Editors
Pierre André • Eckart Haneke
Leonardo Marini • Christopher Rowland Payne

Cosmetic Medicine & Surgery

WITH VITALSOURCE® EBOOK

CRC Press
Taylor & Francis Group

Cosmetic Medicine & Surgery

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Cosmetic Medicine & Surgery

Edited by

Pierre André, MD
Paris Université Laser Skin Clinic, Paris, France

Eckart Haneke, MD
Department of Dermatology, University of Bern, Switzerland
Dermatology Practice Dermaticum, Freiburg, Germany
Department of Dermatology, University of Ghent, Belgium
Centro de Dermatologia Epidermis, Porto, Portugal

Leonardo Marini, MD
Skin Doctors' Centre, Trieste, Italy

Christopher Rowland Payne, MBBS, MRCP
The London Clinic, London, UK

CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

© 2016 by Taylor & Francis Group, LLC
CRC Press is an imprint of Taylor & Francis Group, an Informa business

No claim to original U.S. Government works

Printed on acid-free paper
Version Date: 20160923

International Standard Book Number-13: 978-1-4822-0809-2 (Pack - Book and Ebook)

This book contains information obtained from authentic and highly regarded sources. Reasonable efforts have been made to publish reliable data and information, but the author and publisher cannot assume responsibility for the validity of all materials or the consequences of their use. The authors and publishers have attempted to trace the copyright holders of all material reproduced in this publication and apologize to copyright holders if permission to publish in this form has not been obtained. If any copyright material has not been acknowledged please write and let us know so we may rectify in any future reprint.

Except as permitted under U.S. Copyright Law, no part of this book may be reprinted, reproduced, transmitted, or utilized in any form by any electronic, mechanical, or other means, now known or hereafter invented, including photocopying, microfilming, and recording, or in any information storage or retrieval system, without written permission from the publishers.

For permission to photocopy or use material electronically from this work, please access www.copyright.com (http://www.copyright.com/) or contact the Copyright Clearance Center, Inc. (CCC), 222 Rosewood Drive, Danvers, MA 01923, 978-750-8400. CCC is a not-for-profit organization that provides licenses and registration for a variety of users. For organizations that have been granted a photocopy license by the CCC, a separate system of payment has been arranged.

Trademark Notice: Product or corporate names may be trademarks or registered trademarks, and are used only for identification and explanation without intent to infringe.

Visit the Taylor & Francis Web site at
http://www.taylorandfrancis.com

and the CRC Press Web site at
http://www.crcpress.com

Contents

Contributors . . . . . *ix*

PART I: FUNDAMENTAL ASPECTS

1. **What is beauty? A historical excursus through a continuously evolving subjective and objective perception** **3**
   Eckart Haneke
2. **Body dysmorphic disorder** **7**
   Marie-France Mihout
3. **Pathophysiology of skin aging** **11**
   Laurent Meunier
4. **Clinical signs of aging** **17**
   Claire Beylot
5. **Stem cells and growth factors** **29**
   Klaus Sellheyer
6. **Adipose tissue: Development, physiology, and pathophysiology** **43**
   Max Lafontan
7. **How to evaluate aging skin: Tools and techniques** **59**
   Sophie Mac-Mary, Jean-Marie Sainthillier, and Philippe Humbert
8. **The aesthetic consultation** **67**
   Christopher M.E. Rowland Payne and Uliana Gout

PART II: COSMETIC ASPECTS

9. **Cosmetics and cosmeceuticals** **77**
   Martina Kerscher and Heike Buntrock
10. **Photoprotection** **89**
    Brian L. Diffey
11. **Allergic risks to cosmetics and hypersensitive skin** **99**
    An E. Goossens and Martine Vigan
12. **Hormones and the skin** **107**
    Gérald E. Piérard, Claudine Piérard-Franchimont, and Trinh Hermanns-Lê
13. **Diet and the skin** **113**
    Alessandra Marini
14. **The red face** **119**
    Tamara Griffiths
15. **Pigmentation of the face** **125**
    Lara Tripo, Alice Garzitto, and Ilaria Ghersetich

16. Makeup techniques in dermatology **131**
Zoe Diana Draelos

17. Nail care, nail modification techniques, and camouflaging strategies **139**
Bertrand Richert, Christel Scheers, and Josette André

18. Focal hyperhidrosis: Diagnosis, treatment, and follow-up **155**
Oliver Kreyden

19. Cosmetic tattooing **173**
Nicolas Kluger

20. Body piercings **179**
Nicolas Kluger

PART III: MINIMALLY INVASIVE SURGERY

21. Office surgery for dermatologists **191**
Leonardo Marini

22. Aesthetic suture techniques **207**
Eckart Haneke

23. Dressing systems in cosmetic dermatology **219**
Maurice J. Dahdah and Bertrand Richert

24. Local anesthesia for dermatological surgery **225**
José J. Pereyra-Rodriguez, Javier Domínguez Cruz, and Julian Conejo-Mir

25. Management of abnormal scars **233**
Roland Kaufmann, Eva Maria Valesky, and Markus Meissner

26. Cosmetic surgery of the scalp **249**
Pierre Bouhanna

27. Endovascular procedures for treating chronic venous insufficiency **267**
Claude Garde

28. Phlebectomy **277**
Albert-Adrien Ramelet

29. Nail surgery **287**
Eckart Haneke

30. Superficial and medium-depth chemical peels **303**
Nicolas Bachot, Christopher M.E. Rowland Payne, and Pierre André

31. Deep peels **313**
Nicolas Bachot, Philippe Evenou, and Pierre André

32. Combination chemical peels **319**
Philippe Deprez and Evgeniya Ranneva

33. Dermabrasion **327**
Anthony V. Benedetto

34. 41-Laser dermatology **341**
Serge Mordon and Geneviève Bourg-Heckly

35. Surgical lasers: Ablative and fractional devices **357**
Krystle Wang and Nazanin Saedi

36. Nonablative lasers **371**
Jean-Michel Mazer

37. Intense pulsed light **377**
Hugues Cartier, A. Le Pillouer-Prost, and Saib Norlazizi

38. Photobiomodulation and light-emitting diodes **395**
Michele Pelletier-Aouizérate

39. Radiofrequency **417**
Ines Verner and Boris Vaynberg

40. Fundamentals of ultrasound sources **425**
Shlomit Halachmi and Moshe Lapidoth

41. Lasers for tattoo removal **433**
Isabelle Catoni, Tiago Castro, and Mario A. Trelles

42. Laser and pigmented (melanotic) lesions **473**
Thierry Passeron

43. Lasers, intense pulsed light, and skin redness **481**
Agneta Troilius Rubin

44. Laser and veins **493**
Karin de Vries, Renate R. van den Bos, and Martino H.A. Neumann

45. Lasers and intense pulsed light for hair reduction **501**
Valéria Campos, Luiza Pitassi, and Christine Dierickx

46. Photodynamic therapy for aesthetic indications **511**
Colin A. Morton, Rolf-Markus Szeimies, and Lasse R. Braathen

47. Nonsurgical skin tightening **517**
Ashraf Badawi

48. Cellulite and non-surgical fat destruction **525**
Philippe Blanchemaison and Jade Frucot

49. Cryolipolysis **537**
Hernán Pinto

50. Botulinum toxins: Uses in cutaneous medicine **547**
Uwe Wollina

51. Cosmetic botulinum toxin treatment **557**
Christopher M.E. Rowland Payne and Wolfgang G. Philipp-Dormston

52. Complications and pitfalls of cosmetic botulinum toxin treatment **581**
Christopher M.E. Rowland Payne

53. History of soft-tissue augmentation **591**
Pierre André, Raphael André, and Eckart Haneke

54. Mesotherapy **599**
Philippe Petit and Philippe Hamida-Pisal

55. Hyaluronic acid: Science, indications, and results **617**
Pierre André and Gürkan Kaya

56. Complications of fillers **627**
Eckart Haneke

57. Platelet-rich plasma from science to clinical results **645**
Sabine Zenker

58. Fat grafting **655**
Olivier Claude and Pierre André

59. Liposuction **663**
Daniela Pulcini and Olivier Claude

60. Laser lipolysis **673**
Franck Marie P. Leclère, Serge Mordon, and Mario A. Trelles

61. Soft tissue lifting by suspension sutures **677**
Konstantin Sulamanidze, Marlen Sulamanidze, and George Sulamanidze

62. Blepharoplasty **691**
Serge Morax

PART IV: THE AESTHETIC FACELIFT

63. Facelift: Identity and attractiveness reconstruction **705**
Thierry Besins

64. Development of a therapeutic program: Some rules **707**
Thierry Besins

65. Practical anatomy for face-lifts **709**
Philippe Kestemont and Jose Santini

66. Surgical rejuvenation: Cervico-facial lift technique using the superficial musculoaponeurotic plane technique **717**
Philippe Kestemont and Jose Santini

67. Surgical rejuvenation: The temporal lift **723**
Henry Delmar and Thierry Besins

68. Surgical rejuvenation: Endoscopic brow lift **731**
Henry Delmar

69. Surgical rejuvenation: The midface lift **733**
Henry Delmar

70. Surgical rejuvenation: Autologous adipose grafting **751**
Henry Delmar

71. Positive and negative aspects of face and eyelid cosmetic surgery **757**
Thierry Besins

72. Current and future options for the facelift **759**
Thierry Besins

PART V: OTHER ASPECTS

73. Training in aesthetic and cosmetic dermatology **763**
Argyri Kapellari, Panagiota Riga, and Andreas Katsambas

74. Aesthetic technician **767**
Alexandre Ostojic and Ewa Guigne

75. Internet and e-consultation in aesthetic and cosmetic dermatology **771**
Leonardo Marini

76. Fundamentals of managing and marketing a cosmetic dermatology clinic in the modern world **779**
Wendy Lewis

77. Legal considerations in aesthetic and cosmetic dermatology **789**
David J. Goldberg

Index **795**

Contributors

Josette André Department of Dermatology, St. Pierre–Brugmann and Children's University Hospitals, Université Libre de Bruxelles, Brussels, Belgium

Pierre André Paris Université Laser Skin Clinic, Paris, France

Raphael André Geneva University, Geneva, Switzerland

Nicolas Bachot Private Practice, Paris, France

Ashraf Badawi Laser Institute, Cairo University, Giza, Egypt; Szeged University, Szeged, Hungary; Laser Consultant, Toronto, Ontario, Canada; and European Society for Laser Dermatology, Strasbourg, France

Anthony V. Benedetto Department of Dermatology, Perelman School of Medicine, University of Pennsylvania; and Dermatologic SurgiCenter, Philadelphia, Pennsylvania

Thierry Besins Department of Plastic Surgery, Clinique St. George, Nice, France

Claire Beylot Department of Dermatology, Bordeaux University, Bordeaux, France

Philippe Blanchemaison Department of Vascular Medicine, University of Paris V, Paris, France

Pierre Bouhanna Hair Transplant Clinic, Paris, France

Geneviève Bourg-Heckly Laboratoire Jean Perrin, Université Pierre et Marie Curie–Paris, Paris, France

Lasse R. Braathen University degli Studi Guglielmo Marconi, Rome, Italy; and Dermatology Bern, Bern, Switzerland

Heike Buntrock Division of Cosmetic Science, Department of Chemistry, University of Hamburg, Hamburg, Germany

Valéria Campos Department of Dermatology, University of Mogi das Cruzes, Mogi das Cruzes, Brazil; and Department of Dermatology and Laser, University of Jundiai, Jundiai, Brazil

Hugues Cartier Centre Médical Saint-Jean, Saint-Jean, France

Tiago Castro Laser Division, Instituto Médico Vilafortuny, Cambrils, Spain

Isabelle Catoni Cabinet de Dermatologie Esthétique et Laser, Neuilly sur Seine, France

Olivier Claude Clinique Nescens Spontini, Paris, France

Julian Conejo-Mir Medical-Surgical Dermatology Department, Virgen del Rocio University Hospital, Sevilla, Spain

Maurice J. Dahdah Dermatology Department, American University of Beirut, Beirut, Lebanon

Karin de Vries Department of Dermatology, Erasmus University Medical Center, Rotterdam, The Netherlands

Henry Delmar Private Practice, Antibes, France

Philippe Deprez Clinica Hera, Empuriabrava, Spain

Christine Dierickx Laser and Skin Clinic, Boom, Belgium

Brian L. Diffey Dermatological Sciences, University of Newcastle, Newcastle, United Kingdom

Javier Dominguez Cruz Medical-Surgical Dermatology Department, Virgen del Rocio University Hospital, Sevilla, Spain

Zoe Diana Draelos Dermatology Consulting Services, PLLC, High Point, North Carolina

Philippe Evenou Private Practice, Paris, France

Jade Frucot Biotechnology Engineer

Claude Garde Centre de Sante de la Femme et du Sein, Paris, France

Alice Garzitto Division of Clinical, Preventive, and Oncologic Dermatology, Department of Surgery and Translational Medicine, Florence University, Florence, Italy

Ilaria Ghersetich Division of Clinical, Preventive, and Oncologic Dermatology, Department of Surgery and Translational Medicine, Florence University, Florence, Italy

David J. Goldberg Department of Dermatology, Icahn School of Medicine at Mt. Sinai Fordham Law School, New York, New York

An E. Goossens Department of Dermatology, Katholieke Universiteit Leuven, Leuven, Belgium

Uliana Gout Private Practice, London, United Kingdom

Tamara Griffiths Manchester Academic Health Science Centre, Dermatology Centre, The University of Manchester, Manchester, United Kingdom

Ewa Guigne Clinique Turin, Paris, France

Shlomit Halachmi Herzelia Dermatology and Laser Center, Herzelia Pituach, Israel

Philippe Hamida-Pisal Society of Mesotherapy of the United Kingdom; and Society of Mesotherapy of South-Africa, London, United Kingdom

Eckart Haneke Department of Dermatology, Inselspital, University of Bern, Bern, Switzerland; Dermatology Clinic Dermaticum, Freiburg, Germany; Centro Dermatology, CUF Porto Instituto, Porto, Portugal; Department of Dermatology, Ghent University, Ghent, Belgium

Trinh Hermanns-Lê Department of Dermatopathology, Liège University Hospital, Liège, Belgium

Philippe Humbert Department of Dermatology, Research and Studies Center on the Integument (CERT), Clinical Investigation Center (CIC BT506), Besançon University Hospital, Besançon, France; University of Franche-Comté, Besançon, France

Argyri Kapellari First Dermatology Department, University of Athens, Athens, Greece

Andreas Katsambas First Dermatology Department, University of Athens, Athens, Greece

Roland Kaufmann Department of Dermatology, Venereology and Allergology, Goethe-University Hospital, Frankfurt, Germany

Gürkan Kaya Department of Dermatology, University Hospital of Geneva, Geneva, Switzerland

Martina Kerscher Division of Cosmetic Science, Department of Chemistry, University of Hamburg, Hamburg, Germany

Philippe Kestemont Clinique Esthetique St. George, Nice, France

Nicolas Kluger Department of Dermatology and Allergology, University of Helsinki; and Helsinki University Hospital, Helsinki, Finland

Oliver Kreyden Dermatology and Venereology FMH, Kreyden Dermatology, Kreyden Hyperhidrosis, Kreyden Aesthetics, Praxis Methininserhof, Muttenz, Switzerland

Max Lafontan Max Lafontan Institute of Metabolic and Cardiovascular Diseases, National Institute of Health and Medical Research (Inserm), France; and Paul Sabatier University, Toulouse, France

Moshe Lapidoth Department of Dermatology, Rabin Medical Center, Petach Tikva, Israel; and Herzelia Dermatology and Laser Center, Herzelia Pituach, Israel

Franck Marie P. Leclère Department of Plastic Surgery, Gustave Roussy, Villejuif, France; and Department of Plastic Surgery and Hand Surgery, Inselspital, Bern University, Bern, Switzerland; and Lille University, Lille, France

Wendy Lewis Wendy Lewis & Co Ltd., New York, New York

Sophie Mac-Mary Skinexigence, Besançon, France

Alessandra Marini Institut für Umweltmedizinische Forschung, Leibniz Research Centre for Environmental Medicine at the Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany

Leonardo Marini The Skin Doctors' Center, Trieste, Italy

Jean-Michel Mazer Centre Laser International de la Peau-Paris, Paris, France

Markus Meissner Department of Dermatology, Venereology and Allergology, Goethe-University Hospital, Frankfurt, Germany

Laurent Meunier Department of Dermatology, Hôpital Carémeau, CHU Nîmes, France; and Institute of Biomolecules Max Mousseron, University of Montpellier I, Montpellier, France

Marie-France Mihout Dermatologist and Psychiatrist, Dermatology Clinic, Hôpital Charles Nicolle, Rouen, France (retired)

Serge Morax Department of Ophthalmic Plastic Reconstructive Surgery, Rothschild Ophthalmic Foundation, Paris, France

Serge Mordon University of Lille, Inserm, CHU Lille, U1189 - ONCO-THAI - Image Assisted Laser Therapy for Oncology, Lille, France

Colin A. Morton Department of Dermatology, Stirling Community Hospital, Stirling, United Kingdom

Martino H.A. Neumann Department of Dermatology, Erasmus University Medical Center, Rotterdam, The Netherlands

Saib Norlazizi PulsarLab Ltd., Brynsiriol Pantlasau, Morriston Swansea, United Kingdom

Alexandre Ostojic Department of Dermatology, CHU Henri Mondor, University of Paris-Est, Creteil, France

Thierry Passeron Department of Dermatology & INSERM U1065, C3M, University Hospital of Nice, Nice, France

Michele Pelletier-Aouizérate European Led Academy; Aesthetic and Dermatology Laser Center, Toulon, France

José J. Pereyra-Rodriguez Medical-Surgical Dermatology Department, Virgen del Rocio University Hospital, Sevilla, Spain

Philippe Petit World Anti-Aging Mesotherapy Society, French and International Society of Mesotherapy, Bordeaux, France

Wolfgang G. Philipp-Dormston Hautzentrum Köln, Cologne, Germany

Gérald E. Piérard Department of Clinical Sciences, Liège University Hospital, Liège, Belgium; and Department of Dermatology, University of Franche-Comté, Besançon, France.

Claudine Piérard-Franchimont Department of Clinical Sciences, Liège University Liège, Belgium; and Department of Dermatopathology, Liège University Hospital, Liège, Belgium

A. Le Pillouer-Prost Dermatology Center, Le Grand Prado, Marseille, France

Hernán Pinto Aesthetic Specialties & Aging Research Institute (i2e3), Barcelona, Spain

Luiza Pitassi Department of Dermatology, University of Campinas São Paulo, São Paulo, Brazil

Daniela Pulcini Clinique Nescens Spontini, Paris, France

Albert-Adrien Ramelet Department of Dermatology, Inselspital, University of Bern, Bern, Switzerland

Evgeniya Ranneva Clinica Hera, Empuriabrava, Spain

Bertrand Richert Department of Dermatology, Brugmann–St. Pierre and Children's University Hospitals, Université Libre de Bruxelles, Brussels, Belgium

Panagiota Riga First Dermatology Department, University of Athens, Athens, Greece

Christopher M.E. Rowland Payne The London Clinic, London, United Kingdom

Nazanin Saedi Department of Dermatology and Cutaneous Biology, Thomas Jefferson University, Philadelphia, Pennsylvania

Jean-Marie Sainthillier Skinexigence, Besançon, France

Jose Santini Head and Neck Institute of Nice, Nice, France

Christel Scheers Department of Dermatology, Université Libre de Bruxelles, Brussels, Belgium

Klaus Sellheyer Department of Dermatology, Cleveland Clinic Foundation, Cleveland, Ohio

Konstantin Sulamanidze Private Practice, Tbilisi, Georgia

George Sulamanidze Private Practice, Tbilisi, Georgia

Marlen Sulamanidze Private Practice, Tbilisi, Georgia

Rolf-Markus Szeimies Department of Dermatology and Allergology, Klinikum Vest GmbH, Recklinghausen, Germany

Mario A. Trelles Department Plastic Surgery, Instituto Médico Vilafortuny, Cambrils, Spain

Lara Tripo Division of Clinical, Preventive, and Oncologic Dermatology, Department of Surgery and Translational Medicine, Florence University, Florence, Italy

Agneta Troilius Rubin Department of Dermatology, Centre for Laser & Vascular Anomalies, Skåne University Hospital, Jan Waldenströmsgatan, Sweden

Eva Maria Valesky Department of Dermatology, Venereology and Allergology, Goethe-University Hospital, Frankfurt, Germany

Renate R. van den Bos Department of Dermatology, Erasmus University Medical Center, Rotterdam, The Netherlands

Boris Vaynberg Venus Concept Ltd., Yokneam, Israel

Ines Verner Verner Clinic - Aesthetics, Lasers & Dermatology, Kiriat Ono, Israel

Martine Vigan University Hospital Jean Minjoz Besançon, Besançon, France

Krystle Wang The Menkes Clinic & Surgery Center, Mountain View, California

Uwe Wollina Department of Dermatology and Allergology, Hospital Dresden-Friedrichstadt, Academic Teaching Hospital of the Technical University of Dresden, Dresden, Germany

Sabine Zenker Dermatology Surgery Clinic Munich, Munich, Germany

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

PART I

Fundamental Aspects

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

What is beauty? A historical excursus through a continuously evolving subjective and objective perception

Eckart Haneke

The striving for beauty is as old as the history of mankind. In earlier days, beauty meant leading a healthy life and begetting offspring. Although the meaning of perception of beauty has changed with time, beauty is still an ideal for an important proportion of the world's population. However, the following questions remain: "What is beauty; can it be defined; is it subjective or objective; are there measurable criteria?"

An old saying claims that "beauty is in the eye of the beholder." The origins of this saying can be traced back to the third century BC in Greece, but its current form appeared in the nineteenth century. The literal meaning is that the perception of beauty is subjective. David Hume in *Essays, Moral, Political, and Literary*, 1742, wrote, "Beauty in things exists merely in the mind which contemplates them" [1]. There are endless more meanings and definitions of beauty, which have varied across time, civilizations, religions, and cultures.

Does personal taste actually and really determine beauty? Is beauty just a matter of taste, what you like, or what pleases you, or does it possess more objective qualities? Thomas Dubay [2] defines beauty in line with science: "The beautiful is that which has unity, harmony, proportion, wholeness, and radiance." Plato described the opposite of beauty as the unpleasantness of seeing a body with one excessively long leg. A disproportionate, asymmetrical person lacks harmony and proportion.

Does beauty have a *moral* component? Persons of great personal beauty should not merely be admired based on their form but also on their substance. Personal beauty extends well beyond possessing physical symmetry. Dubay claims that beauty *is* moral. It is a virtue, an image of goodness as well as an image of proportion. "You can recognize truth by its beauty and simplicity" (Richard Feynman, Nobel laureate in physics). A beautiful performance necessitates honesty, integrity, and no cheating. Even a dishonest person appreciates honesty, but appreciation of morality does not require cultivation of morals. However, just because we can recognize the moral component of beauty does not mean that we are, in fact, beautiful [2]. In ancient Greece, this concept of *kalokagathia*, the ideal of the beautiful and good and the unity of physical beauty and moral value, was developed and became important in the civilization of the Middle Ages [3].

Socrates was said to have asked the sophist Hippias of Elis: "What is beauty?" Hippias replied: "Beauty is a pretty girl, beauty is gold; and beauty is to be rich and respected." Socrates was disappointed and said, "They are beautiful, but you do not know what beauty is!" Socrates' answer was "It is not a question of knowing what is beautiful and what is not, but rather to define beauty and to say what makes beautiful things *beautiful*." His three answers were beauty is that which is appropriate, which is useful, and which is favorable, and he added a fourth definition: beauty is the pleasure that comes from seeing and hearing. What was Hippias' mistake? He did not understand the difference between a beautiful object and beauty as a category.

Is beauty really in the eyes of the beholder? This saying reflects what a certain subject *finds* beautiful, but this is no definition of beauty.

Generations of professionals have repeated this assumption, from fashion tsars to beauticians to cosmetic surgeons and particularly the consumer. In Latin, "*de gustibus non est disputandum*" meant you cannot dispute about taste. What is assumed as beauty has a lot to do with taste. And taste is, of course, extremely subjective and varies from person to person.

How should beauty be defined? In the eye of the beholder? Scientifically? Morally? Why? A popular encyclopedia defines the saying in the way that individuals have different inclinations on what is beautiful and that they have different beauty standards [4].

Socrates' question was not what beautiful is, but what *beauty* is. What makes something or somebody that we call beautiful really beautiful? It is *the beauty behind* it.

The German cosmetics producer Nivea performed a survey all over the world: "What do women believe beauty is?" The answers were very ambiguous. First, the interviewers found out what women *find* beautiful. However, despite all cultural, ethnic, and religious differences, the *archetype of a beautiful woman* is universal: not too tall, and having a symmetrical face, smooth skin, shiny long hair, large eyes, and white teeth. This has been confirmed with facial primes in large cohorts [5,6]. Smooth skin is also a relevant factor for hand attractiveness [7]. The value of *beauty* for the industry is enormous: the overall sales of the beauty industry were $330 billion in 2010 [8].

Studies by researchers from cultural, behavioral, and cognitive sciences confirmed the pattern of a general sense of beauty [9]. Brain researchers found cerebral regions associated with the recognition of beauty [10]. These aesthetic centers start being activated when one recognizes symmetry and order [11]. The brain has neurons exclusively reacting to order. Infants just a few days old look longer at beautiful faces. It takes our brain only 1/7 of a second (150 milliseconds) to distinguish between ugly and beautiful. Attractive face recognition is a fast process [12,13]. Handsome men and beautiful women generally have better chances in professional life. Attractive faces are immediately held to be more trustworthy [14], probably due to a shared brain activity for aesthetic and moral judgments [15]. Persons with a cerebral insult in a certain cortical region lose the ability to recognize

a face while still retaining the ability recognize a person by his or her voice or gait. They can also evaluate whether a face is attractive or not.

Research suggests that we view our loved ones through rose-tinted glasses that overlook the crooked noses, bulging tummies, or other attributes that might put others off. This again is in line with the notion of beauty being an advantage in daily life. Aristotle said: "Beauty is a greater recommendation than any letter of introduction." "The three wishes of every man: to be healthy, to be rich by honest means, and to be beautiful" is ascribed to Plato.

On the other hand, beauty was shown to hinder attention switch [16,17].

We can ask again: What is beauty? Is *beauty* really *in the eyes of the beholder*? Whereas almost everybody believes to know what it is, hardly anybody can define beauty.

Researchers have found universal biological aspects of beauty, which may be influenced by culture and historical developments [18,19]. In the 1930s, the American mathematician George David Birkhoff proposed a formula to measure beauty [20]:

$$M = \frac{O}{C}$$

where
M is the aesthetic measure
O is the order
C is the complexity

In case of visual arts, order O depends on geometrical relations among identifiable segments of an evaluated object (e.g., curves or planes). Attributes such as symmetry and balance are considered to be relevant for an intense aesthetic perception. Complexity C is "the number of localities our sight will spontaneously rest on." Complexity negatively affects overall aesthetic measure since complex objects tend to deflect an onlooker's contemplation. Order was refined in more detail in a study of ancient Chinese vases [21]:

$$M = \frac{H + V + P + T}{C}$$

where
- H represents the horizontal order, defined by the number of independent relations of ratios 1:1 and 2:1 within pairs of horizontal distances $hi;hj$ between symmetrical characteristic points, $H \leq 4$.
- V stands for the vertical order, defined by the number of independent relations of ratios 1:1 and 2:1 within pairs of adjacent vertical distances $v_i;v_j$ between characteristic points, $V \leq 4$.
- P stands for the proportional order defined by the number of independent relations of ratios 1:1 and 2:1 within pairs of horizontal and adjacent vertical distances $h_i;v_j$ between characteristic points, $P \leq 2$.
- T represents the tangent order and is defined by the number of the following independent relations $T \leq 4$: Perpendicularity of characteristic tangents, parallelism of nonvertical characteristic tangents, verticality of a characteristic tangent at the terminal or inflex points, and intersection of a characteristic tangent or its normal with the vase center are components of a tangent order.

This formula was intended to aesthetically measure nonliving objects. It wonderfully describes a classical violin. One of the marvels of medieval architecture, the Taj Mahal, or the medieval cathedrals, both romanic and gothic, perfectly fit into the extended aesthetic measure. But is it really restricted to nonliving objects? As shown in the worldwide survey, symmetry and proportion are also valued in persons. Classical sculptures stand out by their proportion; distorting one part is immediately recognized as disturbing. A proportionate sculpture activates the insular cortex; a distorted does not.

If beauty of living individuals cannot clearly be defined, can it at least be differentiated from other positive feelings? Aesthetic, attractiveness, and beauty are often used interchangeably. The question is whether this is correct or not. Whereas beauty, to a large extent and for certain objects, can be measured with the mathematical formula, it is an objective category and does not depend on time and fashion, whereas attractiveness is a personal feeling. It is part of social affinity and the basis of individual communication [22]. In intergender relations, sex appeal is part of this attractiveness. No one will deny that some persons are attractive to one and unattractive to another person.

Is there a sense for beauty in nature? In the Middle Ages, there was a golden rectangle, the particularity of which is when a square is removed, another golden rectangle remains. Its sides are $1 : ([1 + \sqrt{5}] / 2)$, which is $1 + \varphi$ with phi being about 1.618.

In nature, the golden angle exists. Mathematically, it is defined as

$$\frac{a+b}{a} = \frac{a}{b}$$

The golden angle is then the angle subtended by the smaller arc of length b. It measures approximately 137.508° [23]. The golden angle plays a significant role in the theory of phyllotaxis. Most notably, the golden angle is the angle separating the florets on a sunflower [24].

The seeds of the sunflower are arranged in spirals. This is governed by nature. The arrangement of the seeds repeats after every 137.5°, the "golden angle." The full circle of 360° is divided in relation to the "golden section."

In the animal kingdom, males are usually the more beautiful because they have to court the female in order to mate and beget offspring. In mankind, females are called the "beautiful gender" and a man's physical beauty is often replaced by his thick wallet. This is a biological fact: wealthy men can better guarantee a good future for the offspring. In couples where the man is rich, the first child is usually his, whereas the next may come from physically more attractive men.

Test series with male faces and hands showed the same ideals for both genders. Whereas in ancient Hellas, a boy was considered to be a beautiful person, this has now changed as we consider women to be more beautiful. The universal standard of a beautiful woman was already mentioned. But there is much more in the mind of both men and women. When seeing a physically good-looking woman, we may consider her a warm and touching beauty that (almost) everybody would like; a "hot" beauty is more seen as a sexually attractive being, whereas a "cold" beauty may be perfect like a classical statue but without personal radiance.

Color is an important part for perceiving beauty. Red apparently has a particular attraction; in many ethnies, red stands for warm, vivid, and stimulating. In eastern slawic and

Yamomi Indian languages, as well as in some Arabic dialects, red and beautiful/good are the same words, or they have the same origins for the word. In some languages, the words for beauty are also synonyms for balance and symmetry.

However, beauty is not only visual. As found out by researchers, palpation of a smooth skin can also arouse the same feelings as seeing a beautiful object. There is no doubt that acoustic beauty exists. In Bach's organ music, one can find harmony and order.

Olfactory beauty is realized with some classic perfumes or the smell of particular fruits. This is closely linked with taste. Gustatory beauty may also exist, for instance, in a delicious meal, even though we do not speak of food or a drink having a "beautiful taste."

CONCLUSION

"Beauty is in the eyes of the beholder" is not correct—what you *find beautiful* is in your eyes or, better, in *your mind*. There is a universal sense of beauty; however, the differentiation between beauty, aesthetics, and attractiveness is somewhat arbitrary.

REFERENCES

1. Hume D. In: Miller EF, ed. *Essays, Moral, Political, and Literary.* Indianapolis, IN: Library of Economics and Liberty, 1987. http://www.econlib.org/library/LFBooks/Hume/hmMPL.html. Accessed June 1, 2013.
2. Dubay T. *The Evidential Power of Beauty—Science and Theology Meet*. San Francisco, CA: Ignatius Press, 1999.
3. Dürrigl MA. Kalokagathia—Beauty is more than just external appearance. *J Cosmet Dermatol* 2002; 1:208–210.
4. http://en.wiktionary.org/wiki/beauty_is_in_the_eye_of_the_beholder.
5. Stepanova EV, Strube MJ. What's in a face? The role of skin tone, facial physiognomy, and color presentation mode of facial primes in affective priming effects. *J Soc Psychol* 2012; 152:212–227.
6. Jones BC, Little AC, Burt DM, Perrett DI. When facial attractiveness is only skin deep. *Perception* 2004; 33:569–576.
7. Kościński K. Determinants of hand attractiveness—A study involving digitally manipulated stimuli. *Perception* 2011; 40:682–694.
8. Jones G. Globalization and beauty: A historical and firm perspective. *Euramerica* 2011; 41:885–916.
9. Makin AD, Pecchinenda A, Bertamini M. Implicit affective evaluation of visual symmetry. *Emotion* 2012; 12:1021–1230.
10. Jacobsen T. Beauty and the brain: Culture, history and individual differences in aesthetic appreciation. *J Anat* 2010; 216:184–191.
11. Zhang Y, Kong F, Chen H, Jackson T, Han L, Meng J, Yang Z, Gao J, Najam ul Hasan A. Identifying cognitive preferences for attractive female faces: An event-related potential experiment using a study-test paradigm. *J Neurosci Res* 2011; 89:1887–1893.
12. Rellecke J, Bakirtas AM, Sommer W, Schacht A. Automaticity in attractive face processing: Brain potentials from a dual task. *Neuroreport* 2011; 22:706–710.
13. Marzi T, Viggiano MP. When memory meets beauty: Insights from event-related potentials. *Biol Psychol* 2010; 84:192–205.
14. Bzdok D, Langner R, Caspers S, Kurth F, Habel U, Zilles K, Laird A, Eickhoff SB. ALE meta-analysis on facial judgments of trustworthiness and attractiveness. *Brain Struct Funct* 2011; 215:209–223.
15. Tsukiura T, Cabeza R. Shared brain activity for aesthetic and moral judgments: Implications for the Beauty-is-Good stereotype. *Soc Cogn Affect Neurosc* 2011; 6:138–148.
16. Liu CH, Chen W. Beauty is better pursued: Effects of attractiveness in multiple-face tracking. *Q J Exp Psychol* 2012; 65:553–564.
17. Chen W, Liu CH, Nakabayashi K. Beauty hinders attention switch in change detection: The role of facial attractiveness and distinctiveness. *PLOS ONE* 2012; 7(2):e32897.
18. Perrett DI, Burt DM, Penton-Voak IS. Symmetry and human facial attractiveness. *Evol Hum Behav* 1999; 20:295–230.
19. Tomasello M. *The Cultural Origins of Human Cognition*. Boston, MA: Harvard University Press, 2000.
20. Birkhoff GD. *Aesthetic Measure*. Cambridge, MA: Harvard University Press, 1933.
21. Staudek T. On Birkhoff's aesthetic measure of vases. FI-MU-RS 99-06, Faculty of Informatics, Masaryk University, Brno, Czech Republic, 1999.
22. Sattler G. *Auf der anderen Seite des Spiegels: Aus dem Alltag eines Schönheitschirurgen*. München, Germany: Droemer, 2008.
23. http://en.wikipedia.org/wiki/Golden_angle.
24. Prusinkiewicz P, Lindenmayer A. *The Algorithmic Beauty of Plants*. Heidelberg, Germany: Springer-Verlag, 1990, pp. 101–107.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Body dysmorphic disorder

Marie-France Mihout

Body dysmorphic disorder (BDD) is a mental disorder in which the affected person is excessively concerned and preoccupied by a perceived defect in his or her physical features. They are convinced of having visible defects, although most of the time these are nonexistent or only of minor importance. The sufferers may complain of several specific features or one single feature of their general appearance. They waste much time in front of the mirror in looking at themselves inquiringly; the pathologic threshold seems to be more than 1 hour per day, causing psychological distress that impairs occupational and/or social functioning, sometimes to the point of severe depression, severe anxiety, the development of other anxiety disorders, social withdrawal or complete social isolation, and more.

Repeated visits to surgeons or dermatologists in an attempt to correct the defect are common; most of the time, the defect is grossly exaggerated.

It is estimated that 1%–2% of the world's population meets all the diagnostic criteria for BDD. The "dysmorphophobia" is a real phobia: a morbid fear, like others' phobias about snakes or spiders; these persons are convinced of having visible defects and are afraid of their appearance and the way other people look at them. To summarize, this is imaginary ugliness.

BDD is defined by the DSM-IV-TR and is assigned to the larger category of somatoform disorders 1994 (Appendix 4) [1], which are disorders characterized by physical complaints that appear to be medical in origin but that cannot be explained in terms of a physical disease, the result of substance abuse, or another mental disorder (normally without delusion, although it can occur).

The disorder can be seen in earlier literature [2], but the earliest known case of BDD in the medical literature was reported by an Italian physician, Enrique Morselli, in 1891; the disorder was not defined as a formal diagnostic category until the introduction of DSM-III-R in 1987. The World Health Organization did not add BDD to the International Classification of Diseases until 1992. The word "dysmorphic" comes from two Greek words that mean "bad" or "ugly" and "shape" or "form"; BDD was previously known as dysmorphobia [3].

EPIDEMIOLOGY

The usual age of onset is late childhood or early adulthood. In 75% of the cases, troubles will persist. The average age of patients diagnosed with the disorder is 17, but the disorder can remain undiagnosed for a long period. In addition, patients are so often ashamed of grooming rituals and other associated behaviors that they may avoid telling their doctor about them. They are more likely to consult an esthetic surgeon or dermatologist [4]. As many as 50% of patients diagnosed with BDD undergo plastic surgery.

The sex ratio seems to be like that of obsessive compulsive disorder (OCD)/BDD and is often misunderstood to affect mostly women, but research shows that it affects men and women equally, unlike the anxiety disorders whose sex ratio is 2:1 female/male. The DSM-IV-TR classification added references to concern about bodybuilding and excessive weight lifting to DSM-IV's description of BDD, in order to cover "muscle dysmorphia," which mainly affects men.

Causes

The causes of BDD fall into many categories.

Neuropsychological Causes

The problem of body image has to be considered all the way from the purely sensory origin of the perception of the body based on the senses to the more abstract concept of a body schema. Furthermore, the patient's own experiments at manipulating the body schema into the perceived body image become a component of the sense of the self.

It is important to point out that the body schema is broadly the same for any human, but body image is particular to each individual, because it is intimately acquainted with the patient's own story [5], representing the total concept, including conscious and unconscious feelings, thoughts, and perceptions that a person has of his or her own body as an object in space independent and apart from other objects. The body image develops during infancy and childhood from exploration of his or her body surface and orifices (sucking, biting, touching) from the development of physical abilities and from play and comparison of the self with others. Body image is strongly influenced by parental attitudes that give the child a perception of certain body parts as good, clean, and attractive or bad, dirty, and repulsive.

Psychoanalytic Approach

The "Skin-Ego" is a psychoanalytic concept by Anzieu, heir to the Freudian ego (it is, strictly speaking, a fantasy—even according to the author, "a huge metaphor" [6]). For Anzieu, the skin supplies the psychic inner mind with constituent perceptions of oneself [8]. He allocates psychic duties to the skin as follows:

Heaving
Containing protective shield
Developing a personality of one's own intersensorial ability and sexual arousal support
Recharging one's libido-registered sensorial and emotional contents—self-destruction (self–nonself)

The concept of one's body image is more a function of the quality of libidinal "cathexis" than of reality. On one hand, there is the real objective anatomy, while on the other hand the

wished-for anatomy. The mother's role is to mold all the things that have been lived through, feelings and so on. In that way, in some cases, when "organ pleasure identification" fails in the early maternal exchanges, the baby's "affects," those that persist in life, become one experience of mental suffering.

Neurobiological Causes

In neurological and embryological development, brain and skin are formed very early in the development of the embryo from the ectoderm.

Research indicates that patients diagnosed with BDD have serotonin levels that are lower than normal. Serotonin is a neurotransmitter (a chemical produced by the brain that aids in transmitting nerve impulses across the junctions between nerve cells). Low serotonin levels are associated with depression and other mood disorders.

Psychosocial Causes

Another important factor in the development of BDD is the influence of the mass media in developed countries, particularly the role of advertising in spreading images of physically "perfect men and women." Impressionable children and adolescents absorb the message that anything short of physical perfection is unacceptable. They may then develop distorted perceptions of their own faces and bodies [7].

Body Dysmorphic Disorder Has a High Rate of Comorbidity

The prevalence of BDD in psychiatry has been calculated to be about 13%, although some doctors think that it is underdiagnosed because it coexists so often with other psychiatric disorders [8], which means that people diagnosed with the disorders are highly likely to have been diagnosed with another psychiatric disorder [9,10].

Most other commonly associated psychiatric disorders are

- Major depression (about 29% of patients with BDD eventually try to commit suicide)
- OCDs and trichotillomania
- Social phobia
- Drug addiction
- Psychiatric hospitalization (the prevalence is 13%)
- Anorexia nervosa
- Olfactory reference syndrome

And there are many esthetic consequences:

- Incorrectly performed surgery (when disappointed, the patient's condition can become worse)
- Medical nomadism to find a practitioner who will agree to their requests
- Frequent requests for repeated or unnecessary procedures, with discontent with the result

BDD must be evaluated for severity in advance of any treatment [7,11].

Detection

BDD Modification of the Yale Brown Obsessive Compulsive Scale

The *Yale Brown Obsessive Compulsive Scale Modified for BDDs* is a 12-item semistructured clinician-rated instrument designed to rate the severity of BDD [9]. Its purpose is to produce a quick and reliable evaluation of the severity of the illness and to evaluate the threshold of the patient's consciousness of the illness in order to give the appropriate treatment. For each item, the clinician circles the number identifying the response that best characterizes the patient during the previous week.

The scale is a tool for diagnosis to rate the severity of the condition and to give a prognosis for its evolution; it can also be repeated in the course of treatment to reevaluate the severity and prognosis of the condition.

Clinical Aspects

Looking questioningly at the mirror is a compulsive and repetitive activity, reported in 80% of patients. This is a kind of ritualistic behavior performed to manage anxiety, and that takes up excessive amounts of the patient's time; patients are typically upset if someone or something interferes with or interrupts their ritual.

Camouflaging the "problem" feature or body part with makeup, hats, or clothing appears to be the single most common symptom among patients with BDD. (It is reported in 94% of patients [12].)

Treatment

Patients with BDD have in about 40% of cases good self-insight, 20% low self-insight, and 40% bad or no self-insight.

How can the clinician help them? These patients have an incorrect "insight." They are vulnerable because they believe that others are always right. How can they get close to beauty when they think they do not possess it?

Beauty should be fully understood, all things considered, as an emotional reaction. Beauty often easily emerges from ordinary relationships with the others and the world.

These patients need to learn again to live serenely with their body, and one has to make them admit that it is their self-representation that is called into question and not reality. They need to learn to use time and hope.

Primary aims in the consultation are as follows:

- Recognize the patient's suffering.
- Do not discuss the reality of the defect.
- Recognize the strength of the patient's anxious preoccupations.
- Engage with the patient and determine with him or her which treatment could improve the condition.
- Wait for any correction to take place.
- See if the demand for change to their appearance continues.

The standard course of treatment of BDD is a combination of medication and psychotherapy.

In some individuals, the clinician must ensure that the somatic preoccupation is not part of another psychiatric disorder such as anorexia nervosa or gender identity disorder.

When the trouble is severe and there is an "unshakeable conviction" (delusion), the main work will be to bring patients round to consulting a psychiatrist, which can sometimes be very difficult. Unshakeable convictions may reveal borderline or even psychotic personality.

In the case of associated depression, the physician has to be careful about underrating the effect of bad mood, sleep, appetite, tiredness, and so on.

The medications most frequently prescribed for patients with BDD are most commonly the selective serotonin reuptake inhibitors (SSRIs [11]):

- *Fluoxetine* and *sertraline* can reduce sleep.
- *Paroxetine* reduces anxiety.

In fact, it is the relatively high rate of positive responses to SSRIs among BDDs that has led to the hypothesis that disorder has a neurobiological component related to serotonin levels in the body. An associated finding is that patients with BDD require higher dosages of SSRI medications than patients who are being treated for depression with the drugs, which would also explain why OCDs are associated.

The use of neuroleptic drugs in patients with borderline psychosis is disappointing and very ineffective.

The most effective approach to psychotherapy with BDD is cognitive behavioral restructuring.

Cognitive-oriented therapy that challenges inaccurate self-perceptions is more effective than purely supportive approaches. Techniques to stop thoughts and encourage relaxation also work well with BDD patients when they are combined with cognitive restructuring [12].

Some doctors recommend couples therapy or family therapy in order to involve the patient's parents, spouse, or partner in his or her treatment. This approach may be particularly helpful if family members are critical of the patient's looks or are reinforcing his or her unrealistic body image.

In complementary therapies, yoga has helped some persons with BDD acquire more realistic perceptions of their bodies and to replace obsessions about external appearance with new respect for their body's inner structure and functioning.

PROGNOSIS

The prognosis of BDD is considered good for patients receiving appropriate treatment. On the other hand, researchers do not know enough about the lifetime course of BDD to be able to offer detailed statistics.

PREVENTION

Parents, teachers, primary health-care professionals, and other adults who work with young people can point and discuss the pitfalls of trying to look "perfect." In addition, parents or the other adults can educate themselves about BDD and its symptoms and pay attention to any warning signs in their children's dress or behavior.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision, Washington, DC: American Psychiatric Association, 2000.
2. Shakespeare W. In RICHARD III oeuvres completes Traduction francaise de Hugo F.V/Paris éd de la Pléiade Gallimard 1959 ACTE I, scène 1.
3. Thoret Y. La dysmorphophobie: comment s'approcher de la beauté. In *XVII juin journée de psychiatrie du val de Loire-Abbaye de Fontevraud*, juin 2003.
4. Manguel A. Chez Borges. Acte Sud, 2003.
5. Phillips KA. The broken mirror. In *Understanding and Treating Body Dysmorphophobic Disorders*. New York: Oxford University Press, 1996.
6. Jeannerod M. De l'image du corps à l'image de soi. *Rev Neuropsychol* 2010; 2(3):185–194.
7. Corraze J. "The Skin-Ego" or the psychoanalytic marvelous. *Evol Psychmot* 1998; 10(40).
8. Bohbot M. Body dymorphophobic disorder. Diplome d'université MMAA, October 22, 2009.
9. Phillips KA. Questionnaire for aid in diagnosis of BDD. *Am J Psychiatry* 2008; 135:1111–1118.
10. Phillips KA. A severity rating scale for BDD. *Psychopharmacol Bull* 1997; 33(1):17–22.
11. Anzieu D. *The Skin Ego*. New Haven, CT: Yale University Press, 1989 (The International Journal of Psychoanalysis), p. 232. *Le Moi Peau*. Paris: Bordas, 1985.
12. Aouizerate B, Pujol H, Grabot D, Faytout M, Suire K, Braud C, Auriacombe M, Martin D, Baudet J, Tignol J. Body dysmorphic disorder in a sample of cosmetic surgery applicants. *Eur Psychiatry* 2003; 18(7):365–368.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Pathophysiology of skin aging

Laurent Meunier

INTRODUCTION

Skin aging is a complex process determined by genetic factors (intrinsic aging) and cumulative exposure to external factors such as ultraviolet radiation (UVR), smoking, and particle pollution (extrinsic aging) [1–4]. The fine wrinkles and reduced elasticity, which characterize intrinsically aged skin, are exaggerated in photoaged skin, where exposure to UVR is associated with the development of both deep wrinkles and a marked loss of elasticity. Photoaging, like chronological aging, is a cumulative process that depends primarily on the degree of sun exposure and skin pigment. Individuals who have outdoor lifestyles, live in sunny climates, and are lightly pigmented will experience the greatest degree of photoaging [5].

STRUCTURAL AND FUNCTIONAL CHANGES

Major structural and functional changes occur in the dermal extracellular matrix (ECM) where fibrillar collagens, elastic fibers, and proteoglycans are required to confer tensile strength, resilience, and hydration, respectively. The extreme longevity of these biomolecules, compared with intracellular proteins, promotes the accumulation of damage over time, which in turn impacts on their ability to mediate tissue homeostasis [1]. Skin function is mediated primarily by the structure of the epidermal and dermal layers. The two layers are joined by the dermal–epidermal junction (DEJ) in which basal epidermal keratinocytes are secured to a type IV collagen-rich basement membrane (BM) by hemidesmosomes, and the dermis is anchored by collagen VII fibrils and fibrillin-rich microfibril bundles. The disruption of BM at the DEJ in sun-exposed skin may be induced by increased levels of BM-damaging enzymes, such as plasmin and matrix metalloproteinases (MMPs). The impairment of BM structure may be associated with functional changes of epidermal cells and dermal cells and consequently facilitates aging processes by damaging dermal ECM and inducing abnormal keratinocyte responses [6]. Collagens I and III are the most abundant proteins in the dermis and are preferentially distributed in the papillary and deep reticular dermis. Collagen VII is localized to perpendicularly oriented anchoring fibrils that play a key role in securing the dermis to the DEJ. Elastic fibers are composed of multiple components, including cross-linked elastin, fibrillin-rich microfibrils, microfibril-associated glycoproteins, fibulins, and latent transforming growth factor (TGF)-binding proteins. Many ECM proteins are glycoproteins, which have undergone posttranslational modification with numerous oligosaccharides. In contrast, proteoglycans are glycoproteins, in which at least one of the oligosaccharide side chains is a glycosaminoglycan (GAG). Glycoproteins and proteoglycans are distributed throughout the dermis where they play a key role in maintaining skin hydration [1].

In intrinsically aged skin, there is evidence not only for the degradation of fibrous ECM components, including elastin, oxytalan fibers, and collagens I, III, and IV, but also for the loss of the oligosaccharide fraction, which in turn impacts on the ability of skin to retain bound water. Reduced production of type I procollagen is a prominent feature of chronologically aged human skin. Recent findings indicate that downregulation of the TGF-β/Smad/connective tissue growth factor axis likely mediates reduced type I procollagen expression in aged human skin [7].

In severely photoaged skin, there is a loss of not only fibrillar collagens (I and III) throughout the dermis but also the loss of collagen VII anchoring fibrils at the DEJ. In contrast, dermal GAG content, in particular hyaluronic acid (HA) and the chondroitin sulphate–containing GAGs, is increased and redistributed to colocalize with the elastic fiber network [1]. HA is an abundant component of skin ECM matrix, where it plays many roles such as hydration and architectural support. Downregulation of HA during photoaging may be due to regulation of hyaluronidase activity induced by UVB exposure [8]. During the early stages of photoaging, both fibrillin-1 and fibulin-5 are lost from the microfibrillar apparatus (oxytalan fibers) at the DEJ. In severely photoaged skin, however, the reticular dermis is characterized by the distribution of abundant, apparently disorganized elastic fiber proteins including tropoelastin, fibrillin-1, fibulin-2 and fibulin-5, and latent TGF-beta binding protein-1 (LTBP-1) [1].

In contrast to intracellular proteins, whose half-lives are measured in hours or days, many ECM proteins have half-lives that are measured in years. This remarkable longevity is thought to predispose them to the risk of molecular aging. In addition, elastin synthesis and deposition is predominantly confined to fetal and early postnatal skin. Thus, elastic fiber proteins are required to function for many years and may be at risk of accumulating damage.

Although the fundamental mechanisms in the pathogenesis of aged skin are still poorly understood, a growing body of evidence points toward the involvement of multiple pathways.

BIOLOGICAL PROCESS OF SKIN AGING

Recent data indicate that the most important biologic processes involved in skin aging are alterations in DNA repair and stability, mitochondrial function, cell cycle and apoptosis, ECM, lipid synthesis, ubiquitin-induced proteolysis, and cellular metabolism. Among others, a major factor that has been implicated in the initiation of aging is the physiologic decline of hormones occurring with age [9].

Matrix Metalloproteinases

Most studies of photoaging have focused on the upregulation and activation of ECM-degrading MMPs [10]. Elevated MMPs in photodamaged dermis can be divided into following groups: collagenases, MMP-1; gelatinases, MMP-2; stromelysins, MMP-3, MMP-9, and MMP-11; membrane-associated, MMP-17 and the recently identified MMP-27 [1].

Among the 18 MMPs expressed in human skin, 7 are significantly elevated in a photodamaged forearm, compared with sun-protected underarm skin, and all MMPs that are elevated in photodamaged skin, except MMP-3, are primarily expressed in the dermis [11].

MMP-1, MMP-3, and MMP-9 are primary UV-inducible collagenolytic enzymes, and MMP-1 is the major protease capable of initiating degradation of native fibrillar collagens in human skin *in vivo* [10,12]. Epidermal keratinocytes are the major cellular source of UV-induced MMPs. However, dermal cells may also play a role in epidermal production of MMPs by release of growth factors or cytokines, which in turn modulate MMP production by epidermal keratinocytes [10]. Interstitial collagenase (MMP-1) initiates the degradation of type I and III fibrillar collagens, and then further degradation is followed by MMP-3 (stromelysin-1) and MMP-9 (gelatinase B) action.

Increased expression of MMP-1 and reduced production of type I collagen by dermal fibroblasts are prominent features of aged human skin. MMP-1-mediated fragmentation of dermal collagen fibrils alters the function of dermal fibroblasts and may be a key driver of age-related decline of skin function [13–16]. With aging, collagen fragmentation reduces fibroblast-ECM binding and mechanical forces, resulting in fibroblast shrinkage and reduced collagen production. Injection of dermal filler, cross-linked HA, into the skin of individuals over 70 years of age stimulates fibroblasts to produce type I collagen and results in an increase in mechanical forces, which also stimulates fibroblast proliferation, expands vasculature, and increases epidermal thickness [17]. *In vitro* collagen fragmentation recreates many of the abnormalities seen in photodamage *in vivo* [11]. These data indicate that fragmentation of the collagenous ECM in photodamaged dermis alters collagen homeostasis by influencing the function of dermal fibroblasts and indicate that fibroblasts in aged human skin retain their capacity for functional activation, which is restored by enhancing structural support of the ECM. Mechanisms by which ECM microenvironment in photodamaged human skin control fibroblast function are not well understood. Fragmented collagen in photodamaged skin may impair integrin signaling events and induce transcription factors such as activator protein-1 (AP-1), which contributes to elevated MMPs and loss of type I collagen expression [11]. Indeed, activated AP-1 binds to the promoter region of the procollagen gene to inhibit its transcription and also activates the MMP gene enzymes that degrade collagen. The matricellular protein cysteine-rich protein 61 (CCN1), a member of the CCN family, is elevated in replicative senescent dermal fibroblasts and in dermal fibroblasts from UV-exposed skin. This protein may mediate MMP-1-induced alterations of collagen fibrils and may promote cutaneous aging and collagen loss via induction of IL-1beta, inhibition of type I collagen production, and upregulation of MMP-1 [18,19].

Aberrant remodelling of the elastic fiber system is likely to have profound cellular and biochemical effects. In particular, elastin fragments appear to exert an influence on the immune system, upregulate elastase expression, and promote apoptosis. Elastin and fibrillin peptides may induce the expression of several MMPs that have the potential to degrade most major dermal ECM. The fibrillin microfibril may also be degraded by direct UV exposure, and the results of this damage may impact not only the mechanical but also the biochemical functions of the tissue by activating lymphocytes, inducing the expression of proteases, and profoundly influencing TGF-β signalling [1]. Among all four known tissue inhibitor of metalloproteinases (TIMP) genes (TIMP-1, TIMP-2, TIMP-3, and TIMP-4) that are expressed in human dermis, none is preferentially expressed in sun-exposed skin. However, overexpression of TIMP-1 in a human skin xenograft photodamage model resulted in significant inhibition of ECM degradation, as well as suppression of decreased skin elasticity and roughness [20].

Reactive Oxygen Species, Mitochondrial DNA, and Telomere Shortening

Mitochondrial DNA (mtDNA) damage, increased reactive oxygen species (ROS) production, and telomere shortening are thought to play a role in the intrinsic aging process. In contrast, the mechanisms leading to photoaging of the skin are caused mainly by the repetitive adsorption of UVR, which can upregulate the expression of ECM proteases via AP-1 signalling. In addition, UVR can directly damage cutaneous biomolecules, which are rich in chromophores, and may induce the production of ROS, which in turn can act on both cells and matrix components. Free radical damage on the skin by chronic ROS and UV stress plays a major role in photoaging. After UV exposure, ROS trigger the release of proinflammatory cytokines and growth factors (AP-1 and NF-kB), which upregulate key MMPs such as MMP-1, MMP-3, MMP-8, and MMP-9. These proteases degrade the collagen and elastin fibers of the ECM. MMP-1 expression is associated with the presence of mtDNA common deletion, and UV-induced ROS have been shown to decrease TGF-β expression, which decreases collagen production and enhances elastin production. Hence, ROS degrade the structural integrity of skin by way of altering the collagen and elastin components of the ECM.

Mutations of mtDNA such as the 4977 base-pair large-scale deletion, also called common deletion, are increased in photoaged skin, and these mutations seem to represent long-term *in vivo* biomarkers for actinic damage in the human skin [21]. Gradual depletion of mtDNA in human skin fibroblast causes a gene expression profile, which is reminiscent of that observed in photoaged skin [22].

The mitochondrial–free radical theory of aging proposes that aging is caused by damage to macromolecules by mitochondrial ROS that may induce mutations in mtDNA, which in turn leads through a vicious circle to further ROS generation. Elevated ROS levels can cause cumulative damage to various cellular molecules, like proteins, lipids, and nucleic acids, and contribute to a decrease in physiological functions with age. Alternatively, ROS may be associated with aging because they play a role in mediating a stress response to age-dependent damage [23]. Anyway, the extent of age-related mitochondrial dysfunction may vary between different tissues and the mitochondrial oxidative stress theory of aging, and its role for human aging remains to be fully understood.

The accumulation of altered proteins within cells, which is one of the most common symptoms of aging, may be due to decreased elimination of oxidized proteins. The ubiquitin–proteasome pathway is implicated in the degradation of oxidized

proteins [24–26] and plays a major role in signal transduction associated with stress and aging [27–29]. In most cases, proteasome activity was reported to decrease with aging, and functional interplay has been described between mitochondrial and proteasome activity in skin aging [30].

Telomeres are specialized DNA structures at the chromosome ends that undergo progressive shortening unless they are elongated by a ribonucleoprotein named telomerase. In somatic cells lacking telomerase, gradual telomere loss and ultimate senescence are inevitable, and consistent with this model, there is a strong association between cell immortalization and persistent telomerase expression. Progressive telomere loss may be responsible for p53 activation and progerin production during cellular senescence [31]. Furthermore, telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice [32].

Recent data suggest that photoaging may be at least in part a process of damage-accelerated intrinsic aging [33]. Indeed, progerin accumulation, which has been described not only in Hutchinson–Gilford progeria syndrome but also during normal intrinsic aging, may be accelerated by UVA-induced ROS [34].

Although intrinsic aging is accompanied by a decline in DNA repair activities attributed to both base excision repair and nucleotide excision repair [35], chronic sun exposure also induced changes in DNA repair activities [36]. These defects could be partly responsible for nuclear and mitochondrial genomic defects in senescent cells.

Neutrophils and Mast Cells

Neutrophils, which infiltrate sunburned skin, are capable of degrading elastic fibers and collagen fibers, and neutrophil-derived proteolytic enzymes are probably important players in the pathophysiology of photoaging [37,38]. The number of mast cells in sun-exposed skin is higher than in nonexposed skin, and UV exposure leads to increased mast cell numbers and tryptase expression in human skin [39]. The activation of mast cells by UV irradiation may participate in wrinkle formation, ECM proteins modification, and inflammation in UV-exposed skin. Indeed, the mast cell stabilizer ketotifen prevents wrinkle formation in mice chronically exposed to UV irradiation [40].

Aging and Genomic Analysis

Molecular mechanisms involved in aging or photoaging are still poorly understood at the level of global gene expression. Transcriptome analysis of sun-exposed skin suggests that disruption of cutaneous homeostasis and downregulation of skin metabolism may play important roles in the process of photoaging [41]. A recent genome-wide association study in middle-aged Caucasian women pointed out a putative role of STXBP5L and FBX040 genes in facial photoaging [42]. Genetic variations of melanocortin-1 receptor (MC1R) seem to be important determinants for severe photoaging [43], and constitutive activity of the wild-type MC1R in keratinocytes may reduce UVA-induced oxidative stress [44].

Infrared and Visible Radiations

At least 50% of the total energy that is being emitted by the sun and that reaches human skin is in the infrared (IR) range. In addition, within the IR range, IRA rays (770–1400 nm), which represent one-third of the total solar energy, are capable of penetrating human skin and directly affecting cells located in the epidermis, dermis, and subcutis. More than 65% of IRA reaches the dermis, and there is now increasing evidence that IRA, similar to UVB or UVA, significantly contributes to photoaging of human skin [45,46]. Recent work demonstrates that IR and heat exposure each induces cutaneous angiogenesis and inflammatory cellular infiltration, disrupts the dermal ECM by inducing MMPs, and alters dermal structural proteins [47]. The recent analysis of IRA-induced transcriptome in primary human skin fibroblasts identifies IRA as an environmental factor with relevance for skin homeostasis and photoaging [48]. Repetitive IRA irradiation produces significant wrinkle formation in hairless mice [49]. Exposure of human skin fibroblasts *in vitro* [50] and human skin *in vivo* [51] to physiologically relevant doses of IRA causes an increase in MMP-1 without a concomitant upregulation of TIMP-1 expression. IRA exposure also reduces type 1 collagen expression, possibly by reducing the production of procollagen-1-stimulating TGF-β1, TGF-β-2, and TGF-β-3 expression in human skin [52].

The underlying mechanisms responsible for UVB-, UVA-, and IRA-induced MMP-1 expression markedly differ. The major chromophores for UVB appear to be nuclear DNA and cytoplasmic-free tryptophan, whereas the UVA stress response is controlled by the lipid composition of specialized membrane microdomains (rafts) [53]. IRA radiation is strongest absorbed by mitochondria, and the earliest biological event following IRA irradiation of human skin fibroblasts is an increase in mitochondrial production of ROS [54]. Such ROS activate mitogen-activated protein kinase (MAPK) and cause increased transcriptional expression of MMP-1 in the nucleus [55]. IRA exposure induces similar biological effects to UV radiation, but the underlying mechanisms are substantially different since the cellular response to IRA irradiation mostly involves the mitochondrial electron transport chain. Mitochondrial ROS production due to UVA and IRA may trigger retrograde signalling pathways that alter gene expression in fibroblasts in a way that disturbs collagen metabolism and induces neovascularization and that may also be responsible for other features of photoaged skin, for example, the development of an inflammatory infiltrate (dermatoheliosis) [55,56]. Thus, effective sun protection may require specific strategies to prevent IRA-induced skin damage, and mitochondrial-targeted antioxidants may be used to protect human skin against IRA radiation–induced damage [57].

Other portions of the solar spectrum aside from UV, particularly visible light, may also contribute to signs of premature photoaging in skin. Indeed, irradiation of human skin with visible light induces production of ROS, proinflammatory cytokines, and MMP-1 expression [58,59].

REJUVENATION STRATEGIES

Reversing age-related changes remains a major challenge and requires different strategies. Vitamin A treatment reduces MMP expression and stimulates collagen synthesis in naturally aged, sun-protected skin, as it does in photoaged skin [60]. Retinoids may be able to repair intrinsically aged skin as well as photoaged skin by inhibiting the UV-induced induction of c-Jun protein thereby preventing increased MMPs [61,62]. Retinoids influence both the collagenous and elastic dermal matrices. These derivatives of vitamin A may induce the deposition of newly synthesized collagens (I and III) and fibrillin-rich microfibrils in the superficial papillary dermis.

Blockade of MMPs may represent one strategy for preventing UV-initiated photodamage. Peroxisome proliferator–activated receptor (PPAR) δ is a ligand-inducible transcription factor that modulates multiple biological functions pertaining to skin homeostasis. PPARδ-mediated inhibition of MMP-1 secretion prevents some effects of photoaging. Ligand-activated PPARδ confers resistance to UVB-induced cellular senescence by upregulating phosphatase and tensin homolog (PTEN) and thereby modulating PI3K/Akt/Rac1 signalling to reduce ROS generation in keratinocytes [63]. They also attenuate the UVB-induced secretion of MMP-1 by inhibiting ROS generation, in a process mediated by the JNK/MKP-7 signalling pathway [64]. The PPARalpha/gamma activator 5,7-dimethoxyflavone (5,7-DMF) strongly decreases MMP expression, production, and activity. In addition, 5,7-DMF significantly increases PPARalpha/gamma activation and catalase expression, thereby downregulating UVB-induced ROS production, ROS-induced MAPK signalling, and downstream transcription factors [65].

Estrogens play a key role in aging skin. Prevention of skin aging by estrogen/progesterone replacement therapy is effective if administered early after menopause and influences intrinsically aged skin only [66]. A selective estrogen receptor b (ERb) agonist may play a role in preventing the aging process, and estradiol treatment increases the amount of dermal hyaluronan and versican V2 by inducing the release of epidermal growth factor [67].

Heat exposure might exert biological effects on human skin, but the possible role of heat in photoaging is currently controversial [45]. HSP70 inducers could prove beneficial for the prevention of UV-induced wrinkle formation. Indeed, recent data demonstrated that UV-induced skin elasticity and degeneration of ECM as well as wrinkle formation could be suppressed in hairless mice that were concomitantly subjected to a mild heat treatment [68].

Light-emitting diode (LED) at 660 nm may be a safe and effective collagen-enhancement strategy. Indeed, LED therapy has the potential to reverse collagen downregulation and MMP-1 upregulation [69]. This could explain the improvements in skin appearance observed in LED-treated individuals. Broadband light (BBL), also known as intense pulse light, is a commonly available treatment to rejuvenate the skin. Recent data demonstrate that BBL treatment promotes the gene expression pattern of young skin [70]. The precise mechanisms by which BBL alters gene expression are currently not well understood. BBL may influence pathways controlled by NF-kB, whose blockade in aged murine skin is known to restore the gene expression program and phenotypes of young skin [71] and whose accumulation is associated with a reduced type I collagen expression in human skin fibroblasts [72].

Photoprotection is essential for preventing UV-induced premature skin aging, and *in vivo* studies have indicated that the regular application of sunscreen may diminish UV-induced epidermal and dermal changes [73]. Recent data indicate that regular sunscreen use retards skin aging in healthy, middle-aged men and women [74].

REFERENCES

1. Naylor EC, Watson RE, Sherratt MJ. Molecular aspects of skin ageing. *Maturitas* 2011 July; 69(3):249–256.
2. Vierkotter A, Schikowski T, Ranft U et al. Airborne particle exposure and extrinsic skin aging. *J Invest Dermatol* 2010 December; 130(12):2719–2726.
3. Beylot C. Skin aging: Clinicopathological features and mechanisms. *Ann Dermatol Venereol* 2008 February; 135 (Suppl 3):S157–S161.
4. Stoebner PE, Meunier L. Photoaging of face. *Ann Dermatol Venereol* 2008 January; 135(1 Pt 2):1S21–1S26.
5. Fisher GJ, Kang S, Varani J et al. Mechanisms of photoaging and chronological skin aging. *Arch Dermatol* 2002 November; 138(11):1462–1470.
6. Amano S. Possible involvement of basement membrane damage in skin photoaging. *J Investig Dermatol Symp Proc* 2009 August; 14(1):2–7.
7. Quan T, Shao Y, He T, Voorhees JJ, Fisher GJ. Reduced expression of connective tissue growth factor (CTGF/CCN2) mediates collagen loss in chronologically aged human skin. *J Invest Dermatol* 2010 February; 130(2):415–424.
8. Kurdykowski S, Mine S, Bardey V et al. Ultraviolet-B irradiation induces differential regulations of hyaluronidase expression and activity in normal human keratinocytes. *Photochem Photobiol* 2011 Septmber–October; 87(5):1105–1112.
9. Zouboulis CC, Makrantonaki E. Clinical aspects and molecular diagnostics of skin aging. *Clin Dermatol* 2011 January–February; 29(1):3–14.
10. Quan T, Qin Z, Xia W, Shao Y, Voorhees JJ, Fisher GJ. Matrix-degrading metalloproteinases in photoaging. *J Investig Dermatol Symp Proc* 2009 August; 14(1):20–24.
11. Quan T, Little E, Quan H, Qin Z, Voorhees JJ, Fisher GJ. Elevated matrix metalloproteinases and collagen fragmentation in photodamaged human skin: Impact of altered extracellular matrix microenvironment on dermal fibroblast function. *J Invest Dermatol* 2013 May; 133(5):1362–1366.
12. Fisher GJ, Choi HC, Bata-Csorgo Z et al. Ultraviolet irradiation increases matrix metalloproteinase-8 protein in human skin in vivo. *J Invest Dermatol* 2001 August; 117(2):219–226.
13. Xia W, Hammerberg C, Li Y et al. Expression of catalytically active matrix metalloproteinase-1 in dermal fibroblasts induces collagen fragmentation and functional alterations that resemble aged human skin. *Aging Cell* 2013 August; 12(4):661–671.
14. Varani J, Schuger L, Dame MK et al. Reduced fibroblast interaction with intact collagen as a mechanism for depressed collagen synthesis in photodamaged skin. *J Invest Dermatol* 2004 June; 122(6):1471–1479.
15. Fligiel SE, Varani J, Datta SC, Kang S, Fisher GJ, Voorhees JJ. Collagen degradation in aged/photodamaged skin in vivo and after exposure to matrix metalloproteinase-1 in vitro. *J Invest Dermatol* 2003 May; 120(5):842–848.
16. Varani J, Perone P, Fligiel SE, Fisher GJ, Voorhees JJ. Inhibition of type I procollagen production in photodamage: Correlation between presence of high molecular weight collagen fragments and reduced procollagen synthesis. *J Invest Dermatol* 2002 July; 119(1):122–129.
17. Quan T, Wang F, Shao Y et al. Enhancing structural support of the dermal microenvironment activates fibroblasts, endothelial cells, and keratinocytes in aged human skin in vivo. *J Invest Dermatol* 2013 March; 133(3):658–667.
18. Qin Z, Okubo T, Voorhees JJ, Fisher GJ, Quan T. Elevated cysteine-rich protein 61 (CCN1) promotes skin aging via upregulation of IL-1beta in chronically sun-exposed human skin. *Age* 2013 July 24; 36:353–364.
19. Quan T, Qin Z, Voorhees JJ, Fisher GJ. Cysteine-rich protein 61 (CCN1) mediates replicative senescence-associated aberrant collagen homeostasis in human skin fibroblasts. *J Cell Biochem* 2012 September; 113(9):3011–3018.
20. Yokose U, Hachiya A, Sriwiriyanont P et al. The endogenous protease inhibitor TIMP-1 mediates protection and recovery from cutaneous photodamage. *J Invest Dermatol* 2012 December; 132(12):2800–2809.
21. Berneburg M, Plettenberg H, Medve-Konig K et al. Induction of the photoaging-associated mitochondrial common deletion in vivo in normal human skin. *J Invest Dermatol* 2004 May; 122(5):1277–1283.

22. Schroeder P, Gremmel T, Berneburg M, Krutmann J. Partial depletion of mitochondrial DNA from human skin fibroblasts induces a gene expression profile reminiscent of photoaged skin. *J Invest Dermatol* 2008 September; 128(9):2297–2303.
23. Hekimi S, Lapointe J, Wen Y. Taking a "good" look at free radicals in the aging process. *Trends Cell Biol* 2011 October; 21(10):569–576.
24. Coux O, Tanaka K, Goldberg AL. Structure and functions of the 20S and 26S proteasomes. *Annu Rev Biochem* 1996; 65:801–847.
25. Meunier L, Stoebner PE, Marque M, Henry L, Bureau JP, Lavabre-Bertrand T. Proteasome and proteasome inhibitors. *Ann Dermatol Venereol* 2005 November; 132(11 Pt 1):895–898.
26. Aiken CT, Kaake RM, Wang X, Huang L. Oxidative stress-mediated regulation of proteasome complexes. *Mol Cell Proteomics* 2011 January; 10:1–47.
27. Baraibar MA, Friguet B. Changes of the proteasomal system during the aging process. *Prog Mol Biol Transl Sci* 2012; 109:249–275.
28. Shang F, Taylor A. Ubiquitin-proteasome pathway and cellular responses to oxidative stress. *Free Radic Biol Med* 2011 July 1; 51(1):5–16.
29. Low P. The role of ubiquitin-proteasome system in ageing. *Gen Comp Endocrinol* 2011 May 15; 172(1):39–43.
30. Koziel R, Greussing R, Maier AB, Declercq L, Jansen-Durr P. Functional interplay between mitochondrial and proteasome activity in skin aging. *J Invest Dermatol* 2011 March; 131(3):594–603.
31. Cao K, Blair CD, Faddah DA et al. Progerin and telomere dysfunction collaborate to trigger cellular senescence in normal human fibroblasts. *J Clin Invest* 2011 July; 121(7):2833–2844.
32. Jaskelioff M, Muller FL, Paik JH et al. Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice. *Nature* 2011 January 6; 469(7328):102–106.
33. Gilchrest BA, Eller MS, Yaar M. Telomere-mediated effects on melanogenesis and skin aging. *J Investig Dermatol Symp Proc* 2009 August; 14(1):25–31.
34. Takeuchi H, Runger TM. Longwave UV light induces the aging-associated progerin. *J Invest Dermatol* 2013 July; 133(7):1857–1862.
35. Sauvaigo S, Caillat S, Odin F, Nkengne A, Bertin C, Oddos T. Effect of aging on DNA excision/synthesis repair capacities of human skin fibroblasts. *J Invest Dermatol* 2010 June; 130(6):1739–1741.
36. Prunier C, Masson-Genteuil G, Ugolin N, Sarrazy F, Sauvaigo S. Aging and photo-aging DNA repair phenotype of skin cells-evidence toward an effect of chronic sun-exposure. *Mutat Res* 2012 August 1; 736(1–2):48–55.
37. Rijken F, Bruijnzeel-Koomen CA. Photoaged skin: The role of neutrophils, preventive measures, and potential pharmacological targets. *Clin Pharmacol Ther* 2011 January; 89(1):120–124.
38. Rijken F, Bruijnzeel PL. The pathogenesis of photoaging: The role of neutrophils and neutrophil-derived enzymes. *J Investig Dermatol Symp Proc* 2009 August; 14(1):67–72.
39. Kim MS, Kim YK, Lee DH et al. Acute exposure of human skin to ultraviolet or infrared radiation or heat stimuli increases mast cell numbers and tryptase expression in human skin in vivo. *Br J Dermatol* 2009 February; 160(2):393–402.
40. Kim MS, Lee DH, Lee CW et al. Mast cell stabilizer, ketotifen, prevents UV-induced wrinkle formation. *J Invest Dermatol* 2013 April; 133(4):1104–1107.
41. Yan W, Zhang LL, Yan L et al. Transcriptome analysis of skin photoaging in chinese females reveals the involvement of skin homeostasis and metabolic changes. *PLOS ONE* 2013; 8(4):e61946.
42. Le Clerc S, Taing L, Ezzedine K et al. A genome-wide association study in Caucasian women points out a putative role of the STXBP5L gene in facial photoaging. *J Invest Dermatol* 2013 April; 133(4):929–935.
43. Elfakir A, Ezzedine K, Latreille J et al. Functional MC1R-gene variants are associated with increased risk for severe photoaging of facial skin. *J Invest Dermatol* 2010 April; 130(4):1107–1115.
44. Henri P, Beaumel S, Guezennec A et al. MC1R expression in HaCaT keratinocytes inhibits UVA-induced ROS production via NADPH oxidase- and cAMP-dependent mechanisms. *J Cell Physiol* 2012 June; 227(6):2578–2585.
45. Krutmann J, Morita A, Chung JH. Sun exposure: What molecular photodermatology tells us about its good and bad sides. *J Invest Dermatol* 2012 March; 132(3 Pt 2):976–984.
46. Kligman LH. Intensification of ultraviolet-induced dermal damage by infrared radiation. *Arch Dermatol Res* 1982; 272(3–4):229–238.
47. Cho S, Shin MH, Kim YK et al. Effects of infrared radiation and heat on human skin aging in vivo. *J Investig Dermatol Symp Proc* 2009 August; 14(1):15–19.
48. Calles C, Schneider M, Macaluso F, Benesova T, Krutmann J, Schroeder P. Infrared A radiation influences the skin fibroblast transcriptome: Mechanisms and consequences. *J Invest Dermatol* 2010 June; 130(6):1524–1536.
49. Kim HH, Lee MJ, Lee SR et al. Augmentation of UV-induced skin wrinkling by infrared irradiation in hairless mice. *Mech Ageing Dev* 2005 November; 126(11):1170–1177.
50. Schieke S, Stege H, Kurten V, Grether-Beck S, Sies H, Krutmann J. Infrared-A radiation-induced matrix metalloproteinase 1 expression is mediated through extracellular signal-regulated kinase 1/2 activation in human dermal fibroblasts. *J Invest Dermatol* 2002 December; 119(6):1323–1329.
51. Schroeder P, Lademann J, Darvin ME et al. Infrared radiation-induced matrix metalloproteinase in human skin: Implications for protection. *J Invest Dermatol* 2008 October; 128(10):2491–2497.
52. Kim MS, Kim YK, Cho KH, Chung JH. Regulation of type I procollagen and MMP-1 expression after single or repeated exposure to infrared radiation in human skin. *Mech Ageing Dev* 2006 December; 127(12):875–882.
53. Grether-Beck S, Salahshour-Fard M, Timmer A et al. Ceramide and raft signaling are linked with each other in UVA radiation-induced gene expression. *Oncogene* 2008 August 14; 27(35):4768–4778.
54. Schroeder P, Pohl C, Calles C, Marks C, Wild S, Krutmann J. Cellular response to infrared radiation involves retrograde mitochondrial signaling. *Free Radic Biol Med* 2007 July 1; 43(1):128–135.
55. Krutmann J, Schroeder P. Role of mitochondria in photoaging of human skin: The defective powerhouse model. *J Investig Dermatol Symp Proc* 2009 August; 14(1):44–49.
56. Karu TI. Mitochondrial signaling in mammalian cells activated by red and near-IR radiation. *Photochem Photobiol* 2008 September–October; 84(5):1091–1099.
57. Schroeder P, Calles C, Benesova T, Macaluso F, Krutmann J. Photoprotection beyond ultraviolet radiation—Effective sun protection has to include protection against infrared A radiation-induced skin damage. *Skin Pharmacol Physiol* 2010; 23(1):15–17.
58. Liebel F, Kaur S, Ruvolo E, Kollias N, Southall MD. Irradiation of skin with visible light induces reactive oxygen species and matrix-degrading enzymes. *J Invest Dermatol* 2012 February 9; 132(7):1901–1907.
59. Mahmoud BH, Hexsel CL, Hamzavi IH, Lim HW. Effects of visible light on the skin. *Photochem Photobiol* 2008 March–April; 84(2):450–462.
60. Varani J, Warner RL, Gharaee-Kermani M et al. Vitamin A antagonizes decreased cell growth and elevated collagen-degrading matrix metalloproteinases and stimulates collagen accumulation in naturally aged human skin. *J Invest Dermatol* 2000 March; 114(3):480–486.
61. Varani J, Fisher GJ, Kang S, Voorhees JJ. Molecular mechanisms of intrinsic skin aging and retinoid-induced repair and reversal. *J Investig Dermatol Symp Proc* 1998 August; 3(1):57–60.
62. Fisher GJ, Voorhees JJ. Molecular mechanisms of photoaging and its prevention by retinoic acid: Ultraviolet irradiation induces MAP kinase signal transduction cascades that induce Ap-1-regulated matrix metalloproteinases that degrade human skin in vivo. *J Investig Dermatol Symp Proc* 1998 August; 3(1):61–68.
63. Ham SA, Hwang JS, Yoo T et al. Ligand-activated PPARdelta inhibits UVB-induced senescence of human keratinocytes via PTEN-mediated inhibition of superoxide production. *Biochem J* 2012 May 15; 444(1):27–38.
64. Ham SA, Kang ES, Lee H et al. PPARdelta inhibits UVB-induced secretion of MMP-1 through MKP-7-mediated suppression of JNK signaling. *J Invest Dermatol* 2013 May 2.

65. Kim JK, Mun S, Kim MS, Kim MB, Sa BK, Hwang JK. 5,7-Dimethoxyflavone, an activator of PPARalpha/gamma, inhibits UVB-induced MMP expression in human skin fibroblast cells. *Exp Dermatol* 2012 March; 21(3):211–216.
66. Zouboulis CC, Makrantonaki E. Hormonal therapy of intrinsic aging. *Rejuvenation Res* 2012 June; 15(3):302–312.
67. Rock K, Meusch M, Fuchs N et al. Estradiol protects dermal hyaluronan/versican matrix during photoaging by release of epidermal growth factor from keratinocytes. *J Biol Chem* 2012 June 8; 287(24):20056–20069.
68. Matsuda M, Hoshino T, Yamakawa N et al. Suppression of UV-induced wrinkle formation by induction of HSP70 expression in mice. *J Invest Dermatol* 2013 April; 133(4):919–928.
69. Barolet D, Roberge CJ, Auger FA, Boucher A, Germain L. Regulation of skin collagen metabolism in vitro using a pulsed 660 nm LED light source: Clinical correlation with a single-blinded study. *J Invest Dermatol* 2009 December; 129(12):2751–2759.
70. Chang AL, Bitter PH, Jr., Qu K, Lin M, Rapicavoli NA, Chang HY. Rejuvenation of gene expression pattern of aged human skin by broadband light treatment: A pilot study. *J Invest Dermatol* 2013 February; 133(2):394–402.
71. Adler AS, Sinha S, Kawahara TL, Zhang JY, Segal E, Chang HY. Motif module map reveals enforcement of aging by continual NF-kappaB activity. *Genes Dev* 2007 December 15; 21(24):3244–3257.
72. Bigot N, Beauchef G, Hervieu M et al. NF-kappaB accumulation associated with COL1A1 transactivators defects during chronological aging represses type I collagen expression through a -112/-61-bp region of the COL1A1 promoter in human skin fibroblasts. *J Invest Dermatol* 2012 October; 132(10):2360–2367.
73. Sambandan DR, Ratner D. Sunscreens: An overview and update. *J Am Acad Dermatol* 2011 April; 64(4):748–758.
74. Hughes MC, Williams GM, Baker P, Green AC. Sunscreen and prevention of skin aging: A randomized trial. *Ann Intern Med* 2013 June 4; 158(11):781–790.

Clinical signs of aging

Claire Beylot

INTRODUCTION

As life expectancy has increased significantly in industrialized countries, retaining one's youthful appearance has become more and more sought after. Skin and facial aging, which is visible to all, may be a particularly traumatic experience with repercussions in personal life and social relations. Everybody would like to look and stay young for his own well-being, respect for his family and his circle of friends, and also for business needs. Consequently, the correction of facial aging has become the main reason why people look for solutions in cosmetic dermatology and surgery. At a time when self-image and quality of life are becoming increasingly important, this demand, which is especially expressed by women and also by more and more men, should not be thought of a frivolous search for lost youth. In recent years, great progress has been made in the treatment of facial aging, and it is now quite possible to delay and correct aging and even to obtain a more youthful appearance.

To provide the most suitable treatment for each patient, one must analyze how a face has aged. The examination is not limited to skin aging but also involves the underlying structures, facial muscles, fat, and even bones. A similar approach should be taken in the extrafacial areas, especially the neck, back of hands, and forearms, which patients also often would like to see improve.

These components of facial and extrafacial aging are described and evaluated in this chapter, which discusses skin aging extensively, because the other topics are also dealt with in the chapters concerning botulinum toxin, fillers, and surgery. The pathophysiological mechanisms involved are briefly referred to because another author discusses these in detail.

SKIN AGING [1,2]

The skin of people of the same age may vary greatly depending on their genetic profile and their environment with intrinsic (chronological aging and menopause-induced aging) and environmental factors (photoaging and smoking-related aging). A person's phototype is genetic, but the degree of photodamage depends very much on his or her phototype.

Intrinsic Factors

Chronological Aging

Clinical Aspects The signs of chronological aging are difficult to perceive on the face owing to the superposition of photoaging. It is more obvious on unexposed areas of the body, with thinning, puckering, and drying of the skin resembling clothing that is too large (Figure 4.1).

The skin is pallid and the moles progressively disappear with aging as a result of a decrease in the melanocyte count. The wrinkles are fine, crumpled, and almost parallel to each other owing to the atrophy of the skin. These are obvious on the forearms or on the dorsal face of the wrists; they are also visible on the face and the neck. On prints, there is a decrease in the lines and all run in the same direction especially on the dorsal face of the wrists.

Itching is frequent in chronological aging due to dryness of the skin, and it is worsened by inadequate hygiene such as too hot water and/or prolonged baths or showers, too much use of detergent soaps, and consumption of multiple oral drugs [3].

This atrophic skin is fragile and wound healing takes longer.

The hair and the nails are also affected by chronological aging. Scalp hair goes gray and then white, thins out, and grows more slowly. The growth of the nails is slowed down. Whereas the fingernails become fragile and brittle with more longitudinal ridges, the toenails become thicker and difficult to cut with frequent onychomycosis of the big toes.

At the histological level, the following occurs (Figure 4.2a through d):

- Epidermal thinning with a decrease in living Malpighi cells and an increase in dead corneocytes. The number of melanocytes decreases by 10% with each decade.
- Flattening and weakness of the dermoepidermal junction, which is a very complex structure. In aging, the number of each component decreases: integrins of hemidesmosomes, laminin of the lamina lucida, type IV collagen of the lamina densa, type VII collagen of the anchoring fibrils, and fine elastic fibers.
- Disappearance of the thin oxytalan and elaunin elastic network of the papillary dermis, which is a marker of chronological aging. This and the weakness of the dermoepidermal junction explain the decrease in dermoepidermal adhesion.
- Loss of dermal density, with a decrease in all components: collagen, elastic fibers, hyaluronic acid of the extracellular matrix, and sebaceous and sudoral secretions. The loss of dermal density is responsible for vessel dilatation and fragility.

Chronological aging mechanisms are complex and some of them are similar to those of photoaging:

- Genetically determined biological clock, with shortening of the telomeres at every cellular division, leading to replicative senescence with apoptosis or cellular transformation
- Aging-related cellular damage, with 50% decrease in turnover from the age of 20 to 70, less synthesis, and more destruction of collagen

Figure 4.1 Chronological aging. Thinning, puckering, and drying of the skin resembling clothing that is too large.

Menopause-Induced Skin Aging [4]

Signs of Estrogenic Deficiency Menopause-induced aging resembles chronological skin aging. It is due to estrogenic deficiency and sudden skin aging occurs in women who do not take hormonal replacement treatment. The skin fades and becomes thinner and dry with fine wrinkles, especially on the face where there are more estrogen receptors. This skin atrophy is primarily related to a decrease in collagen dermis that is thought to be between 1% and 2% per year. This decrease is correlated with osteoporosis. Climacteric flushing with sweating is sometimes dramatic and embarrassing in early menopause and impacts the quality of life, although it decreases in the postmenopause phase. There are other signs such as palmoplantar keratoderma *climactericum*. Estrogen deficiency also changes the vulvar mucous membrane, which becomes atrophic and dry, leading to pruritus and dyspareunia.

Signs of Relative Hyperandrogenism Hyperandrogenism often occurs owing to a dramatic decrease in ovarian hormones, estradiol and progesterone, whereas the level of androgens decreases to a lesser extent. Cutaneous signs of virilization occur, such as hirsutism and alopecia. These are often mild but deeply affect women since they see it as a visible loss of their femininity.

- Menopausal and postmenopausal alopecia mostly affects the top of the head, making it difficult to adopt any hairstyle, but it spares the thin front hairline. The anagenic phase becomes shorter, leading to depletion of the hair, which becomes thinner like vellus hair. This androgen-dependent process is progressive, frequently beginning many years before the menopause and increasing thereafter.
- Postmenopausal frontal fibrosing alopecia is quite different. An inflammatory lymphocytic lichenoid infiltrate impairs the upper portion of the hair follicle, leading to a symmetrical regression of the frontal and temporal hairline with partial or total loss of the eyebrows. The implication of menopause and androgens has not yet fully been established, but some improvement has been reported with hormonal treatment such as hormonal replacement or antiandrogenic treatment.

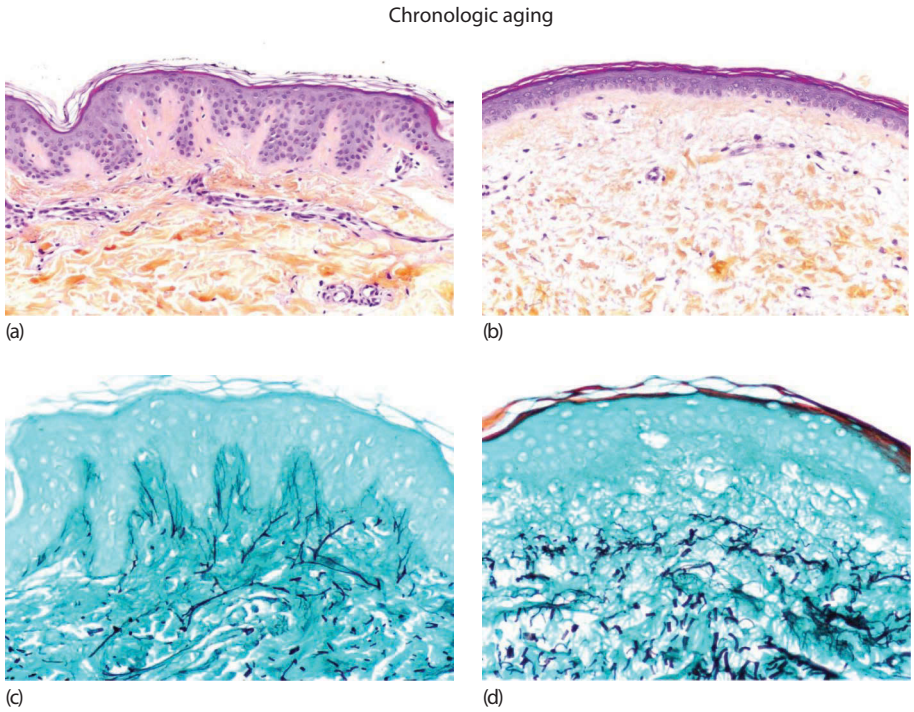


Figure 4.2 From (a) young to (b) old: epidermal thinning, flattening of dermo-epidermal junction, loss of density of dermis with decrease of all its components, especially collagen. From (c) young to (d) old, in papillary dermis, the thin elastic network disappears.

General and Psychiatric Diseases

These diseases, especially depression, accelerate chronological aging.

Environmental Factors [5]

Photoaging [1]

The implication of sun exposure in skin aging was first pointed out by Unna and Dubreuilh in the late nineteenth century. Thereafter, Kligman and Kligman proposed the term of "photoaging" in order to distinguish this process clinically and at the histological level of intrinsic chronological aging, and there have been numerous studies about the very complex mechanisms involved.

In photoaging, genetic factors (phototype) with more severe aging in fair skin and environmental factors (cumulative sun exposure) are closely related and differently combined, explaining the wide variability in appearance between individuals. However, there are also ethnic differences. In fair-skinned Caucasian types, the skin is severely atrophic with multiple telangiectasia and premalignant lesions such as actinic keratosis, whereas in dark-skinned persons, deep wrinkles and furrows occur. In Asians, there are more pigmentary spots but fewer wrinkles [5].

Level of Penetration of UVA and UVB in the Skin and Histological Outcome (Figure 4.3) UVB (290–320 nm), which penetrates the epidermis, and UVA (320–400 nm), which goes deeper into the superficial dermis, are the main causes of photoaging. However, infrared light (740–1400 nm), which reaches as far as the hypodermis, can play a role in this aging process. These levels of penetration of UVA and UVB explain why histologically the changes in photoaging are mainly localized in the upper part of the skin. The main alteration is actinic elastosis. The accumulation of abnormal thick and fragmented elastic fibers in the papillary dermis associated with the decrease in collagen is responsible for the alteration of the biomechanical properties of the skin, loss of elasticity, textural changes, laxity, and wrinkles. Changes also occur in the epidermis, with thinning, excessive, and irregular dispersion of melanin, which is responsible for solar lentigo and cellular atypia, leading to actinic keratosis with a risk of evolution to cancer.

UVB is responsible for epidermal changes, particularly precancerous and cancerous lesions, while UVA exposure leads to aging, especially actinic elastosis. However, the effects are complex, and recent publications demonstrate that UVA also plays an important role in the genesis of cutaneous cancers.

Photoaging Depending on Localization Photoaging is usually predominant on the face, but the skin of the neck, low neck, forearms, and legs are also involved and even the whole body in fanatics of sun-tanning and bed or cabin tanning. Sometimes, there is a dramatic contrast between sun-exposed skin, where the photoaging is severe, and unexposed skin, which appears much younger (Figure 4.4).

On the Face

Aspect and Texture of the Skin On the face, the skin is often thickened owing to solar elastosis and yellowy or gray yellow (Figure 4.5a), with follicular dilated orifices resembling lemon peel. However, the skin sometimes becomes thin particularly in fair persons.

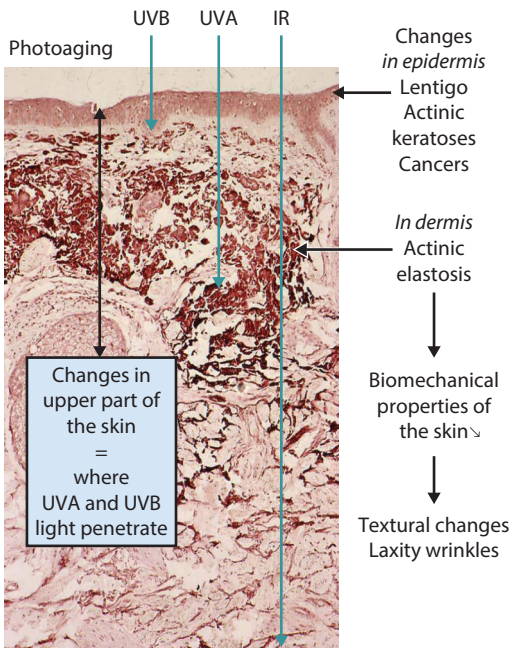


Figure 4.3 The levels of penetration of UVA and UVBA explain why histologically the changes in photoaging are mainly localized in the upper part of the skin.

Figure 4.4 There is a dramatic contrast between sun-exposed skin, where the photoaging is severe, and unexposed skin, which appears much younger.

(a) (b)

Figure 4.5 (a) Solar elastosis, with thickened and yellowy skin. Heliodermic wrinkles of the upper lip ("sun pleated wrinkles"). (b) Dynamic "bar code" wrinkles are deeper and oblique, because they are perpendicular to the direction of contraction of the *orbicularis oris* muscle.

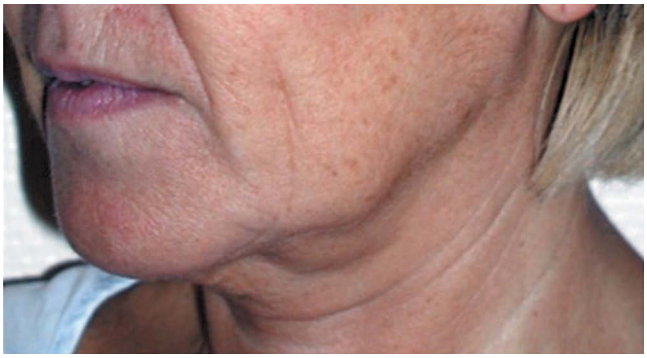


Figure 4.6 Transversal lines of the neck are gravitational wrinkles due to skin and fat ptosis.

Textural changes also occur leading to progressive alteration of the biomechanical properties of the skin. The gradual loss of skin elasticity and its flaccidity, combined with fat ptosis, leads to sagging, with lowering of the eyebrows, upper eye skin excess (dermatochalasis), accentuation of the nasolabial folds, flabby cheeks, and loss of the oval shape of the face.

However, in the patient's opinion, wrinkles are the most noticeable sign of aging.

There are different kinds of wrinkles and it is important to distinguish them because the treatment is not the same [6,7]:

- Elastotic creases (heliodermic wrinkles), which become progressively permanent, develop on sun-exposed areas such as the upper lip (Figure 4.5a). The latter is more exposed than the lower lip because its surface is not quite vertical but slightly oriented upward. The cheeks and nape of the neck are also involved. In these areas, the solar elastosis is hypertrophic, compact, overcompensating the collagen atrophy in volume, and forming a cobblestone sequestrated material making the skin more rigid.
- Dynamic wrinkles due to the underlying muscles and always oriented in a stereotypic pattern perpendicular to the direction of muscular contraction especially in the upper third of the face the glabellar lines, giving the patient an anxious and severe look, forehead lines, crow feet wrinkles, or a perioral area (Figures 4.5b and 4.14a through c). In forehead lines, the role of the thickening and shortening of the retinacula cutis fastening the wrinkle bottom in depth has been demonstrated [8].
- Crumpling wrinkles that are fine and almost parallel to each other are due more to chronological aging and to the atrophy of the skin than to actinic elastosis. They are obvious on the forearms and the dorsal face of wrists but may be visible on the face and the neck.
- Gravitational folds are not really wrinkles, because they are due to tissue ptosis and to fat more than to the skin, with an accumulation above especially in the nasolabial area, the mobile fat of the cheek knocking against the fixed area of the superior lip, thereby hollowing out a deep furrow (Figure 4.17). The same is true for the transversal lines of the neck (Figure 4.6). The main histological change is a loosely and elongated fibrous network in the hypodermis related to gravitational forces followed by a similar elongation of the dermis. When these are mild, fillers can correct such gravitational folds, but lifting is needed if these defects are severe.

Permanent vertical frontal wrinkles and vertical wrinkles of the mid cheek, also known as "pillow wrinkles," are due to the pressure constraints during sleep. They impact aging skin and weaken the underlying structures. Their mechanism of formation is therefore similar to that of gravitational wrinkles.

However, this classification remains artificial, because photoaging with its textural alterations plays an important role even in dynamic wrinkles. Indeed, such dynamic wrinkles are absent in young people, because their skin has biomechanical properties, especially elasticity, allowing muscular movements to occur without the development of permanent wrinkles.

In some localizations such as the upper lip, one must distinguish between heliodermic wrinkles and dynamic wrinkles because the treatment is not the same. The first, i.e., "sun-pleated wrinkles" (Figure 4.5a), are vertical and superficial in a very elastotic skin and require laser treatment or deep peel. The latter, which are sometimes known as "bar code" wrinkles (Figure 4.5b), are deeper and oblique, because they are perpendicular to the direction of contraction of the *orbicularis oris* muscle and are more visible when the patient blows or whistles. These dynamic wrinkles require botulinum toxin. Frequently, however, these two mechanisms are associated and a combined treatment is needed.

Other changes related to photoaging and elastosis are as follows:

- Favre and Racouchot syndrome (*elastosis nodularis cystica et comedonica*) (Figure 4.7): In very elastotic sun-exposed areas such as orbitomalar or laterofrontal eminences and even on bald scalp or the nape of the neck, comedones, sebaceous cysts, and nodules without inflammation may occur. Sebaceous secretions are not increased. The mechanism is simply a sebaceous build-up in distended follicles in flabby skin. These aspects are more frequent and occur earlier in smokers.

Figure 4.7 Favre and Racouchot syndrome *(elastosis nodularis cystica et comedonica*).

Figure 4.8 Large solar lentigines owing to the confluence of several lesions.

- Senile sebaceous hyperplasia: More than age *per se*, photoaging is responsible for these small elevated, soft, yellowish papules that frequently exhibit central umbilication at the site of the ductal opening.
- *Colloid milium*: This occurs in sun-exposed areas, especially the forehead, as skin-colored or yellowish translucent and dome-shaped papules forming plaques. Histology shows extensive deposition of pale homogeneous material in the superficial dermis. The substance is not amyloid but is thought to be due to degeneration of collagen or elastotic material. However, the exact histogenesis is still unresolved.
- *Trichostasis spinulosa* where multiple fine short broken hairs project above the skin surface resembling mucinosis *follicularis*.

Pigmented Lesions

- *Solar lentigines* are very frequent (present in 90% of Caucasians older than 60 years). They present as well-defined, light brown, or tan flat spots. Occasionally, they may be jet black. Surface scaling is minimal or absent. Solar lentigines may be unique or more often multiple, giving a mottled appearance to the skin face. Most solar lentigines are less than 5 mm of diameter, but they may be tiny (1 mm or less) or very large (several centimeters) owing to the confluence of several lesions (Figure 4.8). Histologically, there are an increased number of melanocytes in elongated epidermal rete ridges. Although solar lentigines are benign, they indicate excessive sun exposure with a risk of development of skin cancer. Q-switched lasers or IPL are indicated for their treatment.
- *Actinic keratoses* are the most common premalignant skin condition, affecting nearly 100% of elderly Caucasians and younger fair-skinned people if they have been frequently exposed to sun. These solar keratoses are rough grayish or reddish-brown ill-defined patches with dry adherent scales (Figure 4.9). Often, they are better recognized by palpation than by visual inspection. Frequently, they are multiple in fields of cancerization. Their induration, erosion, or increasing diameter evokes an evolution to squamous cell carcinoma, so a control biopsy is needed. Keratinocytes atypia, with disorderly stratification, hyper- and parakeratosis, breaking of basal membrane, must be sought. Owing to the risk of cancerization, a treatment is indicated. The possibilities are numerous: cryotherapy, 5-fluoro-uracil, curettage and laser abrasion, photodynamic therapy, etc.

Vascular Lesions The first stages of rosacea, erythrosis, and telangiectasias are frequent on sun-exposed areas of the face, particularly the nose and cheeks (Figure 4.10). Thereafter, papulo-pustules and sometimes rhinophyma occur in men. The pathogenesis of rosacea is complex and many factors are involved. However, photoaging plays an important role. The vascular lasers are indicated for these lesions.

Venous ectasia of the lower lip is frequent.

Evaluation of the Degree of Photoaging

Many classifications are available to classify the different grades of photoaging. The Glogau classification in four groups, namely, mild, moderate, advanced, and severe, is the most widely used [9].

The score of intrinsic and extrinsic skin aging proposed by Vierkötter gives a more global evaluation of chronological aging and photoaging [10].

Figure 4.9 Solar keratoses with dry adherent scales. Risk of cancerization.

Figure 4.10 Erythrosis and telangiectasias are frequent on sun-exposed areas of the face, particularly the cheeks.

Figure 4.11 Poikiloderma of Civatte (*erythrosis interfollicularis colli*) is predominant on the lateral face of the neck, sparing a lozenge at the shadow of the chin.

The Body

There is also skin aging in sun-exposed areas of the body:

- *On the neck and low neck*, with poikiloderma of Civatte, a mix of red, white, and brown spots, sparing a lozenge at the shadow of the chin (Figure 4.11). This *erythrosis interfollicularis colli* is predominant on the lateral face of the neck and frequently spreads to the low neck. The skin is red and atrophic between sebaceous follicles that form white micropapules punctuating the erythrotic background.

  Sometimes, there is laxity of the neck skin with transversal wrinkles (Figure 4.6).

  In the nape of the neck, there are deep wrinkles with a rhomboidal arrangement. This is seen in people exposed professionally to the sun like farm workers and sailors.
- *On the sun-exposed areas of the limbs*, the skin is thinner, especially on the dorsal hand (Figure 4.12), where there are solar lentigines, unidirectional grooves, bulging veins, decreased viscoelasticity, and actinic keratosis.

Hypomelanosis guttatae is frequent especially on the legs of women. It is due to the disappearance of the melanocyte transferring the melanosones to the fifty or so keratinocytes associated with an epidermal melanin unit.

Dermatoporosis [11] is a special aspect of photoaging in the elderly. It is seen on the sun-exposed skin of the forearms and legs with severe skin atrophy, senile purpura, stellate white pseudoscars, skin fragility, long-healing skin lacerations (Figure 4.13), and in the most severe grade, nonhealing atrophic ulcers and subcutaneous bleeding with formation of dissecting hematomas, leading to large zones of necrosis. It is not only a cosmetic

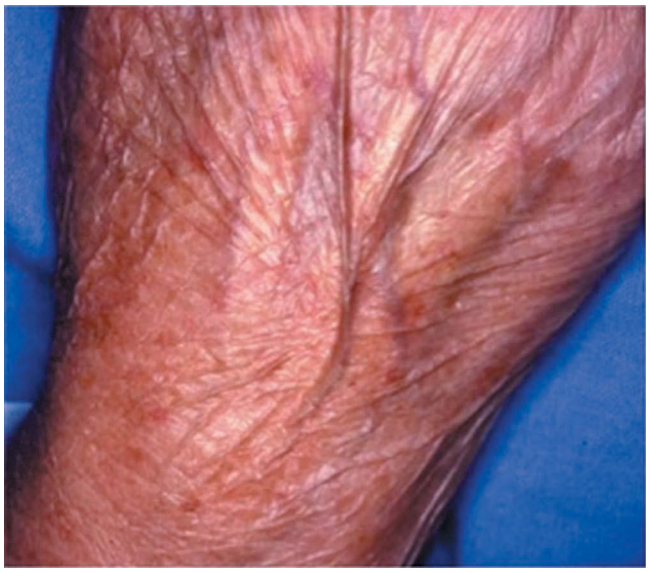


Figure 4.12 On the sun-exposed dorsal hand, the skin is very thin, with decreased viscoelasticity and solar lentigines.

Figure 4.13 *Dermatoporosis* is a special aspect of photoaging in the elderly. On the sun-exposed skin of the forearms and legs: severe skin atrophy, senile purpura, stellate white pseudoscars, skin fragility, long-healing skin lacerations.

problem, except in the mild grades, but really a functional problem related to skin fragility and bruisability, justifying the name of dermatoporosis with reference to the bone fragility occurring in osteoporosis. The molecular mechanisms of dermatoporosis involve a functionally defective hyaluronate CD 44 pathway and are a target for topical treatment, namely, the fragments of hyaluronic acid associated with retinaldehyde.

And Last but Not Least, Photoaging Is Often Associated with Skin Cancers Photoinduced cancers are common: basal cell carcinomas occurring mainly on the face, squamous cell carcinomas often following actinic keratoses in the field of cancerization, and melanoma on all parts of the body, not to be confused on the face with benign solar lentigines. These cancers are not described in detail in this chapter, which primarily deals with the assessment of aging in aesthetic dermatology. Often, these cancers are obvious. However, before an aesthetic procedure, one must take care to diagnose an incipient and still misleading cancer and to do a biopsy if in any doubt.

Photoaging Mechanisms Are Complex

However, there are three major causes:

1. Insufficient repair of UV-induced DNA damage
2. Important role of reactive oxygen species, which are responsible for oxidative stress, inducing damage to DNA, cellular membranes, and proteins, to a decrease in procollagen synthesis, to the modulation of gene fibroblasts with increased gene expression of matricial metalloproteinases, which is responsible for collagen degradation, and the modulation of elastin gene, resulting in production of abnormal elastic fibers and to a lower fibroblast sensitivity to keratinocyte TGF β-1 with a decrease in its capacity to divide
3. Decrease of Langerhans cells responsible for the immunowatching of the skin

Smoke-Induced Skin Aging

Several epidemiological studies have demonstrated the relationship between smoking and skin aging. For some authors, cigarette smoke predisposes skin to aging more than sun exposure, and smoking 20 cigarettes/day is equivalent to almost 10 years of aging. This was confirmed in a study concerning monozygotic twins showing that an increase in apparent age was correlated to years of smoking.

Tobacco-induced skin aging resembles and emphasizes photoaging, with grayish skin, deep wrinkles and furrows, cysts, and comedones. Upper lip heliodermic wrinkles are often marked to such an extent that they are sometimes called smokers' wrinkles. While their depth is greater, the number of furrows is fewer than in nonsmokers.

Cosmetic surgeons need to be cautious with smokers because of the risk of delayed cicatrization and even necrosis, so they must inform their patients about these risks. Excessive tobacco consumption may be a contraindication for surgery [12]. A retrospective study of 345 patients [13] showed that there was an earlier need of cosmetic upper-eyelid surgery in smokers than in nonsmokers (3.5 years) or ex-smokers (3.7 years). This confirms the deleterious effects of smoking on the skin. There was no significant difference between ex-smokers and nonsmokers, suggesting a partial restoration of the skin during smoking cessation time (average cessation time: 204 years).

The mechanisms of aging in smokers are

- Impairment of skin arteries, often with problems in plastic surgery
- Free radicals responsible for degradation of normal elastic fibers and induction of abnormal fibers
- MMPs-1 induction responsible for collagen destruction
- Early menopause with estrogen deficiency

Other Extrinsic Factors

Role of Pollution in Skin Aging This is still poorly documented and difficult to determine because it is associated with other intrinsic and extrinsic factors of skin aging. The pollutants are numerous and long exposure is probably necessary for any effect. An interesting study, however, was performed on 400 Caucasian women aged 70–80 years: comparing a group in the Ruhr exposed to a high density of soot and fine particles related to traffic with another group of women living in a relatively unpolluted residential area [10]. Pollution was associated with 20% more pigment spots on the forehead and cheek but was less correlated to wrinkles. These results confirm the influence of particle pollution on skin aging.

Ozone (O3) and Oxidative Stress [14] O3 is a gaseous oxidant formed by chemical reactions between UV and O2 that can induce oxidative stress in cutaneous tissues. It also induces a significant skin depletion of antioxidants such as vitamins E and C together with an increase in lipid peroxidation, especially involving the stratum corneum. UV and O2 are thought to have additive effects on skin aging.

AGING OF UNDERLYING STRUCTURES

Skin lays on deep planes, superficial muscles, fats, and bones, adopting its curves and contours and reflecting changes in the underlying structures.

Aging also occurs in the superficial muscles that animate the face and give it expression, the fat compartment that confers its curves and fullness, and the bony support beneath.

Facial aging is an indissociable whole and separately analyzing the skin, and each underlying structure is somewhat artificial but necessary for the sake of clarity.

Aging of Muscles

How the Muscles Age [6,15,16]

Every superficial face muscle has a bone and a skin insertion that influences the formation of dynamic wrinkles. These muscles are organized in a superficial tract that is particularly dense and intricated in the periorificial areas. The spaces between the muscles are filled by the superficial fascia, which together with these muscles form the superficial musculoaponeurotic system. All these muscles are even and symmetrical, except the *orbicularis labii oris* muscle, and they are all innervated by the terminal branches of the facial nerve.

Muscle aging is characterized by atrophy and slackening, as the muscles react with permanent compensatory hypertonicity. On the contrary, the skin loses its elasticity and becomes distended without any compensation. It is this differential response of the skin–muscle couple to aging that explains the formation of dynamic expression wrinkles. Facial changes related to aging muscle should be analyzed not only at rest but also during movement, where these dynamic wrinkles are better visualized, so as to schedule their treatment with botulinum toxin (Figure 4.14a through c). For example, five types of glabellar frown can be observed, requiring different doses and points of injection [17].

The areas most affected by the aging muscle and its translation to the skin are those where the muscular network is denser and the skin–muscle couple the most intricate, namely, the periorificial fronto-orbital eyelid zone and the perioral zone. Here, not only wrinkles are visible but the whole facial expression, especially glance and smile, are affected. The aim of botulinum toxin is not only to reduce the wrinkles but also to rejuvenate the expression of the face.

Figure 4.14 Glabellar and frontal dynamic wrinkles should be analyzed not only at rest (a) but also during movement, at frown (b), and looking upward (c) to schedule their treatment with botulinum toxin.

Aging of the Periorificial Fronto-Orbital Area [6,15,16,18]

It is in the upper third of the face, especially the frontoglabellar area, that the superficial muscles play the greatest role in the genesis of dynamic wrinkles. The frontal muscle balance, with a single elevator muscle, the *frontalis*, and several depressor muscles of which the main ones are the *corrugator*, *procerus*, and the upper part of the *orbicularis oculi*, bends to the depressor muscles during aging. The *corrugator*, depressor, and powerful adductor are responsible for vertical frown

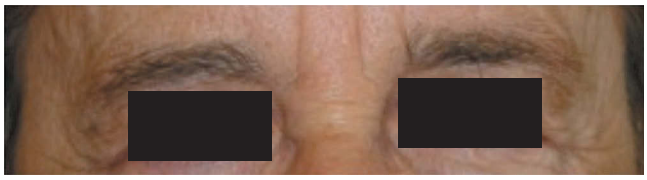


Figure 4.15 The eyebrows fall away, especially in their outer part, on which the *frontalis* muscle does not intervene, but only the *orbicularis oculi*, which acts as a depressor in this area.

Figure 4.16 Permanent wrinkles of the forehead related to hypertonicity and shortening of the *frontalis* muscle, raising the eyebrows and opening of the narrowed palpebral split.

lines that make the face look anxious and severe. The *procerus* is responsible for transverse wrinkles visible at the base of the nose. The eyebrows fall away, especially in their outer part, on which the *frontalis* muscle does not intervene but only the *orbicularis oculi*, which acts as a depressor in this area because of its function as a sphincter (Figure 4.15). This lowering is mainly due to slackening of the front skin and the *galea apeuroneutica* and above all to the weight of the eyebrow and the fat pad of Charpy. This leads to hypertonicity and shortening of the *frontalis* muscle that is sometimes asymmetric because it is stronger on the side of the director eye. This raises the eyebrows and allows opening of the narrowed palpebral split due to the hypertonicity of *orbicularis oculi* muscle, leading to permanent wrinkles of the forehead (Figure 4.16). Crow's feet spread over the temporal region and the upper part of the cheekbone is due to hypertonicity of *orbicularis oculi* muscle. The wrinkles are more pronounced in this area owing to the tight adhesion between the thin skin affected by photoaging and the underlying muscles.

Aging of Peribuccal Area [6,15,19,20]

The *orbicularis labii oris* is a powerful muscle with concentric bundles that functions as a sphincter but also acts on the protraction of the lips. Its motor functions are complex, and it is involved in mouth occlusion when eating, drinking, and sucking. It allows you to talk, blow, whistle, kiss, and smile. It adheres closely to the skin of the lips and its hypertonicity explains the formation of the deep radial wrinkles (cod-bar) that become apparent when the patient is asked to whistle or blow.

To the side of the oral commissure lies the *modiolus*, a muscular crossroads, where intersecting muscles are inserted that draw the commissure laterally (*risorius*), laterally and behind (*buccinator*), upward (*levator anguli oris*) superior and laterally (*zygomaticus major)*, down and laterally (*depressor anguli oris*), and inside (*orbicularis labii oris*).

The *levator labii superioris and alaeque nasi*, the superficial levator of the upper lip and of the ala nose, insert beneath the skin of the juxta-central region of the upper lip. The *levator labii superioris*, which is deeper than the *alaeque nasi*, inserts over almost the entire width of the upper lip. The *depressor labii inferioris* inserts over almost the entire width of the skin of the lower lip and the red border, lowering the lower lip and widening out the free edges. The *mentalis* inserting the skin of the chin tuft creates the middle fossa and raises the skin of the chin. Finally, the high insertions of the platysma at the chin, commissures, and cheek lower the skin of these areas. Owing to their hypertonicity, some of these muscles have a more pronounced effect on facial aging, especially the *depressor anguli oris*, which lowers the commissures and gives a sad-looking face, the *mentalis*, which hollows the lip/chin fold and exacerbates the chin surface irregularities, and the *platysma*, which lowers the tissues of the cheeks, lower lip, and commissures.

However, in this lower third of the face except the deep dynamic wrinkles of the upper lip, the impression of aging stems more from the fat ptosis inducing hollowing of the cheeks, accentuation of the nasolabial fold, which extends lower than the commissures and disturbs the harmony of the facial oval, thereby creating jowls.

And the Nose?

Although this region is rather immobile, the muscular hypertonicity of aging may be also manifested by bunny lines, which are due to the *nasalis pars transversa* muscle, and also to the lower inner part of the *orbicularis oculi* [21]. These wrinkles can appear or become more pronounced as a compensatory mechanism when glabella wrinkles are treated with botulinum toxin. The *depressor septi nasi* is responsible for lowering the tip of the nose, a feature often seen in the elderly.

Muscle Aging in the Neck and Platysmal Cords [6,19,20,22]

Like other muscles, the platysma reacts to atrophy and to elongation related to aging by becoming hypertonic and shorter. It loses its homogeneity and its fibers amalgamate on the muscle edge to form the very unaesthetic platysmal cords, whose relief is especially visible on the anterior face of the neck but also laterally under the distended and creased skin. This hypertonic platysma pulls down the tissues of the mandibular edge, thereby accentuating the ptosis of this area of the face. The platysmal cords can be reduced by botulinum toxin, and the neutralization of the attraction of the lateral platysmal cords and of the platysma on the mandibular edge is the principle of Nefertiti lift [22]. Care should be taken when injecting the platysma anywhere other than the cords, because elsewhere it is very thin and there is a risk of injecting too deep with

severe respiratory adverse events. Moreover, injecting botulinum toxin on this very thin muscle is ineffective for correcting transverse wrinkles of the neck, which are positional wrinkles related to sagging of the skin and are not dynamic wrinkles.

Fat Ptosis and Atrophy

The most affected regions are the midface, where the fat sags, and the inferior third of the face, where the fat arrives and accumulates, transforming the shape of the face from that of an apple in youth to that of a pear in old age [6]. However, other regions such as the temples and even the forehead are also involved by fatty loss.

What Happens to the Midface with Aging ? [6,24–26]

There are deep and superficial fatty compartments in the malar zone separated by the lower half of the muscle *orbicularis oculi*, whose contraction lifts the lower eyelid and the cheek (antiaging effect of the smile). However, this lifting effect does not involve the deep compartment of the malar fat or suborbicularis oculi fat, because it is attached to the orbito-malar bone relief, which determines the contours of the cheekbones. This deep fat remains in place and does not sag during aging. Faces with prominent cheekbones that protrude and are set well above the tissues also age more slowly than others. However, atrophy of the deep malar fat can occur during aging, resulting in a flattening of the cheekbones. On the other hand, the superficial malar fat compartment, which covers the deep fat and *orbicularis oculi* muscle, is fixed only to the skin surface, not in depth. It therefore is drawn down by the sagging skin due to aging and leads to ptosis owing to its own weight and gravity. However, according to the "face recurve" theory, the repeated contraction of the mimic muscles could be the main cause of the changes in fat distribution [23]. Whatever the case, this superficial fat that can be partitioned into three separate compartments, medial, middle, and temporal cheek fat [26], mobilizes down and inward, knocking against the fixed area of the superior lip and accumulating above the nasolabial furrow, which becomes highly marked (Figure 4.17). The fat ptosis also accentuates the palpebro-malar fold, hollowing the dark circles, increasing the height of the lower eyelid and accentuating the mid-jugal fold. The inner part of the palpebro-malar fold and the upper inner part of the mid-jugal form the valley of tears. The tonicity of the inferior eyelid decreases owing to the weakening and spreading down of the *orbicularis oculi* muscle with occasionally scleral show. The ptosis of the orbital fat can form fatty hernias at the level of the inferior eyelids, due to weakening of orbital septum (Figure 4.18). Malar pockets may develop under the external part of the inferior palpebral sulcus.

Fat atrophy sometimes predominates over ptosis and leads to emaciation of the face, which becomes skeletal, with hollowing of the cheeks and the valley of tears and flattening of the cheekbones.

And the Lower Third of the Face?

The fat from the midface accumulates in the lower third of the face, forming jowls due to the sagging of fat and skin, disturbing the oval shape of the face and blurring the definition of the mandibular rim (Figure 4.19). The nasolabial folds extend lower than the commissures of the mouth, forming bitterness folds and making a sad-looking face. These deep furrows create a parenthesis around the mouth that is accentuated by the frequent fat atrophy of the lips. The upper lip looks longer and vertical, with flattening of the philtrum, disappearance of its slight upward orientation, and thinning of the vermilion part. These upper lip alterations are exacerbated by the loss of dental support.

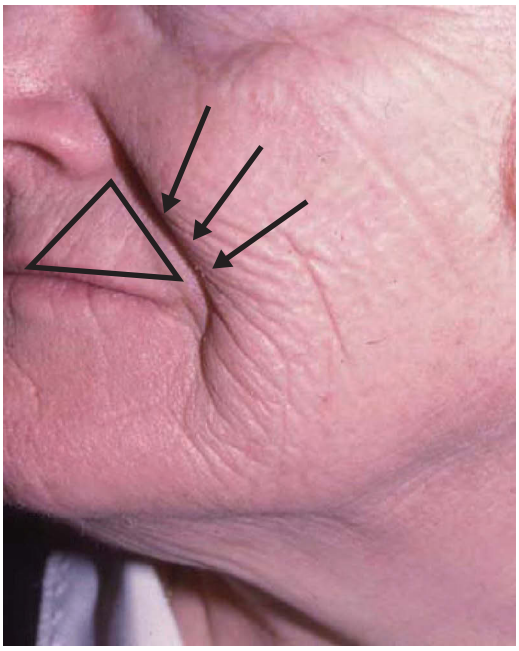


Figure 4.17 The superficial fat mobilizes down and inward, knocking against the fixed area of the superior lip, and accumulating above the nasolabial furrow, which becomes highly marked.

Figure 4.18 The ptosis of the orbital fat can form fatty hernias at the level of the inferior eyelids, due to weakening of orbital septum.

Upper Third of the Face

Aging causes the ptosis of Charpy's pad fat and leads to lowering of the eyebrows. Furthermore, fat is also lost on the forehead, whose convexity disappears and is replaced sometimes by a very marked depression over the eyebrows (Figure 4.20). The fat atrophy is even more visible around the temples, a process beginning at age forty and leading to a skeletal aspect a decade later [27] (Figure 4.20). Orbital fat may be also lost and a ptosis may occur. This fat loss may be pronounced in some individuals and leads to an aspect of deep-set eyes when combined with enlargement of the orbits.

Bony Atrophy

This is always present in aging. Orbital enlargement and atrophy of the maxillary and mandibular bones, often with loss of several teeth, are the most evident signs [28]. There is little

Figure 4.19 The fat from the midface accumulates in the lower third of the face, forming jowls due to the sagging of fat and skin, disturbing the oval shape of the face, and blurring the definition of the mandibular rim.

Figure 4.20 Fat atrophy on the forehead and the temples, leading to a skeletal aspect.

scope for treatment apart from orthodontic care and lipostructure or fillers in some areas.

DISTINCTIVE FACIAL AGING IN MEN COMPARED TO WOMEN

Owing to the influence of androgens, male skin is thicker with a higher density of collagen, more sebaceous secretions, and greater pilosity. Chronological aging is delayed because of this very anabolic hormonal impregnation by the androgens that occurs later in life in men. On the other hand, photoaging is often more pronounced in men because they are more exposed to UV occupationally than women and frequently neglect photoprotection. Other extrinsic factors such as their higher consumption of tobacco act. Their wrinkles and furrows are deep but often less numerous than in women. Their upper lip, which is thicker and denser owing to the presence of numerous proliferative hair follicles, is more resistant to aging and develops wrinkles more slowly. However, this heavier skin ptoses more in some areas such as the eyebrows, which are already horizontal and lower than in women especially in their lower outer part because of the more marked ptosis of Charpy's pad. Furthermore, the jowls are affected, often with dark circles marked by fat pockets in the lower eyelids, sagging neck skin, and fat ptosis with a double chin. The superficial muscles are much more powerful, especially in the glabella, so they need doses of botulinum toxin often twofold greater than those used in woman [29,30]. Botulinum toxin should not be injected too low on the forehead in order to avoid lowering the already low eyebrows. Care should be taken so that fillers injections do not lead to facial feminization by excessive injection of the external malar area or lips. Significant ptosis, a double chin, and lower eyelid fat pockets are good indications for surgery. Androgenic alopecia is a major concern in men, not only owing to its unaesthetic aspect but also because it makes them look older than their age.

CONCLUSION

Careful analysis and evaluation of the various components of aging is needed for guiding the choice of treatment, particularly in the face. Whereas skin aging used to be the focus of attention in the past, the role of the underlying tissues is nowadays taken more and more into account. For skin aging, surface techniques are indicated such as cosmetics, peels, and lasers. To reduce the muscle hypertonicity associated with aging, the treatment is botulinum toxin. For fat ptosis, lipofilling, fillers, radiofrequency, or microfocused ultrasound are the methods of choice when the condition is moderate and surgery if it is more marked. For the atrophy of adipose tissue, the volume may be restored by lipofilling or fillers.

In conclusion, aging of the skin and the underlying structures is a very intricate process. Consequently, a single type of treatment is rarely sufficient; global management is needed and combined treatments are necessary in most cases. Therefore, a personalized treatment plan should be discussed with every patient. Indeed, aging is never the same process, so any treatment plan should take into account both the clinical data and the wishes, priorities, and financial means of the patient.

REFERENCES

1. Beylot C. *Vieillissement cutané. Prévenir. Corriger. Rajeunir.* Paris, France: Med'Com edn, 2007.
2. Debacq-Chaniaux F, Leduc C, Verbeke A et al. UV, stress and aging. *Dermatol Endocrinol* 2012; 4:236–240.
3. Garibyan L, Chiou AS, Elmariah SB. Advanced aging skin and itch: Addressing an unmet need. *Dermatol Ther* 2013; 26:92–103.
4. Blume-Peytavi U, Atkin S, Gieler U et al. Skin academy: Hair, skin, hormones and menopause. Current status/knowledge on the management of hair disorders in menopausal women. *Eur J Dermatol* 2012; 22:310–318.
5. Vierkötter A, Krutmann J. Environmental influences on skin aging and ethnic-specific manifestations. *Dermatol Endocrinol* 2012; 4:227–231.
6. Belhaouari L, Gassia V. *L'art de la toxine botulique en esthétique et des techniques combinées*, 2nd edn. Paris, France: Arnette, Wolters Kluwer, 2013.

7. Quatresooz P, Thirion C, Piérard-Franchimont C et al. The riddle of genuine skin microrelief and wrinkles. *Int J Cosmet Sci* 2006; 28:389–395.
8. Pierard GE, Lapiere Ch M. The microanatomical basis of facial frown. *Arch Dermatol* 1989; 125:1090–1092.
9. Glogau RG. Aesthetic and anatomic analysis of the aging skin. *Semin Cutan Med Surg* 1996; 15:134–138.
10. Vierkötter A, Shikowski T, Ranft U et al. Airborne particle exposure and extrinsic skin aging. *J Invest Dermatol* 2010; 130:2719–2726.
11. Kaya G, Saurat JH. Dermatoporosis: A chronic cutaneous insufficiency/fragility syndrome. Clinicopathological features, mechanisms, prevention and potential treatments. *Dermatology* 2007; 215:284–294.
12. Coon D, Tuffaha S, Christensen J et al. Plastic surgery and smoking: A prospective analysis of incidence, compliance and complications. *Plast Reconstr Surg* 2013; 131:385–391.
13. Deliaert AEK, van den Elsen MEP, van den Kerchkove E et al. Smoking in relation to age in aesthetic facial surgery. *Aesthetic Plast Surg* 2012; 36:853–856.
14. Valachi G, Sticozzi C, Pecorelli A et al. Cutaneous responses to environmental stressors. *Ann N Y Acad Sci* 2012; 127:75–81.
15. Ingallina FM, Trevidic P. *Anatomy and Botulinum Toxin Injections*. Paris, France: E2e Medical Publishing Ed., 2010.
16. Carruthers J, Fournier N, Kerscher M et al. The convergence of medicine and neurotoxine: A focus on botulinum toxin type A and its application in aesthetic medicine. Part II. *Dermatol Surg* 2013; 39:510–525.
17. Trindade De Almeida AR, Da Costa Marques ERM, Banegas R et al. Glabellar contraction patterns: A tool to optimize botulinum toxin treatment. *Dermatol Surg* 2012; 38:1506–1515.
18. Raspaldo H, Baspeyras M, Bellity P et al. Upper- and mid-face anti-aging treatment and prevention using onabotulinumtoxin A: The 2010 multidisciplinary French consensus—Part 1. *J Cosmet Dermatol* 2011; 10:36–50.
19. Raspaldo H, Niforos FR, Gassia V et al. Lower-face and neck antiaging treatment and prevention using onabotulinum toxin A: The 2010 multidisciplinary French consensus-part 1. *J Cosmet Dermatol* 2011; 10:131–149.
20. Gassia V, Beylot C, Bechaux S et al. Les techniques d'injection de la toxine botulique dans le tiers inférieur et moyen du visage, le cou et le décolleté. Le « Néfertiti Lift ». *Ann Dermatol Vénéréol*. 2009; 136 (Suppl 4):S111–S118.
21. Tamura BM, Odo MY, Chang B et al. Treatment of nasal wrinkles with botulinum toxin. *Dermatol Surg* 2005; 31:271–275.
22. Levy PM. The « Nefertiti lift » a new technique for specific recontouring of the jawline. *J Cosmet Laser Ther* 2007; 9:249–252.
23. Le Louarn C. Vieillissement musculaire et son implication dans le vieillissement facial: le concept du Face Recurve. *Ann Dermatol Vénéréol*. 2009; 136 (Suppl 4):S67–S72.
24. Truswell WH. Aging changes of periorbita, cheeks and midface. *Facial Plast Surg* 2013; 29:3–12.
25. Sadick NS, Manhas-Bhutani S, Krueger N. A novel approach to structural facial volume replacement. *Aesth Plast Surg* 2013; 37:266–276.
26. Rohrich RJ, Pessa JE. The fat compartments of the face: Anatomy and clinical implications for cosmetic surgery. *Plast Reconstr Surg* 2007; 119:2219–2227.
27. Raspaldo H. Temporal rejuvenation with fillers: Global face sculpture approach. *Dermatol Surg* 2012; 38:261–265.
28. Shaw RB, Katzel EB, Koltz PF et al. Aging of facial skeleton: Aesthetic implications and rejuvenation. *Plast Reconstr Surg* 2011; 127:374–383.
29. Gassia V. Les injections de toxine botulique en esthétique chez l'homme. *Ann Dermatol Vénéréol*. 2009; 136 (Suppl 4): S119–S124.
30. Monheit G, Lin X, Nelson D et al. Consideration of muscle mass in glabellar line treatment with botulinum toxin type A. *J Drugs Dermatol* 2012; 11:1041S–1045S.

Stem cells and growth factors

Klaus Sellheyer

INTRODUCTION

Stem cell biology influences the practice of modern medicine with an ever-increasing speed. In 2011, Trounson et al. [1] listed a total of 123 clinical trials with mesenchymal stem cells (MSCs)—therapeutically the stem cell type employed most commonly—in the United States alone, addressing various diseases from cancer to diabetes and gastrointestinal diseases (Figure 5.1). These trials are not necessarily done in the United States only. In fact, more than 50% of stem cell trials submitted for approval to the Food and Drug Administration (FDA)—the United States equivalent to the European Medicines Agency (EMA)—involve foreign study sites [2]. Until March 8, 2009, the Bush era–related restriction on federally funded embryonic stem cell research gave Europe a competitive advantage over the United States. With the reversal of the ban by Barack Obama, that advantage is shrinking. A landmark decision in Brüstle versus Greenpeace by the Court of Justice of the European Union (CJEU) published on October 18, 2011, could further influence that balance. The court ruled that any process (including subsequent therapies) involving the derivation of stem cells from a human embryo at the blastocyst stage could not be patented [3]. It remains to be seen what effect that decision has on the patentability of and research on stem cells in Europe that is heavily funded by venture capital investors who consider patents an important part in their decision-making process.

So far, clinical trials with stem cells address mostly otherwise incurable diseases, such as various neurodegenerative disorders, including Parkinson's disease. However, the enormous plasticity of stem cells and the rapid progress in the field make it also increasingly desirable to exploit their potential in other fields of medicine, including aesthetic dermatology. The potential application in the latter has been especially fueled by the 2001 discovery of MSCs in the subcutaneous adipose tissue that is easily accessible [4]. Subsequent studies found that the growth factors secreted by these stem cells play a central role in skin rejuvenation [5,6].

In the following, we will summarize the basic science behind stem cells and outline potential clinical applications in the field of dermatology with special emphasis on aesthetic dermatology.

WHAT IS A STEM CELL AND WHERE IN THE SKIN DO STEM CELLS RESIDE?

A stem cell is defined primarily functionally and not in morphological terms [7,8]. In skin, one of the first population of cells conclusively characterized as a stem cell population is located in the follicular bulge (Figure 5.2). It was initially detected in mice by the ability of the cells to retain radioactively labeled thymidine [9]. Stem cells divide rarely and thus retain radioactivity longer, whereas it becomes diluted and undetectable over the course of several cell cycles in cells that have left the stem cell niche and have committed to differentiate. While subsequently employed immunohistochemical markers are extremely useful in the detection of stem cells *in situ* [10], functional studies are still the gold standard to characterize a stem cell.

Functionally, a stem cell represents an undifferentiated cell that can produce a progeny of other stem cells (self-renewal) or that divides asymmetrically into another stem cell (thereby retaining its undifferentiated status) and a transient amplifying cell, which has lost its capacity for unlimited self-renewal and differentiates down a certain pathway (Figure 5.3).

Stem cells can be totipotent, pluripotent, multipotent, and unipotent. Totipotent stem cells do exist only in the morula stage of the embryo and give rise to the embryo proper as well as to the extraembryonic tissue, the trophoblast (representing the precursor of the placenta). The embryonic stem cells found in the inner cell mass of blastocysts (Figure 5.4) [11], from which the first human embryonic stem cell line was isolated [12], have already lost their capacity to differentiate into the trophoblast and are thus referred to as pluripotent cells. Current dogma holds that totipotent and pluripotent stem cells do not exist in the adult organism. Adult stem cells are either multipotent (differentiating into more than one cell type) or unipotent (differentiating into one cell type only). In skin, the recently identified melanocytic stem cells [13–15] represent an example of the latter, whereas dermal MSCs are multipotent, capable of differentiating into smooth muscle cells, adipocytes, osteocytes, glial cells, and neurons [16–21].

In skin, besides follicular bulge, melanocytic stem cells, and MSCs, the interfollicular epidermis also harbors a special population of stem cells [22]. Sebaceous stem cells have been characterized in the mouse [23], but their existence has not been conclusively demonstrated in the human [24,25]. While technically not considered part of the cutaneous organ, the adipose tissue harbors a large number of stem cells that are therapeutically of great interest, especially for future applications in aesthetic dermatology (see discussion later).

STEM CELL PLASTICITY AND TRANSDIFFERENTIATION

The most appealing characteristic of stem cells is their remarkable plasticity, on which the therapeutic hopes rely. Stem cell transdifferentiation, often used synonymously with plasticity, refers to

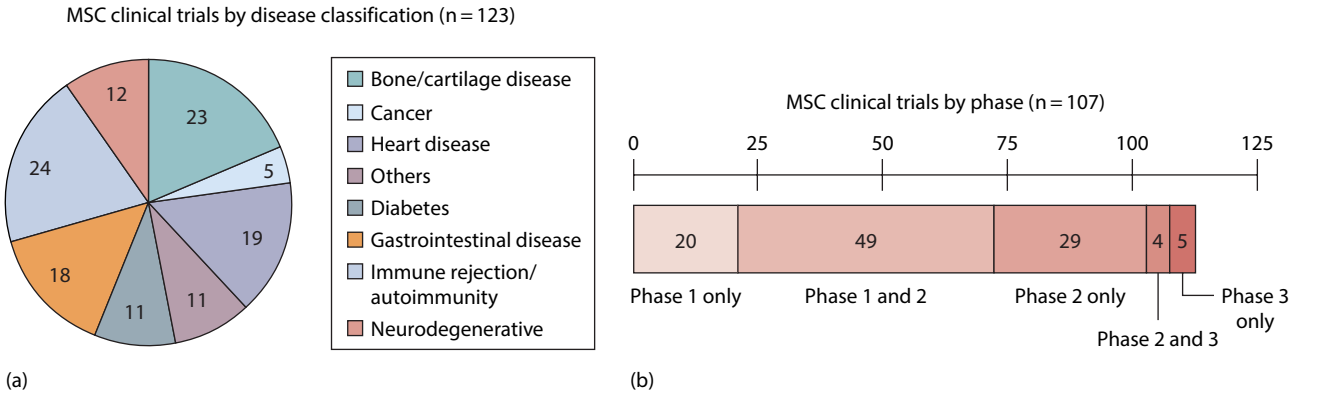


Figure 5.1 (a) Diseases being addressed using bone marrow mesenchymal stem cells (MSCs) for clinical trials (n = number of trials). (b) MSC clinical trials by clinical phase (n = number of trials). (Reprinted from Trounson A et al., *BMC Med*, 9, 52, 2011. With permission; open access journal, CIRM summary/source clinicaltrials.gov. Accessed August 2, 2011.)

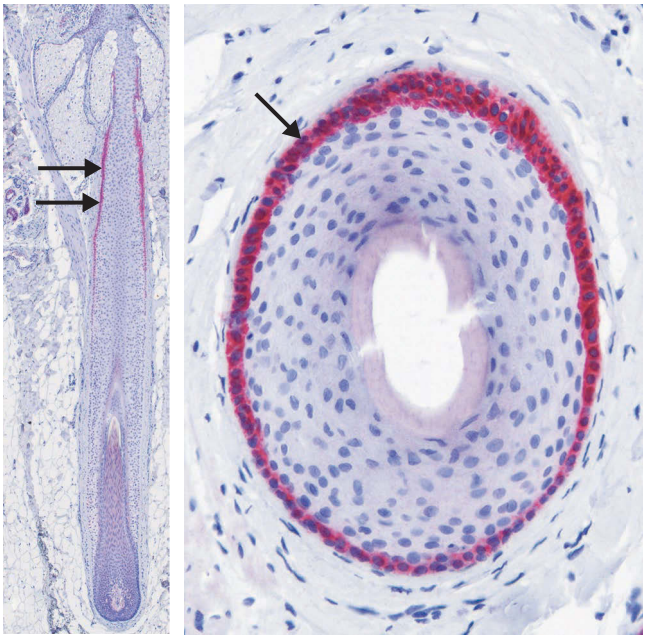


Figure 5.2 Cytokeratin 15 highlights the follicular bulge stem cells (arrows). (a) Longitudinal section of an entire hair follicle. (b) Transverse section through the level of the bulge. (From Sellheyer K: Stem cell markers can help identify adnexal tumor differentiation when evaluated in the context of morphology: Methodology matters. *J Cutan Pathol.* 2011. 38. 460–474. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

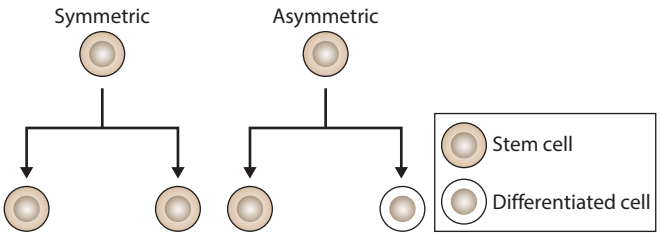


Figure 5.3 Stem cells divide either symmetrically into two stem cells or into one stem cell and a transit amplifying cell. The latter has lost the plasticity of stem cell and is committed to differentiate. (From Koestenbauer S, Zech NH, Juch H, Vanderzwalmen P, Schoonjans L, Dohr G: Embryonic stem cells: Similarities and differences between human and murine embryonic stem cells. *Am J Reprod Immunol.* 2006. 55. 169–180. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

the observation that stem cells can cross germ lines and differentiate into a whole spectrum of cell types other than the germ line lineage or the tissue they derive from. Examples include the differentiation of adult bone marrow–derived MSCs into multiple skin cell types including ectodermally derived keratinocytes [26], of adipose tissue–derived stem cells into hepatocytes [27], and of dermal MSCs into neurons [21,28,29] with the capacity to migrate into the spinal cord after traumatic injury in rats [30]. Such a plasticity of adult stem cells would not even require the use of embryonic cells for future therapeutic applications.

The concept of transdifferentiation is not uncontested, however. Some authors view the actual occurrence of transdifferentiation *in vivo* to be exceedingly rare [31,32] and other phenomena, such as cell fusion, may account for what is interpreted as an extraordinary plasticity of stem cells [33]. According to some reports, bone marrow–derived stem cells regenerate the liver by fusion with preexisting hepatocytes but not by transdifferentiation [34,35]. One study revealed that adult hematopoietic stem cells display little evidence of transdifferentiation [31] but another showed that this cell population has the capacity to transdifferentiate into epithelial cells of the liver, lung, gastrointestinal tract, and skin [36]. Other reports suggest that multiple mechanisms, including transdifferentiation, cell fusion, and production of growth factors, may exist that allow bone marrow–derived MSCs to repair damaged neurons [37]. The different results may have to do to a

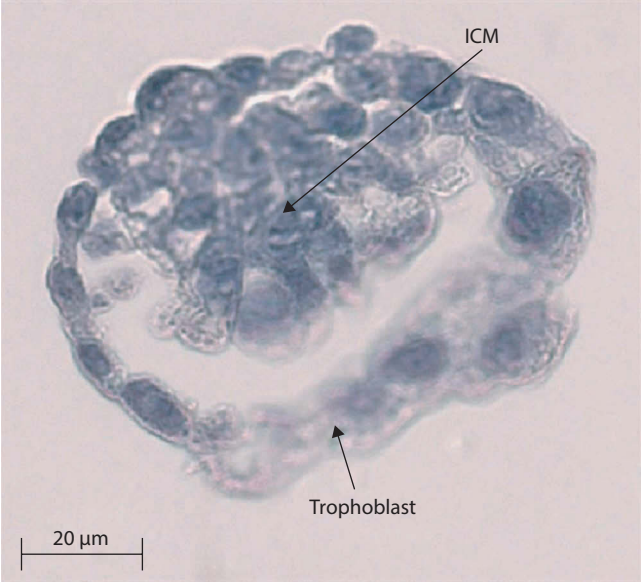


Figure 5.4 Murine blastocyst revealing the transversely cut inner cell mass (ICM) from which the first embryonic stem cell line was established. (From Koestenbauer S, Zech NH, Juch H, Vanderzwalmen P, Schoonjans L, Dohr G: Embryonic stem cells: Similarities and differences between human and murine embryonic stem cells. *Am J Reprod Immunol.* 2006. 55. 169–180. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

large extent with the different experimental techniques used, based on an *in vivo* or an *in vitro* approach.

INDUCED PLURIPOTENT STEM CELLS

The ethical dilemma of employing embryonic stem cells can be bypassed with the use of the recently described induced pluripotent stem cells that have a differentiation potential similar to that of embryonic stem cells. Induced pluripotent stem cells were initially generated from mouse skin fibroblasts [38], shortly thereafter from human skin fibroblasts [39,40], followed by induction of adult human skin keratinocytes [41] and most recently from cells of the hair follicle outer root sheath [42]. Isolated and cultured somatic (differentiated) cells, such as fibroblasts, can be reprogrammed *in vitro* with a cocktail of embryonic transcription factors, most importantly cMYC, SOX2, OCT4, and KLF4 (Figure 5.5). The subsequently generated cells—the induced pluripotent stem cells—behave like embryonic stem cells that can be differentiated into other cells types, e.g., keratinocytes, when incubated under specific culture conditions, such as supplementation with retinoic acid and bone morphogenetic protein-4 (Figure 5.5). That the induced pluripotent stem cells have the same properties as embryonic stem cells can be determined in the teratoma forming assay. The test evaluates the developmental capacity of the induced cells to produce a teratoma in immunodeficient mice (Figure 5.6) [43]. The most stringent test is the tetraploid blastocyst complementation assay. In this assay, successfully induced pluripotent stem cells display the same differentiation potential as embryonic stem cells by producing adult fertile mice [44,45].

One of the major drawbacks of induced pluripotent stem cells is the low yield, varying between 0.01% and 1% [46]. Human keratinocytes can be reprogrammed at a frequency of 100-fold higher than human fibroblasts [41]. Another one is a possible carcinogenic effect since the transgenes encoding the transcription factors are typically inserted via retroviral vectors in the host DNA. The problem can be bypassed with the use of nongenomic DNA integrating adenoviral vectors [41] or by eliminating genetic material in the first place and fusing the transcription factors with proteins instead [41]. The latter technique, however, has an especially low efficiency rate of 0.001% [47]. Another option is the use of modified mRNA [46].

Induced pluripotent stem cells allow for a patient-specific therapeutic approach and eliminate the problem of immunoincompatibility since the cells are derived from the patient himself. The reprogrammed cells can be further genetically altered to correct genetic defects or the effects of skin aging (Figure 5.7). Since they have stem cell characteristics, they can permanently replace diseased or aging cells without the requirement of replacing them after their cell cycles are exhausted.

CLINICAL APPLICATIONS OF STEM CELLS IN AESTHETIC DERMATOLOGY

It needs to be pointed out that the therapeutic use of stem cells is still in its infancy. This is especially true for aesthetic dermatology. Conceptually, however, the use of stem cells should

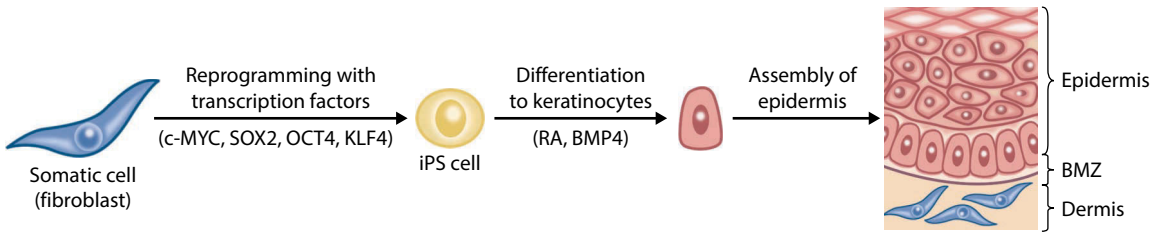


Figure 5.5 Schematic steps of reprogramming somatic cells, such as fibroblasts, into induced pluripotent stem (iPS) cells and subsequent differentiation into epidermal keratinocytes. The latter can be assembled into an epidermis. Reprogramming of somatic cells into iPS cells requires transcription factors (c-MYC, SOX2, OCT4, and KLF4) and differentiation of iPS cells into keratinocytes is done in culture medium supplemented with retinoic acid (RA) and bone morphogenic protein-4 (BMP-4). BMZ, basement membrane zone. (Reprinted by permission from Macmillan Publishers Ltd. *J Invest Dermatol*. Uitto J. 131, 812–814, Copyright 2011).

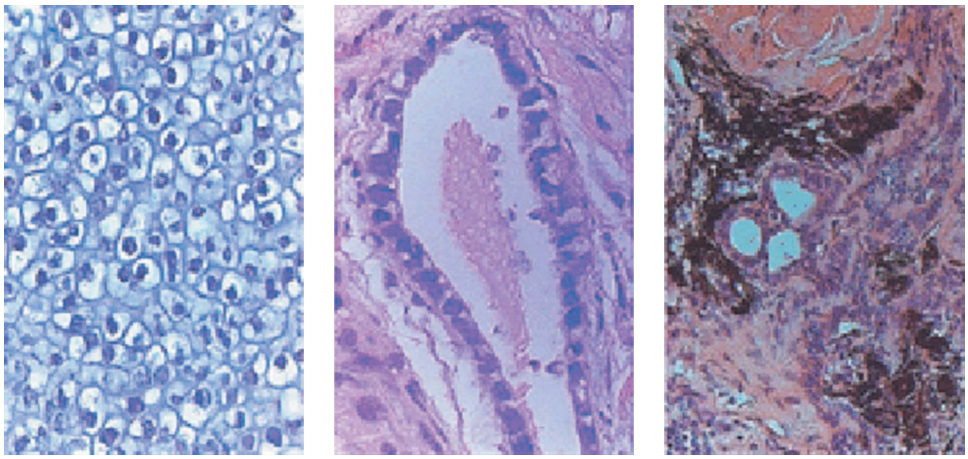


Figure 5.6 In a teratoma forming assay, the potential of human-induced pluripotent stem cells to differentiate into various cell types is examined: (a) cartilage, (b) epithelium, and (c) pigmented cells. (From Galach M and Utikal J: From skin to the treatment of diseases—The possibilities of iPS cell research in dermatology. *Exp Dermatol.* 2011. 20. 523–528. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

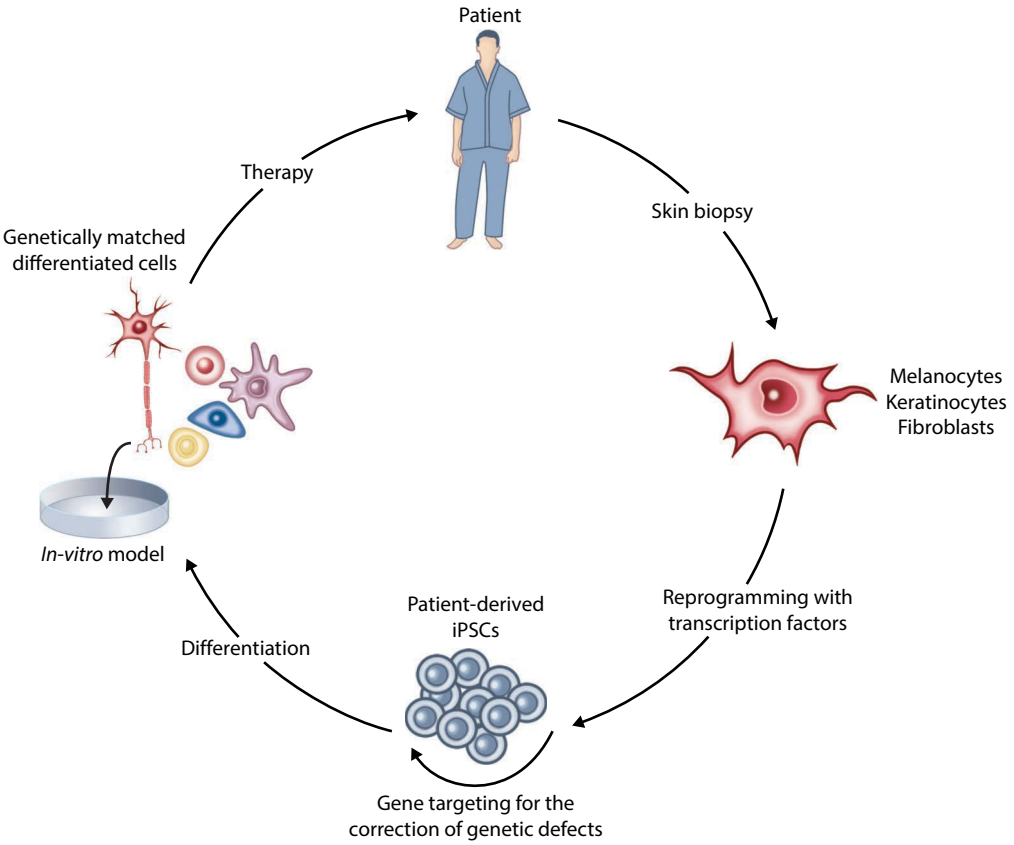


Figure 5.7 Induced pluripotent stem (iPS) cells can be generated from various autologous cell types (e.g., fibroblasts, keratinocytes, or melanocytes) from a diseased patient. Genomic mutations can be corrected *in vitro* and the genetically corrected stem cells can be reintroduced into the same patient, allowing for a permanent correction of a genetic defect. (From Galach M and Utikal J: From skin to the treatment of diseases—The possibilities of iPS cell research in dermatology. *Exp Dermatol.* 2011. 20. 523–528. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

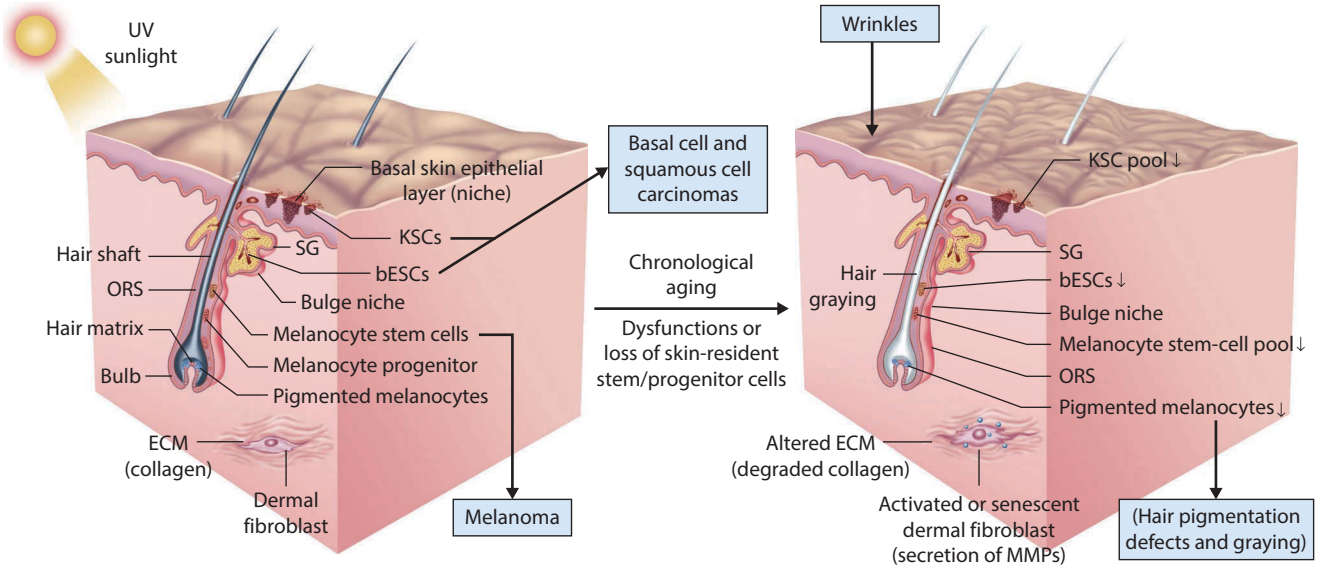


Figure 5.8 Cellular events associated with chronological and photoaging of skin stem cells and dermal fibroblasts. ECM, extracellular matrix; KSCs, keratinocyte stem cells; bKSCs, bulge keratinocyte stem cells; ORS, outer root sheath; SG, sebaceous gland. (From Mimeault M and Batra SK: *J Cell Mol Med.* 2010. 14. 116–134. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

allow for reversing the effects of chronological skin aging by replacing the various stem cells in their anatomical compartments (Figure 5.8) or by modulating their function *in vivo*. Intriguingly, at least epidermal stem cells are maintained at normal levels throughout life and seem to be aging resistant [48]. On the other hand, melanocyte stem cells are lost through premature differentiation (not by apoptosis or senescence), leading to hair graying [49].

The therapeutic use of stem cells does not necessarily involve stem cells that are derived from the integument. In fact, bone marrow–derived stem cells are currently one of the most commonly used subset of stem cells that have been applied clinically, especially in wound healing studies. In aesthetic dermatology, adipose stem cells likewise offer great therapeutic promise, not necessarily merely because of their stem cell characteristics but also especially because of the growth factors they secret [5,6,50]. In the following, we will highlight actual and potential clinical applications of stem cells in aesthetic dermatology. The therapeutic use of stem cells can also be integrated into a multidisciplinary approach combined with the application of gene therapy, the use of biomaterials as well as soluble molecules, especially growth factors (Figure 5.9).

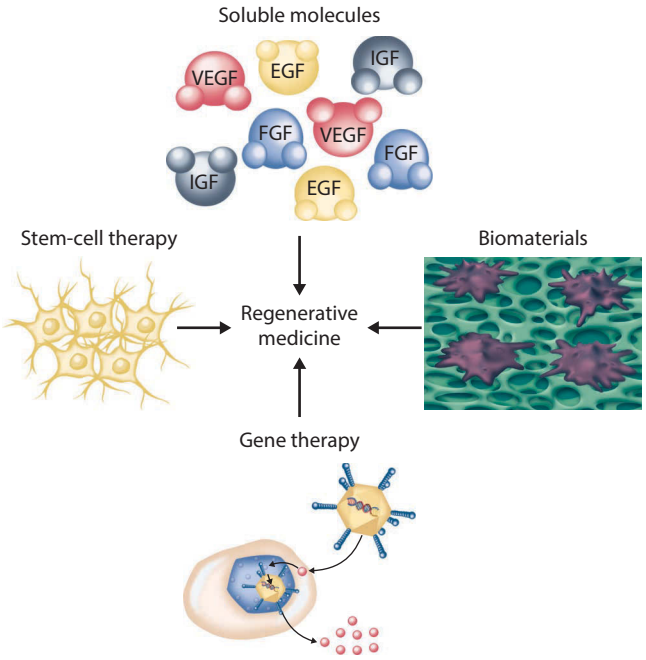


Figure 5.9 The therapeutic use of stem cells can be integrated with gene therapy and use of biomaterials and soluble molecules, especially growth factors. (From Dieckmann C et al.: *Exp Dermatol.* 2010. 19. 697–706. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

Mesenchymal Stem Cells

MSCs, either bone marrow derived, or skin derived, such as dermal or adipose stem cells, offer the greatest potential and have been used most. They have numerous effects on the skin by either differentiating into other cells (primarily dermal fibroblasts but in wound healing also into keratinocytes) and affect surrounding residential cells through secreted growth factors and cytokines. MSCs will be discussed in detail. The other stem cell populations—epidermal, hair follicle bulge, and melanocytic in origin—are currently not at the forefront of applications in aesthetic dermatology and, therefore, will be discussed only briefly. The cells employed so far are all adult stem cells. This eliminates the ethical concerns of embryonic stem cells and their inherent possibility of teratoma formation [51].

Different investigators use different characteristics in defining multipotent MSCs in various organs. Thus, not all cells introduced in the literature as stem cells may in actuality

be stem cells but rather represent transient amplifying or progenitor cells, which have lost their capacity for self-renewal but show a higher proliferative activity than their fully differentiated progeny. In 2006, the International Society for Cellular Therapy published an important position paper outlining the minimal criteria in defining multipotent MSCs [52]. The proposed three criteria comprises

1. Adherence to plastic in standard culture conditions (one of the characteristics of stem cells is their capacity to adhere to the surface of plastic dish used for culture, whereas fully differentiated cells do not)
2. Specific surface antigen expression (most importantly positivity for CD90 and lack of others, such as CD34)
3. Multipotent differentiation potential *in vitro*: osteoblasts, adipocytes, or chondroblasts

These criteria were published with the goal of standardizing the *in vitro* studies and to make a comparison among different laboratories easier, although they are not uniformly accepted. Since many of the studies on cutaneous MSCs were published before 2006 and since the group proposing these criteria is heavily weighted toward investigators with a focus on bone marrow–derived MSCs, reports prior to 2006 and those from researchers more interested in dermal or adipose-derived MSCs may divert from them. It can be expected that they will be modified, as we learn more about MSCs.

Bone Marrow–Derived Mesenchymal Stem Cells

Besides hematopoietic stem cells, the bone marrow harbors multipotent MSCs that are capable of differentiating into mature fibroblasts, endothelial cells, muscle, cartilage, and bone. They are being explored in the regeneration of the intervertebral disc [53], the meniscus [54], or various cartilage defects [55]. One of the first applications in dermatology was their use in the treatment of chronic wounds [56]. In three patients with wounds of more than 1-year duration that did not respond to previous conventional therapy, autologous bone marrow cells applied directly to the debrided wound bed lead to complete wound closure (Figure 5.10a). Skin biopsies showed evidence of dermal regeneration in a short time (Figure 5.10a). The cells delivered to the dermis were CD34-negative and, thus, did not appear to represent hematopoietic but mesenchymal stem cells [56]. Wound epithelialization lagged behind the dermal effects and the authors speculate that the dermal rebuilding process occurs prior to stimulation of the wound epithelialization. In a subsequent paper, the authors described healing of mouse and human wounds upon topical application of cultured bone marrow–derived MSCs that were delivered to the wound bed in a fibrin spray [57]. The latter approach is especially promising in patients with large wounds, such as burn victims, since the MSCs can be expanded in culture before. Limitations, however, are the observed bone marrow suppression in patients with severe burn trauma [58,59] as well as the decrease in the number of bone marrow–derived stem cells with age [60].

One intriguing and clinically useful characteristic of bone marrow–derived MSCs is their immunosuppressive function [61]. Experimental full-thickness cutaneous wounds in rabbits injected with human bone marrow–derived MSCs showed less scar formation and increased tensile strength (Figure 5.11) [62]. The MSCs could be demonstrated up to 21 days after transplantation but did not evoke an immunological response. In another study done on rats, however, donor infusion of mismatched bone marrow–derived MSCs led to faster skin allograft rejection, leading the authors to recommend adequate preclinical experimentation before clinical use [63].

Bone marrow–derived MSCs could be employed in aesthetic dermatology for scar revision (especially in the atrophic variants) or for tissue augmentation and would then compete with dermal mesenchymal and adipose-derived stem cells.

Dermal Mesenchymal Stem Cells

Whereas bone marrow–derived MSCs historically have been one of the first MSC types exploited for their therapeutic potential, dermal MSCs have only recently entered center stage. Although they are far from constituting actual treatment options at this point, it is expected that they will do so in the not so distant future. In contrast to bone marrow–derived MSCs, (1) they have the advantage of being accessible more easily through harvesting at almost every anatomical location, (2) their removal is considerably less painful to the patient, and (3) they are present in abundance.

That MSCs are part of the normal residential cell population in the dermis has first been described in the mouse in 2001 by Toma et al. from the McGill University in Montreal, Canada [16]. Subsequent studies detected dermal MSCs in the pig [19] and shortly thereafter in the human [64–67]. The cells were termed skin-derived precursors [16] and are capable not only of generating mesodermal progeny (adipocytes and smooth muscle cells) *in vitro* but also of differentiating into neurons, thus essentially defining them as stem cells. In line with the three criteria outlined defining multipotent MSCs [52], all four of the human studies demonstrated multilineage differentiation potential of the plastic adherent cells into adipocytes and osteocytes [64,66,67], two of them additionally into a chondrogenic phenotype [64,67]. The surface antigenic profile was positive for CD90 expression [65–67] but differed in regard to negativity for CD34 [66,67]. *In vitro*, skin-derived precursor cells can be expanded for more than a year and retain their normal karyotype [68]. This would allow harvesting the cells from the dermis of patients and to manipulate and expand them for an extended period of time without detrimental changes to the karyotype before implanting them into the patient.

Only a subtype of dermal fibroblasts but not keratinocytes was capable of generating adipocytes, smooth muscle cells, and neurons [16]. Toma et al. [16] early on concluded that the previously unidentified dermal stem cell ("skin-derived precursor"), which generates cells of more than one embryonic lineage, may allow the skin to function as an easily accessible, autologous source for future stem cell transplantation. It is conceivable that harvesting the dermis followed by subsequent isolation and propagation of its stem cells could lead to the treatment of neurodegenerative diseases or traumatic spinal cord injury. It is likewise possible to employ the dermal MSCs for supplementing severely sun-damaged skin with new fibroblasts that are expected to generate from them.

Skin photoaging involves the reduction and cell death of fibroblasts induced by UV irradiation [69]. The transforming growth factor-beta (TGF-β) regulates the extracellular matrix of

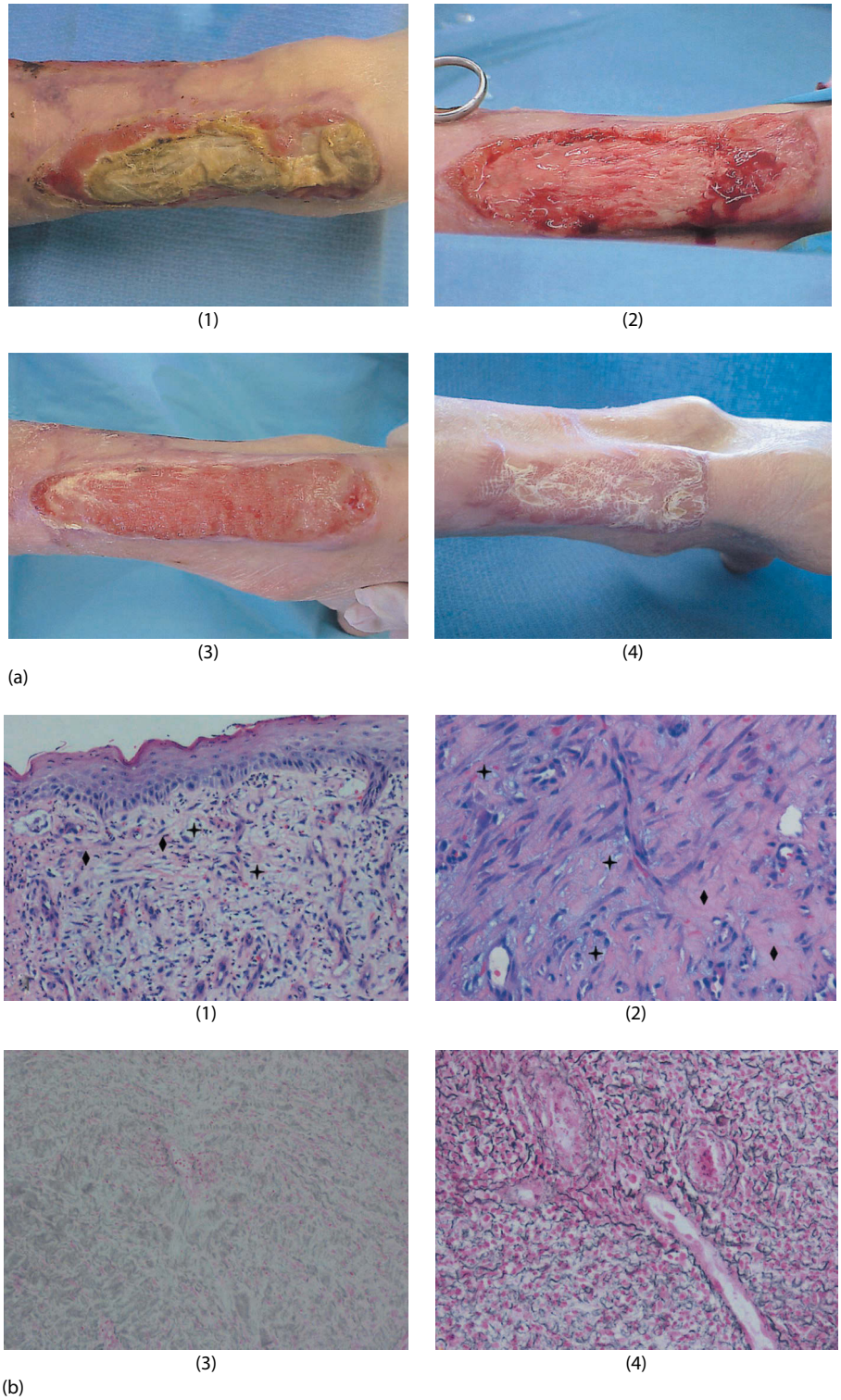


Figure 5.10 (a) Clinical pictures. (1) Visible necrotic Achilles tendon prior to treatment and before wound debridement; (2) appearance immediately after debridement and prior to application of bone marrow aspirate; (3) increased vascularity and evidence of good granulation tissue 5 weeks after application of bone marrow aspirate; and (4) healed wound following administration of bone marrow aspirate and cultured bone marrow cells. (b) Histological pictures. Biopsy specimens obtained after application of bone marrow aspirate and cultured bone marrow cells (1 and 2). Specimens obtained from patient 1 prior to treatment (3) and following application of bone marrow aspirate (4). The wound is epithelialized, with new collagen formation (cross) and mucin deposition (diamond) (1); mucin deposition (diamond) and collagen formation (cross) shown at a higher magnification (2); reticulin stain reveals the absence of reticulin fibers prior to treatment (3) and numerous reticulin fibers after treatment (4). (Reprinted from Badiavas EV and Falanga V, *Arch Dermatol.,* 139, 510, 2003. With permission from the American Medical Association.)

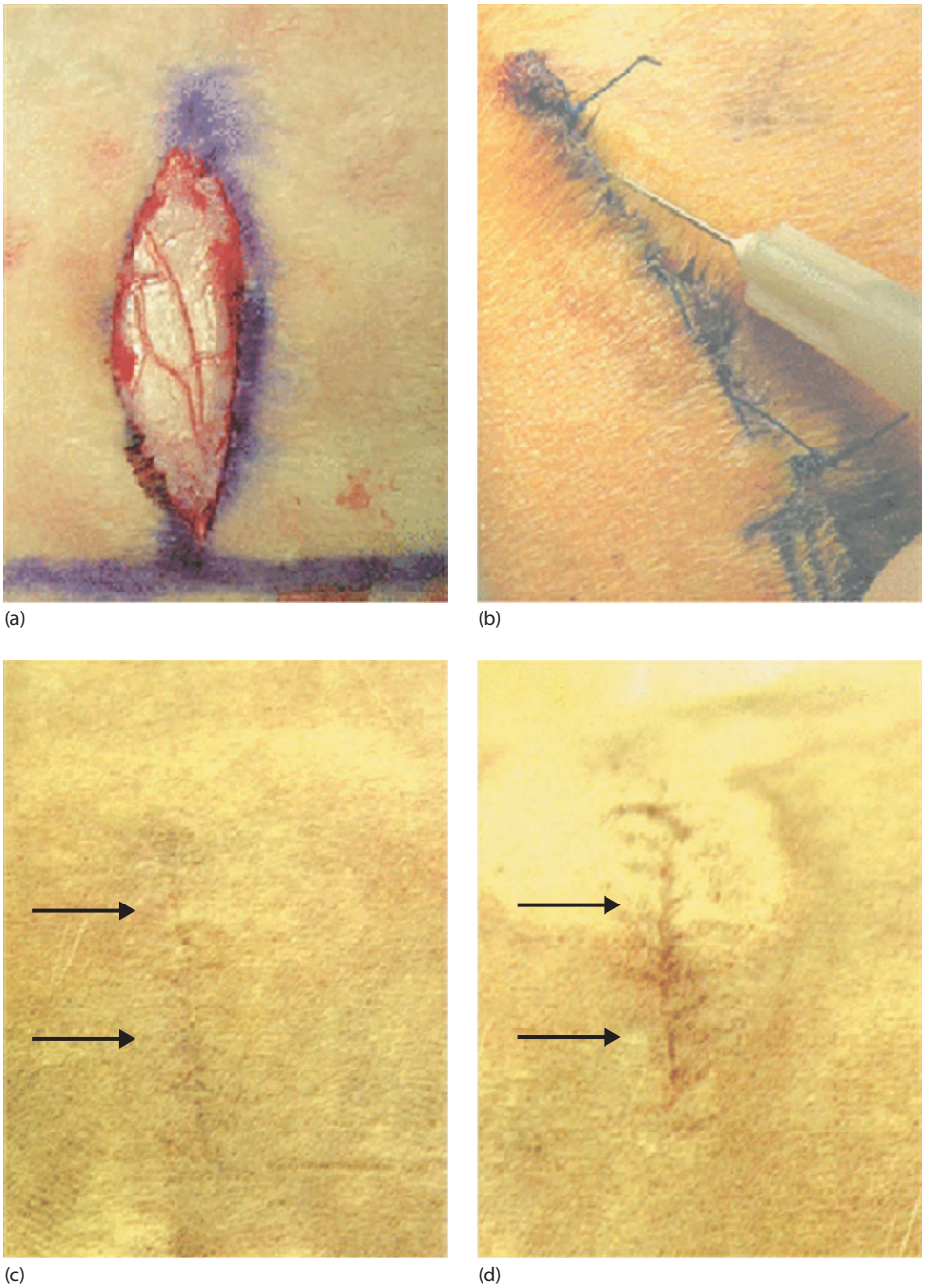


Figure 5.11 Full-thickness 3 cm long incisional wounds in New Zealand rabbits. Wounds were created in the dorsal skin up to the fascia (a) and 1.5 × 106 hMSCs suspended in 100 µL of PBS were injected around the wounds (b). At day 80, the macroscopic appearance of the scarring in incisional wounds treated with hMSCs (c) was less detectable compared with untreated wounds (d). (From Stoff A, Rivera AA, Sanjib Banerjee N et al.: Promotion of incisional wound repair by human mesenchymal stem cell transplantation. *Exp Dermatol.* 2009. 18. 362–369. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

the dermis through its receptor and the intracytoplasmic Smad proteins, a process known as the TGF-β/Smad signaling pathway. Ultraviolet radiation reduces collagen production in photoaged human skin by blocking the pathway in the fibroblasts, leading to collagen breakdown and elastin disorientation [70]. It is hypothesized that implanted dermal MSCs would reverse that effect by stimulating dermal fibroblast proliferation and/or differentiating into fibroblasts, thereby possibly reducing wrinkles and improving skin laxity [69]. Certainly, we are far from such a goal, and *in vitro* results may not necessarily translate into an *in vivo* situation.

The possibilities of skin-derived mesenchymal stems to generate a potpourri of different cells are endless but depend on the culture conditions employed *in vitro*.

Adipose-Derived Stem Cells

Adipose tissue replacement is important in soft tissue reconstruction, especially for large volume defects. Cosmetic and plastic surgeons typically use vascular pedicles composed of skin and subcutaneous tissue that provide appropriate volume. Lipotransfer for midface contouring is a popular procedure in aesthetic dermatology and uses free fat grafting [71]. Stem cell–enriched soft tissue augmentation with adipose-derived stem cells is increasingly being investigated [72,73]. If successful, stem cell transplantation would avoid the donor site defect of vascular pedicles, the unpredictable resorption rate of autologous fat grafts, as well as fibrosis and infection associated with synthetic materials [74].

The multilineage potential of stem cells derived from human adipose tissue has first been characterized in 2001 by Zuk et al. [4]. The cells were initially termed processed lipoaspirate (PLA) cells since they were isolated from lipoaspirates. The stem cells are derived from the stromal-vascular fraction that is left after enzymatic digestion of the extracellular matrix of the harvested adipose tissue with collagenase, red blood cell lysis, and subsequent centrifugation. This cell population contains not only adipose-derived stem cells but also endothelial stem cells [75]. This is clinically important since it allows not only for neoadipogenesis but for neoangiogenesis as well. Graft loss in free fat transfer is frequently attributed to the lack of vascularization [76]. Comparable to dermal MSCs, adipose-derived stem cells also can differentiate into neurons, oligodendrocytes, Schwann cells, smooth muscle cells, and numerous other cells [77]. Due to the abundance of adipose tissue, adipose-derived stem cells are even easier to harvest than dermal mesenchymal cells. Moreover, compared to bone marrow, adipose tissue harbors 100–1000× more stem cells per gram of tissue [78]. This bypasses the need for prior *in vitro* propagation and facilitates the use of the cells shortly after harvesting.

There are regional anatomical differences in the apoptotic susceptibility of human adipose-derived stem cells as well as age-related changes in function that need to be taken into consideration when selecting patients and cell harvest sites. Stem cells derived from the superficial abdominal depot are significantly more resistant to apoptosis than those derived from the upper arm, medial thigh, trochanter, and the deep abdominal depots [79]. Cell proliferation on the other hand is related primarily to age and not anatomical site with younger patients showing a higher proliferative capacity of their adipose-derived stem cells than older ones [79].

It is not sufficient after harvesting to transplant the adipose-derived stem cells to a tissue defect in the hope the cells will regenerate into functional adipose tissue. Without an accompanying mechanical support, typically in the form of a scaffold, adipogenesis would not occur [80]. The three different types of scaffolds include hydrogels (e.g., fibrin glue, hyaluronic acid, polyethylene glycol-diacrylate, alginate), preformed sold scaffolds (e.g., hyaluron-based sponges, collagen, and poly-L-lactic acid seeded scaffolds), and a combination of solid particles embedded within a hydrogel (e.g., polyglycolic acid fiber–based matrices with poly-L-lactic acid and with a fibrin-/adipose-derived stem cell mixture) [74]. Ideally, the scaffold does not degrade fast enough before mature adipose tissue is formed and allows for angiogenesis. The scaffold needs to promote attachment, proliferation, and differentiation of the stem cells.

While the number of stem cells is higher in adipose tissue than in, e.g., bone marrow, one study found that the harvesting technique can have a profound influence on the stem cell survival [81]. Harvesting is typically done with a standard liposuction blunt-tipped cannula. The yield of adipose-derived stem cells is lower, however, in aspirated versus excised whole fat [81]. Aspirated fat also contained fewer large vascular structures than excised one [81]. When the aspirated human fat was transplanted subcutaneously into severe combined immunodeficiency mice—used because the mice do not reject human tissue—adipose tissue supplemented with stem cells (= cell-assisted lipotransfer) survived better (35% larger on average) and developed more prominent microvasculature than mice transplanted with fat not supplemented with previously isolated adipose-derived stem cells [81]. The finding could explain the frequent lack of long-term survival of adipose tissue in free fat transfer.

A natural scaffold for adipose-derived stem cells is the lipoaspirate of adipose tissue itself. Adipose-derived stem cell–assisted lipotransfer has clinically already been applied for cosmetic breast augmentation [82,83] (Figure 5.12). The augmentation

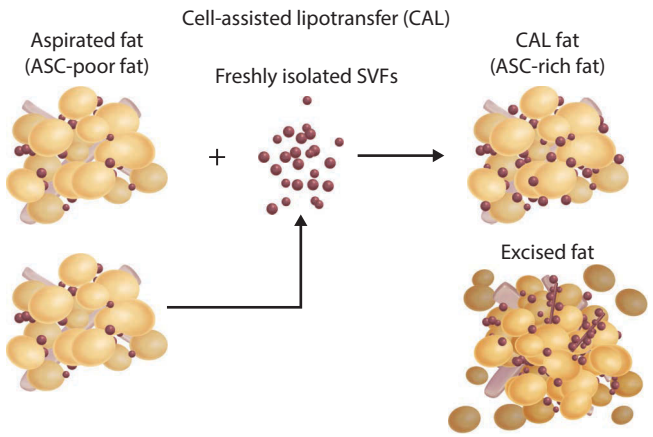


Figure 5.12 Procedure of cell-assisted lipotransfer. Half of the volume of the aspirated fat is processed for isolation of the stromal-vascular fraction containing the stem cells. During the isolation process, the other half of the aspirated fat is prepared for grafting. Then the freshly isolated stem cells are attached to the aspirated fat and the fat acts as a living scaffold. Finally, the stem cell–enriched fat is injected into the target sites. (From Yoshimura K, Sato K, Aoi N, Kurita M, Hirohi T, Harii K: Cell-assisted lipotransfer for cosmetic breast augmentation: Supportive use of adipose-derived stem/stromal cells. *Aesthetic Plast Surg.* 2008. 32. 48–55. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

effects were higher in patients who underwent cell-assisted lipotransfer compared to those with conventional autologous lipoinjection.

Using platelet-rich plasma as a scaffold and combined with a 3D, polymerized hyaluronic acid–medicated biologic dressing, adipose-derived stem cells lead to a significant healing-time reduction of lower limb wounds in 30 patients [84].

Adipose-derived stem cells were also useful in 29 cases requiring soft tissue augmentation in hostile recipient areas, such as the areas of facial atrophy in patients with Parry–Romberg syndrome or iatrogenic soft tissue defects due to subcutaneous steroid injection [72]. The authors injected adipose-derived stem cells, harvested and enriched on the same day, into the areas that previously underwent autologous fat grafting in the morning. They observed minimal postoperative atrophy of the injected areas and no volume change after 8 weeks and a mean follow-up period of 10 months. Lipoatrophy is frequent complication of free fat transfer. The early ischemia—thought to be a cause for the atrophy following free fat transfer—is suspected to be mitigated by the angiogenic effect of the additionally injected stem cells [72].

With further optimization and standardization, the use of adipose-derived stem cells for a broader spectrum of cosmetic applications is likely in the future.

Epidermal Stem Cells

The use of epidermal stem cells has not reached the field of aesthetic dermatology yet, but first attempts have been made to correct the gene defect in patients with inherited skin diseases confined to the epidermis. Junctional epidermolysis bullosa, caused by mutations in the gene encoding laminin 5 located in the epidermal basement membrane, has been treated with genetically altered epidermal stem cells. Epidermal stem cells from an adult patient affected by laminin5-beta3-deficient junctional epidermolysis bullosa were transduced with a retroviral vector expressing LAMB3 cDNA (encoding laminin5-beta3) [85]. Subsequently, the genetically corrected epidermal stem cells were transplanted onto the open wounds of the patient's legs. Expression of normal levels of functional laminin 5 was observed and the blisters subsided. Targeting the epidermal stem cells ensures that laminin 5 expression continues throughout life. It is conceivable that a similar approach could be used in wound healing with large epidermal defects.

Hair Follicle Bulge Stem Cells

Bulge stem cells, also representing keratinocytes, could be employed for wound healing purposes as well. Even more intriguing would be their use in the construction of entire hair follicles that could be used by hair transplant surgeons for hair replacement. Animal experimental data are already quite promising. Mixing cultured bulge-derived stem cells with primary dermal papilla cells from vibrissae hair follicles of rats followed by subsequent injection into the back of immunodeficient mice, it was possible to generate intact mature hair follicles [86] (Figure 5.13). In the mouse, bioengineered hair follicles were generated from embryonic epidermal and dermal skin–derived cells as well as from adult vibrissa stem cells of

Figure 5.13 In mice, entire hair follicles including the follicular papillae can be reconstructed from a combination of hair bulge–derived stem cells with follicular papilla cells. (a) Gross picture. (b) Histological picture. (Reprinted by permission from Macmillan Publishers Ltd. *Gene Ther.* Sugiyama-Nakagiri Y, Akiyama M, Shimizu H, Hair follicle stem cell-targeted gene transfer and reconstitution system, 13, 732–737, Copyright 2006.)

the hair follicle bulge and the follicular papilla [87–89]. The bioengineered hair follicles showed normal hair structures; developed the proper connections to the surrounding structures, including the epidermis, arrector pili muscle, and nerve fibers; underwent hair cycles; and were capable of piloerection. The technique is certainly extremely time consuming, expensive, and still far away from a clinical applicability in the human. The animal experimental data nevertheless demonstrate, however, that bioengineering of hair follicles from stem cells is possible.

Melanocytic Stem Cells

Dermabrasion alone is capable of inducing regimentation in vitiligo patients [90]. It is theorized that functionally this is achieved via stimulation of melanocytic stem cells located in the hair follicle bulge. Indeed, the application of autologous cell solutions from the follicular outer root sheath with its residing melanocytes and melanocytic stem cells to abraded skin in patients with vitiligo stimulates repigmentation [91,92]. It is possible that hair graying can be treated in the future by the modification of residing melanocytic stem cells and by targeted injection of melanocytic stem cells cultivated *in vitro*.

STEM CELLS AND GROWTH FACTORS

Stem cells do not only exert their effects on organs by differentiating into other cell types but also through secretion of growth factors [5,6,51]. It is the latter effect that is closest to an industrial-style clinical application. For dermatological applications, it has been mostly studied in adipose-derived stem cells.

The conditioned cell culture media used to propagate human adipose–derived stem cells were found to contain numerous growth factors and extracellular matrix proteins known to have an effect on photoaged skin, including vascular endothelial growth factor (VGEF), basic fibroblast growth factor (bFGF), transforming growth factor (TGF)-β1 and TGF-β2, keratinocyte growth factor (KGF), platelet-derived growth factor (PDGF)-AA, type I collagen, and fibronectin [5]. When intradermally injected into the skin of a micropig, adipose-derived stem cells and their culture medium showed a small but not definite increase in dermal thickness, but a Western blot analysis revealed a distinctive increase in collagen expression in injected skin [5].

UVB-induced wrinkles in hairless mice improved significantly after subcutaneous injection of adipose-derived stem cells and collagen production increased (Figure 5.14) [51]. The effect is apparently mediated through paracrine secretion of growth factors by the stem cells. *In vitro*, UVB irradiation reduced the proliferation of human dermal fibroblasts. Prior incubation of the fibroblasts with conditioned culture medium from adipose-derived stem cells, however, protects the cells from UVB-induced apoptotic cell death in a dose-dependent manner [51]. In addition, an increase in collagen type I and a reduction in matrix metalloproteinase 1 in dermal fibroblasts were observed when incubated in conditioned medium from stem cells [51].

In a pilot study on a single patient with photoaged skin intradermal injections with autologous PLA containing an increased number of adipose-derived stem cells, the authors observed improvement of general skin texture and wrinkles 2 months after the second injection (Figure 5.15) [5].

FUTURE DIRECTIONS

The use of adult stem cells, most importantly MSCs and especially those from adipose tissue, is very promising for the field of cosmetic dermatology and bypasses the use of ethically questionable embryonic stem cells. The potential use of induced pluripotent stem cells further eliminates the necessity of the latter. However, controlled clinical studies with large number of patients evaluating the effect of stem cells and their growth factors on aesthetic skin conditions that are desired to be treated are still required and currently missing. The basic science is largely worked out. It will be the next step to optimize the application of stem cells on a clinical level.

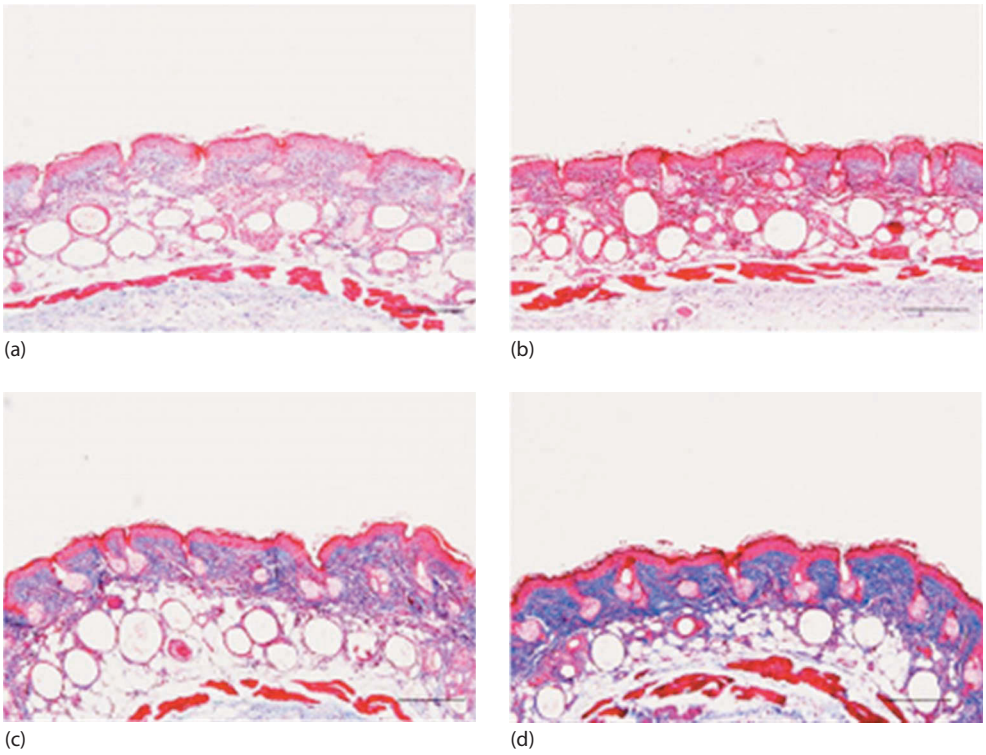


Figure 5.14 On Masson's trichrome staining to highlight collagen (blue), there was a significant increase in collagen deposition in UV-radiated mice when injected with middle and high doses of adipose-derived stem cells. Control (a), 1×10^3 cells (b), 1×10^4 cells (c), and 1×10^5 cells (d). (Reprinted from *J Dermatol Sci*, 53, Kim WS, Park BS, Park SH, Kim HK, Sung JH, Antiwrinkle effect of adipose-derived stem cell: Activation of dermal fibroblast by secretory factors, 96–102, Copyright 2009, with permission from Elsevier.)

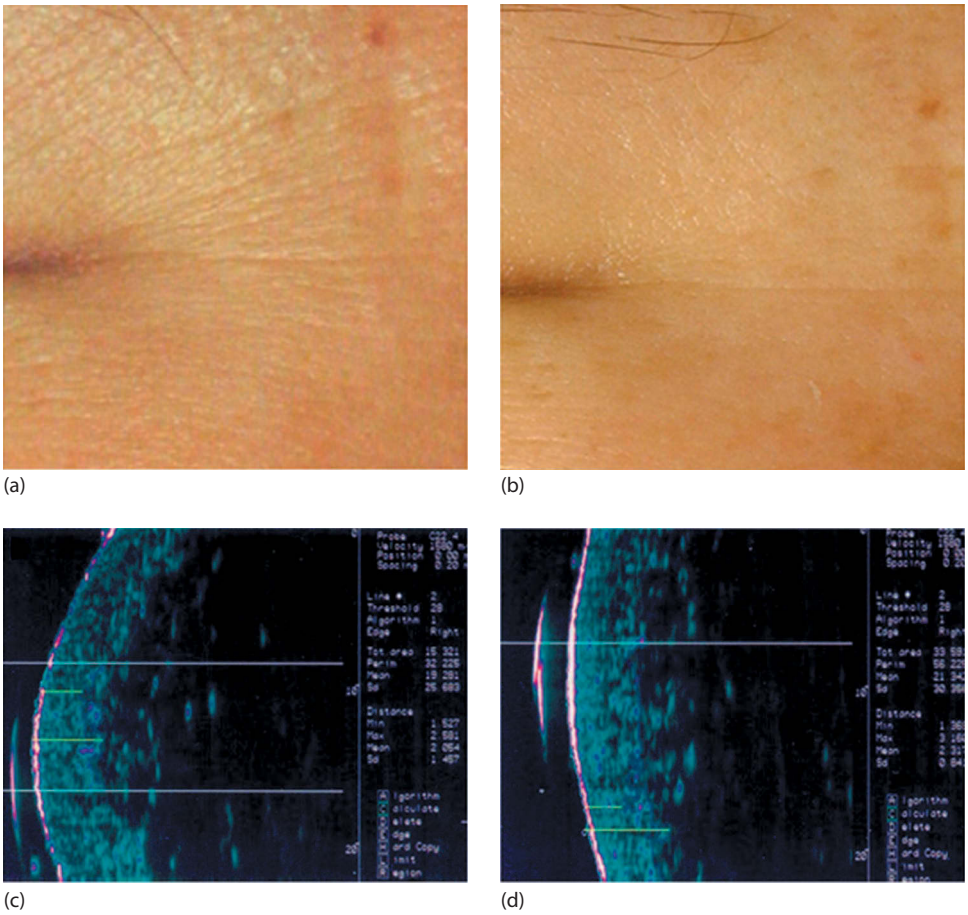


Figure 5.15 In a clinical pilot study on one patient undergoing intradermal injections with autologous processed lipoaspirate cells containing adipose-derived stem cells, amelioration of periorbital wrinkles was noted. Medical photographs of periorbital wrinkle were taken (a, before treatment; b, after treatment) and dermal thickness was measured by an ultrasonograph (c and d). Improved skin texture and dermal thickness (2.054 mm vs. 2.317 mm) were clearly observed 2 months after injection of PLA cells (b and d). (From Park BS, Jang KA, Sung JH, Park JS, Kwon YH, Kim KJ, Kim WS: Adipose-derived stem cells and their secretory factors as a promising therapy for skin aging. *Dermatol Surg.* 2008. 34. 1323–1326. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

REFERENCES

1. Trounson A, Thakar RG, Lomax G, Gibbons D. Clinical trials for stem cell therapies. *BMC Med* 2011; 9:52–58.
2. Levinson DR. Challenges to FDA's ability to monitor and inspect foreign clinical trials. Report of the Office of Inspector General, Department of Health and Human Services. June 2010, OEI-01-08-00510. http://oig.hhs.gov/oei/reports/oei-01-08-00510.pdf.
3. Koch NJ, Baum E, Trounson A. European court ruling on embryonic stem cells: Ripple effects. *Cell Stem Cell* 2011; 9:499–500.
4. Zuk PA, Zhu M, Mizuno H, Huang J, Futrell JW, Katz AJ, Benhaim P, Lorenz HP, Hedrick MH. Multilineage cells from human adipose tissue: Implications for cell-based therapies. *Tissue Eng* 2001; 7:211–228.
5. Park BS, Jang KA, Sung JH, Park JS, Kwon YH, Kim KJ, Kim WS. Adipose-derived stem cells and their secretory factors as a promising therapy for skin aging. *Dermatol Surg* 2008; 34:1323–1326.
6. Yang JA, Chung HM, Won CH, Sung JH. Potential application of adipose-derived stem cells and their secretory factors to skin: Discussion from both clinical and industrial viewpoints. *Expert Opin Biol Ther* 2010; 10:495–503.
7. Blau HM, Brazelton TR, Weimann JM. The evolving concept of a stem cell: Entity or function? *Cell* 2001; 105:829–841.
8. van der Kooy D, Weiss S. Why stem cells? *Science* 2000; 287:1439–1441.
9. Cotsarelis G, Sun TT, Lavker RM. Label-retaining cells reside in the bulge area of pilosebaceous unit: Implications for follicular stem cells, hair cycle, and skin carcinogenesis. *Cell* 1990; 61:1329–1337.
10. Sellheyer K. Stem cell markers can help identify adnexal tumor differentiation when evaluated in the context of morphology: Methodology matters. *J Cutan Pathol* 2011; 38:460–474.
11. Koestenbauer S, Zech NH, Juch H, Vanderzwalmen P, Schoonjans L, Dohr G. Embryonic stem cells: Similarities and differences between human and murine embryonic stem cells. *Am J Reprod Immunol* 2006; 55:169–180.
12. Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, Jones JM. Embryonic stem cell lines derived from human blastocysts. *Science* 1998; 282:1145–1147.
13. Nishimura EK, Jordan SA, Oshima H et al. Dominant role of the niche in melanocyte stem-cell fate determination. *Nature* 2002; 416:854–860.

14. Nishimura EK, Granter SR, Fisher DE. Mechanisms of hair graying: Incomplete melanocyte stem cell maintenance in the niche. *Science* 2005; 307:720–724.
15. Osawa M, Egawa G, Mak SS et al. Molecular characterization of melanocyte stem cells in their niche. *Development* 2005; 132:5589–5599.
16. Toma JG, Akhavan M, Fernandes KJ, Barnabé-Heider F, Sadikot A, Kaplan DR, Miller FD. Isolation of multipotent adult stem cells from the dermis of mammalian skin. *Nat Cell Biol* 2001; 3:778–784.
17. Toma JG, McKenzie IA, Bagli D, Miller FD. Isolation and characterization of multipotent skin-derived precursors from human skin. *Stem Cells* 2005; 23:727–737.
18. Jahoda CA, Whitehouse J, Reynolds AJ, Hole N. Hair follicle dermal cells differentiate into adipogenic and osteogenic lineages. *Exp Dermatol* 2003; 12:849–859.
19. Dyce PW, Zhu H, Craig J, Li J. Stem cells with multilineage potential derived from porcine skin. *Biochem Biophys Res Commun* 2004; 316:651–658.
20. Gingras M, Champigny MF, Berthod F. Differentiation of human adult skin-derived neuronal precursors into mature neurons. *J Cell Physiol* 2007; 210:498–506.
21. Kruse C, Bodó E, Petschnik AE, Danner S, Tiede S, Paus R. Towards the development of a pragmatic technique for isolating and differentiating nestin-positive cells from human scalp skin into neuronal and glial cell populations: Generating neurons from human skin? *Exp Dermatol* 2006; 15:794–800.
22. Schreder A, Pierard GE, Paquet P, Reginster MA, Pierard-Franchimont C, Quatresooz P. Facing towards epidermal stem cells. *Int J Mol Med* 2010; 26:171–174.
23. Horsley V, O'Carroll D, Tooze R, Ohinata Y, Saitou M, Obukhanych T, Nussenzweig M, Tarakhovsky A, Fuchs E. Blimp1 defines a progenitor population that governs cellular input to the sebaceous gland. *Cell* 2006; 126:597–609.
24. Lo Celso C, Berta MA, Braun KM, Frye M, Lyle S, Zouboulis CC, Watt FM. Characterization of bipotential epidermal progenitors derived from human sebaceous gland: Contrasting roles of c-Myc and beta-catenin. *Stem Cells* 2008; 26:1241–1252.
25. Sellheyer K, Krahl D. Blimp-1: A marker of terminal differentiation but not of sebocytic progenitor cells. *J Cutan Pathol* 2010; 37:362–370.
26. Sasaki M, Abe R, Fujita Y, Ando S, Inokuma D, Shimizu H. Mesenchymal stem cells are recruited into wounded skin and contribute to wound repair by transdifferentiation into multiple skin cell type. *J Immunol* 2008; 180:2581–2587.
27. Taléns-Visconti R, Bonora A, Jover R, Mirabet V, Carbonell F, Castell JV, Gómez-Lechón MJ. Human mesenchymal stem cells from adipose tissue: Differentiation into hepatic lineage. *Toxicol In Vitro* 2007; 21:324–329.
28. Joannides A, Gaughwin P, Schwiening C, Majed H, Sterling J, Compston A, Chandran S. Efficient generation of neural precursors from adult human skin: Astrocytes promote neurogenesis from skin-derived stem cells. *Lancet* 2004; 364:172–178.
29. Yang LY, Zheng JK, Liu XM, Hui GZ, Guo LH. Culture of skin-derived precursors and their differentiation into neurons. *Chin J Traumatol* 2004; 7:91–95.
30. Gorio A, Torrente Y, Madaschi L et al. Fate of autologous dermal stem cells transplanted into the spinal cord after traumatic injury (TSCI). *Neuroscience* 2004; 125:179–189.
31. Wagers AJ, Sherwood RI, Christensen JL, Weissman IL. Little evidence for developmental plasticity of adult hematopoietic stem cells. *Science* 2002; 297:2256–2259.
32. Wagers AJ, Weissman IL. Plasticity of adult stem cells. *Cell* 2004; 116:639–648.
33. Vassilopoulos G, Russell DW. Cell fusion: An alternative to stem cell plasticity and its therapeutic implications. *Curr Opin Genet Dev* 2003; 13:480–485.
34. Vassilopoulos G, Wang PR, Russell DW. Transplanted bone marrow regenerates liver by cell fusion. *Nature* 2003; 422:901–904.
35. Wang X, Willenbring H, Akkari Y, Torimaru Y, Foster M, Al-Dhalimy M, Lagasse E, Finegold M, Olson S, Grompe M. Cell fusion is the principal source of bone-marrow-derived hepatocytes. *Nature* 2003; 422:897–901.
36. Krause DS, Theise ND, Collector MI et al. Multi-organ, multilineage engraftment by a single bone marrow-derived stem cell. *Cell* 2001; 105:369–377.
37. Hokari M, Kuroda S, Shichinohe H, Yano S, Hida K, Iwasaki Y. Bone marrow stromal cells protect and repair damaged neurons through multiple mechanisms. *J Neurosci Res* 2008; 86:1024–1035.
38. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* 2006; 126:663–676.
39. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* 2007; 131:861–872.
40. Yu J, Vodyanik MA, Smuga-Otto K et al. Induced pluripotent stem cell lines derived from human somatic cells. *Science* 2007; 318:1917–1920.
41. Aasen T, Raya A, Barrero MJ et al. Efficient and rapid generation of induced pluripotent stem cells from human keratinocytes. *Nat Biotechnol* 2008; 26:1276–1284.
42. Aasen T, Izpisúa Belmonte JC. Isolation and cultivation of human keratinocytes from skin or plucked hair for the generation of induced pluripotent stem cells. *Nat Protoc* 2010; 5:371–382.
43. Lensch MW, Schlaeger TM, Zon LI, Daley GQ. Teratoma formation assays with human embryonic stem cells: A rationale for one type of human-animal chimera. *Cell Stem Cell* 2007; 1:253–258.
44. Boland MJ, Hazen JL, Nazor KL, Rodriguez AR, Gifford W, Martin G, Kupriyanov S, Baldwin KK. Adult mice generated from induced pluripotent stem cells. *Nature* 2009; 461:91–94.
45. Stadtfeld M, Apostolou E, Akutsu H, Fukuda A, Follett P, Natesan S, Kono T, Shioda T, Hochedlinger K. Aberrant silencing of imprinted genes on chromosome 12qF1 in mouse induced pluripotent stem cells. *Nature* 2010; 465:175–181.
46. Galach M, Utikal J. From skin to the treatment of diseases—The possibilities of iPS cell research in dermatology. *Exp Dermatol* 2011; 20:523–528.
47. Zhou H, Wu S, Joo JY et al. Generation of induced pluripotent stem cells using recombinant proteins. *Cell Stem Cell* 2009; 4:381–384.
48. Giangreco A, Qin M, Pintar JE, Watt FM. Epidermal stem cells are retained in vivo throughout skin aging. *Aging Cell* 2008; 7:250–259.
49. Inomata K, Aoto T, Binh NT, Okamoto N, Tanimura S, Wakayama T, Iseki S, Hara E, Masunaga T, Shimizu H, Nishimura EK. Genotoxic stress abrogates renewal of melanocyte stem cells by triggering their differentiation. *Cell* 2009; 137:1088–1099.
50. Kim WS, Park BS, Park SH, Kim HK, Sung JH. Antiwrinkle effect of adipose-derived stem cell: Activation of dermal fibroblast by secretory factors. *J Dermatol Sci* 2009; 53:96–102.
51. Blum B, Benvenisty N. The tumorigenicity of human embryonic stem cells. *Adv Cancer Res* 2008; 100:133–158.
52. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, Deans R, Keating A, Prockop Dj, Horwitz E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy* 2006; 8:315–327.
53. Huang YC, Leung VY, Lu WW, Luk KD. The effects of microenvironment in mesenchymal stem cell-based regeneration of intervertebral disc. *Spine J* January 19, 2013.
54. Haddad B, Pakravan AH, Konan S, Adesida A, Khan W. A systematic review of tissue engineered meniscus strategies: Experimental preclinical studies. *Curr Stem Cell Res Ther* Janurary 7, 2013.
55. Veronesi F, Giavaresi G, Tschon M, Borsari V, Nicoli Aldini N, Fini M. Clinical use of bone marrow, bone marrow concentrate, and expanded bone marrow mesenchymal stem cells in cartilage disease. *Stem Cells Dev* 2013; 22:181–192.
56. Badiavas EV, Falanga V. Treatment of chronic wounds with bone marrow-derived cells. *Arch Dermatol* 2003; 139:510–516.

57. Falanga V, Iwamoto S, Chartier M, Yufit T, Butmarc J, Kouttab N, Shrayer D, Carson P. Autologous bone marrow-derived cultured mesenchymal stem cells delivered in a fibrin spray accelerate healing in murine and human cutaneous wounds. *Tissue Eng* 2007; 13:1299–1312.
58. Gamelli RL, He LK, Liu H. Recombinant human granulocyte colony-stimulating factor treatment improves macrophage suppression of granulocyte and macrophage growth after burn and burn wound infection. *J Trauma* 1995; 39:1141–1156.
59. Shoup M, Weisenberger JM, Wang JL, Pyle JM, Gamelli RL, Shankar R. Mechanisms of neutropenia involving myeloid maturation arrest in burn sepsis. *Ann Surg* 1998; 228:112–122.
60. Rao MS, Mattson MP. Stem cells and aging: Expanding the possibilities. *Mech Ageing Dev* 2001; 122:713–734.
61. Stagg J, Galipeau J. Immune plasticity of bone marrow-derived mesenchymal stromal cells. *Handb Exp Pharmacol* 2007; 180:45–66.
62. Stoff A, Rivera AA, Sanjib Banerjee N et al. Promotion of incisional wound repair by human mesenchymal stem cell transplantation. *Exp Dermatol* 2009; 18:362–369.
63. Sbano P, Cuccia A, Mazzanti B et al. Use of donor bone marrow mesenchymal stem cells for treatment of skin allograft rejection in a preclinical rat model. *Arch Dermatol Res* 2008; 300:115–124.
64. Chen FG, Zhang WJ, Bi D et al. Clonal analysis of nestin(-) vimentin(+) multipotent fibroblasts isolated from human dermis. *J Cell Sci* 2007; 120:2875–2883.
65. Lysy PA, Smets F, Sibille C, Najimi M, Sokal EM. Human skin fibroblasts: From mesodermal to hepatocyte-like differentiation. *Hepatology* 2007; 46:1574–1585.
66. Lorenz K, Sicker M, Schmelzer E, Rupf T, Salvetter J, Schulz-Siegmund M, Bader A. Multilineage differentiation potential of human dermal skin-derived fibroblasts. *Exp Dermatol* 2008; 17:925–932.
67. Kroeze KL, Jurgens WJ, Doulabi BZ, van Milligen FJ, Scheper RJ, Gibbs S. Chemokine-mediated migration of skin-derived stem cells: Predominant role for CCL5/RANTES. *J Invest Dermatol* 2009; 129:1569–1581.
68. Toma JG, McKenzie IA, Bagli D, Miller FD. Isolation and characterization of multipotent skin-derived precursors from human skin. *Stem Cells* 2005; 23:727–737.
69. Zhong J, Hu N, Xiong X, Lei Q, Li L. A novel promising therapy for skin aging: Dermal multipotent stem cells against photoaged skin by activation of TGF-β/Smad and p38 MAPK signaling pathway. *Med Hypotheses* 2011; 76:343–346.
70. Quan T, He T, Kang S, Voorhees JJ, Fisher GJ. Solar ultraviolet irradiation reduces collagen in photoaged human skin by blocking transforming growth factor-beta type II receptor/Smad signaling. *Am J Pathol* 2004; 165:741–751.
71. Wollina U, Goldman A, Berger U, Abdel-Naser MB. Esthetic and cosmetic dermatology. *Dermatol Ther* 2008; 21:118–130.
72. Tiryaki T, Findikli N, Tiryaki D. Staged stem cell-enriched tissue (SET) injections for soft tissue augmentation in hostile recipient areas: A preliminary report. *Aesthetic Plast Surg* 2011; 35:965–771.
73. Tabit CJ, Slack GC, Fan K, Wan DC, Bradley JP. Fat grafting versus adipose-derived stem cell therapy: Distinguishing indications, techniques, and outcomes. *Aesthetic Plast Surg* 2012; 36:704–713.
74. Brayfield CA, Marra KG, Rubin JP. Adipose tissue regeneration. *Curr Stem Cell Res Ther* 2010; 5:116–121.
75. Lin K, Matsubara Y, Masuda Y, Togashi K, Ohno T, Tamura T, Toyoshima Y, Sugimachi K, Toyoda M, Marc H, Douglas A. Characterization of adipose tissue-derived cells isolated with the Celution system. *Cytotherapy* 2008; 10:417–426.
76. Ersek RA. Transplantation of purified autologous fat: A 3-year follow-up is disappointing. *Plast Reconstr Surg* 1991; 87:219–227.
77. Zuk PA. The adipose-derived stem cell: Looking back and looking ahead. *Mol Biol Cell* 2010; 21:1783–1787.
78. Fraser JK, Wulur I, Alfonso Z, Hedrick MH. Fat tissue: An underappreciated source of stem cells for biotechnology. *Trends Biotechnol* 2006; 24:150–154.
79. Schipper BM, Marra KG, Zhang W, Donnenberg AD, Rubin JP. Regional anatomic and age effects on cell function of human adipose-derived stem cells. *Ann Plast Surg* 2008; 60:538–544.
80. Moseley TA, Zhu M, Hedrick MH. Adipose-derived stem and progenitor cells as fillers in plastic and reconstructive surgery. *Plast Reconstr Surg* 2006; 118 (3 Suppl):121S–128S.
81. Matsumoto D, Sato K, Gonda K, Takaki Y, Shigeura T, Sato T, Aiba-Kojima E, Iizuka F, Inoue K, Suga H, Yoshimura K. Cell-assisted lipotransfer: Supportive use of human adipose-derived cells for soft tissue augmentation with lipoinjection. *Tissue Eng* 2006; 12:3375–3382.
82. Yoshimura K, Sato K, Aoi N, Kurita M, Hirohi T, Harii K. Cell-assisted lipotransfer for cosmetic breast augmentation: Supportive use of adipose-derived stem/stromal cells. *Aesthetic Plast Surg* 2008; 32:48–55.
83. Yoshimura K, Asano Y, Aoi N, Kurita M, Oshima Y, Sato K, Inoue K, Suga H, Eto H, Kato H, Harii K. Progenitor-enriched adipose tissue transplantation as rescue for breast implant complications. *Breast J* 2010; 16:169–175.
84. Cervelli V, De Angelis B, Lucarini L, Spallone D, Balzani A, Palla L, Gentile P, Cerulli P. Tissue regeneration in loss of substance on the lower limbs through use of platelet-rich plasma, stem cells from adipose tissue, and hyaluronic acid. *Adv Skin Wound Care* 2010; 23:262–272.
85. Mavilio F, Pellegrini G, Ferrari S et al. Correction of junctional epidermolysis bullosa by transplantation of genetically modified epidermal stem cells. *Nat Med* 2006; 12:1397–1402.
86. Sugiyama-Nakagiri Y, Akiyama M, Shimizu H. Hair follicle stem cell-targeted gene transfer and reconstitution system. *Gene Ther* 2006; 13:732–737.
87. Asakawa K, Toyoshima KE, Ishibashi N et al. Hair organ regeneration via the bioengineered hair follicular unit transplantation. *Sci Rep* 2012; 2:424.
88. Toyoshima KE, Asakawa K, Ishibashi N, Toki H, Ogawa M, Hasegawa T, Irié T, Tachikawa T, Sato A, Takeda A, Tsuji T. Fully functional hair follicle regeneration through the rearrangement of stem cells and their niches. *Nat Commun* 2012; 3:784.
89. Sato A, Toyoshima KE, Toki H, Ishibashi N, Asakawa K, Iwadate A, Kanayama T, Tobe H, Takeda A, Tsuji T. Single follicular unit transplantation reconstructs arrector pili muscle and nerve connections and restores functional hair follicle piloerection. *J Dermatol* 2012; 39:682–687.
90. Awad SS. Dermabrasion may repigment vitiligo through stimulation of melanocyte precursors and elimination of hyperkeratosis. *J Cosmet Dermatol* 2012; 11:318–322.
91. Vanscheidt W, Hunziker T. Repigmentation by outer-root-sheath-derived melanocytes: Proof of concept in vitiligo and leucoderma. *Dermatology* 2009; 218:342–343.
92. Mohanty S, Kumar A, Dhawan J, Sreenivas V, Gupta S. Noncultured extracted hair follicle outer root sheath cell suspension for transplantation in vitiligo. *Br J Dermatol* 2011; 164:1241–1246.

6

Adipose tissue: Development, physiology, and pathophysiology

Max Lafontan

INTRODUCTION

Fat deposits serve as caloric stores and help survival during periods of famine or food deprivation. For a long time, adipose tissue (AT) was considered to be a rather passive storage site with an early fixed number of cells possessing rather limited functions. AT is now recognized as the hub of an intricate regulatory network that modulates many body functions. Multiple diseases can result from AT dysfunction. Dysregulation of the AT mass, including obesity, genetic disorders of AT development/differentiation such as lipoatrophy/lipodystrophy, is associated with a wide range of multiple endocrine and metabolic disorders. AT is a buffer for daily lipid influx [1,2]. In conditions of energy excess, expansion of AT occurs and includes both mature adipocyte hypertrophy as well as an increase in the number of adipocytes (hyperplasia). Through their important fat-storing possibilities, adipocytes exert a protective action against fatty acid–induced lipotoxic damage to lean tissues: this is referred to as lipotoxicity (lipid-induced dysfunction) or as lipoapoptosis (lipid-induced programmed cell death) [3].

Fat biology represents a "black hole" in the field of dermatology and reconstruction procedures. Surgeons have long since used AT as a "filler" in tissue reconstruction. Problems to maintain the reconstituted volume are now evident. Today, the demand for surgical procedures involving the manipulation of subcutaneous AT (i.e., surgical removal, fat transplantation, liposuction, and lipofilling procedures) is rising every year. Dermatologists and surgeons sucking out AT and placing it elsewhere with rather crude technology must consider carefully the major disturbances induced in the AT and in the cells they manipulate.

In addition to its role as an energy reservoir, AT secretes hormones and other key signaling molecules that impact on multiple target tissues and organs. AT is not limited to fat cells (e.g., adipocytes); it includes connective tissue matrix, sympathetic nervous system (SNS) nerve terminals, vessels, capillaries, and a number of other cell types present in its stroma-vascular fraction (SVF), which all contribute in an integrated way to the regulation of AT biology and physiology. AT produces an array of factors with endocrine, paracrine, and autocrine actions. Some of these factors can contribute, together with the fatty acids released by the hydrolysis of adipocyte triglycerides, to the development of glucose intolerance, insulin resistance, and beta-cell dysfunction leading not only to type 2 diabetes, but also to hypertension and various cardiovascular dysfunctions [4–9]. More recently, obesity was found to be associated with a chronic systemic low-grade inflammatory state, and inflammation is becoming one of the suspected mechanisms leading to obesity-related morbidities [10,11]. In this chapter, key features of AT biology and physiology will be summarized. Tables, figures, and summary boxes are included to facilitate reading.

ADIPOSE TISSUE DISTRIBUTION: FAT REDISTRIBUTION IN OBESITY AND AFTER LIPOSUCTION

AT is a specialized tissue that functions to store and mobilize energy under the form of lipids; it is the body's major energy reservoir. Energy is stored in the adipocyte as triacylglycerols (TAGs) (e.g., triglycerides). In mammals, AT is found under two forms: white AT (WAT) and brown AT (BAT) (Box 6.1). The main function of BAT is the maintenance of body temperature through SNV-mediated activation of cold-induced thermogenesis. Two reviews on BAT by B. Cannon and J. Nedergaard and E. Ravussin offer the most comprehensive information on its functional and physiological role to date [12,13]. In humans, recent morphological and scanning studies using fluorodeoxyglucose and positron emission tomography have revealed that the abundance of BAT was higher than previously thought [13–17].

AT Distribution

AT is one of the largest body compartments; it is also the most variable compartment of the organism. AT reserves are increased during pregnancy to support the development of the fetus and facilitate energy storage before the postpartum lactation period. The distribution pattern of AT differs strikingly between men and women. AT is located predominantly in the upper body in men and various terms have been used to define this situation such as android, central, male, upper body segment, or "apple" distribution. When AT accumulates preferentially in the lower body, the terms gynoid, female, lower-body segment, or "pear" distribution are used. The pattern of fat distribution changes with aging; an increment of upper body fat could occur in untreated menopausal women.

The 70 kg "reference" man has 15 kg of AT representing 21% of body mass. The percentage increases in women, the elderly, and overweight subjects. AT is usually subcategorized into subcutaneous and internal fat deposits as detailed in Table 6.1 [18]. Visceral AT conveys the highest health risks among the currently measurable AT compartments in humans [7,19–21]. Pericardiac AT may also play a role in the development of an unfavorable cardiovascular risk profile [22,23]. Subcutaneous AT is subdivided into deep (i.e., the layer found between the muscle fascia and a fascial plane in the lower trunk and gluteal thigh areas) and superficial (i.e., the layer found between the skin and the fascial plane in the lower trunk and gluteal-thigh area) compartments. The protective barrier of our body, the skin, consists of three layers: epidermis, dermis, and a subcutaneous layer mainly composed of AT. Studies on the role of subcutaneous AT in dermatology have mainly focused on its thermoregulatory functions and AT has remained the

BOX 6.1 BROWN AND WHITE ADIPOSE TISSUES

- Adipose tissue (AT), initially considered to be limited to mechanical protection, heat insulation, and thermoregulation, rapidly became the most important tissue for its function in energy storage. Two types of AT can be distinguished by histological analysis and functional challenges: white adipose tissue (WAT) and brown adipose tissue (BAT). Adipocytes of both ATs store lipid in the form of triacylglycerols (TAGs).
- BAT is specialized in the production of heat; it is a very important tissue in hibernating animals, small rodents, and numerous mammals. BAT depots are limited in human adults and the specific mitochondrial protein of BAT fat cell (i.e., uncoupling protein-1) is expressed at low levels in humans. Recent studies have led to the reconsideration of the role of BAT in humans. BAT may contribute to thermogenesis in humans, but its role remains to be fully established.
- As the major site of energy storage, AT provides a buffer during energy imbalances when energy intake is not equal to energy output. Storing excess energy in the form of TAG is an efficient way to store excess energy. AT contributes to the "buffering" of the influx of fatty acids into the circulation that occurs after meals and also to the delivery of fatty acids into the circulation according to the body's energy needs. Hydrolysis of adipocyte TAG stores (i.e., lipolysis) is under a strict and sophisticated hormonal control. Insulin, catecholamines, and natriuretic peptides are the major acute regulators of lipolysis.
- Beyond body weight control, AT is also involved in a broad range of other physiological processes including glucose homeostasis, reproduction, immunity, and vascular homeostasis. These new functions rely on the ability of AT (i.e., adipocytes and various cells of the stroma-vascular fraction of AT) to synthesize and secrete a large number of enzymes, hormones, growth factors, cytokines, complement factors, and matrix and membrane proteins.
- AT represents an abundant and quite accessible source of adult stem cells (i.e., adipose-derived stromal cells [ASCs]), which possess the ability to differentiate along multiple lineage pathways. ASCs have been shown to exhibit a perivascular but also stromal phenotype in human AT.

Table 6.1 Classification and Distribution of Total Body Adipose Tissue (AT) according to the Proposals of Shen et al.

1. *Total adipose tissue*: total AT excluding bone marrow, head, hands, and feet AT
2. *Subcutaneous adipose tissue*
   a. *Superficial subcutaneous adipose tissue*: AT between the skin and a fascial plane in the lower trunk and gluteal-thigh area
   b. *Deep subcutaneous adipose tissue*: AT between the muscle fascia and a fascial plane in the lower trunk and gluteal thigh areas
3. *Internal adipose tissue*
   a. *Visceral adipose tissue*
      i. Intrathoracic adipose tissue
         - Intrapericardial
         - Extrapericardial
      ii. Intra-abdominopelvic
         - Intraperitoneal (e.g., omental and mesenteric)
         - Extraperitoneal
           - Intra-abdominal
             – Preperitoneal
             – Retroperitoneal (e.g., perirenal, pararenal, periaortic, and peripancreatic)
           - Intrapelvic (e.g., parametrial, retropubic, paravesical, retrouterine, pararectal, and retrorectal)
   b. *Nonvisceral internal adipose tissues*
      i. Intramuscular adipose tissue (AT within a muscle, between fascicles)
      ii. Perimuscular adipose tissue (AT inside the muscle fascia)
         - Intermuscular adipose tissue (AT between muscles)
         - Paraosseal adipose tissue (AT in the interface muscle/bone)
      iii. Other nonvisceral adipose tissues: orbital adipose tissue; aberrant and pathological AT (various kinds of lipomas)

Source: Shen W et al., *Obes Res*, 11, 5, 2003.

neglected element of skin biology although skin manifestations of obesity are well recognized [24].

Impact of Routine Liposuction

Routine liposuction is commonly used to remove some subcutaneous AT deposits; it is considered innocuous and to have low perioperative complication rates. Large-volume liposuctions have been proposed because they could have some potential to reduce obesity-associated metabolic disturbances. However, the benefits of such techniques remain a highly debated question [25–30]. Subcutaneous AT has storage capacities and metabolic functions related to its absolute amount as it plays a major role in sequestration of fatty acids into TAG and limits their accumulation in other tissues [1,31]. Removal of large amounts of subcutaneous AT might be more detrimental than initially suspected. A study of the impact of

liposuction has been carried out in mildly obese patients of both sexes (i.e., the amount of fat removed by large-volume liposuction was >1000 cc). One-third of the women had a mean increase of 16% in the proportion of visceral fat. In the 12 men included in the study, liposuction also resulted in a 14% increase in the ratio of visceral to subcutaneous fat. Although large-volume subcutaneous AT liposuction removed relatively little body fat (compared with total fat), it led to increases in the proportion of visceral AT. Since the proportion of visceral AT is a risk factor for metabolic complications of obesity, the metabolic effects of large-volume liposuction need to be evaluated more precisely [32]. Two recent studies have confirmed that abdominal liposuction does trigger a compensatory increase in visceral fat [29,30] although the mechanisms controlling such compensatory events remain unknown. Interestingly, visceral fat increase was counteracted by physical activity [30].

HISTOGENESIS AND THE FINE STRUCTURE OF ADIPOSE TISSUE

The pioneering studies on AT histology and its development before 1965 are summarized in the Handbook of Physiology devoted to AT [33,34]. The histological atlas of Saverio Cinti is the best updated and useful document on BAT and WAT histology [35]. AT is composed of spherical lipid-laden adipocytes organized in fat lobules. Most of the fat cell volume is occupied by a single lipid droplet surrounded by a thin cytoplasm rim: the mitochondria, small Golgi, granular endoplasmic reticulum with occasional lysosomes, and the nucleus are pushed to the periphery of the fat cell. About 95% of the total lipid content of the lipid droplet is represented by TAG. The lipid droplet is separated from the cytoplasmic matrix by a coat of proteins at the interface between the cytosol and the droplets. The first of these proteins to be discovered was perilipin [36] and since then other proteins have also been described [37]. These proteins play critical roles in regulating neutral lipid metabolism by coordinating the access of lipolytic enzymes (i.e., the lipases) to the TAG of the lipid droplet [38,39].

Unilocular adipocytes characteristic of AT range in diameter from 25 to 200 μm. Adipocyte enlargement is limited: once a maximum capacity is attained (i.e., average 1000 pL for human adipocytes), the formation of new adipocytes from the precursor pool will take place [19,40]. In obese women, hyperplasia is predominant in the subcutaneous AT, whereas fat cell hypertrophy is observed both in the omental and subcutaneous compartments [41]. A thin external lamina called the basal lamina surrounds all fat cells. At light microscopy level, capillaries can be seen coursing among adipocytes. WAT is less richly vascularized than BAT, but each adipocyte is in contact with at least one capillary. Fat cells are surrounded by connective fibers clustering into lobules receiving an innervation via nerve fibers following the vascular network. There is no direct innervation of each white adipocyte. Adipocytes contribute around 45%–70% of the mass of AT in adults but only represent about 25%–30% of the total cell population in AT. AT is not only composed of adipocytes as various other cell types constitute the SVF. Blood cells, macrophages, T-lymphocytes, fibroblasts, pericytes, microvascular endothelial cells as well as fat cell precursors and some stem cells account for the remaining 70%–75% of the total cell population of AT.

PHYSIOLOGICAL FEATURES OF WHITE AT INNERVATION

The fat cell is under multiple influences including that of the autonomous sympathetic nervous system (sympathetic and parasympathetic), local blood flow variations, and various hormones and factors delivered from the plasma or produced locally in the fat pad by the various cell types of the SVF [1].

Autonomic Innervation of AT

Most of the studies on the autonomic innervation of AT have been carried out in animals, and it is difficult to extrapolate the results to the human situation. AT is innervated by the nerve endings of the autonomic nervous system, which mediates both vascular and metabolic responses within the AT. The involvement of the SNS in the innervation of AT to mobilize lipid is undeniable. Adrenergic fibers lie along arterioles with some innervation of small venules and, putatively, a limited number of adipocytes seem to be in direct contact with nerve varicosities. Stimulation of organs via sympathetic innervation has demonstrated the corelease of noradrenaline, neuropeptide Y (NPY), and ATP from axon terminals [42]. Surgical sympathectomy reduces lipolysis in the denervated AT depot, while electrical stimulation of SNS nerve endings stimulates lipolysis in animals and also in humans [43,44].

Sensory Innervation of AT

Sensory innervation of tissues is the rule. There is a sensory innervation in rodent WAT (e.g., WAT afferents have been demonstrated by several methods [45,46]). However, the functions monitored by sensory nerves in AT are not clearly established and unknown in humans. Pain is a feature of many disorders of fat tissue; inflammatory conditions are able to produce pain. Painful fat deposits in Dercum's disease (*adiposis dolorosa*) [47] and other causes of painful fat have been reported [48–51], but they are poorly defined. It remains to establish the respective role of autonomic and sensory nerves in painful fat in humans. Liposuction methods used to remove unwanted AT may promote alterations in the sympathetic nerve plexus and sensory nerves in AT and disturb the function of the remaining tissues. This aspect of the question has often been neglected.

Denervation and Accumulation of Fat

The important role played by nerves in the storage of lipids in WAT was first realized when it was noted that patients with regional denervations exhibited large increases in adipose mass in the denervated areas. Denervation is associated with accumulation of WAT within the denervated area in rats and it is related to an increase in fat cell number [43]. Norepinephrine, the major transmitter of SNS, is decreased by 80% in the denervated fat pad, where it is suspected to be the main actor. Recent findings suggest that the SNS plays a major role in the growth of fat pads, not only by controlling fat cell size through lipolysis, but also through a control of fat cell numbers. It must be noted that a number of obesities, often due to an increase in fat cell numbers in rodents and humans [52], are associated with a decrease in the SNS activity in AT [53]. In terms of clinical relevance of such observations, if sympathetic innervation would inhibit the development of AT in humans, it must be questioned if liposuction-induced alteration of sympathetic nerve plexus and afferent fibers may be followed by a proliferation of fat cell precursors and initiate compensatory growth of AT in the long term. This view fits with recent results [29,30].

BLOOD FLOW REGULATION IN ADIPOSE TISSUE IN HUMANS

Tissue-specific regulation of blood flow in AT is needed to meet the local metabolic and physiological demands [54]. The standard reference human AT blood flow (ATBF) value of about 28 mL/min/kg is based on ^{133}Xenon washout measurements in subcutaneous AT [55,56]. Enhancement of ATBF is important in metabolic physiology since it facilitates plasma triglyceride extraction and facilitates or enables signaling between AT and other tissues involved in the regulation of metabolism. ATBF plays an integral role in oxygen supply: tissue O_2 partial pressure (pO_2) reflects the balance between O_2 delivery and consumption. Overall, results from a number of studies in experimental animals show that hypoxia occurs in AT depots in obesity, at least in rodents [57]. In human AT, future studies should be devoted to improve pO_2 determinations, with a special focus on the metabolic responses induced by pO_2 changes within human physiological ranges (3%–11% O_2) [58].

Sympathetic Nervous System and the Control of Adipose Tissue Blood Flow

SNS activation strongly modulates ATBF. The stimulation of SNS supplying the vasculature of WAT results in several phenomena that depend on the intensity and duration of stimulation. Major actions are depicted in Box 6.2. Several mechanisms have been proposed, and norepinephrine is considered to act directly via $beta_2$-, $alpha_1$-, and $alpha_2$-adrenergic receptors located on endothelial cells or smooth muscle cells to cause vasodilation or contraction and promote an increase in vascular permeability.

Regulation of Adipose Tissue Blood Flow by Nutrient Intake

Glucose [59] and ingestion of a mixed meal [60] promote a strong increase in ATBF, while fat alone does not elicit a blood flow response [61–63]. In subcutaneous AT, postprandial, the ATBF response is largely blocked by propranolol [64,65]. Beta-adrenergic receptor stimulation elevates ATBF [66–68] and results from local beta-adrenergic receptor stimulation [65]. Insulin-driven activation of SNS seems to play a major role in postprandial ATBF increase [69]; it is impaired in insulin resistance [70]. The direct effect of insulin is not proven so far: a possible indirect effect on postprandial ATBF via SNS activation has been suspected. The lack of glucose-stimulated ATBF is associated with resistance to sympathetic activation in AT [71]. NO seems to determine the absolute level of ATBF, whereas a major proportion of the postprandial enhancement of ATBF is under the beta-adrenergic regulation *in vivo* in humans [65].

DEVELOPMENT OF ADIPOSE TISSUE: ORGANIZATION AND DYNAMICS

An expanded AT mass increases the risk of many pathologies, and therefore, it is imperative to understand the mechanisms by which fat pads expand [72] (Figure 6.1). AT, like muscle and bone, is generally considered as having a mesodermal origin. Adipocytes differentiate from stellate or fusiform precursor cells of mesenchymal origin [73]. Spatial and temporal relationships between fetal vascular and fat cell development exist with depot- and genetic-dependent arteriolar differentiation having been described. Adipogenesis is also regulated by factors that drive angiogenesis [74,75].

The adipocyte number is a major determinant for the fat mass in adults. The total number of adipocytes is set during childhood and adolescence, while the number of fat cells remains practically constant in adulthood in lean and also in obese individuals. Determination of fat cell turnover shows that approximately 10% of fat cells are renewed annually at all adult ages and levels of body mass index. A tight regulation of fat cell number is maintained during adulthood; neither adipocyte death nor generation rate is noticeably altered, at least in early-onset obesity [76] though the question remains open in late-onset obesity. Assessment of *in situ* progenitor cell proliferation has revealed that the fraction of proliferative progenitor cells in human adult AT could be modulated by the degree of adiposity. Changes in the progenitor cell microenvironment

BOX 6.2 NERVOUS CONTROL OF ADIPOSE TISSUE BLOOD FLOW (ATBF) IN WHITE ADIPOSE TISSUE

1. Adipose tissue (AT) receives adrenergic (noradrenaline) and peptidergic nerves, but apparently no functionally important cholinergic nerves. Most fat cells are not in direct synaptic contact with adrenergic nerves (less than 5%).
2. Adrenergic nerves play the dominant role in short-term regulation, but peptidergic nerves may play a role in the long-term regulation of adipose tissue blood flow (ATBF).
3. Activation of sympathetic nerves to AT leads to a reduced blood flow and a decreased blood volume with increased vascular permeability. The effects are mainly mediated via alpha-adrenergic receptors.
4. An autoregulatory escape is promoted during prolonged nerve stimulation. It is mediated in part by noradrenaline acting on beta-adrenergic receptors and in part by locally formed adenosine.
5. Nerve stimulation increases oxygen consumption, but at the same time, oxygen and glucose delivery is limited by vasoconstriction.
6. Important interactions exist between ATBF and metabolism (e.g., extraction of plasma TAG and fatty acids). In shock conditions, activation of metabolism and reduction of blood flow may be combined to produce damage in the tissue.
7. ATBF is increased by glucose and mixed meal uptake but not by fat intake. It is of considerable importance in the regulation of metabolism.
8. Postprandial enhancement of ATBF coincides with an increase in plasma insulin concentration that might activate the sympathetic nervous system.
9. Nitric oxide (NO) seems to be involved in fasting ATBF regulation.
10. Circulating angiotensin II (Ang. II) appears to be a regulator of fasting ATBF but has no major effect on the postprandial enhancement of ATBF.

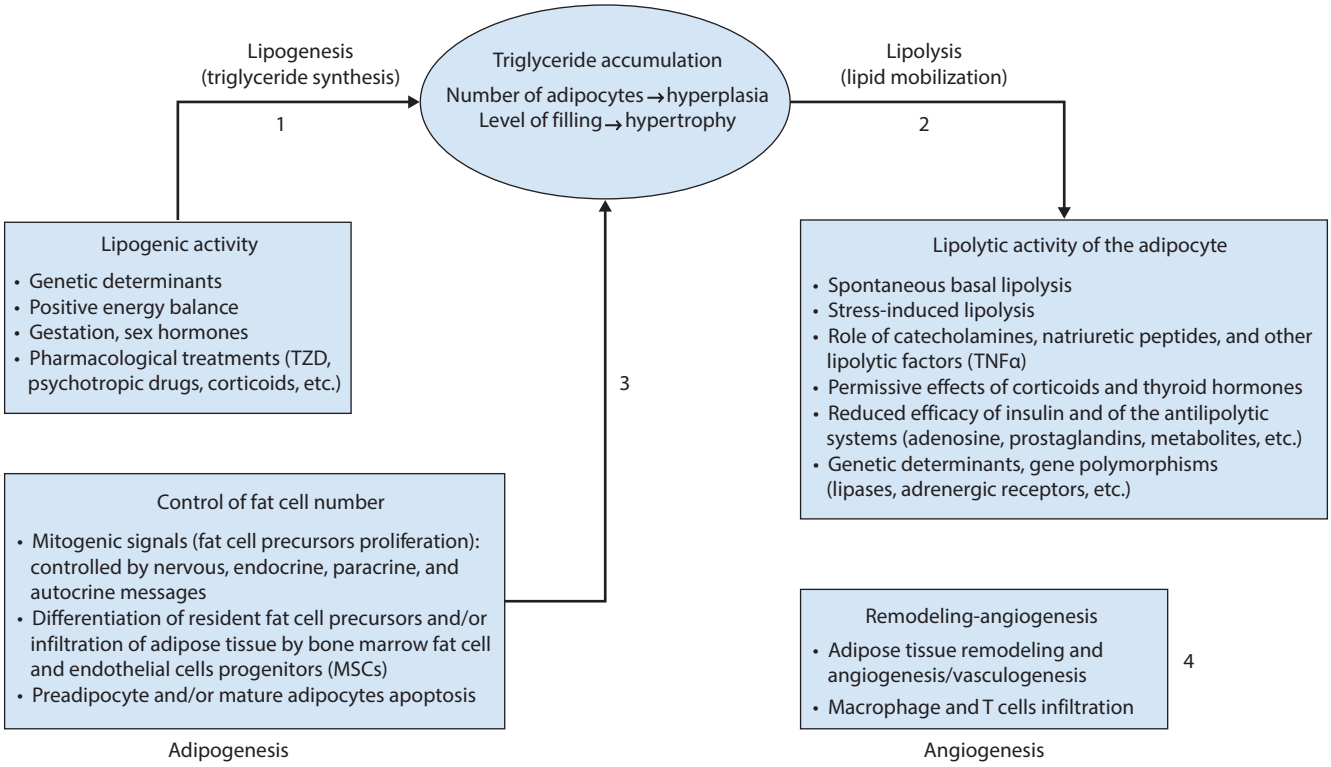


Figure 6.1 Diagram summarizing the major factors involved in the control of adipose tissue extension and homeostasis.

involving adipokines, hypoxia, and oxidative stress might play a key role in the control of the self-renewal of the local pool of AT progenitor cells [77].

The studies on fat mass accretion in humans during the establishment of obesity have shown that a phase of hyperplasia is observed when the maximal storage capacity of the adipocytes is reached [19,52,78]. When optimal adipocyte hypertrophy is attained in some morbidly obese individuals, more adipocytes are necessary to store the excess of fatty acids and avoid storage in non-AT locations and lipotoxic processes [3,79]. "AT expandability theory" proposes that once the AT expansion limit is reached, AT is unable to store energy efficiently. Thus, lipids begin to accumulate in other tissues. Ectopic lipid accumulation in nonadipocyte cells causes various lipotoxic insults including insulin resistance, apoptosis, and inflammation [80].

FAT CELL PRECURSORS AND THE HETEROGENEITY OF THE CELL TYPES IN ADIPOSE TISSUE

The primordial fat pad depot is populated by mesenchymal stem cells (MSCs) and a range of cell phenotypes common to red bone marrow, which include preadipocyte and endothelial progenitors, immature macrophages and macrophages, mast cells, fibroblast-like perivascular cells, and pericytes. Adult AT also contains a mixed population of cells in the SVF.

Preadipocyte Progenitors

The preadipocyte progenitor cells able to enter the adipocyte lineage are located among the SVF cell population [81,82]. MSCs are recruited from bone marrow and the vascular stroma of AT and provide a quite unlimited supply of adipocyte precursors. Members of the bone morphogenetic proteins (BMP) and secreted signaling glycoproteins Wnt (whose effects are mediated through the frizzled receptor) are key mediators of stem cell commitment to produce preadipocytes. Cellular and molecular mechanisms of adipogenesis leading to adipocyte formation have been extensively studied [73]. All the complex events controlling the evolution from the stem cell to adipocyte have recently been reviewed [83] and are summarized in Box 6.3.

The different steps of the sequential differentiation program of adipocyte precursors (i.e., preadipocytes) have been extensively studied. Orchestration of the differentiation program leading to mature adipocytes expressing the enzymes of lipogenesis and lipolysis, hormone receptors controlling afferent messages to AT, and important adipokines has been extensively studied (schematically illustrated in Figure 6.2). Since mature adipocytes are unable to proliferate, the increase in adipocyte number within AT was thought to originate from the proliferation/differentiation of adipocyte precursors, the so-called preadipocytes present in the SVF. The accepted belief was that new adipocytes appearing with the fat mass increase arose from a population of "resident preadipocyte progenitors" located in the SVF and maintained in a "dormant" state [84,85].

The preadipocytes isolated from the SVF of AT were, in fact, multipotent and were able to differentiate into mature adipocytes but also osteoblasts and chondrocytes [86]. Similarities exist in cell immunophenotype between adipose-derived stem cells (ASCs) (also known as adipose-derived stromal cells; the preferred name now [87]) and bone marrow–originating MSCs [88,89].

BOX 6.3 ADIPOGENESIS (SEE REVIEW BY TANG ET AL. [83])

Excessive caloric intake and high-fat diets lead to an increase in adiposity and adipocyte hyperplasia (increased fat cell number) followed by hypertrophy of mature adipocytes. Neoformation of adipose tissue (AT) requires new adipocytes and the concomitant organization of the vascular bed. The processes by which mesenchymal stem cells (MSCs) commit to the adipose lineage and differentiate into adipocytes is adipogenesis. It is tightly linked to the formation of new capillaries and vessels (i.e., angiogenesis).

Adipocytes originate from pluripotent MSCs that have the capacity to develop into several cell types, i.e., adipocytes, myocytes, chondrocytes, and osteocytes. MSCs comprise a minor fraction of bone marrow cells and other tissues, with bone marrow MSCs constituting a mere 0.00001%–0.01% of all bone marrow nucleated cells. In contrast, AT contains at least 100,000 stem/stromal progenitor cells (ASCs) in each gram of fat.

MSCs reside in the bone marrow and as adipose-derived stromal cells (ASCs) along the vascular bed and in the AT stroma. When stimulated by appropriate factors, MSCs undergo a multistep process of commitment, during which the progenitor cells become restricted to the adipocyte lineage.

Several established cell lines, useful for investigators, mimic the functional characteristics of the mesenchymal pluripotent cell type *in vitro* and can be induced to undergo commitment to adipose, muscle, cartilage, and bone lineages.

1. Diets enriched in fat and/or excessive caloric intake increase adiposity that is the result of adipocyte hyperplasia (increased fat cell number) followed by hypertrophy of the adipocytes (e.g., cells can shift from a diameter of 20–150/180 μm in the long term).
2. Adipocyte hyperplasia is caused by recruitment of pluripotent mesenchymal stem cells (MSCs) and ASCs from the vascular stroma of adipose tissue.
3. The bone morphogenetic proteins (BMPs) and Wnt protein families are key mediators of MSC commitment to produce preadipocytes.
4. Exposure of growth-arrested preadipocytes to differentiation inducers (insulin-like growth factor-1 [IGF-1], glucocorticoid, and cyclic AMP) triggers DNA replication, reentry of the cell cycle (a process known as mitotic clonal expansion), and a transcription factor cascade, which leads to the expression of a large number of adipocyte genes → mature adipocyte.
5. After induction of differentiation, the major operating transcription factors include
   - Cyclic AMP response element-binding protein (CREB)
   - The CCAAT/enhancer-binding protein family (C/EBPα, C/EBPβ, C/EBPδ, and CHOP10) that possesses a DNA-binding domain and an adjacent C-terminal leucine zipper dimerization domain
   - Peroxisome proliferator–activator receptor γ (PPARγ1 and PPARγ2) transcribed from the same gene
   - Sterol regulatory element-binding protein (SREBP1c/ADD1)
6. Schematically, the transcription factor cascade operates according to the following steps: induction of CREB and of its phosphorylation [CREB → **P**CREB] → repression of CHOP10 → induction of C/EBPβ and its phosphorylation by kinases (MAP kinase and GSK3β) [C/EBPβ → **P2**-C/EBPβ] → induction of [C/EBPα/PPAR]γ → induction of SREBP1c/ADD1 → induction of adipocyte genes.
7. A number of microRNAs (endogenous small noncoding RNAs that regulate gene expression) appear to play a role in adipogenesis. Some of these microRNAs seem to accelerate adipogenesis, while others negatively regulate it.

Furthermore, MSCs are able to differentiate into adipocytes under adipogenic *in vitro* culture conditions [90,91].

An approach allowing isolation of different cell populations present in the SVF from human AT was developed by using magnetic microbeads coupled to antibodies directed against cell surface marker antigens CD34, CD31 (marker for endothelial cells, monocyte/macrophage lineage, and platelets), and CD14/CD45 (markers for the monocyte/macrophage lineage, leucocytes, and the granulocytes). Among the different subsets of cells, the $CD45^-/CD34^+/CD31^-$ cells were the unique cell fraction able to differentiate into adipocytes in adipogenic culture conditions [92]. Endothelial progenitor cells have been found in the same subset of the $CD45^-/CD34^+/CD31^-$ cell population that also differentiate *in vitro* into endothelial cells when cultured in a pro-angiogenic culture medium. Moreover, *in vivo*, they participate in the revascularization of the ischemic hindlimb in mice [93]. Paracrine regulation of angiogenesis and adipocyte differentiation was shown during *in vivo* adipogenesis [94] in rodents AT. Recent studies using rodent models have clarified the complex mechanisms of *de novo* generation of white adipocytes from the myeloid lineage [95–97]. Hematopoietic progenitors generate bone marrow derived–adipocytes and adipocyte precursors via myeloid intermediates. Accumulation of bone marrow–derived adipocytes over time in a given fat deposit is age dependent (e.g., accumulation with age), fat depot location related, and gender specific. A higher number of these adipocytes have been found in visceral versus subcutaneous AT, and in the female rather than in the male [95].

To conclude, the search for fat cell progenitors has provided a number of answers and has revealed the existence of ASCs in AT SVF. Treatment procedures and potential utility of ASCs in tissue engineering have been reviewed [98]. To summarize the benefits of ASC administration, major points could be noted: (1) ASCs are able to contribute to newly formed tissues

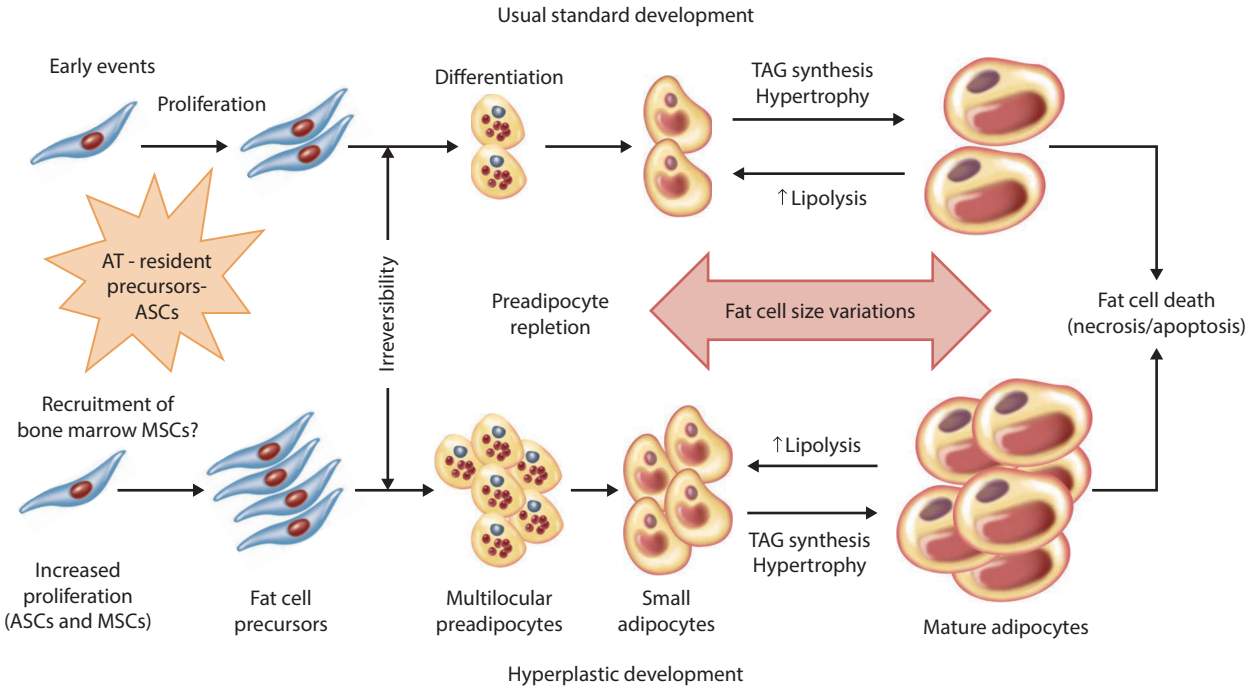


Figure 6.2 Essential steps of normal and excessive development of adipose tissue. Comparison of the usual standard development and the hyperplastic development. After initial proliferation of fat cell precursors and of an irreversibility step, preadipocytes repletion will be followed by final adipocyte differentiation and repletion (see Box 6.4). Mature adipocytes do not proliferate. In the adult, a large part of adipose tissue extension will be governed by variations in fat cell size. The number of fat cells remains practically constant in adulthood in lean and also in obese individuals. Fat cell turnover exists (i.e., apoptosis of mature adipocytes and appearance of new adipocytes); approximately 10% of fat cells are renewed annually at adult ages irrespective of the body mass index.

through their differentiation (bone reconstruction, chondrogenic potencies, angiogenic potential, etc.); (2) ASCs possess potent paracrine activities with the production of numerous growth factors that may exert pleiotropic actions (e.g., formation of neovessels, control of cell survival, modulation of inflammation, etc.); and (3) ASCs possess immunomodulating properties. It must be remembered that adverse effects such as undesirable differentiation or negative interaction with cells could perturb the safety of ASC treatments.

Macrophages and Endothelial Cells

These cells identified by fluorescence-activated cell sorter analysis (FACS) have also been isolated from human AT from various fat depots using antibody-coated microbeads. The number of resident macrophages present in human AT was found to correlate positively with BMI [99]. Such a correlation was confirmed by using other approaches in human subcutaneous fat depots [100–105] and has also been observed in various mouse models of obesity [100,106]. A significant level of lymphocytes has been identified in the SVF of rodent white AT [107] and an increase in T cell markers also exists in the fat pads of obese patients [108]. Defining the role played by AT blood vessels in homing and integrating various circulating lymphocytes and monocytes and bone marrow–derived progenitor cells remains a fascinating challenge. Various experiments in mice have shown that disturbing AT vascularization has a major impact on AT development in genetic and fat-feeding-induced obesity [109–111].

MECHANISMS INVOLVED IN THE CONTROL OF FAT DEPOSITION AND FAT MOBILIZATION

Fat deposition and fat mobilization are under the control of powerful mechanisms that have been extensively detailed in a number of reviews [1,112–114] (Table 6.2). They will not be detailed here and are summarized in the Figures 6.3 through 6.5 and Box 6.4.

De Novo Lipogenesis

In human AT, *de novo* lipogenesis is controversial. Nevertheless, it cannot be ruled out that *de novo* lipogenesis might operate to a significant extent in human AT when there is a need to dispose of "excess" carbohydrate [115,116] (Figure 6.3).

Lipoprotein Lipase Uptake of TAG–Fatty Acids

The major route for TAG deposition in human WAT is the uptake of preexisting fatty acids from circulating TAG (existing in chylomicrons or very-low-density lipoprotein [VLDL] particles) (Figures 6.3 and 6.4).

Uptake of Fatty Acids by Adipocytes

Efficient uptake and channeling of long-chain fatty acids (LCFAs) are critical cell functions. The mechanism by which fatty acids enter the adipocyte is complex and still debated. A large body of evidence supports the presence of protein-mediated carrier systems operating at low substrate

Table 6.2 Hormones and Other Factors Involved in the Regulation of Body Fat Distribution and Adipose Tissue Functions

Hormones and factors	Main biological functions
Insulin	Increasing LPL activity. Increasing glucose and fatty acid uptake. Increase in TAG synthesis in fat cells. Potent antilipolytic hormone. Stimulation of leptin mRNA expression.
Glucocorticoids	GC receptors (GR) highly expressed in visceral AT. Local production of GC by 11β-HSD1 in visceral AT. Increased LPL activity (synergism with insulin). Increase proliferation of fat cell precursors → adipogenesis.
Mineralocorticoids	Presence of aldosterone synthase CYP11B2 in preadipocytes and adipocytes → aldosterone production. Mineralocorticoid receptors (MRs) in adipocytes and preadipocytes.
Growth hormone	Stimulation of basal and catecholamine-induced lipolysis. Increase in hormone-sensitive lipase activity. Variants involved in lipolysis stimulation and lipogenesis inhibition. Inhibition of adipocyte differentiation and stimulation of preadipocyte proliferation.
Catecholamines (adrenaline [A], noradrenaline [NA])	NA acts via stimulation of $beta_{1-2}$- and $alpha_2$-adrenergic receptors. Lipolytic response results from the interplay between both receptor subtypes (see Figure 6.5). Other effects: stimulation of IL-6 release; inhibition of leptin release.
Neuropeptide Y (NPY)	NPY is a sympathetic cotransmitter (colocalized with NA within the sympathetic nerves). NPY receptors (NPY-Y_2) exist in adipocytes and preadipocytes; their stimulation inhibits lipolysis. NPY stimulates preadipocyte proliferation and angiogenesis.
Iodothyronines	Stimulation of lipolysis and increased ATBF. Synergism with catecholamine action. Increase expression of $beta_{1-2}$-adrenergic and decrease expression of $alpha_2$-adrenergic receptors.
Estrogens	Estrogen receptors are expressed in gluteofemoral adipocytes. Inhibition of LPL activity. Increased expression of $alpha_2$-adrenergic receptors. At menopause, gluteofemoral adipocytes convert estradiol to estrone (the estrogen after menopause).
Progesterone	Receptors in SVF fraction. Increase of LPL activity.
Androgens (testosterone)	Receptors highly expressed in visceral AT. Stimulation of lipolysis and reduced LPL activity in males. Reduced femoral lipolysis in females (reduction of HSL expression and $beta_2$-adrenergic receptors). Testosterone inhibits adipocyte differentiation.
Leptin	Mainly secreted by the hypertrophic subcutaneous adipocytes. Paracrine effects on lipogenesis (inhibition) and angiogenesis (stimulation). Proinflammatory effects on endothelial cells.
Interleukin-6 (IL-6)	Mainly released by cells of the SVF (mainly in visceral fat). Increase of lipolysis and decreased LPL activity. Downregulated by glucocorticoid treatment.
Natriuretic peptides	Secreted by cardiomyocytes (atria and ventricle).
Atrial (ANP) and B-type (BNP) natriuretic peptides	Act via stimulation of fat cell NPR-A receptors. Stimulation of lipolysis and ATBF.
Tumor necrosis factor-α (TNF-α)	Mainly released by cells of the SVF. Production in different AT depots (essentially by macrophages). Stimulation of lipolysis on the long term via various pathways. Stimulation of IL-6 production from AT. Inhibition of leptin synthesis.

Note: Main biological impacts and mechanisms of action (endocrine and paracrine) on fat cells.
Abbreviations: A, adrenaline; AT, adipose tissue; ATBF, adipose tissue blood flow; CYP11B2, aldosterone synthase; 11β-HSD1, 11β-hydroxysteroid dehydrogenase 1; GC, glucocorticoids; GH, growth hormone; GR, glucocorticoid receptor, HSL, hormone sensitive lipase; IL-6, interleukin-6; LPL, lipoprotein lipase; MR, mineralocorticoid receptor; NA, noradrenaline; NPY, neuropeptide Y; NPY-Y_2, type 2 NPY receptor; SVF, stroma-vascular fraction; TAG, triacylglycerol.

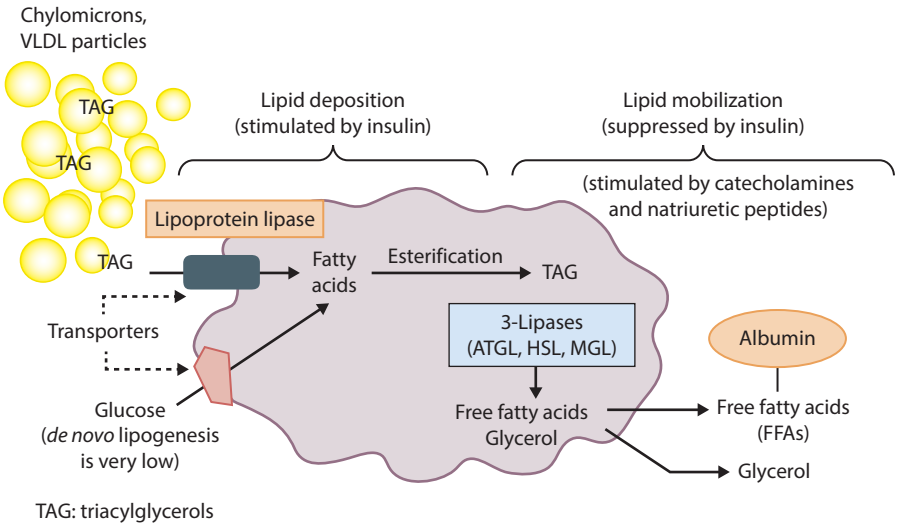


Figure 6.3 Basic pathways leading to lipid deposition and lipid mobilization. The processing of triglyceride-rich lipoproteins by lipoprotein lipase (LPL) is the central event in plasma lipid metabolism. Adipocyte triacylglycerols (TAGs) are synthesized from fatty acids (FAs) and glucose uptake. Specific and selective transporters are involved in the transfer of both metabolites. LPL located in the capillary lumen releases FA from TAGs transported by chylomicrons or very-low-density lipoprotein (VLDL) particles. When stored in the adipocyte, TAGs must be hydrolyzed under the form of free fatty acids (FFAs) (also called nonesterified fatty acids [NEFAs]). Their hydrolysis, i.e., lipolysis, is under the control of three separate lipases themselves under the control of lipolytic and antilipolytic hormones. Plasma FFAs are bound to albumin in the plasma.

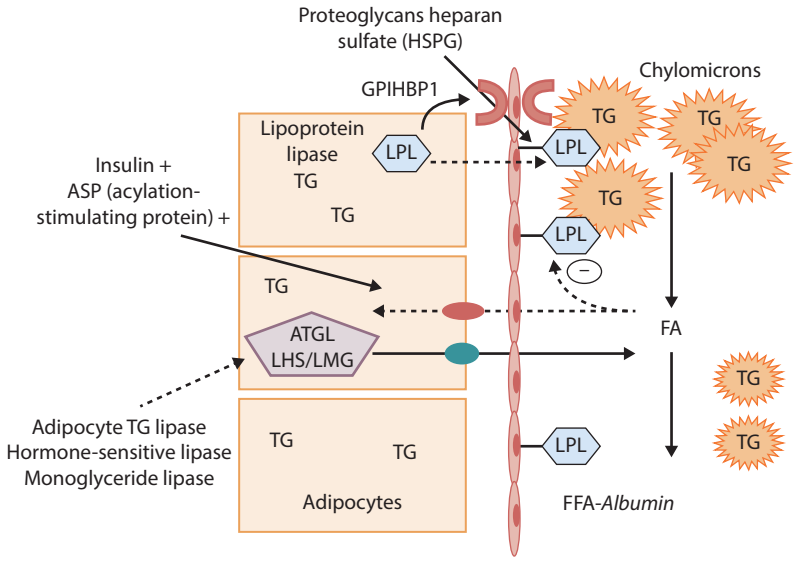


Figure 6.4 Lipoprotein lipase transfer to the capillary lumen and uptake of triacylglycerol (TAG)–fatty acids (FAs) and their transfer across endothelium. The major route for TAG deposition in human white adipose tissue (WAT) is the uptake of preexisting FAs from circulating TAG (existing in chylomicrons or very-low-density lipoprotein [VLDL]) particles. Lipoprotein lipase (LPL) is synthesized in the adipocyte and transferred to the capillary lumen by an endothelial cell protein (the glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1 [GPIHBP1]) via a transcytosis mechanism. LPL is anchored to the endothelial cells by GPIHBP1 and the proteoglycan heparan sulfate. FAs released by LPL activation are rapidly taken up by endothelial cells and transferred to the adipocyte for TAG synthesis (under the control of insulin and acylation-stimulating protein [ASP]). Some FAs bound to albumin can be cleared from AT. When activated by lipolytic hormones, the lipases hydrolyze TAGs and contribute to the recirculation of FAs.

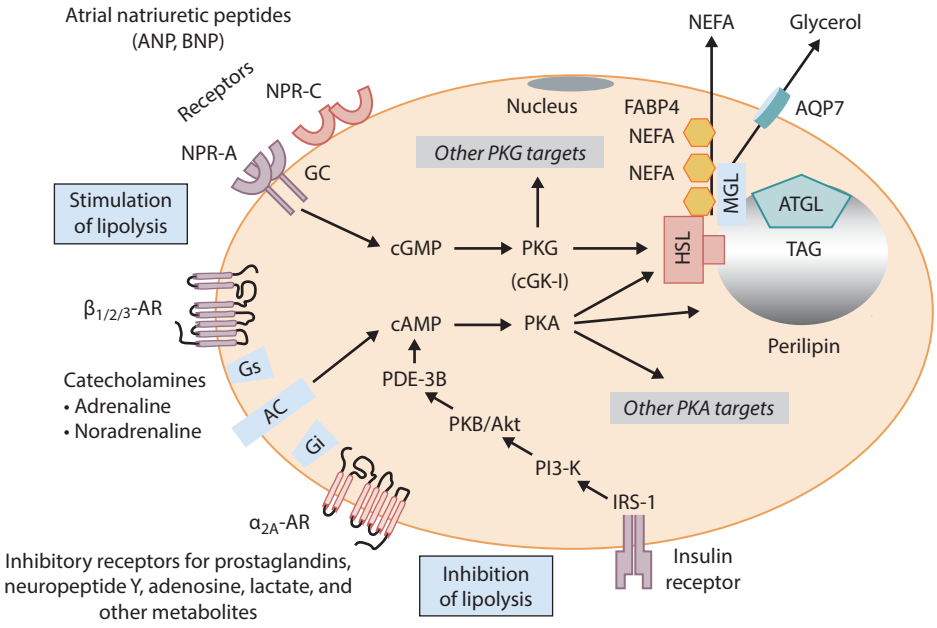


Figure 6.5 Major pathways involved in the regulation of human fat cell lipolysis. Identification of signal transduction pathways for catecholamines, insulin, autacoids, metabolites (lactate), and natriuretic peptides (atrial and brain natriuretic peptides [ANP] and B-type natriuretic peptide [BNP]). Three lipases are necessary for the complete hydrolysis of TAG: adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and monoacylglycerol lipase (MGL). Human fat cells express several adrenergic receptors (i.e., the receptors of catecholamines): both beta$_{1-2}$ and alpha$_2$-adrenergic receptors. Acting through beta$_{1-2}$-adrenergic receptors (coupled to stimulatory GTP-binding protein [Gs]), catecholamines stimulate fat cell membrane adenylyl cyclase and production of cyclic AMP (cAMP) from ATP. In contrast, selective stimulation of alpha$_2$-adrenergic receptors (coupled to inhibitory GTP-binding protein [Gi]) inhibits lipolysis. Various other receptors coupled to Gi protein operate similarly to inhibit lipolysis. Natriuretic peptides, acting via type A natriuretic peptide receptors (NPR-A), that possess a guanylyl cyclase activity, generate cyclic GMP (cGMP). The two second messengers (e.g., cAMP and cGMP) are able to stimulate lipolysis via activation of their corresponding kinases, PKA and PKG, respectively. Protein kinases (PKA and PKG [cGK-I]) are involved in phosphorylation of perilipin and HSL. Perilipin phosphorylation induces a structural modification of the surface droplet that facilitates access of activated HSL to TAGs of the droplet for the initiation of lipolysis. In addition, perilipin phosphorylation releases ABHD5, a specific regulator of ATGL. HSL phosphorylation promotes its translocation from the cytosol to the surface of the lipid droplet. Docking of adipocyte lipid-binding protein (FABP4) to HSL favors the outflow from the cell of NEFAs released by the hydrolysis of triacylglycerols. Glycerol outflow operates via aquaporin 7 (AQP7). Insulin, via stimulation of fat cell insulin receptors and phosphodiesterase-3B stimulation, promotes cAMP degradation and antilipolytic effects, while it is not active on cGMP-dependent pathways (not shown in the diagram). ATGL, adipose triglyceride lipase; AQP7, aquaporin 7; FABP4, adipocyte fatty acid–binding protein 4; GC, guanylyl cyclase; Gi, inhibitory GTP-binding protein; Gs, stimulatory GTP-binding protein; HSL, hormone-sensitive lipase; MGL, monoacylglycerol lipase; NEFA, nonesterified fatty acid; NPR-A, type A natriuretic peptide receptor; NPR-C, type C natriuretic peptide receptor; TAG, triacylglycerols.

concentrations [117]. Proteins are important mediators of LCFA trafficking into cells and various proteins have been suggested to be involved in this process [118,119]. The membrane transport of fatty acids is intimately linked to their "activation" (esterification with coenzyme A) [120,121]. Fatty acid esterification to form TAG involves the sequential addition of acyl-CoA to a glycerol "backbone" in adipocytes [122].

To summarize the regulation of TAG synthesis in AT, it is stimulated by insulin at multiple stages: (1) activation of LPL, (2) activation of the uptake of fatty acids across the fat cell membrane, (3) activation of the pathway of *de novo* fatty acid synthesis, (4) and stimulation of fatty acid esterification to form TAG. The net effect of insulin on WAT TAG stores is strongly "anabolic."

MECHANISMS INVOLVED IN THE CONTROL OF FAT MOBILIZATION

This is achieved by a highly active and regulated pathway: lipolysis, whereby TAGs stored in the adipocyte are hydrolyzed, and fatty acids delivered to the plasma. The detailed regulatory processes have been published in recent reviews [114,123,124]. Lipolytic and antilipolytic pathways control lipolysis. Lipolysis is acutely stimulated by catecholamines (adrenaline and noradrenaline) and natriuretic peptides (e.g., peptide hormones secreted by cardiomyocytes) [125], while insulin is the major inhibitor of lipolysis. A number of other agents acting via paracrines and autocrines also exert lipolytic and antilipolytic actions though the physiological relevance of some of them remains to be elucidated. All the elements of the lipolytic system of the human fat cell are summarized in Figure 6.5.

BOX 6.4 ADIPOSE TISSUE UPTAKE AND MOBILIZATION OF FATTY ACIDS

Lipid storage and synthesis of triacylglycerol (TAG)

- Meal fat that is not oxidized is mainly stored in adipose tissue (AT).
- A greater percentage of dietary fat is stored in subcutaneous AT in females compared with males. [114]
- AT uptake of meal-derived fatty acids carried by chylomicron TAGs involves postprandial lipoprotein lipase (LPL) activity.[1]
- TAG synthesis in AT is stimulated by insulin at multiple stages:
  Activation of LPL and TAG hydrolysis in capillary lumen
  Activation of uptake of fatty acids and glucose across the fat cell membrane
  Activation of the pathway of *de novo* fatty acid synthesis (low in humans)
  Stimulation of fatty acid esterification to form TAG
- Excess energy intake, achieved by a high-fat meal, results in preferential storage of dietary fat in lower-body subcutaneous AT in lean women compared with lean men. The phenomenon is linked to greater postprandial activation of LPL in femoral (leg) fat.
- However, regional differences in meal fatty acid uptake into AT do not fully account for sex-based differences in body fat distribution under energy balance conditions.

Lipid mobilization

- Fasting, cold exposure, and physical activity promote lipid mobilization.
- Physical activity increases the oxidation of dietary fatty acids mobilized from AT by skeletal muscle.
- Insulin, catecholamines, and natriuretic peptides are the major acute regulators of lipid mobilization in humans.[2]
- Catecholamines (adrenaline, noradrenaline) stimulate lipolysis by activating bêta$_1$- and bêta$_2$-adrenergic receptors and inhibit lipolysis via stimulation of alpha$_2$-adrenergic receptors.
- Alpha$_2$-adrenergic receptors predominate in women's femoral AT; in men, they are abundant in abdominal adipocytes of the obese. Alpha$_2$-adrenergic receptors are overexpressed (versus bêta$_1$- and bêta$_2$-adrenergic receptors) in hypertrophied adipocytes.
- Natriuretic peptides (ANP and BNP) stimulate lipolysis by stimulating type A natriuretic peptide receptors (NPR-A) and stimulation of cGMP production.
- Tumor necrosis factor-α and IL-6 also stimulate lipolysis.[3]
- Adenosine, prostaglandins, neuropeptide Y/peptide YY, lactate, and nicotinic acid inhibit lipolysis by stimulating receptors negatively coupled to adenylyl cyclase and inhibition of cAMP production.
- Lipolytic activity is greater in upper-body subcutaneous than in femoral (leg) AT (per kg of fat) in lean and obese women and in lean and obese men.
- Upper-body subcutaneous AT is the major source of systemic fatty acids, while femoral (leg) fat is the lesser contributor.
- Visceral AT contributes to hepatic nonesterified fatty acid delivery in subjects having an increased visceral AT mass.
- This biological issue still remains a puzzle: if regional differences in AT nonesterified fatty acid release fully account for the sex-based differences in body fat distribution under fasted, fed, or exercise conditions.

[1] Langin D, Arner P. Importance of TNFalpha and neutral lipases in human adipose tissue lipolysis. *Trends Endocrinol Metab* 2006; 17:314–320.
[2] Votruba SB, Jensen MD. Regional fat deposition as a factor in FFA metabolism. *Annu Rev Nutr* 2007; 27:149–163.
[3] Wang H, Eckel RH. Lipoprotein lipase: From gene to obesity. *Am J Physiol Endocrinol Metab* 2009; 297:E271–E288.

Site-related differences in the *in vitro* effects of catecholamines have been reported in fat cells from men and women [126–128] and confirmed *in vivo* [129,130]. An enhanced alpha$_2$-adrenergic responsiveness associated with a concomitant decrease in beta$_{1-2}$-adrenergic responsiveness explains the lower lipolytic effect of catecholamines in the gluteal/femoral fat cells of normal and obese women [131] and abdominal fat cells in obese men. Whatever the sex, functional changes in beta$_{1-2}$/alpha$_2$-adrenergic receptor balance are related to the extent of the fat mass and the degree of fat cell hypertrophy. The hypertrophic subcutaneous (abdominal, femoral) fat cells are known to have increased basal lipolysis but to be less responsive to the lipolytic action of catecholamines; they have the highest number of alpha$_2$-adrenergic receptors and the lowest number of beta$_{1-2}$-adrenergic receptors.

ADIPOSE TISSUE PRODUCTIONS, ADIPOKINES, AND THEIR MAJOR ACTIONS

In addition to the metabolic disturbances resulting from altered NEFA handling, AT can exert a substantial impact on systemic glucose homeostasis, insulin resistance, and the initiation of cardiovascular disorders through dysregulated production and release of numerous factors. Some of them are known to act as hormones while many others are limited to an autocrine or paracrine action between the various cell

types within the AT. This section will be limited since a number of recent reviews [132–135] and a book entirely devoted to adipokines are available [136]. The AT secretome is very complex and it is not intended here to present a review of the question. AT secretions and their major actions are summarized in Box 6.5. It must be noted that nonfat cells of AT express and release noticeable amounts of most of the inflammatory factors [137].

To make the story short, the two major hormones of AT, leptin and adiponectin, are involved in the regulation of whole-body energy metabolism. Hypoadiponectinemia and leptin resistance are associated with the development of insulin resistance in obesity-related disorders and type 2 diabetes. The two major adipokines are regulated in opposite ways. Unlike leptin, which is correlated to increased BMI, adiponectin is decreased and increases after weight reduction [134].

BOX 6.5 ADIPOSE TISSUE PRODUCTIONS (ADIPOCYTES AND CELLS OF THE STROMA-VASCULAR FRACTION) AND THEIR INVOLVEMENT IN THE CONTROL OF VARIOUS FUNCTIONS

Metabolism of lipids and lipoproteins

- Lipoprotein lipase
- Acylation-stimulating protein (ASP)
- Prostaglandin E2, prostacyclin
- Autotaxin (lysophospholipase D) + phosphatidylcholine → lysophosphatidic acid
- Retinol-binding protein4 (RBP-4)
- Cholesterol esters transfer protein (CETP)
- Angiopoietine-like-4 (ANGPTL-4)
- Pigment epithelium-derived factor (PEDF)

Food intake and activation of the sympathetic nervous system

- Leptin
- Nesfatin
- Omentin

Metabolism and energy homeostasis

- Leptin
- Adiponectin
- Resistin
- Interleukin-6 and interleukin-8
- Visfatin/nicotinamide phosphoribosyltransferase (NAMPT)

Insulin sensitivity of muscle, hepatocyte, and adipocytes

- Leptin
- Adiponectin
- Apelin
- Resistin
- Visfatin/nicotinamide phosphoribosyltransferase (NAMPT)
- Interleukin-6
- Adipsin and acylation-stimulating protein (ASP)
- Dipeptidyl peptidase 4 (DPP4)

Vascular tonus and angiogenesis

- Vascular endothelial growth factor (VEGF)
- Hepatocyte growth factor (HGF)
- Monobutyrin
- Leptin
- Adiponectin
- Apelin
- Angiopoietin-like 4 (ANGPTL-4)/fasting-induced adipose factor (FIAF)/(peroxisome proliferator-activated receptor γ angiopoietin-related gene (PGAR)
- Angiopoietin-2
- Angiotensinogen/angiotensin-2
- Omentin

- Nesfatin
- Visfatin/nicotinamide phosphoribosyltransferase (NAMPT)
- Interleukin-6
- Adipose-derived relaxing factor (ADRF)

Metabolism of extracellular matrix

- Type 6 collagen
- Plasminogen activator inhibitor-1 (PAI-1)
- Metalloproteases (gelatinases MMP-2 et MMP-9)
- Tissue inhibitors of metalloproteases (TIMP-1 to -3)

Immune system and inflammation acute phase proteins

Pro-inflammatory adipokines

- Leptin
- Tumor necrosis factor-α (TNF-α)
- Interleukins (IL-1β, IL-6, IL-8, IL-18)
- Monocyte chemoattractant protein-1 (CCL2/MCP-1)—binding to CCR2 receptor
- Regulated on activation, normal T expressed and secreted (CCL5/RANTES) (binding to CCR5 receptor)
- Eotaxin (CCL11)
- Epithelial cell–derived neutrophil-activating peptide (78/CXCL5)—binding to CXCR2 receptor
- Visfatin/nicotinamide phosphoribosyltransferase (NAMPT)
- Retinol-binding protein-4 (RBP4)
- Lipocaline2 (*neutrophil gelatinase-associated lipocalin and 24p3*)
- Visfatin/nicotinamide phosphoribosyltransferase (NAMPT)
- Macrophage inflammatory protein-1α,-β et -3α (CCL3/MIP-1α et CCL4/MIP-1β et CCL20/MIP-3α)
- Growth-related oncogene factor-α (CXCL1/GRO-α)—binding to CXCR2 receptor

Anti-inflammatory adipokines

- Adiponectin
- Secreted frizzled-related protein 5 (SFRP5)—ligand of WNT5a
- Interleukin-1 receptor antagonist (IL-1Ra)

Other factors

- Adipsin, factors C3, B et D of the alternative complement system—α1-acid glycoprotein
- Serum amyloïd A 3 (SAA3)
- Haptoglobin
- Pentraxin-3
- Metallothionein
- Cathepsin S

See also [136].

FUTURE TRENDS

The processes participating in the control of energy balance, as well as in the regulation of the intermediary lipid and carbohydrate metabolism, are intricately controlled by neurohumoral mediators. The coordination of the biochemical and molecular pathways involved underlies, at least in part, the large number of intracellular and secreted proteins produced by AT with autocrine, paracrine, and endocrine effects. The discovery that AT secretes a plethora of pleiotropic adipokines at the same time and that adipocytes express receptors for a huge range of compounds will lead to an expansion in the insights into the functions of AT at both the basic and clinical levels. The factors that determine body fat distribution still remain unknown. The combinations of genetic, hormonal, and nutritional factors that promote fat accumulation in some fat deposits relative to other deposits remain to be clarified in humans. New experimental approaches are required to address such issues.

ACKNOWLEDGMENTS

The author acknowledges the following colleagues: P. Arner, A. Bouloumié, J. Galitzky, K.N. Frayn, G. Fruhbeck, D. Langin, N. Viguerie, and R. Zechner for their contribution to the discussion of some points. Their long-lasting involvement in the study of AT biology and physiology has been punctuated with a number of original discoveries.

REFERENCES

1. Frayn KN. Adipose tissue as a buffer for daily lipid flux. *Diabetologia* 2002; 45:1201–1210.
2. Frayn KN, Karpe F, Fielding BA et al. Integrative physiology of human adipose tissue. *Int J Obes Relat Metab Disord* 2003 August; 27(8):875–888.
3. Unger R. Lipid overload and overflow: Metabolic trauma and the metabolic syndrome. *Trends Endocrinol Metab* 2003; 14:398–403.
4. Fruhbeck G. The adipose tissue as a source of vasoactive factors. *Curr Med Chem Cardiovasc Hematol Agents* 2004 July; 2(3):197–208.
5. Lafontan M. Fat cells: Afferent and efferent messages define new approaches to treat obesity. *Annu Rev Pharmacol Toxicol* 2005; 45:119–146.
6. Fantuzzi G. Adipose tissue, adipokines, and inflammation. *J Allergy Clin Immunol* 2005 May; 115(5):911–919.
7. Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature* 2006 December 14; 444(7121):881–887.
8. Han SH, Quon MJ, Kim JA et al. Adiponectin and cardiovascular disease: Response to therapeutic interventions. *J Am Coll Cardiol* 2007 February 6; 49(5):531–538.
9. Fox CS, Coady S, Sorlie PD et al. Increasing cardiovascular disease burden due to diabetes mellitus: The Framingham Heart Study. *Circulation* 2007 March 27; 115(12):1544–1550.
10. Hotamisligil GS. Inflammation and metabolic disorders. *Nature* 2006 December 14; 444(7121):860–867.
11. Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. *J Clin Invest* 2011 January; 121(6):2111–2117.
12. Cannon B, Nedergaard J. Brown adipose tissue: Function and physiological significance. *Physiol Rev* 2004 January; 84(1): 277–359.
13. Ravussin E, Galgani JE. The implication of brown adipose tissue for humans. *Annu Rev Nutr* 2011 August 21; 31:33–47.
14. Hany TF, Gharehpapagh E, Kamel EM et al. Brown adipose tissue: A factor to consider in symmetrical tracer uptake in the neck and upper chest region. *Eur J Nucl Med Mol Imaging* 2002 October; 29(10):1393–1398.
15. Gelfand MJ, O'Hara S M, Curtwright LA et al. Pre-medication to block [(18)F]FDG uptake in the brown adipose tissue of pediatric and adolescent patients. *Pediatr Radiol* 2005 October; 35(10):984–990.
16. Nedergaard J, Bengtsson T, Cannon B. Unexpected evidence for active brown adipose tissue in adult humans. *Am J Physiol Endocrinol Metab* 2007 August; 293(2):E444–E452.
17. Enerback S. Human brown adipose tissue. *Cell Metab* [Research Support, Non-U.S. Gov't Review]. 2010 April 7; 11(4):248–252.
18. Shen W, Wang Z, Punyanita M et al. Adipose tissue quantification by imaging methods: A proposed classification. *Obes Res* 2003 January; 11(1):5–16.
19. Björntorp P. Adipose tissue distribution and function. *Int J Obesity* 1991; 15:67–81.
20. Nicklas BJ, Penninx BW, Cesari M et al. Association of visceral adipose tissue with incident myocardial infarction in older men and women: The Health, Aging and Body Composition Study. *Am J Epidemiol* 2004 October 15; 160(8):741–749.
21. Nicklas BJ, Cesari M, Penninx BW et al. Abdominal obesity is an independent risk factor for chronic heart failure in older people. *J Am Geriatr Soc* 2006 March; 54(3):413–420.
22. Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: Anatomic, biomolecular and clinical relationships with the heart. *Nat Clin Pract Cardiovasc Med* 2005 October; 2(10):536–543.
23. Iacobellis G, Sharma AM. Epicardial adipose tissue as new cardio-metabolic risk marker and potential therapeutic target in the metabolic syndrome. *Curr Pharm Des* 2007; 13(21):2180–2184.
24. Yosipovitch G, DeVore A, Dawn A. Obesity and the skin: Skin physiology and skin manifestations of obesity. *J Am Acad Dermatol* 2007 June; 56(6):901–916; quiz 17–20.
25. Giese SY, Bulan EJ, Commons GW et al. Improvements in cardiovascular risk profile with large-volume liposuction: A pilot study. *Plast Reconstr Surg* 2001 August; 108(2):510–519.
26. Giugliano G, Nicoletti G, Grella E et al. Effect of liposuction on insulin resistance and vascular inflammatory markers in obese women. *Br J Plast Surg* 2004 April; 57(3):190–194.
27. Klein S, Fontana L, Young VL et al. Absence of an effect of liposuccion on insulin action and risk factors for coronary heart disease. *N Engl J Med* 2004; 350:2549–2557.
28. Esposito K, Giugliano G, Giugliano D. Metabolic effects of liposuction—Yes or no? *N Engl J Med* 2004 September 23; 351(13): 1354–1357.
29. Hernandez TL, Kittelson JM, Law CK et al. Fat redistribution following suction lipectomy: Defense of body fat and patterns of restoration. *Obesity (Silver Spring)* 2011 July; 19(7):1388–1395.
30. Benatti F, Solis M, Artioli G et al. Liposuction induces a compensatory increase of visceral fat which is effectively counteracted by physical activity: A randomized trial. *J Clin Endocrinol Metab* 2012 July; 97(7):2388–2395.
31. Manolopoulos KN, Karpe F, Frayn KN. Gluteofemoral body fat as a determinant of metabolic health. *Int J Obes* 2010 June; 34(6):949–959.
32. Matarasso A, Kim RW, Kral JG. The impact of liposuction on body fat. *Plast Reconstr Surg* 1998 October; 102(5):1686–1689.
33. Wasserman F. The development of adipose tissue. *Hanbook of Physiology, Adipose Tissue: Section 5*. Washington, DC: American Physiological Society, 1965, pp. 87–100.
34. Napolitano L. The fine structure of adipose tissues. *Hanbook of Physiology, Adipose Tissue: Section 5*. Washington, DC: American Physiological Society, 1965, pp. 109–123.
35. Cinti S. *The Adipose Organ*. Kurtis Editrice, Milano, Italy, 1999.
36. Greenberg AS, Egan JJ, Wek SA et al. Perilipin, a major hormonally regulated adipocyte-specific phosphoprotein associated with the periphery of lipid storage droplets. *J Biol Chem* 1991 June 15; 266(17):11341–11346.
37. Brasaemle DL. Thematic review series: Adipocyte Biology. The perilipin family of structural lipid droplet proteins: Stabilization of lipid droplets and control of lipolysis. *J Lipid Res* 2007 December; 48(12):2547–2559.
38. Wolins NE, Brasaemle DL, Bickel PE. A proposed model of fat packaging by exchangeable lipid droplet proteins. *FEBS Lett* 2006 October 9; 580(23):5484–5491.
39. Girousse A, Langin D. Adipocyte lipases and lipid droplet-associated proteins: Insight from transgenic mouse models. *Int J Obes (Lond)* 2012 April; 36(4):581–594.
40. Hirsch J, Batchelor B. Adipose tissue cellularity in human obesity. *Clin Endocrinol Metab* 1976 July; 5(2):299–311.
41. Drolet R, Richard C, Sniderman AD et al. Hypertrophy and hyperplasia of abdominal adipose tissues in women. *Int J Obes* 2007 February; 32(2):283–291.
42. Lundberg JM, Franco-Cereceda A, Hemsen A et al. Pharmacology of noradrenaline and neuropeptide tyrosine (NPY)-mediated sympathetic cotransmission. *Fundam Clin Pharmacol* 1990; 4(4):373–391.
43. Cousin B, Casteilla L, Lafontan M et al. Local sympathetic denervation of white adipose tissue in rats induces preadipocyte proliferation without noticeable changes in metabolism. *Endocrinology* 1993; 133:2255–2262.
44. Bartness TJ, Song CK. Thematic review series: Adipocyte biology. Sympathetic and sensory innervation of white adipose tissue. *J Lipid Res* 2007 August; 48(8):1655–1672.
45. Fishman RB, Dark J. Sensory innervation of white adipose tissue. *Am J Physiol* 1987 December; 253(6 Pt 2):R942–R944.
46. Bartness TJ, Song CK. Brain-adipose tissue neural crosstalk. *Physiol Behav* 2007 July 24; 91(4):343–351.
47. Wortham NC, Tomlinson IP. Dercum's disease. *Skinmed* 2005 May–June; 4(3):157–162; quiz 63–64.
48. Stallworth JM, Hennigar GR, Jonsson HT, Jr. et al. The chronically swollen painful extremity. A detailed study for possible etiological factors. *JAMA* 1974 June 24; 228(13):1656–1659.
49. Woerdeman MJ, van Dijk E. Piezogenic papules of the feet. *Acta Derm Venereol* 1972; 52(5):411–414.

50. Faille RJ. Low back pain and lumbar fat herniation. *Am Surg* 1978 June; 44(6):359–361.
51. Duri ZA, Aichroth PM, Dowd G. The fat pad. Clinical observations. *Am J Knee Surg* 1996 Spring; 9(2):55–66.
52. Knittle JL, Timmers K, Ginsberg-Fellner F et al. The growth of adipose tissue in children and adolescents. Cross-sectional and longitudinal studies of adipose cell number and size. *J Clin Invest* 1979 February; 63(2):239–246.
53. Bray GA. Obesity—A state of reduced sympathetic activity and normal or high adrenal activity (the autonomic and adrenal hypothesis revisited). *Int J Obes* 1990; 14 Suppl 3:77–91.
54. Sotornik R, Brassard P, Martin E et al. Update on adipose tissue blood flow regulation. *Am J Physiol Endocrinol Metab* 2012 May 1; 302(10):E1157–E1170.
55. Williams LR, Leggett RW. Reference values for resting blood flow to organs of man. *Clin Phys Physiol Meas* 1989 August; 10(3):187–217.
56. Larsen OA, Lassen NA, Quaade F. Blood flow through human adipose tissue determined with radioactive xenon. *Acta Physiol Scand* 1966 March; 66(3):337–345.
57. Trayhurn P. Hypoxia and adipose tissue function and dysfunction in obesity. *Physiol Rev* 2013 January; 93(1):1–21.
58. Goossens GH, Blaak EE. Adipose tissue oxygen tension: Implications for chronic metabolic and inflammatory diseases. *Curr Opin Clin Nutr Metab Care* 2012 November; 15(6):539–546.
59. Bulow J, Astrup A, Christensen NJ et al. Blood flow in skin, subcutaneous adipose tissue and skeletal muscle in the forearm of normal man during an oral glucose load. *Acta Physiol Scand* 1987 August; 130(4):657–661.
60. Coppack SW, Evans RD, Fisher RM et al. Adipose tissue metabolism in obesity: Lipase action in vivo before and after a mixed meal. *Metabolism* 1992 March; 41(3):264–272.
61. Evans K, Clark ML, Frayn KN. Effects of an oral and intravenous fat load on adipose tissue and forearm lipid metabolism. *Am J Physiol* 1999 February; 276(2 Pt 1):E241–E248.
62. Evans K, Clark ML, Frayn KN. Carbohydrate and fat have different effects on plasma leptin concentrations and adipose tissue leptin production. *Clin Sci (Lond)* 2001 May; 100(5):493–498.
63. Fugmann A, Millgard J, Sarabi M et al. Central and peripheral haemodynamic effects of hyperglycaemia, hyperinsulinaemia, hyperlipidaemia or a mixed meal. *Clin Sci (Lond)* 2003 December; 105(6):715–721.
64. Simonsen L, Bulow J, Astrup A et al. Diet-induced changes in subcutaneous adipose tissue blood flow in man: Effect of beta-adrenoceptor inhibition. *Acta Physiol Scand* 1990 June; 139(2):341–346.
65. Ardilouze JL, Fielding BA, Currie JM et al. Nitric oxide and beta-adrenergic stimulation are major regulators of preprandial and postprandial subcutaneous adipose tissue blood flow in humans. *Circulation* 2004 Januray 6; 109(1):47–52.
66. Blaak EE, van Baak MA, Kemerink GJ et al. Beta-adrenergic stimulation and abdominal subcutaneous fat blood flow in lean, obese, and reduced-obese subjects. *Metabolism* 1995 February; 44(2):183–187.
67. Samra JS, Simpson EJ, Clark ML et al. Effects of epinephrine infusion on adipose tissue: Interactions between blood flow and lipid metabolism. *Am J Physiol* 1996 November; 271(5 Pt 1):E834–E839.
68. Millet L, Barbe P, Lafontan M et al. Catecholamine effects on lipolysis and blood flow in human abdominal and femoral adipose tissue. *J Appl Physiol* 1998 July; 85(1):181–188.
69. Karpe F, Fielding BA, Ardilouze JL et al. Effects of insulin on adipose tissue blood flow in man. *J Physiol* 2002 May 1; 540(Pt 3):1087–1093.
70. Karpe F, Tan GD. Adipose tissue function in the insulin-resistance syndrome. *Biochem Soc Trans* 2005 November; 33(Pt 5):1045–1048.
71. Ardilouze JL, Sotornik R, Dennis LA et al. Failure to increase postprandial blood flow in subcutaneous adipose tissue is associated with tissue resistance to adrenergic stimulation. *Diabetes Metab* 2012 February; 38(1):27–33.
72. Gesta S, Tseng YH, Kahn CR. Developmental origin of fat: Tracking obesity to its source. *Cell* 2007 October 19; 131(2):242–256.
73. Rosen ED, MacDougald OA. Adipocyte differentiation from the inside out. *Nat Rev Mol Cell Biol* 2006 December; 7(12):885–896.
74. Hausman GJ, Richardson RL. Adipose tissue angiogenesis. *J Anim Sci* 2004 March; 82(3):925–934.
75. Nishimura S, Manabe I, Nagasaki M et al. Adipogenesis in obesity requires close interplay between differentiating adipocytes, stromal cells, and blood vessels. *Diabetes* 2007 June; 56(6):1517–1526.
76. Spalding KL, Arner E, Westermark PO et al. Dynamics of fat cell turnover in humans. *Nature* 2008 June 5; 453(7196):783–787.
77. Maumus M, Sengenes C, Decaunes P et al. Evidence of in situ proliferation of adult adipose tissue-derived progenitor cells: Influence of fat mass microenvironment and growth. *J Clin Endocrinol Metab* 2008 October; 93(10):4098–4106.
78. Gregoire FM, Smas CM, Sul HS. Understanding adipocyte differentiation. *Physiol Rev* 1998 July; 78(3):783–809.
79. Heilbronn L, Smith SR, Ravussin E. Failure of fat cell proliferation, mitochondrial function and fat oxidation results in ectopic fat storage, insulin resistance and type II diabetes mellitus. *Int J Obes Relat Metab Disord* 2004 December; 28 Suppl 4:S12–S21.
80. Virtue S, Vidal-Puig A. Adipose tissue expandability, lipotoxicity and the Metabolic Syndrome—An allostatic perspective. *Biochim Biophys Acta* 2010 March; 1801(3):338–349.
81. Hausman GJ, Campion DR, Martin RJ. Search for the adipocyte precursor cell and factors that promote its differentiation. *J Lipid Res* 1980 August; 21(6):657–670.
82. Hausman DB, DiGirolamo M, Bartness TJ et al. The biology of white adipocyte proliferation. *Obes Rev* 2001 November; 2(4): 239–254.
83. Tang QQ, Lane MD. Adipogenesis: From stem cell to adipocyte. *Annu Rev Biochem* 2012; 81:715–736.
84. Ailhaud G, Grimaldi P, Negrel R. Cellular and molecular aspects of adipose tissue development. *Annu Rev Nutr* 1992; 12:207–233.
85. Tang W, Zeve D, Suh JM et al. White fat progenitor cells reside in the adipose vasculature. *Science* 2008 October 24; 322(5901): 583–586.
86. Zuk PA, Zhu M, Ashjian P et al. Human adipose tissue is a source of multipotent stem cells. *Mol Biol Cell* 2002 December; 13(12):4279–4295.
87. Phinney DG, Prockop DJ. Concise review: Mesenchymal stem/multipotent stromal cells: The state of transdifferentiation and modes of tissue repair—Current views. *Stem Cells* 2007 November; 25(11):2896–2902.
88. Gronthos S, Franklin DM, Leddy HA et al. Surface protein characterization of human adipose tissue-derived stromal cells. *J Cell Physiol* 2001 October; 189(1):54–63.
89. De Ugarte DA, Alfonso Z, Zuk PA et al. Differential expression of stem cell mobilization-associated molecules on multi-lineage cells from adipose tissue and bone marrow. *Immunol Lett* 2003 October 31; 89(2–3):267–270.
90. Ryden M, Dicker A, Gotherstrom C et al. Functional characterization of human mesenchymal stem cell-derived adipocytes. *Biochem Biophys Res Commun* 2003 November 14; 311(2):391–397.
91. Dicker A, Le Blanc K, Astrom G et al. Functional studies of mesenchymal stem cells derived from adult human adipose tissue. *Exp Cell Res* 2005 August 15; 308(2):283–290.
92. Sengenes C, Lolmede K, Zakaroff-Girard A et al. Preadipocytes in the human subcutaneous adipose tissue display distinct features from the adult mesenchymal and hematopoietic stem cells. *J Cell Physiol* 2005 October; 205(1):114–122.
93. Miranville A, Heeschen C, Sengenes C et al. Improvement of postnatal neovascularization by human adipose tissue-derived stem cells. *Circulation* 2004 July 20; 110(3):349–355.
94. Fukumura D, Ushiyama A, Duda DG et al. Paracrine regulation of angiogenesis and adipocyte differentiation during in vivo adipogenesis. *Circ Res* 2003 October 31; 93(9):e88–e97.
95. Majka SM, Fox KE, Psilas JC et al. De novo generation of white adipocytes from the myeloid lineage via mesenchymal intermediates is age, adipose depot, and gender specific. *Proc Natl Acad Sci USA* 2010 August 17; 107(33):14781–14786.

96. Sera Y, LaRue AC, Moussa O et al. Hematopoietic stem cell origin of adipocytes. *Exp Hematol* 2009 September; 37(9):1108–1120, 20 e1–e4.
97. Tomiyama K, Murase N, Stolz DB et al. Characterization of transplanted green fluorescent protein+ bone marrow cells into adipose tissue. *Stem Cells* 2008 February; 26(2):330–338.
98. Gimble JM, Katz AJ, Bunnell BA. Adipose-derived stem cells for regenerative medicine. *Circ Res* 2007 May 11; 100(9):1249–1260.
99. Curat CA, Miranville A, Sengenes C et al. From blood monocytes to adipose tissue-resident macrophages: Induction of diapedesis by human mature adipocytes. *Diabetes* 2004 May; 53:1285–1292.
100. Weisberg SP, McCann D, Desai M et al. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 2003 December 15; 112:1796–808.
101. Clément K, Viguerie N, Poitou C et al. Weight loss regulates inflammation-related genes in white adipose tissue of obese subjects. *FASEB J* 2004; 18:1657–1669.
102. Cancello R, Henegar C, Viguerie N et al. Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. *Diabetes* 2005 August; 54(8):2277–2286.
103. Cancello R, Tordjman J, Poitou C et al. Increased infiltration of macrophages in omental adipose tissue is associated with marked hepatic lesions in morbid human obesity. *Diabetes* 2006 June; 55(6):1554–1561.
104. Harman-Boehm I, Bluher M, Redel H et al. Macrophage infiltration into omental versus subcutaneous fat across different populations: Effect of regional adiposity and the comorbidities of obesity. *J Clin Endocrinol Metab* 2007 June; 92(6):2240–2247.
105. Bourlier V, Zakaroff-Girard A, Miranville A et al. Remodeling phenotype of human subcutaneous adipose tissue macrophages. *Circulation* 2008 Februray 12; 117(6):806–815.
106. Xu H, Barnes GT, Yang Q et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest* 2003 December 15, 2003; 112:1821–1830.
107. Caspar-Bauguil S, Cousin B, Galinier A et al. Adipose tissues as an ancestral immune organ: Site-specific change in obesity. *FEBS Lett* 2005 July 4; 579(17):3487–3492.
108. Wu H, Ghosh S, Perrard XD et al. T-cell accumulation and regulated on activation, normal T cell expressed and secreted upregulation in adipose tissue in obesity. *Circulation* 2007 February 27; 115(8):1029–1038.
109. Rupnick MA, Panigrahy D, Zhang CY et al. Adipose tissue mass can be regulated through the vasculature. *Proc Natl Acad Sci USA* 2002 August 6; 99(16):10730–10735.
110. Kolonin MG, Saha PK, Chan L et al. Reversal of obesity by targeted ablation of adipose tissue. *Nat Med* 2004 June; 10(6): 625–632.
111. Brakenhielm E, Cao R, Gao B et al. Angiogenesis inhibitor, TNP-470, prevents diet-induced and genetic obesity in mice. *Circ Res* 2004 June 25; 94(12):1579–1588.
112. Horowitz JF. Fatty acid mobilization from adipose tissue during exercise. *Trends Endocrinol Metab* 2003 October; 14(8):386–392.
113. Langin D, Lafontan M. Lipolysis and lipid mobilization in human adipose tissue. In: Bray GA and Bouchard, C, eds., *Handbook of Obesity Etiology and Pathophysiology.* New York: Marcel Dekker, Inc., 2004, pp. 515–532.
114. Lafontan M, Langin D. Lipolysis and lipid mobilization in human adipose tissue. *Prog Lipid Res* 2009 September; 48(5):275–297.
115. Acheson KJ, Schutz Y, Bessard T et al. Glycogen storage capacity and de novo lipogenesis during massive carbohydrate overfeeding in man. *Am J Clin Nutr* [Research Support, Non-U.S. Gov't]. 1988 August; 48(2):240–247.
116. Aarsland A, Chinkes D, Wolfe RR. Hepatic and whole-body fat synthesis in humans during carbohydrate overfeeding. *Am J Clin Nutr* 1997 June; 65(6):1774–1782.
117. Pohl J, Ring A, Hermann T et al. Role of FATP in parenchymal cell fatty acid uptake. *Biochim Biophys Acta* 2004 November 8; 1686(1–2):1–6.
118. Stahl A, Evans JG, Pattel S et al. Insulin causes fatty acid transport protein translocation and enhanced fatty acid uptake in adipocytes. *Dev Cell* 2002; 2:477–488.
119. Hajri T, Abumrad NA. Fatty acid transport across membranes: Relevance to nutrition and metabolic pathology. *Annu Rev Nutr* 2002; 22:383–415.
120. Gargiulo CE, Stuhlsatz-Krouper SM, Schaffer JE. Localization of adipocyte long-chain fatty acyl-CoA synthetase at the plasma membrane. *J Lipid Res* 1999 May; 40(5):881–892.
121. Lobo S, Wiczer BM, Smith AJ et al. Fatty acid metabolism in adipocytes: Functional analysis of fatty acid transport proteins 1 and 4. *J Lipid Res* 2007 March; 48(3):609–620.
122. Coleman RA, Lee DP. Enzymes of triacylglycerol synthesis and their regulation. *Prog Lipid Res* 2004 March; 43(2):134–176.
123. Zechner R, Strauss JG, Haemmerle G et al. Lipolysis: Pathway under construction. *Curr Opin Lipidol* 2005 June; 16(3):333–340.
124. Langin D. Adipose tissue lipolysis as a metabolic pathway to define pharmacological strategies against obesity and the metabolic syndrome. *Pharmacol Res* 2006; 53:482–491.
125. Moro C, Lafontan M. Natriuretic peptides and cGMP signaling control of energy homeostasis. *Am J Physiol Heart Circ Physiol* 2013 February 1; 304(3):H358–H368.
126. Lafontan M, Berlan M. Fat cell alpha 2-adrenoceptors: The regulation of fat cell function and lipolysis. *Endocr Rev* 1995 December; 16(6):716–738.
127. Arner P. Catecholamine-induced lipolysis in obesity. *Int J Obes* 1999; 23 Suppl 1:10–13.
128. Jensen MD. Lipolysis: Contribution from regional fat. *Annu Rev Nutr* 1997; 17:127–139.
129. Stich V, deGlisezinski I, Crampes F et al. Activation of alpha2-adrenergic receptors impairs exercise-induced lipolysis in SCAT of obese subjects. *Am J Physiol* 2000; 279:R499–R504.
130. Manolopoulos KN, Karpe F, Frayn KN. Marked resistance of femoral adipose tissue blood flow and lipolysis to adrenaline in vivo. *Diabetologia* 2012 November; 55(11):3029–3037.
131. Mauriege P, Galitzky J, Berlan M et al. Heterogeneous distribution of beta and alpha-2 adrenoceptor binding sites in human fat cells from various fat deposits: Functional consequences. *Eur J Clin Invest* 1987 April; 17(2):156–165.
132. Ceddia RB. Direct metabolic regulation in skeletal muscle and fat tissue by leptin: Implications for glucose and fatty acids homeostasis. *Int J Obes* 2005 October; 29(10):1175–1183.
133. Lafontan M, Viguerie N. Role of adipokines in the control of energy metabolism: Focus on adiponectin. *Curr Opin Pharmacol* 2006 December; 6(6):580–585.
134. Kadowaki T, Yamauchi T, Kubota N et al. Adiponectin and adiponectin receptors in insulin resistance, diabetes and the metabolic syndrome. *J Clin Invest* 2006; 116:1784–1792.
135. Bastard J-P, Vatier C, Fève B. Adiponectin: An adipokine with multiple faces. In: Bastard JP and Fève, B, eds. *Physiology and Physiopathology of Adipose Tissue*. Paris, France: Springer Verlag France, 2013, pp. 187–200.
136. Preedy V, Hunter RJ, eds. *Adipokines.* Boca Raton, FL: CRC Press, 2011.
137. Fain JN. Release of interleukins and other inflammatory cytokines by human adipose tissue is enhanced in obesity and primarily due to the nonfat cells. *Vitam Horm* 2006; 74:443–477.

How to evaluate aging skin: Tools and techniques

Sophie Mac-Mary, Jean-Marie Sainthillier, and Philippe Humbert

Aging skin is the result of several processes: natural aging (including the specific influence of menopause in women: hormonal aging), repeated sun exposure, and environmental and catabolic factors. All these elements have histological and functional impacts that are revealed by clinical modifications [42–44,52]. From biology to skin imaging, biometrological assessments to clinical scoring, numerous and valuable scientific tools are available to quantify aging skin as well as the efficacy of aesthetic treatments (Table 7.1).

BIOLOGY

From the biological perspective, there are several mechanisms to assess the aging process, including oxidative stress, mitochondrial dysfunction, telomere shortening, and various genetic mechanisms [10,40,55,68,69].

Up to now, biological research has mostly focused on particular types of skin cells (keratinocyte [25], fibroblast [23], melanocyte [15]) or a section of the skin (epidermis, dermis, connective tissue), ignoring the overall biological network of the whole skin. However, reconstructed skin is a model in constant progress [31–33,39,59]: it can be now pigmented, immunocompetent, or endothelialized or include a hypodermis.

In current years, microarray technology has become a valuable tool for screening the genetic material in order to map genes and pathways involved in the pathogenesis of aging [45,49 (Figure 7.1), 68].

However, these studies depend on the collection of human skin samples that is associated with major practical and ethical obstacles, and the formation of reconstructed skin is long and difficult to perform (from cell isolation to the creation of model equivalent, only a few samples of all those cultured will be useable).

Skin explants are very convenient models to visualize and quantify modifications in histological markers and biological targets (incubation of the explants in a deprived medium, study of the effects of UV or pollution, etc.). Unfortunately, these models can be studied only over the course of a few days (<14 days).

Thanks to technical progresses in noninvasive structural and molecular analyses such as infrared, confocal, and Raman spectroscopy, optical biopsies can now be performed.

These techniques were used at the beginning mostly to measure water content in skin, but their combination with statistical analyses such as principal component analysis (PCA) now provides also qualitative and quantitative information about the structure, as well as the intra- and interchain organization of extracted or biomimetic lipid mixtures [42,47,65,66]. It is therefore possible to estimate changes in barrier function of stratum corneum (SC) lipids, expressed as molecular changes occurring in the conformational and organizational states [65]. All these techniques are among the most promising techniques, but their use is currently limited because of their high cost and restriction to a reduced study area (inducing difficulties of repositioning) and because the interpretation of the results is still complex.

INSTRUMENTATION

Objective quantification of the impact of these physiological modifications can be performed non-invasively, thanks to the numerous biometrological instruments that are now available. The key signs of aging skin such as loss of elasticity, firmness, sebum secretion, hydration, smoothness, and radiance can all be assessed.

However, these investigations require a disciplined approach to their use [14]. It is necessary to perform the measurements with the same experienced clinician, in a controlled atmosphere (temperature and hygrometry), on the same anatomical area of the skin, on a skin without makeup or product, and on volunteers remaining at rest at least 15 minutes before examination in order to be in stable conditions of blood flow and skin temperature.

With Aging, Skin Elasticity Decreases

The assessment of mechanical properties allows access to the intrinsic mechanical properties and functional condition of the skin such as its elastic components (elastic fibers, connective bundle weaving, stratum corneum pliability) or components with a viscous behavior (interstitial fluid mobility and viscosity, friction within the tissues) [2].

Several constraints can be applied by twisting the skin (with the Torque Meter® from DTM), by suction (Cutometer® from Courage & Khazaka or DermaLab® Elasticity from Cortex Technologies), or by indentation (ballistometer® from Diastron, which assesses the rebound of a light hammer falling with a given energy onto a surface [1]). All these techniques quantify related but not identical aspects of the skin: the suction method measures predominantly elasticity, whereas indentation skin measures stiffness [34]. Moreover, correlation between these assessments is often difficult to perform because the area involved and the conditions of the measurement change, which are of importance to the results (Cutometer as well as Torque Meter can be used with different settings).

Table 7.1 Main Factors to Be Studied for Assessing Aging Skin

Biology [10,66]	Histology [31,66]	Biometrology [14]	Clinical scoring [4,14,51]
Changes in the molecular structure of DNA, proteins lipids, and prostaglandins	Epidermal thinning (or thickening with photoaging)	Sebum (↘)	Xerosis
Mitochondrial dysfunction	Dermoepidermal junction flattening	Hydration (↘)	Fine wrinkles (↗)
Telomere shortening	Loss of connective tissue and atrophy of the dermis	Elasticity (↘)	Roughness (↗)
Upregulation of apoptosis	Fragmentation of elastic fibers and thickening	Skin microrelief	Wrinkles (↗)
Ceramide composition (↘)	Dermal papillae (↘)	Skin macrorelief (wrinkle depth and volume, fringe projection)	Skin transparency
Keratinocyte proliferation (↘)	Number and size of fibroblasts (↘)	Sagging (fringe projection, stereoimaging)	Volume changes/ptosis/eyebags, etc.
Epithelial cell turnover (↘)	Number and size of melanocytes (↘) and heterogeneity in terms of pigment distribution	Skin color and homogeneity	Skin firmness/elasticity
Procollagen synthesis (↘)			Skin radiance/complexion homogeneity
Glycosaminoglycans (↘)			Lentigos/skin heterogeneity
Superoxide dismutase, catalase, and glutathione peroxidase (↘)			
Enzyme expression (metalloproteinases) (↗)			
Elastase synthesis (↗)			
Elastin expression (↗)			
Free radical production (↗)			
Advanced protein end product (↗)			

Note: From biology investigations to clinical scoring.

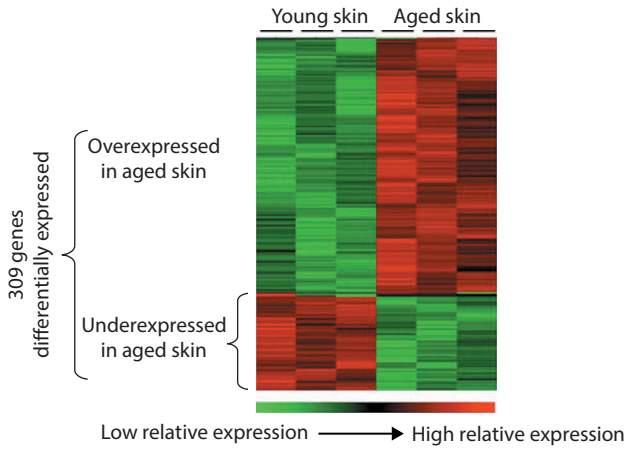


Figure 7.1 Differential gene expression between young (26 years) and old skin (56 years) identified through hierarchical clustering analysis. Most of the overexpressed genes encoded proteins that are related to senescence and oxidative stress, whereas those underexpressed are related to the barrier function and reepithelialization processes. (From Montastier.)

Many parameters can be determined from these assessments (Figure 7.2). Previous studies suggest that skin final retraction is strongly correlated with age [53]. Age induces a decrease of skin tonicity (Ur) and elasticity (Ur/Ue) [15]. Other parameters such as skin distensibility (Ur/Uf), gross elasticity (Ua/Uf), as well as maximum recovery also seem suitable to show its influence [37], irrespective of the studied site (cheek, neck, forearm, hand). Assessments performed on temples also suggest an increase in skin fluidity (Uv/Ue) [12].

With Menopause in Females and with Photoaging, Sebaceous Gland Activity Decreases [71]

Quick estimation of the sebum level can be performed by collecting devices such as Sebutape® from Cuderm or Sebufix® from Courage & Khazaka. After applying firmly against the skin for 5 seconds, oiliness is revealed by dark spots. A clinical scoring can be thus performed by comparing it with reference pattern, or sebum level can be assessed through image analysis. Casual sebum level can also be easily measured through grease spot photometry (Sebumeter®, Courage & Khazaka) [57].

With Aging, the Skin Becomes More Transparent, Dryer, and Wound Healing Is Delayed

In healthy skin, there is an equilibrium between the proliferation/differentiation process of the keratinocytes and the desquamation of corneocytes. Every day, a layer of stratum corneum is eliminated and the epidermis underneath synthesizes a new layer. The stratum corneum is renewed in about 20 days in young adults as opposed to 10 days in older people [28]. This technique involves the assessment of the disappearance of a marker dye (chloruredansyl, assessed by fluorescence or dihydroxyacetone, assessed by chromametry [56]).

The water content of the stratum corneum is linked to its aesthetic aspect as well as its function. Skin dryness can be easily assessed through adhesive sampling and analysis of this sampling (D-Squame® from Cuderm or Corneofix® from Courage & Khazaka). Clinical scoring can be performed by comparing the appearance of the sample to a reference pattern, or quantification by image analyses and calculation of a scaling index [9]. Assessment of the dielectric properties of the skin (capacitance through the Corneometer® from Courage & Khazaka, impedance through the DPM9003® from NOVA™ Technology Corporation, or conductance through the

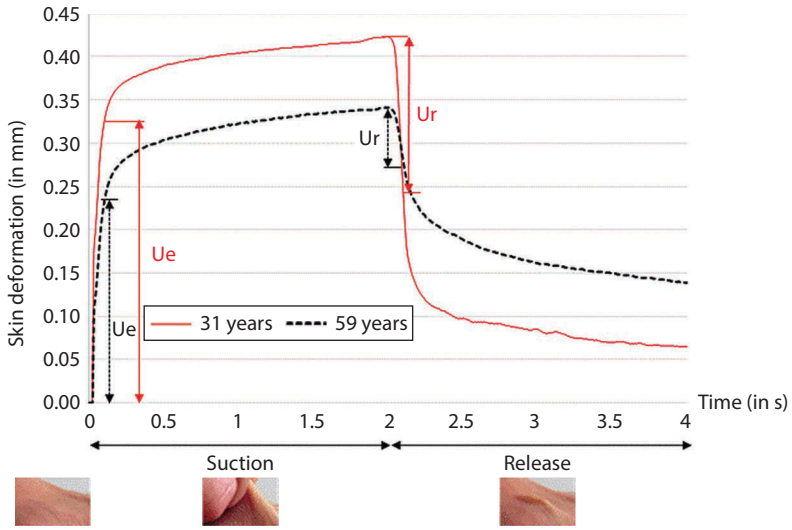


Figure 7.2 Curves obtained with the cutometer on the skin's temple of women aged 31 (red line) and 59 (black dotted line). The skin is much less tonic and elastic in the older woman (Ur and Ur/Ue are lower: Ur/Ue = 0.554 for the young woman and 0.329 for the older).

Skicon-200EX® from IBS) provides indirect assessment of the hydration of the skin surface. Skin hydration can also be measured not only on the surface but also in depth, thanks to the MoistureMeter from Delfin Technologies [3].

With Aging, the Skin Becomes Rougher (Wrinkles Become Wider) and Anisotropic [7,37,38]

Previous works have well demonstrated the strong influence of skin surface topography [63] as well as color homogeneity [46] on the perception of age.

Optical profilometry is probably the most widely used technique today to acquire 3D images (DermaTop®, Eotech, and Primos®, GFM) with a high resolution. The principle of this technique is to project structured light, i.e., a network of fringes, onto the investigated surface [30,62,64]. Fringes are deformed (modulated) by the relief. Several acquisitions with different phases of the projected network are recorded by a camera; after processing by dedicated software, the tridimensional profile of the studied area is reconstructed within a few seconds. This is particularly interesting in the study of morphological transformations, which take place on the forehead, crow's feet, or cheeks such as appearance of wrinkles, ptosis of jawline, eyebags, and/or periorbital dark circles (Figure 7.3). The advantages of this technique are to obtain accurate measurements of surfaces without any contact and to offer the possibility to study the skin directly *in vivo* or from replicas. It is therefore well adapted to the skin and its constraints. With the possibility to adapt the size of the measurement field to the studied object, it is a very interesting tool in clinical evaluation. However, this technique still remains expensive and needs technical, practical, and computing competence.

Optical 2D systems such as Visioscan provide semi-quantitative information on roughness and texture [22]. These systems are cheaper and easier to use but are influenced by skin color.

With Aging, the Skin Becomes Darker and Its Color Is Heterogeneous, a Universal Phenomenon

Inhomogeneity of the skin complexion, light-diffusion properties of the skin, and lightness seem to influence most particularly consumer's perception of the skin's visual appearance for its age [58].

Difficulties in assessing color arise from its dependency on three interacting factors: the light source, the skin, and the observer (the color of the skin is due to the light it reflects after an internal course in every direction during which an important absorption of light takes place, especially of specific wavelengths) [60]. If one of them varies (nature and intensity of the light source, reflection and absorption of the light by the skin, sensitivity of the observer as well as his position in relation to the skin), the color measured changes too. Specific guidelines have been published for the assessment of skin color [24].

Instrumental assessments, which are exclusively based on the laws of physics, have been developed, giving more reliable and objective quantification of human skin color than the eye, which gives only an interpretation that is sometimes even individual specific [61]. The advantages of skin reflectance measurement devices such as spectrophotometers and colorimeters are to control the illuminating source and the observer. Spectrophotometry uses either a broadband or selected wavelengths in the visible range, with measurement of absorbance and reflectance (spectrophotometer CM2600® from KonicaMinolta) or tristimulus (blue, red, green) analysis of light reflected from skin structures (Chromameter CR400® from KonicaMinolta, Colorimeter CL400® from Courage & Khazaka, DSMII ColorMeter® from

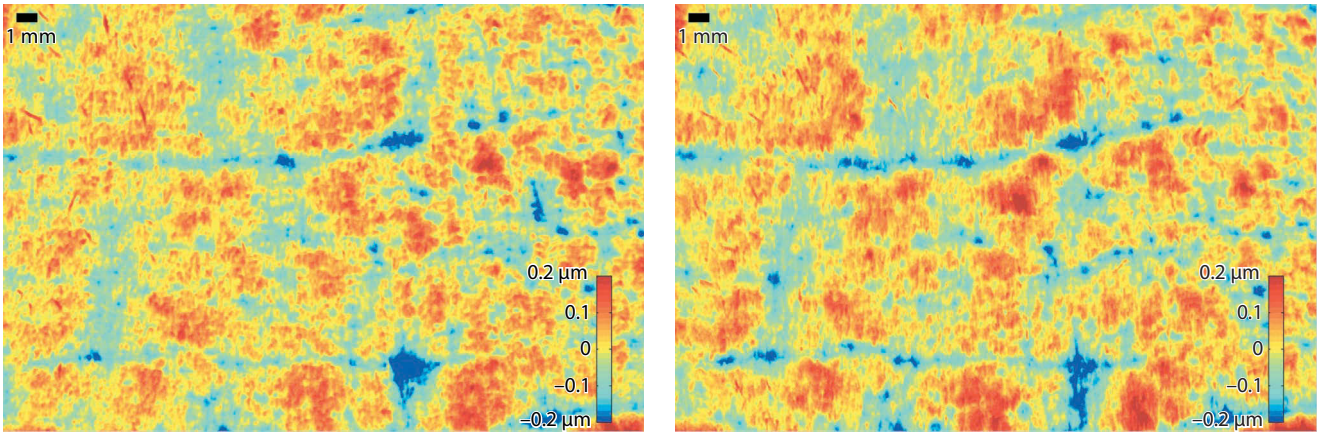


Figure 7.3 Two images of the forehead (30 × 20 mm) of a woman, made 3 years apart: (a) 39-year old; (b) 41-year old (same woman). A slight increase of the relief is visible: the 2 discontinued horizontal wrinkles are barely visible in the first image, and they then become deeper and continuous. These changes represent a 5% increase of volume.

Cortex Technology). Skin color is usually expressed in the L*a*b* color space defined by the Commission Internationale de l'Eclairage (CIE), which gives a 3D representation of human color perception. In this system, L* characterizes surface brightness (black–white axis), a* a point along the green–red axis, and b* along the blue–yellow axis. Previously published works have demonstrated that L* in Caucasian facial skin may be related to antiaging treatment efficacy [70].

Narrowband spectrophotometer dedicated to the assessment of skin pigmentation and erythema has also been developed (DermaSpectrometer® from Cortex Technology, Mexameter MX18® from Courage & Khazaka) as well as non-invasive fluorescence devices [54] assessing yellow–brown deposits of advance glycation end products. However, these systems only allow the assessment of skin color locally.

With standardized photography, it is possible not only to illustrate but also to associate morphometry to color analyses (photography uses the tristimulus [red, blue, green] like colorimeters). Moreover, with photography, it is possible to reveal or increase the visibility of pigmentation and vascular disorders with filters (UV or cross-polarization of light) (Figure 7.4). Quantification can be possible only after ensuring that the colors assessed are as close as possible to reality and that shooting is reproducible. This implies the use of the same

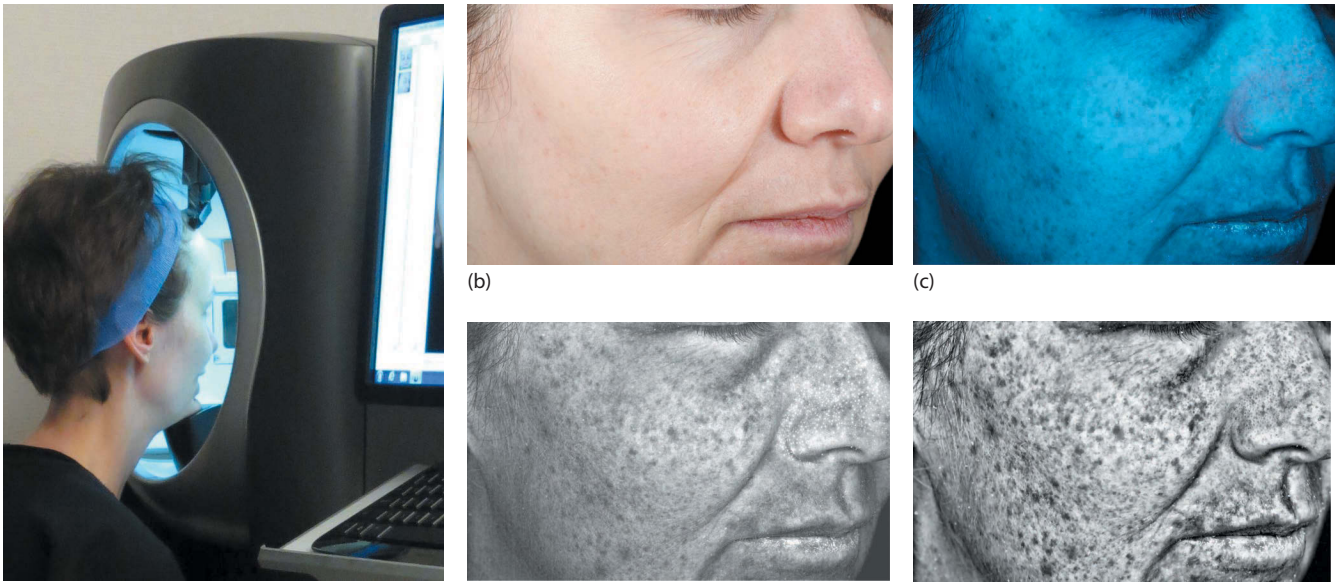


Figure 7.4 Example of photos taken with Visia (a) in normal light (b) and UV mode (c). From such images, numerical filters can be applied to distinguish information relating to the fluorescence of porphyrins (d) or relating to photoaging (e).

camera, in the same lighting conditions, with the same settings of exposure, focal length, and white balance. The subject must always be in the same position and must not wear makeup or visible jewels. Hairs must not be apparent and clothes are covered with a black garment. A color chart should be put in the scene to correct colorimetric deviation on the face of the volunteer if necessary. It is then possible to select the area(s) of interest; then, thanks to image processing, calculate the average color before displaying the L*a*b* coordinates. Many advances have been made in recent years; dedicated systems and software programs are now available to take and compare simply and accurately photographs at different times. Stereotactical tables (Visio-3D® from Eotech, Mona-photo RC05® from Monaderm, etc.) and light boxes have been developed to ensure that all these conditions are met (Chromasphere® from L'Oréal [17], Visioface from Courage & Khazaka, Visia® from Canfield, Visiosphere® from Eotech, etc.).

Changes in skin microcirculation can be assessed quantitatively as well as qualitatively through videocapillaroscopy [41].

CLINICAL SCORING

Clinical scoring remains the easiest, quickest, and cheapest way to assess aging skin. As for instrumentation, it must be performed under standardized conditions: air-conditioned room, homogeneous and stable lighting (Evalux® Bench from Orion TechnoLab, Figure 7.5), same clinician at each assessment, skin without makeup, patient has rested for 15 minutes before scoring, etc.

Assessments can be carried out globally (appearance, grade of maturity of the skin [60], wrinkles intensity) and/or gradually by focusing with increased accuracy on the patient and his or her skin (intensity of wrinkles of the forehead, crow's feet, etc.). They can be performed either by the patient himself/herself or by an expert, directly in the presence of the patient or at a later time from photographs. The advantage of the patients' self-assessments is that they take into account subjective feelings such as discomfort, itching, and stinging, but the assessments performed by a trained clinician are more sensitive and objective.

Visual scoring (visibility of spots, wrinkles, eyebags, ptosis, etc.) is usually associated with tactile assessments (skin roughness, softness, laxness, elasticity, etc.). It can be performed using descriptive grading systems (nominal scoring), visual analogue scales, and/or photographic systems [21,26,35]. Nominal scoring uses words or sentences characterizing the clinical status (for example, none, mild, moderate, and severe aging) [21,26,35]. These grades can also be replaced by numbers (0, 1, 2, 3) and become an ordinal scale. On an ordinal scale, the number of grades should be related to the maximum sensitivity of the investigator. If the number of grades is high, it approaches a continuous scale and thus could justify instead the use of an analogue scale. These systems are usually well correlated, although in women over the age of 60, analogue scales seem to underestimate them, whereas ordinal scales tend to overestimate them.

In recent years, many articles have been published, which suggest useful advice to perform objective assessments and which help to reduce the subjectivity of the psychosensorial assessment and facilitate interstudy and intercenter comparison. They include photographical scales [4–6,20], color charts [17,36,50], or composite clinical scores, allowing for global evaluation of the age of the skin [11,29,51,67]. Moreover, photographical scales are now available for Caucasian, Asian, Afro-American [4–6], and Indian skin [8].

Figure 7.5 Example of environmental conditions used in clinical scoring. Bench ensuring homogeneous lightening of the skin for clinical scoring as well as self-assessment. These assessments must be performed in standardized conditions: natural light must be avoided, as well as any object that could interfere with the evaluation such as hairs, jewels, clothes, and makeup. In addition, the subject must always be placed in the same position and examined from the same angle.

There have been a wide increase in the number of aesthetic treatments administered in the last decade. A set of validated, quantitative scales has been specifically developed in association with experts from different specialties within aesthetic medicine to evaluate the key signs of aging targeted by cosmetic procedures [11].

CONCLUSION

Aging is a global phenomenon with an impact on most characteristics of the skin, either physiological, mechanical, or visual. These numerous changes account for the wide range of available instrumental techniques, from genomic analysis to visual scoring and including 3D analysis of skin relief.

The use of these tools requires a disciplined approach. They improve our knowledge about the cellular and molecular mechanisms of aging skin as well as their clinical impact.

Moreover, these techniques are useful for the modeling of aging as well as for the development and testing of new treatments. Many researchers have therefore tried to achieve modeling by combining clinical scores with biometrological assessments to obtain a parameter characterizing skin age [18,29,48] or perceived age [13,27,67]. Thanks to the combination of technological approaches (gene therapy, stem cell transplantation, tissue engineering, and reprogramming of cell and tissue types), recent developments have been made in regenerative medicine [19].

REFERENCES

1. Adhoute H, Berbis E, Privat Y. Ballistometric properties of aged skin. In: Lévêque JL, Agache P, eds. *Ageing Skin: Properties and Functional Changes*. New York: Marcel Dekker, 1993, pp. 39–48.
2. Agache P, Varchon D. Mechanical behavior assessment. In: Agache P, Humbert P, eds. Measuring the skin. Berlin, Germany: Springer-Verlag, 2004, pp. 33–39.
3. Alanen E, Nuutinen J, Nicklen K, Lahtinen T, Mönkkönen J. Measurement of hydration in the *stratum corneum* with the MoistureMeter and comparison with the corneometer. *Skin Res Technol* 2004; 10:32–37.
4. Bazin R, Doublet E. *Atlas du vieillissement cutané: Volume 1, Population européenne*. Paris, France: Ed Med Com, 2007.
5. Bazin R, Flament F. *Atlas du vieillissement cutané: volume 2, Asian type.* Paris, France: Ed Med Com, 2010.
6. Bazin R, Flament F, Giron F. *Atlas du vieillissement cutané: volume 3, population Afro-Américaine*. Paris, France: Ed Med Com, 2012.
7. Bazin R, Leveque JL. Longitudinal study of skin ageing: From microrelief to wrinkles. *Skin Res Technol* 2011; 17:135–140.
8. Bernois A, Huber A, Derome C, Drouault Y et al. A photographic scale for the evaluation of facial skin ageing in Indian women. *Eur J Dermatol* 2011; 21:700–704.
9. Black D, Boer J, Lagarde JM. Image analysis of skin scaling using D-Squame((T)) samplers: Comparison with clinical scoring and use for assessing moisturizer efficacy. *Int J Cosmet Sci* 2006; 28:35–44.
10. Callaghan TM, Wilhelm KP. A review of ageing and an examination of clinical methods in the assessment of ageing skin. Part I: Cellular and molecular perspectives of skin ageing. *Int J Cosmet Sci* 2008; 30:313–322.
11. Carruthers A, Carruthers J. A validated facial grading scale: The future of facial ageing measurement tools? *J Cosmet Laser Ther* 2010; 12:235–241.
12. Choi JW, Kwon SH, Huh CH et al. The influences of skin viscoelasticity, hydration level and ageing on the formation of wrinkles: A comprehensive and objective approach. *Skin Res Technol* 2013; 19:e349–e355.
13. Christensen K, Thinhhaard M, MacGue M et al. Perceived age as clinically useful biomarker of ageing: Cohort study. *Br Med J* 2009; 339:b5262.
14. Clary P, Barel O. New European Legislation concerning efficacy claims of cosmetic products. An overview of different methods of evaluation. In: *Handbook of Cosmetic Science and Technology*. Fourth Edition. Barel O, Paye M, Maibach HI (Eds.), New York: Edition Informa Healthcare, 2014, pp. 637–645.
15. Costin G, Hearing V. Human skin pigmentation: Melanocytes modulate skin color in response to stress. *FASEB J* 2007; 21:976–994.
16. Couturaud V, Coutable J, Khaiat A. Skin biomechanical properties: In vivo evaluation of influence of age and body site by a non-invasive method. *Skin Res Technol* 1995; 1:68–73.
17. De Rigal J, Abella ML, Giron F et al. Development and validation of a new skin color chart. *Skin Res Technol* 2007; 13:101–109.
18. Dicanio D, Sparacio R, Declercq L, Corstjens H. Calculation of apparent age by linear combination of facial skin parameters: A predictive tool to evaluate the efficacy of cosmetic treatments and to assess the predisposition to accelerated ageing. *Biogerontology* 2009; 10:757–772.
19. Dieckmann C, Renner R, Milkova L, Simon JC. Regenerative medicine in dermatology: Biomaterials, tissue engineering, stem cells, gene transfer and beyond. *Exp Dermatol* 2010; 19:697–706.
20. Ezure T, Hosoi J, Amano S, Tsuchiya T. Sagging of the cheek is related to skin elasticity, fat mass and mimetic muscle function. *Skin Res Technol* 2009; 15:299–305.
21. Faivre B, Agache P. Aged skin: Clinical signs and methodologic aspects. In: Leveque JL, Agache P, eds. *Ageing Skin Properties and Functional Changes*. Chap. 1. New York: M. Dekker, 1992, pp. 1–14.
22. Ferreira MR, Costa PC, Bahia FM. Efficacy of anti-wrinkle products in skin surface appearance: A comparative study using non-invasive methods. *Skin Res Technol* 2010; 16:444–449.
23. Fisher G, Varani J, Voorhees J. Looking older: Fibroblast collapse and therapeutic implications. *Arch Dermatol* 2008; 144:666–672.
24. Fullerton A, Fischer T, Lahti A et al. Guidelines for measurement of skin colour and erythema. *Contact Dermatitis* 1996; 35:1–10.
25. Gilchrest B. In vitro assessment of keratinocyte aging. *J Invest Dermatol* 1983; 81:184s–189s.
26. Glogau RG. Aesthetic and anatomic analysis of the ageing skin. *Sem Cutan Med Surg* 1996; 15:134–138.
27. Goodman GJ, Halstead MB, Rogers JD et al. A software program designed to educate patients on age-related skin changes of facial and exposed extrafacial regions: The results of a validation study. *Clin Cosmet Invest Dermatol* 2012; 5:23–31.
28. Grove GL, Kligman AM. Age-associated changed in human epidermal cell renewal. *J Gerontol* 1983; 38:137–142.
29. Guinot C, Malvy DJM, Ambroisine L et al. Relative contribution of intrinsic vs extrinsic factors to skin ageing as determined by a validated skin age score. *Arch Dermatol* 2002; 138:1454–1460.
30. Hayashi S, Mimura K and Nishijima Y. Changes in surface configuration of the skin caused by ageing and application of cosmetics; three-dimensional analysis according to a new system based on image analysis and Fourier transformation. *Int J Cosmet Sci* 1989; 11:67–85.
31. Humbert P, Viennet C, Legagneux K et al. In the shadow of the wrinkle: theories. *J Cosmet Dermatol* 2011; 11:72–78.
32. Humbert P, Viennet C, Legagneux K et al. In the shadow of the wrinkle: Experimental models. *J Cosmet Dermatol* 2011; 11:79–83.
33. Jeanmaire C, Danoux L, Pauly G. Glycation during human dermal intrinsic and actinic ageing: An in vivo and in vitro model study. *Br J Dermatol* 2001; 145:10–18.
34. Jemec GB, Selvaag E, AgrenM, Wulf HC. Measurement of the mechanical properties of skin with ballistometer and suction cup. *Skin Res Technol* 2001; 7:122–126.
35. Kappes UP. Skin ageing and wrinkles: Clinical and photographic scoring. *J Cosmet Dermatol* 2004; 3:23–25.
36. Konishi N, Kawada A, Morimoto Y et al. New approach to the evaluation of skin color of pigmentary lesions using skin tone color scale. *J Dermatol* 2007; 34:441–446.
37. Krueger N, Luebberding S, Oltmer M et al. Age-related changes in skin mechanical properties: A quantitative evaluation of 120 female subjects. *Skin Res Technol* 2013; 17:141–148.
38. Lagarde JM, Rouvrais C, Black D. Topography and anisotropy of the skin surface with ageing. *Skin Res Technol* 2005; 11:110–119.
39. Lebonvallet N, Jeanmaire C, Danoux L et al. The evolution and use of skin explants: Potential and limitations for dermatological research. *Eur J Dermatol* 2010; 20:671–684.
40. Le Clerc S, Taing L, Ezzedine K et al. A genome-wide association study in caucasian women points out a putative role of the STXBP5L gene in facial photoageing. *J Invest Dermatol* 2013; 133:929–935.
41. Li L, Mac-Mary S, Sainthillier JM et al. Age related-changes of the cutaneous microcirculation in vivo. *Gerontology* 2006; 52:142–153.

42. Longo C, Casari A, Beretti F et al. Skin ageing: In vivo microscopic assessment of epidermal and dermal changes by means of confocal microscopy. *J Am Acad Dermatol* 2013; 68:e73–e82.
43. Mac-Mary S, Viennet C. Vieillissement cutané (visible) et dommages cellulaires (invisibles). *Dermatologie Pratique* 2012; 361:2–3.
44. Mac-Mary S, Sainthillier JM, Jeudy A, Sladen C, Williams C, Bell M, Humbert P. Assessment of the UVA cumulative exposure through the study of asymmetrical facial damage. *Clin Interv Aging* 2010; 5:277–284.
45. Makrantonaki E, Brink TC, Zampeli V, Elewa RM. Identification of biomarkers of human skin ageing in both genders. Wnt signaling, a label of skin ageing ? *PLOS ONE* 2012; 7:e50393.
46. Matts PJ, Fink B, Grammer K et al. Color homogeneity and visual perception of age, health, and attractiveness of female facial skin. *J Am Acad Dermatol* 2007; 57:977–984.
47. Miyamae Y, Yamakawa Y, Kawabata M, Ozaki Y. A combined near-infrared diffuse reflectance spectroscopy and principal component analysis method of assessment for the degree of photoageing and physiological ageing of human skin. *Anal Sci* 2012; 28:1159–1164.
48. Miyamoto K, Inoue Y, Hsueh K et al. Characterization of comprehensive appearances of skin ageing: An 11-year longitudinal study on facial skin ageing in Japanese females at Akita. *J Dermatol Sci* 2011; 64:229–236.
49. Montastier C, Mac-Mary S, Lati E et al. In vitro and in vivo study of the angi-aging properties of a botanical complex. Anti-aging Medicine World Congress, Monaco, France, March 29–31, 2012.
50. Musnier C, Piquemal P, Beau P, Pittet JC. Visual validation in vivo of "complexion radiance" using the CLBT sensoring methodology. *Skin Res Technol* 2004; 10:50–56.
51. Nkengne A, Roure R, Rossi AB, Bertin C. The skin ageing index: A new approach for documenting anti-ageing products or procedures. *Skin Res Technol* 2013; 0:1–8.
52. Nkengne A, Bertin C. Aging and facial changes—Documenting clinical signs, part 1: Clinical changes of the aging face. *Skinmed* 2012; 10:284–289.
53. Ohshima H, Kinoshita S, Oyobikawa M et al. Use of cutometer area parameters in evaluating age-related changes in the skin elasticity of the cheek. *Skin Res Technol* 2013; 19:e238–e242.
54. Ohshima H, Oyobikawa M, Tada A et al. Melanin and facial skin fluorescence as markers of yellowish discoloration with ageing. *Skin Res Technol* 2009; 15:496–502.
55. Osborne R, Hakozaki T, Laughlin T, Finlay DR. Application of genomics to breakthroughs in the cosmetic treatment of skin ageing and discoloration. *Br J Dermatol* 2012; 166 Suppl s2:16–19.
56. Piérard GE, Piérard-Franchimont C. Dihydroxyacetone test as a substitute for the dansyl chloride test. *Dermatology* 1993; 186:133–137.
57. Pierard-Franchimont C, Martalo O, Richard A et al. Sebum rheology evaluated by two methods in vivo. Split-face study of the effect of a cosmetic formulation. *Eur J Dermatol* 1999; 9:455.
58. Puccetti G, Nguyen T, Strover C. Skin colorimetric parameters involved in skin age perception. *Skin Res Technol* 2011; 17:127–134.
59. Rollin G, Placet V, Jacquet E et al. Development and characterization of a human dermal equivalent with physiological mechanical properties. *Skin Res Technol* 2012; 18:215–218.
60. Sainthillier JM, Mac-Mary S, Monnier D et al. Exploratory study of the typology of various grades of mature skin. *Skin Res Technol* 2013; 19:e507–e514.
61. Sainthillier JM, Gabard B. Mesure de la couleur de la peau. EMC (Elsevier Masson SAS, Paris), Cosmétologie et Dermatologie esthétique. 50-140-F-10, 2010.
62. Sainthillier JM, Mac-Mary S, Humbert P. Analyse du relief cutané. EMC (Elsevier Masson SAS, Paris), Cosmétologie et Dermatologie esthétique, 50-140-E-10, 2011.
63. Samson N, Fink B, Matts P. Interaction of skin color distribution and skin surface topography cues in the perception of female facial age and health. *J Cosmet Dermatol* 2011; 10:78–84.
64. Takeda M, Ina H, Kobayashi S. Fourier-transform method of fringe-pattern analysis for computer-based topography and interferometry. *J Opt Soc Am* 1982; 72(1):156–160.
65. Tfayli A, Guillard E, Manfait M, Baillet-Guffroy A. Raman spectroscopy: Feasibility of in vivo survey of stratum corneum lipids, effect of natural ageing. *Eur J Dermatol* 2012; 22:36–41.
66. Waller JM, Maibach HI. A quantitative approach to age and skin structure and function: Protein, glycosaminoglycan, water, and lipid content and structure. In Barel AO, Paye M, Maibach HI, eds. *Handbook of Cosmetic Science and Technology*, 3rd ed. New York: Edition Informa Healthcare, 2009, pp. 243–260.
67. Williams LM, Alderman JE, Cussell G et al. Patient's self-evaluation of two education programs for age-related skin changes in the face: A prospective, randomized, controlled study. *Clin Cosmet Invest Dermatol* 2011; 4:149–159.
68. Yan W, Zhang LL, Yan L et al. Transcriptome analysis of skin photoageing in Chinese females reveals the involvement of skin homeostasis and metabolic changes. *PLOS ONE* 2013; 8:e61946.
69. Yan W, Zhao ZM, Zhang LL et al. Identification of estrogen-associated intrinsic ageing genes in Chinese Han female skin by cDNA microarray technology. *Biomed Environ Sci* 2011; 24:364–373.
70. Zedayko T, Azriel M, Kollias N. Caucasian facial L* shifts may communicate anti-ageing efficacy. *Int J Cosmet Sci* 2011; 33:450–454.
71. Zouboulis CC, Boschnakow A. Chronological ageing and photoageing of the human sebaceous gland. *Clin Exp Dermatol* 2001; 26:600–607.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

The aesthetic consultation

Christopher M.E. Rowland Payne and Uliana Gout

BEFORE THE CONSULTATION

Referrals

The patient would have found the doctor either by referral from another doctor or from another patient or by word of mouth or through the media, including magazines, newspapers, and the Internet. Most referrals depend upon the reputation of the doctor.

Reputation

Ultimately, the reputation of a doctor depends upon the advice and treatment that patients get from that doctor.

Patient's First Contact with Your Practice

The patient will usually telephone or send an email requesting an appointment. They may have a shortlist of potential doctors to contact. It is clear that the doctor who has a swift, efficient, and approachable appointments' secretary is immediately at an advantage compared with one who uses an answering machine. The voice of your appointments' secretary is likely to be the patient's first direct contact with your practice and much depends upon that initial impression.

Booking the Appointment

It is helpful to the patient if the appointments secretary can explain some important information at the time when the appointment is booked. This helps prepare the patient so that the consultation will set off on the right foot and flow freely. Thus, this telephone conversation might include an indication of the likely duration and extent of the consultation. If it is your usual practice to offer total skin examination (TSE) at the initial consultation, it is helpful that this is explained during this telephone conversation. Patients should be asked to bring all existing medicines to the consultation, including prescribed topical applications, preferably in a transparent plastic bag to avoid stickiness on your desk. It is best that the patient is also told at this point about the likely cost of the appointment. A note should be made of more than one means of communication, e.g., two or three telephone numbers and/or an email address. If during this conversation the prospective patient distinguishes themselves in any way, in the estimation of the appointments' secretary, this may be of great importance and should be relayed to the doctor. People who are unreasonable or rude to the secretary may include some who are depressed and who may therefore particularly benefit from the doctor's assistance, others with personality disorders who may be difficult to please, and some who are simply ill mannered.

Confirmation of the Appointment

Immediately following the booking of the appointment, it is helpful to send the patient written confirmation and also an information sheet. If the appointment is booked more than a few days hence, a confirmatory telephone call a day or two before the consultation will help prevent the wasted time and frustration of a no show.

Managing the Day

If there are any delays, even though it may be too late for patients to modify their plans, it is polite and desirable to telephone to warn them.

Arriving at the Clinic

First impressions matter. The patient will be reassured by a professional address, a front door with gravitas and a clean and welcoming entrance hall and waiting room. The initial greeting should be polite and respectful and warm and welcoming. The patient should be made comfortable and given a simple registration form to complete in their own handwriting. If there are any delays, apologies should be tendered. If the delay will last more than 10 minutes, fulsome apologies should be made; coffee or tea might be offered and the patient informed every 10–15 minutes of progress. Patients who are public figures may require meeting at the door of the clinic. Celebrities may prefer to enter by a more discreet side entrance. A supplementary waiting area may be helpful.

Preparing to Meet the Patient

The doctor should review what the patient has written on the registration form. By observing the patient's handwriting, one of us (CMERP) diagnoses two cases of Parkinsonism each year before even meeting these patients. If the patient has seen the doctor beforehand, the old notes should be reviewed. They may well contain pertinent information. If many years have elapsed since the last visit, the patient will be favorably impressed if the old notes are in the doctor's hands. It is worthwhile also having available the notes of other close family members (though usually these are best not seen by the patient).

Meeting the Patient

It is courteous if the doctor goes to the waiting room to meet the patient. This practice has many advantages over the method of the patient being brought to the doctor. After years

of experience of life and medical practice, much is immediately apparent *à coup d'oeuil*. Is the patient well or unwell, happy or discontented, fashionably attired and made up with attention to detail or unkempt? Eye contact and verbal exchange, essential steps in the consultation, begin at this moment. Shaking hands while saying one's own name helps break the ice. The handshake may detect Dupuytren's contracture. Having read the name of the referring doctor from the registration form completed by the patient, an opening gambit might be: "Dr. So & So has asked me to see you." If there are shopping bags, the doctor may carry them. The doctor can open the consulting room door for the patient. The patient's gait may be observed. The doctor may take the patient's coat and draw back one chair for the patient to sit on and another on which the patient may rest coat and bags.

HISTORY

Initiating the History

"How can I help?" will usually begin the story. Often a patient will begin by saying "Do you do xxxx treatment?" The best response is: "What would you like to achieve?" Patients often present with preconceived notions of treatments they would like. Such ideas are often based upon articles they have read in the media that have been driven by the advertising or public relations budgets of companies selling expensive machines, medicines, or new treatments. Alternatively, a mirror may be proffered and the doctor might say: "What do you regard as your weak point?"

History of the Presenting Complaint

The patient should be encouraged to explain what they wish to discuss, treat, alter, improve, or achieve. Much depends on taking the time to listen and understand exactly what the patient requests. Many patients find it difficult to give a clear history. Typically, they will wish to tell you of the treatments they were given by previous doctors. This information should be recorded but is likely to be of relatively little interest, since the patient would probably not be seeing you if the last treatment had met with their satisfaction.

When this vein of conversation falters, you may wish to ask a question or two related to your own area of expertise.

In the case of a dermatological patient, the patient will need to be guided through the usual questions of the medical history of any presenting complaint: "Where on your body did it begin?" Press the point and ask for more precision: "Left or right, ankle or shin?" "Where did it go next?" "And then where?" Repeat the order back to the patient and offer them the chance to put the anatomical sites in a different order as you help them recount the history of their malady. "What was the first symptom?" "Was it an itch or a rash or pain?" "When was that?" "What came next… itch after rash or rash after itch?" Such detail is always informative. "What were you doing when and just before it started?" "Where were you?" "What makes the problem worse?" This volley of questions often opens the door to pertinent information. "Is it worse in bed or in the day?" "After bathing or in the evening?" "Is it worse in summer or winter?" The questions need to be asked gently and in an unrushed fashion.

As a dermatologist, it is also helpful to ask: "Are there any other spots, rashes, or moles you would like to ask about?" "Any problems with hair, nails, private parts, or mouth?"

Continuing the History

Further prompts may be useful, "Are there any other things I can help you with?" For women, "Any other cosmetic questions?" And for men, "Any questions about appearance?" Far more often than not, these direct questions will elicit further matters about which the patient would also like to ask advice.

The history is best continued according to the medical model, with questions next about past medical, surgical, and gynecological history and the history of any cosmetic interventions, including botulinum or fillers. Then the family history, current treatment, and history of allergies are recorded.

Systemic Review

Direct questions into the patient's general health provide specific information as well as a general idea of the patient's health, happiness, and disposition. Additional questions may concern the history of sun exposure and alcohol, smoking, and dietary habits. Particularly helpful questions concern headaches/migraine, change in bowel habit or weight, duration of menstrual cycle, and susceptibility to blushing and sweating. The physician can later use this information to guide and advise the patient on which life factors may be modified, not only to avoid an impaired complexion but also to assist the patient to live a longer and more healthy life.

Sleep

The single most important direct question concerns sleep. If sleep is not perfect, further questions are indicated. Early morning waking, especially if combined with impairment of concentration, memory, or energy, suggests depression. If there is also increased irritability, with either tearfulness in women or decreased libido in men, depression is likely. Difficulty in getting to sleep may suggest anxiety. Tactful and diplomatic active listening often elicits a great deal of highly relevant information. Stressors may be manifold, but often there is a focus upon one or more of the usual: friends, family, firm,* finances, and future (Table 8.1).

EXAMINATION

All doctors practicing in the cosmetic field will wish to examine their patients. At the least, the examination must include examination of the presenting complaint and probably also examination of the face and any other parts of the body mentioned

Table 8.1 Stressors

Boyfriend or spouse
Bairns[a]
Bereavement
Brass[b]
Boss
Business
Busyness[c]

Source: After O'Doherty, personal communication.
[a] A Scottish word for children.
[b] A Yorkshire word for money.
[c] Having too many things to deal with.

* Meaning job.

by the patient in the history. This is best accomplished using by a good light and a magnifying glass (e.g., Luxo mobile illuminated magnifier LFM-101(15), www.luxoonline.co.uk). Examination of suspect pigmented lesions is greatly facilitated by using a dermoscope (e.g., 3Gen DermLite Carbon, www.dermlite.com). All findings should be recorded by the doctor. Body map diagrams assist greatly.

The more thorough the examination,
The more the doctor will be able to help the patient.

The great majority of patients appreciate a thorough examination. All the better for the patient and the patient's confidence in you if your examination also reveals other important matters of a non-cosmetic nature that you can help.

Experience has taught me (CMERP) that the best approach is a systematic one that begins with TSE and proceeds to examination of the face and then to examination of the presenting complaint.

Total Skin Examination Has Many Benefits

TSE almost always reveals information of interest to the patient, often reveals clinically useful information and sometimes life-saving information. Each week, TSE allows one of us (CMERP, a dermatologist) to discover at least one or two skin malignancies of which the patient had been completely unaware. Several times a year, melanomas are diagnosed in this way. In a series of 102 consecutive melanomas, 30 were discovered on routine TSE; neither the patient nor the referring doctor had been aware of any of these 30 melanomas (Rowland Payne, 1995).

TSE also facilitates the identification of other disorders that the patient may well wish to have treated. The examination may reveal hands with solar lentigoes and tortuous ectatic veins, upper limbs with guttate hypomelanosis, a décolleté with helioderma and sleep rhytids, a trunk with seborrhoeic warts and Campbell de Morgan angiomas, lower limbs with reticulate telangiectasia, toes with onychodystrophy, heels with radial fissuring, and a scalp with one or more types of alopecia. All findings should be recorded on body map diagrams. It is indispensible that non-dermatologists active in cosmetic practice have some knowledge of these common disorders.

Usually, TSE takes less than 3 minutes.

Examination of the Face

The skin of the face, having borne the brunt of the patient's cumulative lifetime exposure to ultraviolet light, is often the most fruitful in terms of actinic lesions, whether brown spots or wrinkles, textural changes or new growths. The various fat compartments of the face are subject to obesity, gravity, and involution.

Examination of the Presenting Complaint

At this point, the focus of the examination may shift to the presenting complaint. If the request is for botulinum or filler, the patient is asked to sit upright. The lighting is adjusted so that it shines from above downward in the most unforgiving way, "elevator lighting." The patient should be observed at rest and in animation. Before treatment, it is helpful to demonstrate to the patient, in a hand mirror, any facial asymmetries. Often patients are entirely unaware of quite major facial asymmetries. Records should be made.

Clinical Photography

Clinical photography is a useful aspect in monitoring treatment success, as well as in providing supporting evidence should it ever be required. Many advocate that photographs should be taken before and after all treatments and stored in a clinical database, but this may not always be practical and some patients may decline. Many imaging systems are available commercially. The camera in a smart phone is excellent for most purposes. Every effort should be made to standardize images: same background, same lighting, similar environmental conditions, same patient positioning, and same ½ zoom setting for the camera (in order to minimize distortion).

DIAGNOSIS

While the patient dresses, time should be taken by the doctor to review the notes made during the history and examination. An attempt should be made to marshal all the findings and gather them together into one or more diagnoses. Whatever happens, at least one diagnosis should be made. The discipline of making a diagnosis helps to concentrate the mind of the doctor and so reduces the chance of sloppy thinking and inappropriate treatment.

The basis of good treatment is firm diagnosis.

Frequently, multiple diagnoses are made. For example, a patient who attends asking for botulinum may have (1) animation rhytids, (2) eyebrow ptosis, (3) solar lentigoes, (4) sebaceous hyperplasia, (5) rosaceous telangiectasia, (6) the atypical nevus syndrome, and (7) venous insufficiency of lower limbs.

Thorough Consultation Has Many Benefits

In a prospective study of 200 consecutive patients, who saw one of us (CMERP), *apart from their presenting problem* (and apart from any known current or previous illnesses), in the course of the study period and any prior visits, a large range of other disorders, which they did not know they had, were also diagnosed. In these 200 patients, these *additional diagnoses* included 41 patients with at least 117 skin malignancies (including 6 patients with melanomas and 1 with cutaneous T-cell lymphoma), as well as 1 patient with prostate cancer, 1 with an aggressive desmoid tumor, 3 patients with myelodysplasia (preleukemia), 13 with autoimmune disease (including one with systemic lupus erythematosus and 2 with systemic sclerosis), and 39 with psychological disorders (most often anxiety disorder or depression).

DISCUSSION

Each diagnosis is explained to the patient. The discussion should be tailor-made to suit each particular patient.

Proposing Treatment

One or more diagnoses may require treatment for medical reasons, e.g., a suspicious pigmented lesion. Other diagnoses may be more or less cosmetic and, if the patient shows interest, the possible treatment options and their likely outcomes are outlined. The best potential treatment options should be discussed, regardless of whether or not they are available from you or your immediate associates. It goes without saying that the doctor should only propose to perform treatments that the

doctor considers will benefit the patient and that the doctor should only propose to carry out treatments, which lie within the compass of the doctor's competence. The doctor should be cognizant of and prepared to cope with the known potential unwanted effects of any proposed treatment. Patient advice sheets may be helpful.

Patient Selection

Patient selection for any particular treatment is of critical importance in cosmetic patients. Good results depend not only upon correct diagnosis, appropriate choice of treatment, and its skillful execution but also upon correct patient selection.

Patient selection is a two-way process. Much depends on taking the time to listen and understand exactly what the patient requests. On occasions, it is better for patient and doctor if the doctor does not intervene. Some patients are unsuitable for various treatments, perhaps by reason of concurrent medical or psychological illness or simply because of unrealistic expectations or because the treatment desired by the patient may be aesthetically unsuitable. Sometimes, patients need to be dissuaded from pushing a treatment beyond the limits of beauty and into the realms of ugliness. It is usually best that any concurrent psychological disorder is treated before any interventional cosmetic treatment is given. Whenever possible, at the initial consultation, it is best to recognize people who are unreasonable and to avoid performing any interventional treatment on them.

Patient Expectations

Managing patient demands and expectations are delicate aspects of the consultation. For an optimum outcome, the patient's expectations of benefit must not be more optimistic than those of the doctor. The risk/benefit ratio of each proposed treatment should be discussed, the likely downtime explained and any likely relevant adverse effects mentioned. It is best not to be overoptimistic about likely benefits and not to downplay any likely downtime. Realistic patient expectations are essential.

> *Satisfaction equals perceptions minus expectations.*
>
> **—Maister, 1993**

The more that can be explained to a patient preoperatively about what they can expect, the less that needs to be explained postoperatively.

> *Preoperative explanation is "knowledge."*
> *Postoperative explanation is "excuses."*

Letter

At this point, in some countries, it is customary to dictate a medical report or letter about the patient to the patient's referring doctor. It is best to dictate this in front of the patient and to send a copy of the letter to the patient. It assists communication and acts as a reminder of the consultation and treatment plan. It is also a legal record.

Fees

At the end of the consultation, the doctor may wish to explain to the patient the cost of any possible treatments.

To Treat or Not to Treat?

Ultimately, the decision as to whether or not the patient decides to proceed with the treatment advocated by the doctor rests, of course, with the patient. The doctor is ultimately only the patient's advisor.

TREATMENT

Treatment the Same Day

Should the patient wish to pursue one or more of the treatments mentioned, it is often helpful to the patient to offer to begin some of the simpler treatments at the initial visit. This saves time for the patient. It often also reassures the patient that the treatment is mild in terms of discomfort and possible downtime. Sometimes there may be medical reasons to begin interventional treatment without delay; e.g., it may be advisable to excise a suspicious pigmented lesion at the initial consultation.

Treatment Later

More invasive treatments (especially larger elective procedures) are usually often better scheduled for a later date, in order to allow the patient time to reflect on the matter and to plan a date that will make any downtime least inconvenient. This delay also allows the patient the opportunity, without embarrassment, to cancel or postpone the planned treatment.

Consent

Informed consent is crucial prior to any interventional treatment. There are two types of consent, verbal and written. Written consent is preferable prior to interventional treatment. It records an agreement between the patient and the treating physician.

DOCTOR–PATIENT RELATIONSHIP

The initial consultation is the anvil upon which the doctor–patient relationship is forged. It provides an unrivalled opportunity for communication between patient and doctor. Verbal exchange and eye contact are essential steps in this process. Every minute of the initial consultation is precious.

> *A minute spent at the initial consultation*
> *is worth two later.*

In an ideal doctor–patient relationship, the patient will have trust and confidence in the doctor and there will be a mutual understanding. The formalized setting of the consultation is the ideal opportunity for the patient to develop trust and confidence in the doctor and for mutual understanding to develop.

Trust and Confidence

Most patients arrive at the initial consultation in a spirit of *trust*, trusting the doctor because of the doctor's own reputation or the reputation of doctors in general. The initial consultation provides the patient the opportunity to further develop their trust in the doctor's knowledge, experience, technical competence, professionalism, integrity, and good judgment. It is trust that allows the patient to allow the doctor the privilege of having access to the patient's private thoughts and feelings, of physically examining the patient and of treating

the patient. Thorough and professional attention to all of these steps increases patient *confidence*.

Mutual Understanding

The consultation allows both doctor and patient the opportunity to develop a professional relationship with one another and so develop the *mutual understanding* that will allow doctor and patient to work together most efficiently and most fruitfully.

The Magic of Medicine and the Placebo Response

It is trust and confidence that is the bedrock of the doctor–patient relationship and upon this bedrock is built the magic of medicine that is the placebo response. An important element of any therapeutic response is attributable to the placebo response. If the doctor does not or cannot foster the placebo response, the patient is the poorer.

Patients who have confidence in their doctor and who are positive in their approach to treatment will find the experience of treatment sessions easier and often less uncomfortable than patients who are more doubtful or diffident. The patient who has confidence in the doctor is more likely to tolerate well any minor inconveniences of treatment, such as small bruising.

Professionalism

Professionalism lies at the heart of medical practice and comprises many aspects, including putting the patient first, integrity, and confidentiality.

Pressures on Professionalism

The physician must be wary of pressures from media, industry, and patients to perform the latest *à la mode* techniques. The physician must eschew financial pressures, for example to amortize expensive equipment such as lasers. Good judgment must be exercised. Physicians must always be guided by their patients' best interests.

Medical Model

The medical model of a thorough and systematic consultation that considers the whole patient has many benefits. It allows sufficient time to establish the doctor–patient relationship. It facilitates the incidental finding of concurrent medically important illness. It allows time for the doctor to help the patient further, either by treating any other illnesses identified during the consultation or, when indicated, by referring the patient back to the referring doctor or to another specialist. All of these factors serve to foster trust, confidence, and mutual understanding.

Client or Patient?

All of the aforementioned draws upon the *medical model* of doctor and patient. On the other hand, some would argue that the aesthetic industry is merely a retailer of treatments and that it is for the industry to lay out its offering and for *clients* to take their pick. In this *retail model*, the client is a person who is healthy and simply looking for an enhancing treatment and, as such, would prefer to be considered a "client" or a "customer" rather than a "patient" with its connotations of illness. At its extreme lies the "botox party." Such an approach will lack the many benefits described earlier that may flow from a doctor–patient relationship. Most critically important, the retail model does not facilitate consideration of pertinent psychological aspects.

PSYCHOLOGICAL CONSIDERATIONS

Psychological aspects are integral to every step of the aesthetic consultation. Beauty and appearance are inextricably linked with psychological well-being and inner feelings.

The doctor involved in aesthetic medicine needs to be familiar with the psychological factors that drive people to request treatment. The initial consultation should aim to elucidate any psychological concerns and manage properly such patients from the outset. No consultation is complete without considering this aspect, which, in some cases, is the most important aspect of the aesthetic consultation. These patients require a holistic approach to treatment, which may include the prescription of psychotropic drugs and/or talking therapies or referral to a psychiatrist or psychologist.

Look behind the Patient's Expression

It is important to look behind the patient's expression and remember that 49% of cosmetic surgery patients have a body image disorder and 19% a personality disorder (Dakanalis et al., 2013). Of cosmetic rhinoplasty patients, 41% had an associated psychiatric disorder and 25% had body dysmorphic disorder (BDD) (Alavi et al., 2011). Of persons seeking appearance-enhancing treatment, such as cosmetic surgery and dermatological/minimally invasive treatments, 5%–15% have BDD (Crerand et al., 2006; Sarwer and Spitzer, 2012).

Of general dermatology patients, 25% exhibit psychiatric morbidity (Picardi et al., 2000). Of dermatology patients, 20%–25% have obsessive-compulsive behavior/disorder, of which four out of five are previously undiagnosed and untreated (Fineberg, 2003; Demet et al., 2005; Kestenbaum, 2013). Of general dermatology patients, 10% have major depression (Cohen et al., 2006).

Psychological Symptoms and Signs

Certain psychological symptoms and signs help identify patients in whom psychological factors may be important.

Psychological Syndromes

A syndrome is a recognizably characteristic cluster of symptoms and/or signs. Just as a symptom or sign is not, in itself, a diagnosis, neither is a syndrome. Each is a clue, a piece of the clinical jigsaw that, when assembled, will indicate the underlying diagnosis. Treatment of symptoms, signs, and syndromes has its place, but a successful outcome is more likely to follow treatment of the underlying diagnosis.

Certain psychological syndromes may be apparent, such as BDD, obsessive-compulsive behavior, and destructive behavior (including anorexia nervosa, bulimia, acne excoriée, dermatitis artefacta [DA], and self-harm) and conversion syndrome. These are not diagnoses in themselves. They are best regarded as syndromes. In any particular patient, an attempt should be made to elucidate the underlying diagnosis as this will affect the choice of optimum treatment (Table 8.2).

Table 8.2 Psychological Syndromes Occurring in Cosmetic Patients

Psychological syndromes	Possible underlying psychological diagnosis
BDD	Depression/anxiety/ personality disorder/OCD/ psychosis
Obsessive-compulsive behavior	Depression/anxiety/ personality disorder/OCD/ psychosis
Destructive behavior (including anorexia nervosa, bulimia, acne excoriée, DA, self-harm)	Depression/anxiety/ personality disorder/ psychosis

Body Dysmorphic Disorder (BDD)

Patients with BDD, also known as dysmorphophobia, dwell unnaturally upon their appearance. In a German nationwide survey, the prevalence of BDD in the general population was 1.8%; persons with BDD reported more cosmetic surgery (16% vs. 3%) and higher rates of suicidal ideation (31% vs. 3.5%) and of suicide attempts due to appearance concerns (22% vs. 2%) (Buhlmann et al., 2010). BDD is present in 5%–15% of patients seeking cosmetic surgery (Crerand et al., 2006, Sarwer and Spitzer, 2012), in 14% of general dermatology patients (Conrado et al., 2010), in 25% of persons seeking cosmetic botulinum (Misra, 2002), in 25% of cosmetic rhinoplasty patients (Alavi et al., 2011), and in 30%–40% of persons seeking laser therapy (Cotterill, 2002). Often, the treatment for these patients should not be botulinum, fillers, or face lifts. These patients require a diagnosis of the underlying psychological disorder, which may be a personality disorder (Phillips and McElroy, 2000), especially avoidant (Phillips and McElroy, 2000), schizotypal or paranoid personality disorders (Bellino et al., 2006), obsessive-compulsive disorder (OCD) (Coles et al., 2006), major depression (Coles et al., 2006), anxiety, social phobia (Coles et al., 2006), or psychosis and sometimes a combination of more than one of these (Table 8.3). BDD patients are generally unsatisfied with the results of aesthetic medical treatments (Sarwer and Spitzer, 2012) and dermatological treatments (Conrado et al., 2010). BDD patients have a risk of suicide (Phillips and Dufresne, 2000). BDD patients are litigious (Crerand et al., 2006). At least two surgeons have been murdered by patients who probably had BDD (Goin and Goin, 1981; Yazel, 1999).

Obsessive-Compulsive Behavior

This may be a manifestation of depression, anxiety, personality disorder, OCD, or psychosis. Obsessive-compulsive (anankastic) personality (OCP) and OCD have many similarities, for example, in attention to detail, perfectionism, and ritualistic behavior. They are differentiated by the way in which the subject views his or her own behavior patterns. In OCD, the *subject* feels these behaviors to be a burden or even a curse, "If only I could be free of this burden! If only I could be in step with everyone else!" In OCP, the *subject* feels these behaviors are admirable and worthy: "If only everyone else shared my high standards! If only everyone else could be in step with me!"

Table 8.3 Some Psychological Disorders Encountered in Cosmetic Patients

Type of disorder	Underlying diagnosis
Affective disorder	Depression Anxiety OCD
Personality disorder	Avoidant Narcissistic Dependant Sociopathic Paranoid Schizotypal OCP
Psychosis	Monosymptomatic hypochondriacal psychosis (MSHP)

Underlying Psychological Diagnoses

Whatever the psychological presentation, an attempt should be made at making an underlying psychological diagnosis as this will determine the choice of treatment.

The basis of good treatment is firm diagnosis.

In cosmetic patients, a number of underlying psychological diagnoses are common, in particular, depression and personality disorder. OCD is not uncommon. Less common but important to recognize is psychosis, notably MSHP (Table 8.3).

Depression

Depression not uncommonly presents with cosmetic requests. Sleep disturbance, especially early morning waking and some other symptoms and signs, may point to this diagnosis (Table 8.4).

Anxiety

Anxiety is suggested when patients describe themselves as "being a worrier" or by a history of difficulty in getting off to sleep or panic attacks or by symptoms, such as jaw clenching and nocturnal teeth grinding, or by signs, such as tremor, rapid blink rate, fidgeting, and nail biting.

Treatment of the Underlying Psychological Disorder

Some may be best first treated psychologically before any interventional cosmetic treatment is given. Some are best dissuaded from any interventional cosmetic treatment at all. If the patient lacks insight, this can sometimes put the doctor in an extremely difficult position with the good doctor declining the patient's

Table 8.4 Symptoms and Signs of Depression

Symptoms	Signs
Early morning waking Concentration ↓ Memory ↓ Energy ↓ Tearfulness/low libido	Flexed gait and posture Psychomotor retardation Melancholic/angry/anxious demeanor Dressed unremittingly in black Tinted spectacles (Howard and Valori, 1989)

expressed wish for a cosmetic intervention and instead urging the patient to start a psychological intervention, which the patient may reject.

Treatment of Depressed Patients

Depressed patients often benefit from cosmetic treatments, but if a patient is depressed, treatment of the depression may well be the first priority. Depressed patients have a lower tolerance of pain (Gormsen et al., 2004). Patient's satisfaction is harder to achieve in patients who are depressed. Of patients undergoing facial plastic surgery, patients currently being treated for depression had higher rates of satisfaction than other patients (Hessler et al., 2010). However, this is not a hard and fast rule. Indeed, botulinum treatment of the face improves major depression (Finzi and Rosenthal, 2014; Magid et al., 2014), even in patients whose depression did not respond sufficiently when prescribed antidepressant therapy (Wollmer et al., 2012). An improvement in appearance may result in an improvement in self-confidence or mood.

Look better, feel better.

If an angry-faced person enters a room full of people who are smiling or laughing, the smiles and laughter will be dampened. The reverse is equally true. Effacement of negative expressions can improve the way in which other people treat the patient.

Smile and the world smiles with you.

Who Should Treat the Psychological Patient Who Presents Cosmetically?

It may be desirable and necessary to liaise with the patient's family doctor or a psychiatrist or a clinical psychologist. Some patients may well benefit from psychological treatment, though many may be relatively unwilling to accept it. Most British patients will reject referral to a psychiatrist or clinical psychologist. If a patient perceives their problem to be cosmetic, the patient will usually not accept psychiatric referral. Therefore, if the doctor, who the patient has consulted cosmetically, does *not* treat this sort of patient psychologically, the patient is likely to go untreated. It could be argued therefore that it is incumbent upon every doctor practicing in the cosmetic field to be competent in treating such patients psychologically.

The doctor who practices interventional cosmetics should be well versed in the diagnostic and therapeutic aspects of psychological medicine.

SECOND OPINION PATIENTS

These fall into two groups that require different handling:

1. *The easy-to-please patient*. These may have been referred to you (or may have found you) because they seek your special expertise in some clinical domain: these are likely to be patients who will benefit from your services and appreciate your help.
2. *The less easy-to-please patient.* These patients always take extra time. They are unlikely to have achieved satisfaction with the treatment provided by the previous doctor. It is best to listen and note down all the points the patient wishes to recount. The consultation should proceed in your usual way. Towards the end of the examination, the patient should be given a mirror and asked to demonstrate the flaws in their appearance and these should be examined with care and, if present, acknowledged. It is helpful if you can point out any good aspects of the previous treatment. If the results were suboptimal or not as good as the patient had hoped, you may be able to improve on them. If the results were good but the patient is not pleased, it will have been a problem of either the patient's overexpectation or disordered perception. If the patient's perception is disordered, by BDD for example, the underlying psychological diagnosis should be identified and, if possible, treated.

DISCONTENTED PATIENTS

Difficult-to-Please Patients

These patients are best recognized early and require special handling. Your appointment staff should be encouraged to tell you if they find a caller unreasonable or rude. They may present stating that they have seen numerous practitioners and none of them could achieve a good result. This doctor shopping and negative name-dropping is a red flag warning sign as, all too often, such patients will repeat this behavior. Some such patients may be depressed, anxious, or psychotic and may well benefit from your care. Others may have a personality disorder or may simply be unreasonable or ill mannered. Most medicolegal complaints and litigation come from difficult-to-please patients. It may well be prudent to avoid interventional treatment in some such patients.

Patients who may be difficult to please may exhibit a range of red flag clinical features (Table 8.5).

Complaining or Litigious Patients

Sometimes patients complain. Sometimes complaints are justified, sometimes not. Patients may consult you because they are litigious toward another doctor. It may happen one day that a patient may be unhappy with you. If so, this requires immediate attention from you.

A complaint is a medical emergency.

—Cotterill, 2002

Contact the patient immediately. Try to see the complaint from the patient's point of view, especially if it is about your own treatment that the patient is complaining. Communication may have been inadequate. Listen carefully to all the patient says, examine the patient, and assess the problem. Explain potential treatments, and consider the benefits of time. Mistakes happen.

Table 8.5 Difficult-to-Please Patients May Exhibit Some of These Traits

Unreasonable/rude to appointments staff
Dissatisfied with previous doctors
Doctor shopper
Preoccupied with appearance
Mirror gazer
Unwilling to be examined
Secretive
Angry

Source: After Cotterill JA, *J Cosmet Dermatol*, 1, 211, 2002.

If appropriate, apologize early. Early effective communication will almost always neutralize patient's anger. Legible and appropriate clinical notes are important (Cotterill, 2002).

Some litigious patients have a well-placed grievance and seek acknowledgment, apology, and possibly redress. Others may be unreasonable or psychologically unwell, especially those with depression or BDD (Crerand et al., 2010).

Prevention of Patient Discontent

Patient selection is particularly important for cosmetic procedures. For best results, the patient should have an expectation and a disposition that are reasonable and the patient and the doctor should share a mutual understanding. Any procedures envisaged must of course be within the compass of the technical competence of the doctor.

Whenever possible, it is best to recognize the unreasonable patient at the initial consultation and to avoid performing any interventional treatment on them. Likewise, the psychologically unwell are best identified at the initial consultation. Any psychological illness is usually best treated before any cosmetic intervention is undertaken.

CONCLUSIONS

The consultation is an unrivalled opportunity for both the doctor and the patient. It is at the consultation that the diagnosis is made and the chosen treatment selected for a particular patient. It is at the initial consultation that the doctor–patient relationship is first forged.

REFERENCES

Alvavi M, Kalafi Y, Dehbozorgi GR, Javadpour A. Body dysmorphic disorder and other psychiatric morbidity in aesthetic rhinoplasty candidates. *J Reconstr Aesthet Surg* 2011; 64(6):738–741.

Bellino S, Zizza M, Paradiso E, Rivarossa A, Fulcheri M, Bogetto F. Dysmorphic concern symptoms and personality disorders: A clinical investigation in patients seeking cosmetic surgery. *Psychiat Res* 2006 September 30; 144(1):73–78.

Buhlmann U, Glaesmer H, Mewes R, Fama JM, Wilhelm S, Brahler E, Rief W. Updates on the prevalence of body dysmorphic disorder: A population-based survey. *Psychiat Res* 2010; 178(1):171–175.

Cohen AD, Ofek-Shlomai A, Vardy DA, Weiner Z, and Shvartzman P. Depression in dermatological patients identified by the Mini International Neuropsychiatric Interview questionnaire. *J Am Acad Dermatol* 2006 January; 54(1):94–99.

Coles ME, Phillips KA, Menard W, Pegano ME, Fay C, Weisberg RB, Stout RL. Body dysmorphic disorder and social phobia: Cross-sectional and prospective data. *Depress Anxiety* 2006; 23(1):26–33.

Conrado LA, Hounie AG, Diniz JB, Fossaluza V, Torres AR, Miguel EC, Rivitti EA. Body dysmorphic disorder among dermatologic patients: Prevalence and clinical features. *J Am Acad Dermatol* 2010 August; 63(3):235–243.

Cotterill JA. Damage limitation in cosmetic dermatology. *J Cosmet Dermatol* 2002; 1:211–213.

Crerand CE, Franklin ME, Sarwer DB. Body dysmorphic disorder and cosmetic surgery. *Plastic Reconstr Surg* 2006 December; 118(7):767e–780e.

Crerand CE, Menard W, Phillips KA. Surgical and minimally invasive cosmetic procedures among persons with body dysmorphic disorder. *Ann Plast Surg* 2010 July; 65(1):11–16.

Dakanalis A, Di Mattei VE, Zanetti AM, Clerici M, Madeddu F, Riva G, Lanfranchi L, Baruffaldi Preis F. Personality and body image disorders in cosmetic surgery settings: Prevalence, comorbidity and evaluation of their impact on post-operative patients' satisfaction. *Eur Psychiatry* 2013; 28 Suppl 1:1.

Demet MM, Deveci A, Taskin EO, Ermertcan AT, Yurtsever F, Deniz F, Bayraktar D, Ozunturkcan S. Obsessive-compulsive disorder in a dermatology outpatient clinic. *Gen Hosp Psychiat* 2005 November–December; 27(6):426–430.

Fineberg NA, O'Doherty C, Rajagopal S, Reddy K, Banks A, Gale TM. How common is obsessive-compulsive disorder in a dermatology outpatient clinic? *J Clin Psychiatry* 2003 February; 64(2):152–155.

Finzi E, Rosenthal NE. Treatment of depression with onabotulinumtoxinA: A randomized, double-blind, placebo controlled trial. *J Psychiatr Res* 2014; 52:1–6.

Goin MK, Goin JM. Midlife reactions to mastectomy and subsequent breast reconstruction. *Arch Gen Psychiatry* 1981 February; 38(2):225–227.

Gormsen L, Ribe AR, Raun P, Rosenberg R, Videbech P, Vestergaard P, Bach FW, Jensen TS. Pain thresholds during and after treatment of severe depression with electroconvulsive therapy. *Eur J Pain* 2004; 8(5):487–493.

Hessler JL, Moyer CA, Kim JC, Baker SR, Moyer JS. Predictors of satisfaction with facial plastic surgery: Results of a prospective study. *Arch Facial Plast Surg* 2010; 12(3):192–196.

Howard RJWM, Valori RM. Hospital patients who wear tinted spectacles—Physical sign of psychoneurosis: A controlled study. *J R Soc Med* 1989; 82:606–608.

Kestenbaum T. Obsessive-compulsive disorder in dermatology. *Sem Cutan Med Surg* 2013 June; 32(2):83–87.

Magid M, Reichenberg JS, Poth PE, Robertson HT, LaViolette AK, Kruger TH, Wollmer MA. Treatment of major depressive disorder using botulinum toxin a: A 24-week randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2014; 75(8):837–844.

Maister DH. Managing the professional service firm. New York: Free Press, 1993.

Misra VP. The changed image of botulinum toxin. *Br Med J* 2002; 23; 325(7374):1188.

Phillips KA, Dufresne RG Jr, Wilkel CS, Vittorio CC. Rate of body dysmorphic disorder in dermatology patients. *J Am Acad Dermatol* 2000 March; 42(3):436–441.

Philips KA, McElroy SL. Personality disorders and traits in patients with body dysmorphic disorder. *Compr Psychiatry* 2000 July–August; 41(4):229–236.

Picardi A, Abeni D, Melchi CF, Puddu P, Pasquini P. Psychiatric morbidity in dermatological outpatients: An issue to be recognized. *Br J Dermatol* 2000; 143(5):983–991.

Rowland Payne CME. 32 melanomas diagnosed by opportunistic total skin examination. *Br J Dermatol* 1995; 113 (Suppl 45):24.

Sarwer DB, Spitzer JC. Body image dysmorphic disorder in persons who undergo aesthetic medical treatments. *Aesthet Surg J* 2012; 32(8):999–1009.

Wollmer MA, de Boer C, Kalak N et al. Facing depression with botulinum toxin: A randomized controlled trial. *J Psychiatr Res* 2012; 46(5):574–581.

Yazel L. The serial-surgery murder. *Glamour* 1999 May; 108–114.

PART II

Cosmetic Aspects

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Cosmetics and cosmeceuticals

Martina Kerscher and Heike Buntrock

SUMMARY

Cosmetics and cosmeceuticals are innovative rapidly developing fields of dermatology. In recent years, the number of new cosmetic agents has increased considerably and has resulted in a broad range of cosmeceutical products and antiaging strategies. This chapter will briefly present the problems of distinguishing between cosmetics, cosmeceuticals, over-the-counter (OTC) drugs, and prescribed drugs and summarize important new developments in raw materials, carrier systems, and ingredients from the dermatological point of view. Especially, new evidence-based active ingredients against skin aging, here in particular antioxidants (e.g., vitamin C, niacinamide, polyphenols) and cell regulators (e.g., retinol, polypeptides, growth factors), are reviewed. Cosmeceuticals are extremely interesting and important to the daily practice of dermatology. The practical application of the Hamburg skin aging score will enable dermatologists to make a structured product selection and improve patients' clinical results. Important parameters for the quality assessment of cosmeceuticals are evidence-based *in vivo* and *in vitro* efficacy and sustainability as well as scientifically proven wanted and unwanted effects. Due to the continual development of new skin care products on the one side and the lack of controlled studies on the other, generally accepted guidelines for quality and scientific documentation of new active cosmetic ingredients have yet to be developed.

INTRODUCTION

The word "cosmetic" comes from Greek from the adjective "kosmétikos" or the verb "kosméo" and can be translated as "to decorate." However, cosmetics have been understood as products for beauty care that serve the preservation and restoration or improvement of the beauty of the human body. In current evidence-based medicine, the traditional term of cosmetics has been expanded and is thus defined as cosmetics based on scientific and technological research. But the differentiation between cosmetics, OTC drugs, and prescribed drugs can be highly difficult depending on the purpose and mechanism of action. For example, cosmetic products can indeed serve as protection against pathological lesions, and/or OTC products (e.g., skin protectants, acne treatments, antiperspirants) can be expressly employed to prevent, treat, or alleviate diseases [1]. The borders are increasingly becoming indistinct, and the list of products on the borderline of the respective product groups is long. The term "cosmeceuticals," introduced by Albert Kligman in the 1980s, combines the English terms "cosmetics" and "pharmaceuticals" and is used for products that have a positive effect on the skin, but not a medical-therapeutic effect, thus attempting to close this gap [2]. They are more than merely cosmetics, yet are not true drugs and can be defined as a subcategory of cosmetics. The U.S. Food and Drug Administration does not recognize cosmeceuticals as a category and views them as cosmetics [1,3]. The attention that the cosmetic and pharmaceutical industries pay to the development of "pharmacologically" active cosmetics and to cosmetically oriented medications is increasing the medical importance of cosmeceuticals [4].

The immense abundance of cosmetic products against skin aging demands a critical evaluation of the promised effects. Cosmeceuticals whose quality is established should possess an adequate scientifically documented proof of *in vivo* and *in vitro* efficacy and scientifically founded wanted and unwanted effects. Cosmetic products whose efficacy and tolerability have been demonstrated in scientific *in vivo* and *in vitro* studies are much in demand, and the cosmetic and pharmaceutical industry responds to this trend with a multitude of modern skin care products. Due to the continual development of new skin care products with new active ingredients, minimum requirements for quality and scientific documentation are a primary goal [5].

BASES AND VEHICLE COMPONENTS

Efficacy, tolerability, and properties of the use of cosmeceuticals are determined not only by actives but also by the vehicle. It is established that a well-formulated base adapted to the individual skin condition can have numerous positive effects on the skin (e.g., hydration, stabilization of the epidermal barrier). Further, the specific galenic preparation has great significance, as the effects of many cosmeceutical active agents depend largely on the overall formulation. While, for example, petrolatum allows for only moderate penetration of vitamin E into the skin, a micro- or nanoemulsion can improve effectiveness distinctly [6,7]. The overall formulation with interaction between vehicle, active ingredient, and skin influences the effects of the preparation as well as the liberation of the active ingredient. Important basic and auxiliary ingredients of cosmeceuticals are summarized in Table 9.1.

Innovative Vehicles

Derma Membrane Structure

Derma membrane structure (DMS) multilayer creams are lamellar preparations that are comparable to physiologic skin lipids with respect to structure (lipid double membrane) and ingredients. These novel galenic formulations are not based on the conventional W/O or O/W principle, but, with their lamellar structure, imitate the lipids of the intercellular substance, of the stratum corneum and thus are intended to improve the skin barrier.

Table 9.1 Important Ingredients in Vehicles

Vehicle components in cosmeceuticals	
Hydrophilic vehicle components	Water 2-Propanol Propylene glycol
Hydrophobic vehicle components	Petrolatum Triglycerides Silicon oils
Emulsifiers	Anionic tensides Cationic tensides Ambiphilic tensides Non-ionic tensides
Gel-forming agents	Hydroxyethyl cellulose
Preservatives	Sorbic acid Benzyl alcohol
Antioxidants	Tocopherol (acetate) Ascorbyl palmitate

Source: Daniels R and Knie U, *J. Dtsch Dermatol Ges*, 5(5), 367, 2007.

Table 9.2 Moisturizers in Cosmeceuticals

Type	Examples	*In vivo* effect
Emollients	Lanolin, mineral oil, petrolatum	Increased corneocyte cohesion
Occlusive agents	Paraffin, soy bean oil, propylene glycol, squalene, lanolin	Reduced transepidermal water loss (TEWL)
Moisture-retaining substances	Glycerol, urea, hyaluronic acid	Increased stratum corneum hydration

Nanodisperse Systems

Nanodisperse carrier systems, such as liposomes, nanoemulsions, or lipid nanoparticles, are increasingly gaining significance as vehicle and carrier systems for active cosmetic ingredients, as they can, for example, increase penetration of active ingredients that are difficult to bring into the skin. The most frequently employed water-soluble phospholipid in cosmeceuticals is phosphatidylcholine, which is derived from soybean lecithin and can increase skin hydration and reduce skin roughness [9,10].

Moisturizers

Moisturizing creams, that both protect from dryness and smooth a rough skin surface, contain emollients, occlusive agents and moisture-retaining substances. Thus, they not only serve as lipid-replenishing and rehydrating skin care of dry skin, but also help maintain the health of aging skin [11] (Table 9.2).

ACTIVE COSMECEUTICAL INGREDIENTS AGAINST SKIN AGING

Due to the enormous number of active ingredients presently employed in cosmeceuticals, only a few active substances, whose efficacy in the prevention and repair of signs of skin aging has been proven in scientific *in vivo* studies, can be described in an exemplary fashion in this chapter. Both intrinsically and extrinsically aged skin exhibits loss of elasticity and wrinkles; extrinsically prematurely aged skin is also characterized by pigmentary irregularities (hyper-/hypopigmentation) and solar/senile lentigines, whose therapy will not be discussed here.

The basis of an effective maintenance regime on existing aging and in particular for the prevention of skin aging is a daily consistent protection against ultraviolet (UV) and infrared (IR) radiation [12]. This daily UV protection, which should include both adequate UVA/UVB and IR filter substances, can be usefully combined with antioxidants and cell regulators. Antioxidants, such as vitamins, coenzymes, and botanicals (plant materials), act by reducing the concentration of free radicals, which lowers the concentration of matrix metalloproteinase and thus counteracts collagen degradation; cell regulators, such as retinol, peptides, and growth factors, directly influence the metabolism of fibroblasts and increase their synthesis performance.

Antioxidants

Antioxidants are a heterogeneous group of agents that reduce the concentration of free radicals in the skin. Antioxidants are significantly reduced during aging and by numerous extrinsic factors (e.g., UV radiation [13,14] and smoking [15,16]). Based on the theory of promotion of aging by free radicals [17–21], an attempt has been made with the help of diverse cosmeceutical products to supply the skin with antioxidants from the outside [11,22]. Some of the most commonly employed antioxidants are vitamins: at present, vitamin C (L-ascorbic acid) and vitamin B_3 (niacinamide) are the most common cosmeceuticals to treat premature skin aging [23–30].

Moreover, vitamin E (α-tocopherol), various botanicals such as flavonoids like green tea polyphenols, resveratrol, a polyphenolic phytoalexin, or pycnogenol can act in a photoprotective manner and counteract skin photoaging in topical use [31–37].

Vitamin C (L-Ascorbic Acid)

The water-soluble, heat-labile molecule, L-ascorbic acid (vitamin C), is a hexuronic acid that can irreversibly be destroyed by oxidation. In addition to its antioxidative effects in the skin and its capacity to reduce the concentration of free radicals, vitamin C also provides preservative properties for the skin care product itself. There is very good and evidence-based documentation in the international literature regarding the antiaging effects of vitamin C preparations at a concentration of up to 15% based on double-blind, placebo-controlled studies. The topical application of vitamin C thus leads to a stimulation of connective tissue metabolism in the dermis with the induction of type I and III collagen, of enzymes required for collagen biosynthesis, and of the tissue inhibitor of matrix metalloproteinase 1 (collagenase 1) [28,38–40]. Traikovich and Rubino et al. were able to document in different studies a significant reduction of wrinkles using optical profilometry in clinical studies with half-side comparison after a 3-month treatment with 10% vitamin C [41,42]. Further, according to Fitzpatrick et al., subsequent histology demonstrated an increase of collagen and an increased expression of the gene for type I collagen [43]. In addition to its effects on collagen metabolism and the synthesis of elastin, vitamin C also promotes epidermal differentiation. In reconstructed skin, Ponec et al. were able to show that vitamin C increases the degree of differentiation of

ceramides in the region of the epidermal barrier and that the formation of an effective epidermal barrier is dependent on vitamin C [29]. Pinnell et al. demonstrated in clinical studies that the antioxidant protection of vitamins C and E in combination is higher than that of vitamin C or E alone and also in comparison with other antioxidants. In further studies, combinations of 15% vitamin C, 1% vitamin E, and 0.5% of ferulic acid (an antioxidant extracted from the plant *Ferula*), and of vitamin C, ferulic acid, and phloretin (an antioxidant extracted from the bark of fruit trees) significantly reduced UV-induced damage to human skin [44].

Niacinamide (Vitamin B_3)

Niacinamide is a substance contained in all human cells. Nicotinamide adenine dinucleotide (NAD) or NAD phosphate (NADP) serves as an antioxidant in a number of enzymatic reactions. The reduced forms NADH and NADPH act as redox coenzymes. Niacinamide regulates cellular metabolism and cell renewal and, due to its cosmetic advantages, has been increasingly used in recent years often in concentrations of up to 5% as an antiaging agent in cosmeceuticals [45]. Newer double-blind, vehicle-controlled studies were able to demonstrate that a 3-month topical treatment with a 5% niacinamide cream significantly reduces signs of skin aging such as hyperpigmentation, skin redness, senile lentigines, yellow discoloration, and large pores. Further, niacinamide, with very good tolerability, leads to a significant improvement of skin elasticity and fine wrinkles [23,24,30,46]. By the activation of serine palmitoyl transferase and increased synthesis of free fatty acids, cholesterol and ceramides, in topical use it reduces transepidermal water loss and stabilizes the epidermal barrier and is also suitable as an antiaging agent even in hypersensitive skin. According to Hakozaki et al. and Draelos et al., possible mechanisms of action beyond antioxidative effects include increased collagen synthesis shown *in vitro* in fibroblast cultures as well as normalization of glycosaminoglycan synthesis [23,24,47,48].

Vitamin E (α-Tocopherol)

Vitamin E is a fat-soluble, heat-stable molecule that belongs to the lipophilic antioxidants and is found today in concentrations of 2%–20% in countless skin care products [49]; it has very good tolerability with positive effects on the skin and can also protect skin care products from oxidation. Beyond physiologic anti-inflammatory, immunostimulatory, and antiproliferative effects, it is supposed (although the effects are clearly weaker than those of vitamin C and B_3) to smoothen skin surface relief, increase the moisture-retaining capacity of the stratum corneum, have antiaging effects, accelerate epithelialization of the skin, increase enzyme effects, and have photoprotective effects [50–52]. Mayer et al. were able to detect a skin-smoothening effect in a clinical study on 20 women after a 4-week treatment with topical vitamin E [51]. In a double-blind, randomized, and vehicle-controlled study on 10 test subjects Zhai et al. were able to show photoprotective effects of an emulsion containing vitamin E. In comparison to the carrier system without active ingredients, the vitamin E emulsion displayed a higher antioxidative capacity and was better able to prevent UV-induced erythema and inflammatory skin damage [50].

α-Lipoic Acid

The coenzyme α-lipoic acid is a lipophilic antioxidant that plays an important role in the citric acid cycle and has the ability to neutralize peroxide radicals, hydroxyl radicals, superoxide radicals, and nitrogen oxides. In a double-blind, randomized, and vehicle-controlled study, Beitner demonstrated distinct antioxidative effects and a significant improvement of age-related skin changes by topically applied α-lipoic acid [17].

Plant Materials (Botanicals)

A variety of plant constituents termed "secondary plant materials" can have positive effects on the skin. Polyphenols are a large family of naturally occurring plant materials. Their main sources are fruits, vegetables, nuts, bark, leaves, and seeds such as cacao, coffee, tea, juice, and wine. The most common polyphenols are flavonoids, phenolic acids, catechins, stilbenes, proanthocyanidins, ellagitannins, and anthocyanins. The group of flavonoids includes flavanols, flavanones, anthocyanidines, flavones, flavonols, and isoflavones. They are most commonly known for their strong antioxidant activity and have been reported to possess substantial skin photoprotective effects [53,54].

Polyphenolic epicatechins found in *green tea* extract are naturally occurring antioxidants used in numerous cosmetics. Their effects on the cellular stress system are very complex: both direct effects on signal transduction and alteration in connection with the prevailing antioxidative status of the cell could be shown [55,56].

Sirtuin 1, one of seven sirtuins in humans, is an enzyme that is part of signal transduction and can slow the initiation of cell death. Sirt1 is inter alia activated by *resveratrol*, an ingredient of blue grapes.

Resveratrol belongs to the polyphenolic phytoalexins and has pronounced antioxidant, anti-inflammatory, antiproliferative, and sirtuin-activating properties. In a comparative study, a commercially available resveratrol-based skin care product (1% resveratrol) demonstrated a 17 times greater antioxidant activity than 1% idebenone [57]. Moreover, resveratrol is known to be a phytoestrogen, and further studies on the potential of resveratrol to attenuate the symptoms of menopause are warranted [58].

A further antiaging substance is the plant antioxidant *pycnogenol*, a standardized extract of pro(antho)cyanidines from the bark of the French sea pine (*Pinus pinaster, ssp. atlantica*). Oligomeric procyanidins belong to the flavonoids and are among the most effective antioxidants with the ability to neutralize every naturally occurring oxygen radical species. It has thus been established that pycnogenol is a much more active antioxidant than coenzyme Q10, α-lipoic acid, and grape seed extract [59–61].

However, *grape seed* proanthocyanidins have been shown to be potent antioxidants and free radical scavengers with a significantly stronger antioxidant capacity than vitamin C or vitamin E. A 4-week twice-daily application of a grape seed extract containing serum improved the main clinical signs of photoaged skin in humans [62].

Emblica, a standardized extract won from the plant *Phyllanthus emblica* (syn. *Emblica officinalis*), the Indian gooseberry or amla, contains various phenolic compounds and has antioxidant and anti-inflammatory properties. It is supposed to reduce free radicals and inhibit metal-induced oxidation by forming chelate complexes with iron and copper. This chelation prevents the formation of damaging hydroxyl radicals [63].

Pomegranate, from the tree *Punica granatum*, is also a rich source of polyphenols and possesses strong antioxidant, anti-inflammatory, and anticarcinogenic properties [53,64].

Further plant extracts employed as antiaging substances include isoflavones from *soy* or *red clover*, whose results are attributed to a phytoestrogen effect via specific interaction with the estrogen receptors, as well as extracts from *coffee berry, curcumin, ectoin, delphinidin*, or even maritime plant extracts like those from *algae or microalgae* [53,60,64–66]. A current systematic review of only randomized or controlled clinical trials concluded that a significant reduction in skin wrinkling was proved for *rosaceae, date kernel, cork, peony, and soy extracts*, although there is no evidence that the reduction is enduring [67].

Cell Regulators

While antioxidants reduce the concentration of free radicals in the skin and thus counteract collagen degradation, cell regulators, such as vitamin A acid derivatives and retinol, and also polypeptides and growth factors, directly influence dermal metabolism and stimulate the synthesis of collagen or elastic fibers as well as extracellular matrix.

Retinol (Vitamin A) and Its Derivatives

Vitamin A is the generic term for a series of natural and synthetic compounds with a similar chemical structure but in part differing biological activities. This group of agents consists of various substances or derivatives such as fat-soluble vitamin A (retinol), aldehyde–retinal (retinaldehyde), and vitamin A acid (retinoic acid/tretinoin). The most commonly used substance in modern antiaging preparations is at present retinol, which in comparison to tretinoin (drug requiring prescription) is less irritating to the skin [68–70] and generally better tolerable in topical use [68,70]. At a maximal concentration of up to 0.3%, retinol is today considered as the "gold standard" of cosmetic antiaging agents. The synthetic retinoic acid (tretinoin), which requires a prescription, is a non-aromatic retinoid of the first generation and is not licensed for use in cosmetic products in Germany. In the United States, this agent is licensed, up to a concentration of 0.05% tretinoin cream, for the treatment of signs of skin aging and known under the trademarks Renova™ and Retin-A™.

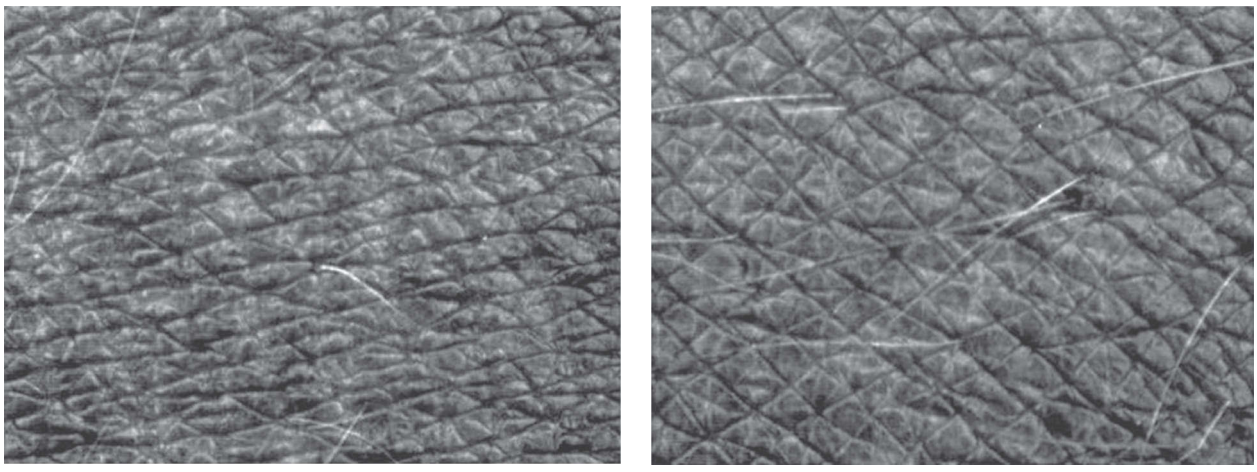
Vitamin A derivatives belong to the antiaging substances whose clinical efficacy has been scientifically well studied and proven [71–73]. Topical therapy with vitamin A derivatives can be used both for prevention and for treatment of already photodamaged skin. Varani et al. showed, for example, that retinol has positive effects not only on extrinsic but also on intrinsic skin agents and has similar effects as retinoic acid [70]; 0.1% tretinoin can markedly reduce typical signs of UV-induced premature skin aging, such as wrinkles, loss of elasticity of the skin, pigmentation irregularities, and keratoses [74], which was confirmed by Bhawan in placebo-controlled studies and clinically even with the help of histological examinations [75].

Scientifically well documented are the positive effects on collagen metabolism. Studies on topical use, for example, demonstrated that retinol and vitamin A acid (retinoic acid) can induce collagen synthesis. In addition to induction of collagen biosynthesis, vitamin A derivatives can also reduce the expression of collagen-degrading enzymes such as matrix metalloproteinase 1 (collagenase 1). Just as for tretinoin and retinol, Boisnic et al. were able to show a stimulation of collagen synthesis with retinaldehyde. Collagenase activity declined and, in part, damaged collagen fibers were reconstituted with a restructuring of the connective tissue [76]. In a randomized, double-blind, vehicle-controlled *in vivo* study of 90 subjects, Creidi et al. applied 0.5% retinaldehyde daily with good tolerability over 44 weeks.

Optical profilometry of the wrinkles at the lateral corner of the eye revealed a significant reduction of wrinkle depth and skin surface roughness [77] (Figure 9.1).

Polypeptides

Through advances in technology, it became possible to produce peptide sequences that imitate the body's own molecules, such as collagen or elastin, and thus attain the capability of influencing bodily processes such as collagen



(a) (b)

Figure 9.1 Skin surface morphology before (a) and after (b) 4 months of topical treatment containing retinol (smoother skin surface).

Table 9.3 Peptides in Cosmeceuticals

Type	*In vitro* mechanisms of action	Postulated *in vivo* effects
Signal peptides, e.g., Pal-KTTKS, Pal-KT	Activation of fibroblasts by specific peptide sequences	Increased collagen and elevated elastin, proteoglycan, glycosaminoglycans, and fibronectin proliferation
Carrier peptides, e.g., copper tripeptide	Via inward transport of trace elements (e.g., copper) enzyme activation of collagen synthesis	Increased collagen neosynthesis
Neurotransmitter-inhibitor peptides, e.g., acetyl hexapeptide-3, pentapeptide-3	Inhibited the release of acetylcholine at the neuromuscular junction	Reduced muscle activity
Enzyme-inhibitor peptides. Mostly extracted from botanical sources, e.g., silk protein, soy peptide, or rice peptide	Directly or indirectly inhibited the function of a key enzyme in some metabolic process	Inhibited the formation of proteases or matrix metalloproteinase activity or lipid peroxidation, tyrosinase activity, and keratinocyte apoptosis

Sources: Lupo MP, Cole AL, *Dermatol Ther*, 20(5), 343, 2007; Gorouhi F, Maibach HI, *Int J Cosmet Sci*, 31(5), 327, 2009.

synthesis or transmission at the neuromuscular synapse. Therefore, peptides are used in cosmeceuticals to improve skin aging features, be they due to increased muscular activity or increased collagen degradation [78]. In addition to the aforementioned signal peptides whose effects are covered very well, carrier, neurotransmitter-inhibitor, and enzyme-inhibitor peptides are also used in cosmeceuticals. The four groups of peptides are differentiated and summarized in Table 9.3.

Signal Peptides

In various *in vivo* studies with double-blind, vehicle-controlled, and randomized design, it was shown that palmitoyl pentapeptide-3 (Pal-KTTKS), a signal peptide, with good tolerability already after 12 weeks of daily application, led to a stimulation of connective tissue metabolism with induction of type I and III collagen. Clinically, this was seen in the form of increased collagen content of the dermis, that could be detected histopathologically in the form of increased skin thickness and density measured by 20 MHz sonography, as well as in a reduction of skin surface roughness and an increase in skin smoothness (Figure 9.2) [80]. In a further study, Lintner et al. compared the clinical efficacy of a topical preparation containing palmitoyl pentapeptide with the efficacy of a preparation containing retinol. The effects on collagen metabolism did not differ significantly; the tolerability of application of the pentapeptide was markedly improved [81].

Growth Factors

In multiple clinical studies, it has been shown that the topical application of human growth factors reduces the signs and symptoms of skin aging, including a statistically significant reduction in fine lines and wrinkles and an increase in dermal collagen synthesis [82].

Epidermal growth factor (EGF) is a 53-amino-acid peptide generated by platelets and several subtypes of white blood cells and is implicated in keratinocyte migration, fibroblast function, and the formation of granulation tissue. The EGF therapeutic efficacy of EGF in wound healing and its excellent tolerability have been widely demonstrated in earlier research studies [83,84]. It has been observed that the stimulatory effects of EGF itself on fibroblasts lead to increased production of collagen 1 and therefore increased dermal thickness [85], but, with age both, the number of functional EGF receptors and the EGFR response decreases [86,87]. Given these findings, it is not unexpected that the topical application of human growth factors plays an important role in reversing the effects of skin aging mediated by chronological and environmental factors [82]. In a recent 3-month, open-label study, Schouest et al. investigated the efficacy of a unique serum containing barley bioengineered, human-like EGF protein specifically in improving visible signs of photodamage and aging in facial skin. Twenty-nine females with clinically significant signs of aging/photoaging applied twice daily the EGF serum and additionally a basic sunscreen and facial cleaner. Clinical evaluations, subject self-assessment, and clinical photography showed statistically significant improvements in fine lines and rhytides, skin texture, pore size, and dyschromatic conditions within the first month of use. After 3 months subjects rated a moderate to great improvement in skin smoothness of 80%, in fine lines and brown spotting of 60%, and in wrinkles of 45% [88].

Madecassoside, a growth factor extracted from the plant *Centella asiatica*, beyond well-documented effects on wound healing is supposed also to support the synthesis of type I collagen fibers and protect collagen fibers from enzymatic degradation. Thus, in various studies on subjects with extrinsically aged skin, the clinical efficacy of a topically applied facial cream containing 0.1% madecassoside and 5% vitamin C was examined. In a randomized double-blind study, Haftek et al. documented a significant improvement of skin elasticity, clinical score, and self-evaluation (e.g., wrinkle depth, skin roughness, hydration) after 6 months [38] (Figure 9.3).

COMBINATION POSSIBILITIES

According to recent studies, the combination of various active ingredients against skin aging reduces clinical signs of aging significantly and improves regeneration of the skin [90]. Combinations of different antioxidants or the combination of antioxidants and cell regulators seem to be of great value (Figure 9.4).

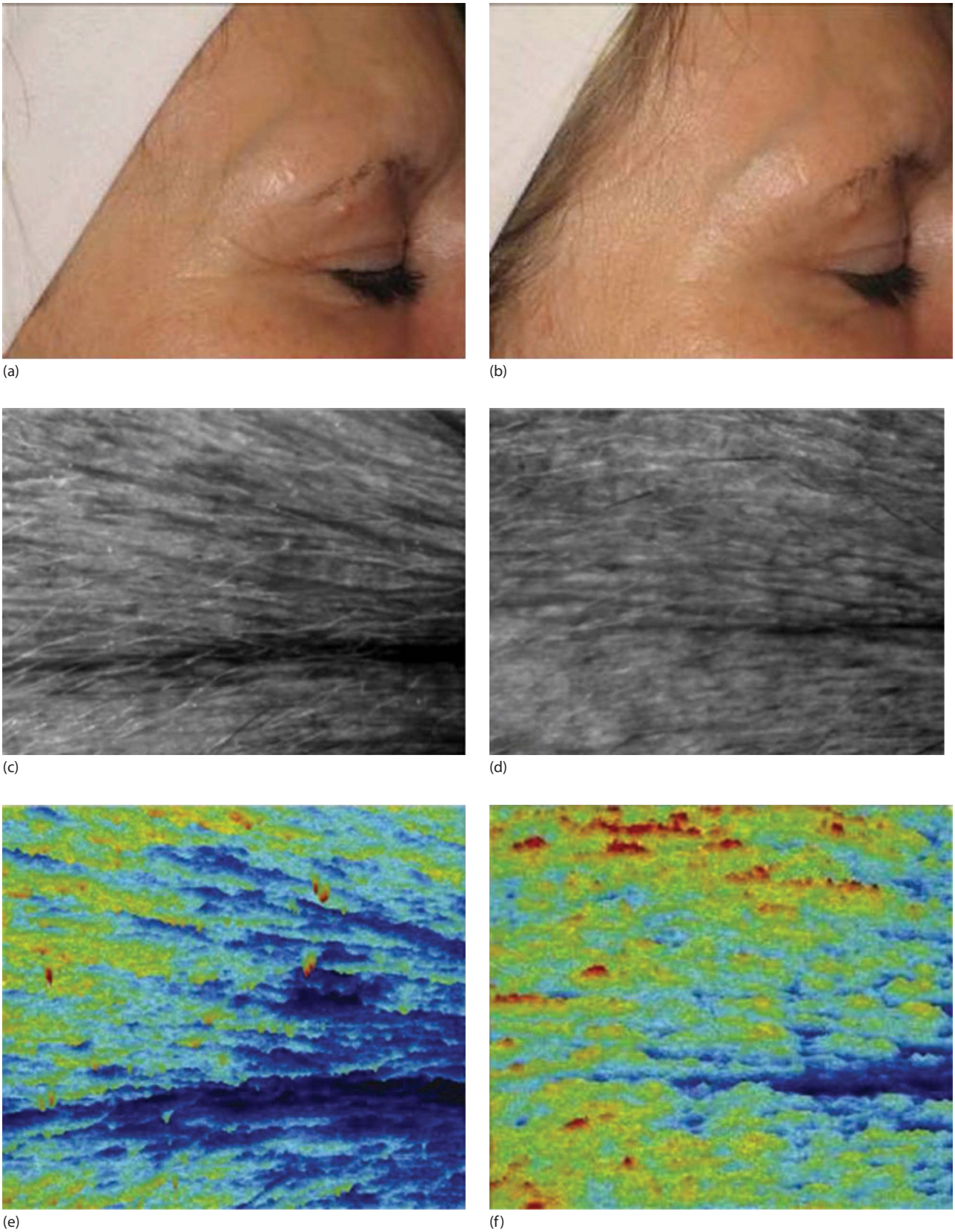
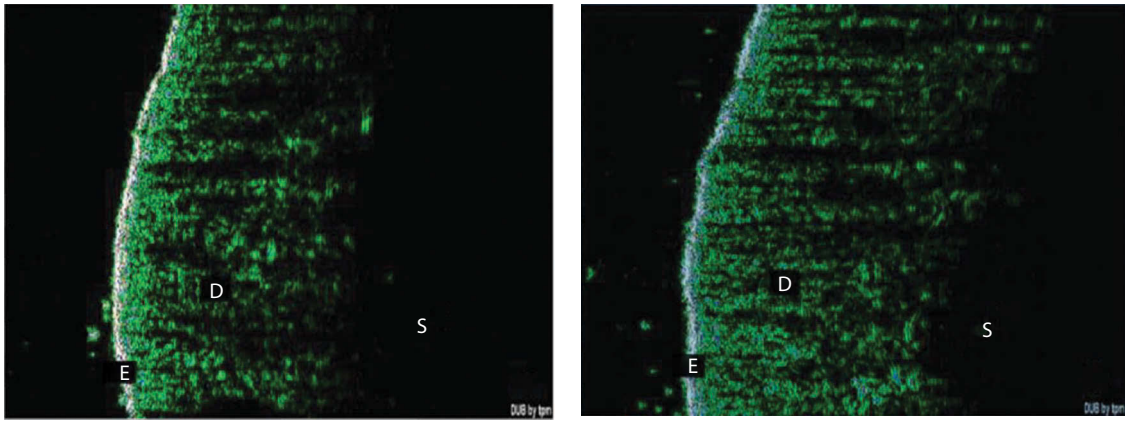
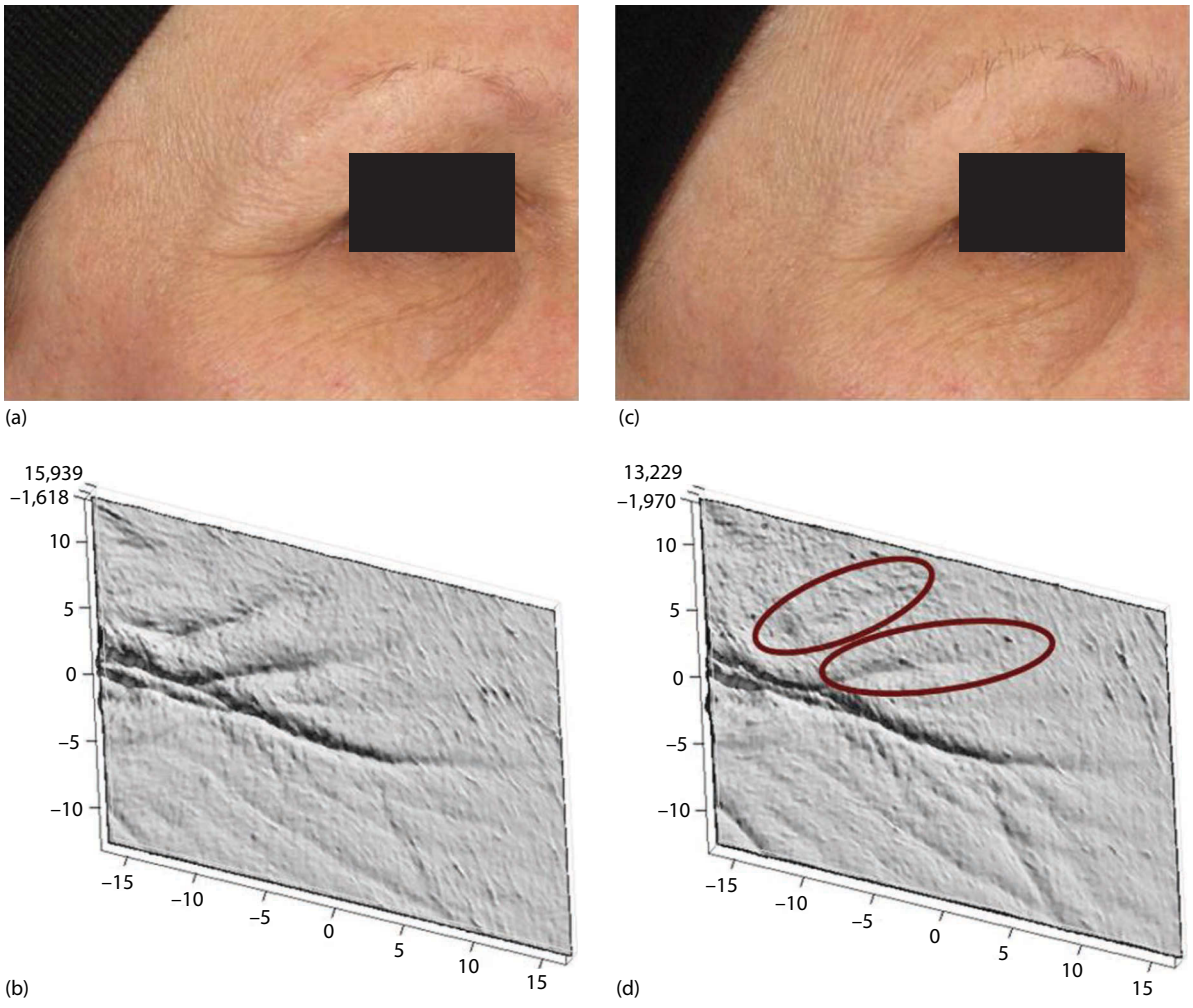


Figure 9.2 Corner of the eye before (a) and after (b) 12 weeks of topical treatment containing palmitoyl pentapeptide, grayscale visioscans (c, d), and color images (e, f) of calculated 3D models taken at baseline and after 12 weeks of topical treatment containing palmitoyl pentapeptide. (From Krueger N et al., Palmitoyl Pentapeptide in skin aging: A randomized, double-blind, half-sided evaluation using bioengineering methods, *16th Congress of the European Academy of Dermatology and Venereology*, EADV 2007, Vienna, Austria, May 16–19 [Poster].)



(a) (b)

Figure 9.3 20 MHz sonography before (a) and after (b) 12 weeks pf topical treatment with 0.1% madecassoside and 5% vitamin C. (From Krueger N et al., Biophysical and clinical evaluation of a topical treatment with 5% vitamin C and 0.1% madecassoside on skin physiology after 12 weeks, *18th Congress of the European Academy of Dermatology and Venereology*, EADV 2009, Berlin, Germany [Poster].)



(a) (c)

(b) (d)

Figure 9.4 Standardized photography and calculated 3D models of the corner of the eye before (a, b) and after (c, d) 28 days of topical treatment containing niacinamide, peptides, and a retinylester. (From Krueger N et al., Randomisierte, kontrollierte Untersuchung der Effekte eines dermatokosmetischen Pflegeregimes mit Niacinamide, Peptiden und einem Retinylester auf die Hautqualität im Gesicht, *46th Tagung der Deutschen Dermatologischen Gesellschaft*, DDG 2011, Dresden, Germany [Poster].)

THE HAMBURG APPROACH

As youth and perception of beauty are increasingly considered to be of great importance, the science behind skin aging has become increasingly popular in the past decade and has resulted in the development of cosmetic products full of innovation and complex formulations. New cosmetic agents to improve various signs of skin aging are appearing at an astounding and increasing pace in the cosmeceutical market.

In order to facilitate the use of aforementioned agents in everyday dermatological routine, the agents can be categorized according to the mechanisms of action (antioxidants, cell regulators). Furthermore, the classification of patients into different skin aging stages can be helpful (Figure 9.5) [92]. Therefore, the Hamburg skin aging score was developed, which can be filled out within minutes during the patient dialog (Figure 9.6). Depending on the individual skin aging stage, the particular degree of specific clinical signs of skin aging and skin condition, as well as possible past minimally invasive procedures, individual treatment strategies that have both a preventive and a reparative character can be developed for each patient (Figure 9.7). For optimal prevention of light-induced signs of skin aging, additional daily UVA/UVB and IR protection, possibly in combination with DNA repair enzymes and antioxidants, is indispensable in every skin aging stage. The use of antioxidants is recommended for skin aging stages I and II, while cell regulators in combination with antioxidants, but also as monotherapy, are particularly suitable for skin aging stages III and IV (approx. from the fourth decade of life) as well as peri- and postmenopausally. Thus, newer studies by Haftek et al. and Fu et al. show especially that the combination of cosmeceutical agents leads to increased clinical effects [38,90].

CONCLUSIONS

In the targeted recommendation of specific agents and combinations of agents, sufficiently documented scientific *in vivo* and *in vitro* proof of efficacy, sustainability, and tolerability in a sufficient number of subjects is of great importance. Even though the number of published studies on cosmeceutical products is rising almost exponentially, a frequent problem in the confirmation or comparison of cosmetic products is still a lack of controlled, evidence-based studies.

CONFLICTS OF INTEREST

None.

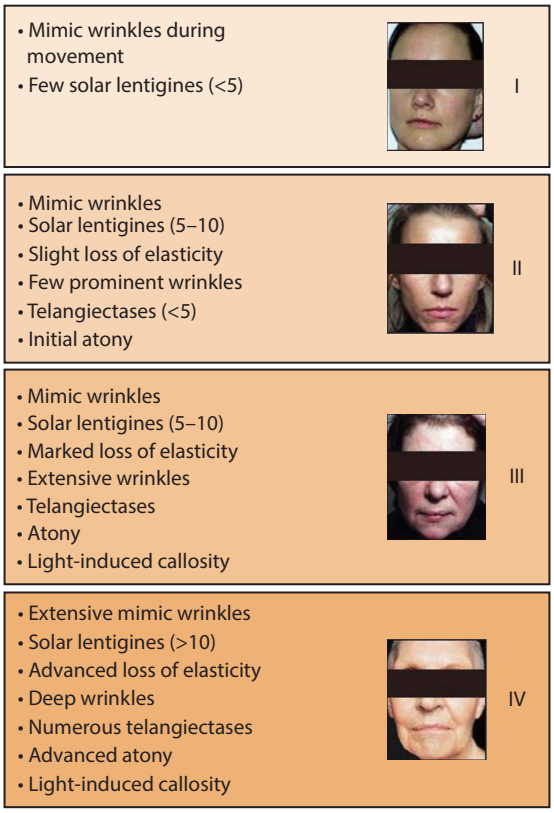


Figure 9.5 Skin aging scale (according to the Hamburg skin aging score). (From Krueger N et al., Evaluation of skin physiology with biophysical measurements using four skin aging stages, *68th Annual Meeting of the American Academy of Dermatology*, AAD 2010, Miami Beach, FL [Poster].)

Age: _____ years	Clinical grade			
	Missing	Low	Medium	Strong
Actinic elastosis	0	1	2	3
Loss of elasticity and firmness	0	1	2	3
Pale and thin skin	0	1	2	3
Glabella fold	0	1	2	3
Thickening of the stratum corneum	0	1	2	3
Horizontal forehead lines	0	1	2	3
Non-mimic creases, e.g. nasolabial fold	0	1	2	3
Marionette lines	0	1	2	3
Crow's feet	0	1	2	3
Lentigo senilis	0	1	2	3
Age-related skin dryness	0	1	2	3
Marked and deep folds	0	1	2	3

Sum score of the questions with blue background:	
Sum score of the questions with yellow background:	
Sum score of the questions with orange background:	

The color with the highest sum score corresponds to the prevalent skin aging type.

	X
Myo skin aging	
Intrinsic skin aging	
Extrinsic skin aging	

Figure 9.6 Hamburg skin aging score.

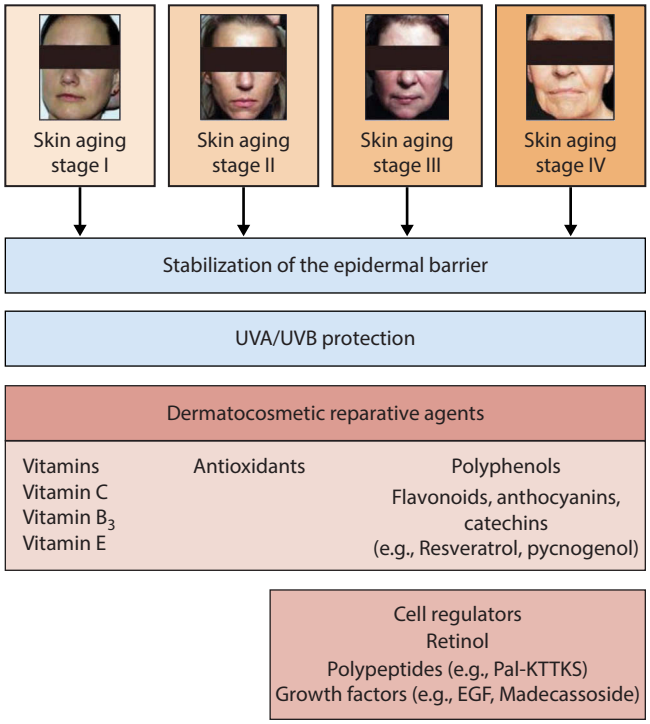


Figure 9.7 Treatment options depending on skin aging stage.

REFERENCES

1. Draelos ZD. Cosmetics, categories, and the future. *Dermatol Ther* 2012; 25(3):223–228.
2. Amer M, Maged M. Cosmeceuticals versus pharmaceuticals. *Clin Dermatol* 2009; 27(5):428–430.
3. Reszko AE, Berson D, Lupo MP. Cosmeceuticals: Practical applications. *Dermatol Clin* 2009; 27(4):401–416.
4. Zesch A. Cosmetics: Definition and legal aspects of the term. *Hautarzt* 1999; 50(4):243–249.
5. Leitlinie GD. Dermokosmetika gegen Hautalterung. GD Gesellschaft für Dermopharmazie e.V. March 22th, 2010.
6. Ehrlich M, Rao J, Pabby A et al. Improvement in the appearance of wrinkles with topical transforming growth factor beta(1) and l-ascorbic acid. *Dermatol Surg* 2006; 32(5):618–625.
7. Martini MC, Bobin MF, Flandin H et al. Role of microemulsions in the percutaneous absorption of alpha-tocopherol. *J Pharm Belg* 1984; 39(6):348–354.
8. Daniels R, Knie U. Galenics of dermal products—Vehicles, properties and drug release. *J Dtsch Dermatol Ges* 2007; 5(5):367–383.
9. Artmann C, Röding J, Ghyczy M et al. Influence of various liposome preparations on skin humidity. *Parfümerie Kosmetik* 1990; 5:326–327.
10. Ghyczy M, Gareiss J, Kovats T. Liposomes from vegetable phosphatidylcholine. Their production and effects on the skin. *Cosmet Toiletries* 1994; 109:75–80.
11. Böni R, Burg G. Aging skin: Physiological bases, preventive measures and therapeutic modalities. *Schweiz Med Wochenschr* 2000; 130(36):1272–1278.
12. Krutmann J. Actives. A central component of modern light protection. *Hautarzt* 2009; 60(4):294–300.
13. Brenneisen P, Wenk J, Klotz LO et al. Central role of Ferrous/Ferric iron in the ultraviolet B irradiation-mediated signaling pathway leading to increased interstitial collagenase (matrix-degrading metalloprotease (MMP)-1) and stromelysin-1 (MMP-3) mRNA levels in cultured human dermal fibroblasts. *J Biol Chem* 1998; 273(9):5279–5287.
14. Fisher GJ, Wang ZQ, Datta SC et al. Pathophysiology of premature skin aging induced by ultraviolet light. *N Engl J Med* 1997; 337(20):1419–1428.
15. Francès C. Smoker's wrinkles: Epidemiological and pathogenic considerations. *Clin Dermatol* 1998; 16(5):565–570.
16. Lahmann C, Bergemann J, Harrison G et al. Matrix metalloproteinase-1 and skin ageing in smokers. *Lancet* 2001; 357(9260): 935–936.
17. Beitner H. Randomized, placebo-controlled, double blind study on the clinical efficacy of a cream containing 5% alpha-lipoic acid related to photoageing of facial skin. *Br J Dermatol* 2003; 149(4):841–849.
18. Sander CS, Chang H, Salzmann S et al. Photoaging is associated with protein oxidation in human skin in vivo. *J Invest Dermatol* 2002; 118(4):618–625.
19. Scharffetter-Kochanek K, Wlaschek M, Brenneisen P et al. UV-induced reactive oxygen species in photocarcinogenesis and photoaging. *Biol Chem* 1997; 378(11):1247–1257.
20. Sohal RS, Weindruch R. Oxidative stress, caloric restriction, and aging. *Science* 1996; 273(5271):59–63.
21. Wlaschek M, Tantcheva-Poór I, Naderi L et al. Solar UV irradiation and dermal photoaging. *J Photochem Photobiol B* 2001; 63(1–3):41–51.
22. Friedland JA, Buchel EW. Skin care and the topical treatment of aging skin. *Clin Plast Surg* 2000; 27(4):501–506.
23. Bissett D. Topical niacinamide and barrier enhancement. *Cutis* 2002; 70(6):8–12; discussion 21–23.
24. Bissett DL, Oblong JE, Berge CA. Niacinamide: A B vitamin that improves aging facial skin appearance. *Dermatol Surg* 2005; 31(7 Pt 2): 860–865.
25. Colven RM, Pinnell SR. Topical vitamin C in aging. *Clin Dermatol* 1996; 14(2):227–234.

26. Soma Y, Kashima M, Imaizumi A et al. Moisturizing effects of topical nicotinamide on atopic dry skin. *Int J Dermatol* 2005; 44(3):197–202.
27. Seité S, Bredoux C, Compan D et al. Histological evaluation of a topically applied retinol-vitamin C combination. *Skin Pharmacol Physiol* 2005; 18(2):81–87.
28. Nusgens BV, Humbert P, Rougier A et al. Topically applied vitamin C enhances the mRNA level of collagens I and III, their processing enzymes and tissue inhibitor of matrix metalloproteinase 1 in the human dermis. *J Invest Dermatol* 2001; 116(6):853–859.
29. Ponec M, Weerheim A, Kempenaar J et al. The formation of competent barrier lipids in reconstructed human epidermis requires the presence of vitamin C. *J Invest Dermatol* 1997; 109(3):348–355.
30. Bissett DL, Miyamoto K, Sun P et al. Topical niacinamide reduces yellowing, wrinkling, red blotchiness, and hyperpigmented spots in aging facial skin. *Int J Cosmet Sci* 2004; 26(5):231–238.
31. Dreher F, Gabard B, Schwindt DA et al. Topical melatonin in combination with vitamins E and C protects skin from ultraviolet-induced erythema: A human study in vivo. *Br J Dermatol* 1998; 139(2):332–339.
32. Gallarate M, Carlotti ME, Trotta M et al. On the stability of ascorbic acid in emulsified systems for topical and cosmetic use. *Int J Pharm* 1999; 188(2):233–241.
33. Hoppe U, Bergemann J, Diembeck W et al. Coenzyme Q10, a cutaneous antioxidant and energizer. *Biofactors* 1999; 9(2–4):371–378.
34. Ricciarelli R, Maroni P, Ozer N et al. Age-dependent increase of collagenase expression can be reduced by alpha-tocopherol via protein kinase C inhibition. *Free Radic Biol Med* 1999; 27(7–8):729–737.
35. Werninghaus K, Meydani M, Bhawan J et al. Evaluation of the photoprotective effect of oral vitamin E supplementation. *Arch Dermatol* 1994; 130(10):1257–1261.
36. Wei H, Zhang X, Zhao JF et al. Scavenging of hydrogen peroxide and inhibition of ultraviolet light-induced oxidative DNA damage by aqueous extracts from green and black teas. *Free Radic Biol Med* 1999; 26(11–12):1427–1435.
37. Wolf R, Wolf D, Ruocco V. Vitamin E: The radical protector. *J Eur Acad Dermatol Venereol* 1998; 10(2):103–117.
38. Haftek M, Mac-Mary S, Le Bitoux M-A et al. Clinical, biometric and structural evaluation of the long-term effects of a topical treatment with ascorbic acid and madecassoside in photoaged human skin. *Exp Dermatol* 2008; 17(11):946–952.
39. Humbert PG, Haftek M, Creidi P et al. Topical ascorbic acid on photoaged skin. Clinical, topographical and ultrastructural evaluation: Double-blind study vs. placebo. *Exp Dermatol* 2003; 12(3):237–244.
40. Raschke T, Koop U, Düsing H-J et al. Topical activity of ascorbic acid: From in vitro optimization to in vivo efficacy. *Skin Pharmacol Physiol* 2004; 17(4):200–206.
41. Traikovich SS. Use of topical ascorbic acid and its effects on photodamaged skin topography. *Arch Otolaryngol Head Neck Surg* 1999; 125(10):1091–1098.
42. Rubino C, Farace F, Dessy LA et al. A prospective study of anti-aging topical therapies using a quantitative method of assessment. *Plast Reconstr Surg* 2005; 115(4):1156–1162; discussion 1163–1164.
43. Fitzpatrick RE, Rostan EF. Double-blind, half-face study comparing topical vitamin C and vehicle for rejuvenation of photodamage. *Dermatol Surg* 2002; 28(3):231–236.
44. Murray JC, Burch JA, Streilein RD et al. A topical antioxidant solution containing vitamins C and E stabilized by ferulic acid provides protection for human skin against damage caused by ultraviolet irradiation. *J Am Acad Dermatol* 2008; 59(3):418–425.
45. Matts PJ, Oblong JE, Bisset DL. A review of the range of effects of niacinamide in human skin. *Int fed Soc Cosmet Chem Mag* 2002; 5:285–289.
46. Bissett DL. Common cosmeceuticals. *Clin Dermatol* 2009; 27(5):435–445.
47. Draelos ZD, Ertel K, Berge C. Niacinamide-containing facial moisturizer improves skin barrier and benefits subjects with rosacea. *Cutis* 2005; 76(2):135–141.
48. Hakozaki T, Minwalla L, Zhuang J et al. The effect of niacinamide on reducing cutaneous pigmentation and suppression of melanosome transfer. *Br J Dermatol* 2002; 147(1):20–31.
49. Kästner W. Vitamin E: Absicherung bei der Verwendung in Externa. *Fat Sci Technol* 1989; 91:305–312.
50. Zhai H, Behnam S, Villarama CD et al. Evaluation of the antioxidant capacity and preventive effects of a topical emulsion and its vehicle control on the skin response to UV exposure. *Skin Pharmacol Physiol* 2005; 18(6):288–293.
51. Mayer P, Pittermann W, Wallat S. The effects of vitamin E on the skin. *Cosmet Toiletries* 1993; 108:99–109.
52. Möller A, Ansmann A, Wallat S. Wirkungen von Vitamin E auf die Haut bei topischer Anwendung. *Fat Sci Technol* 1989; 91:295–305.
53. Afaq F, Katiyar SK. Polyphenols: Skin photoprotection and inhibition of photocarcinogenesis. *Mini Rev Med Chem* 2011; 11(14):1200–1215.
54. Nichols JA, Katiyar SK. Skin photoprotection by natural polyphenols: Anti-inflammatory, antioxidant and DNA repair mechanisms. *Arch Dermatol Res* 2010; 302(2):71–83.
55. Elmets CA, Singh D, Tubesing K et al. Cutaneous photoprotection from ultraviolet injury by green tea polyphenols. *J Am Acad Dermatol* 2001; 44(3):425–432.
56. Katiyar SK, Matsui MS, Elmets CA et al. Polyphenolic antioxidant (-)-epigallocatechin-3-gallate from green tea reduces UVB-induced inflammatory responses and infiltration of leukocytes in human skin. *Photochem Photobiol* 1999; 69(2):148–153.
57. Baxter RA. Anti-aging properties of resveratrol: Review and report of a potent new antioxidant skin care formulation. *J Cosmet Dermatol* 2008; 7(1):2–7.
58. Farris PK. Innovative cosmeceuticals: Sirtuin activators and anti-glycation compounds. *Semin Cutan Med Surg* 2011; 30(3):163–166.
59. Rohdewald P. A review of the French maritime pine bark extract (Pycnogenol), a herbal medication with a diverse clinical pharmacology. *Int J Clin Pharmacol Ther* 2002; 40(4):158–168.
60. Berson DS. Natural antioxidants. *J Drugs Dermatol* 2008; 7(7):7–12.
61. Packer L, Rimbach G, Virgili F. Antioxidant activity and biologic properties of a procyanidin-rich extract from pine (Pinus maritima) bark, pycnogenol. *Free Radic Biol Med* 1999; 27(5–6):704–724.
62. Cronin H, Draelos ZD. Top 10 botanical ingredients in 2010 anti-aging creams. *J Cosmet Dermatol* 2010; 9(3):218–225.
63. Chaudhuri RK. Emblica cascading antioxidant: A novel natural skin care ingredient. *Skin Pharmacol Appl Skin Physiol* 2002; 15(5):374–380.
64. Fowler JF Jr, Woolery-Lloyd H, Waldorf H et al. Innovations in natural ingredients and their use in skin care. *J Drugs Dermatol* 2010; 9(6):72–81.
65. Baumann L, Woolery-Lloyd H, Friedman A. "Natural" ingredients in cosmetic dermatology. *J Drugs Dermatol* 2009; 8(6):5–9.
66. Thornfeldt C. Cosmeceuticals containing herbs: Fact, fiction, and future. *Dermatol Surg* 2005; 31(7 Pt 2):873–880.
67. Hunt KJ, Hung SK, Ernst E. Botanical extracts as anti-aging preparations for the skin: A systematic review. *Drugs Aging* 2010; 27(12):973–985.
68. Kafi R, Kwak HSR, Schumacher WE et al. Improvement of naturally aged skin with vitamin A (retinol). *Arch Dermatol* 2007; 143(5):606–612.
69. Kang S, Duell EA, Fisher GJ et al. Application of retinol to human skin in vivo induces epidermal hyperplasia and cellular retinoid binding proteins characteristic of retinoic acid but without measurable retinoic acid levels or irritation. *J Invest Dermatol* 1995; 105(4):549–556.
70. Varani J, Warner RL, Gharaee-Kermani M et al. Vitamin A antagonizes decreased cell growth and elevated collagen-degrading matrix metalloproteinases and stimulates collagen accumulation in naturally aged human skin. *J Invest Dermatol* 2000; 114(3):480–486.

71. Kligman AM, Grove GL, Hirose R et al. Topical tretinoin for photoaged skin. *J Am Acad Dermatol* 1986; 15(4 Pt 2):836–859.
72. Olsen EA, Katz HI, Levine N et al. Tretinoin emollient cream: A new therapy for photodamaged skin. *J Am Acad Dermatol* 1992; 26(2 Pt 1):215–224.
73. Sendagorta E, Lesiewicz J, Armstrong RB. Topical isotretinoin for photodamaged skin. *J Am Acad Dermatol* 1992; 27(6 Pt 2): 15–18.
74. Goldfarb MT, Ellis CN, Weiss JS et al. Topical tretinoin therapy: Its use in photoaged skin. *J Am Acad Dermatol* 1989; 21(3 Pt 2):645–650.
75. Bhawan J. Short- and long-term histologic effects of topical tretinoin on photodamaged skin. *Int J Dermatol* 1998; 37(4):286–292.
76. Boisnic S, Branchet-Gumila MC, Le Charpentier Y et al. Repair of UVA-induced elastic fiber and collagen damage by 0.05% retinaldehyde cream in an ex vivo human skin model. *Dermatology* 1999; 199(1):43–48.
77. Creidi P, Humbert P. Clinical use of topical retinaldehyde on photoaged skin. *Dermatology* 1999; 199(1):49–52.
78. Lupo MP, Cole AL. Cosmeceutical peptides. *Dermatol Ther* 2007; 20(5):343–349.
79. Gorouhi F, Maibach HI. Role of topical peptides in preventing or treating aged skin. *Int J Cosmet Sci* 2009; 31(5):327–345.
80. Krueger N, Bayrhammer J, Sy M, Kerscher M. Palmitoyl Pentapeptide in skin aging: A randomized, double-blind, half-sided evaluation using bioengineering methods. *16th Congress of the European Academy of Dermatology and Venereology*, EADV 2007, Vienna, Austria, May 16–19 (Poster).
81. Lintner K. Promoting production in the extracellular matrix without compromising barrier. *Cutis* 2002; 70(6):13–16.
82. Mehta RC, Fitzpatrick RE. Endogenous growth factors as cosmeceuticals. *Dermatol Ther* 2007; 20(5):350–359.
83. Berlanga-Acosta J, Gavilondo-Cowley J, López-Saura P et al. Epidermal growth factor in clinical practice—A review of its biological actions, clinical indications and safety implications. *Int Wound J* 2009; 6(5):331–346.
84. Hardwicke J, Schmaljohann D, Boyce D et al. Epidermal growth factor therapy and wound healing—Past, present and future perspectives. *Surgeon* 2008; 6(3):172–177.
85. Nanney LB. Epidermal and dermal effects of epidermal growth factor during wound repair. *J Invest Dermatol* 1990; 94(5):624–629.
86. Shiraha H, Gupta K, Drabik K et al. Aging fibroblasts present reduced epidermal growth factor (EGF) responsiveness due to preferential loss of EGF receptors. *J Biol Chem* 2000; 275(25):19343–19351.
87. Tran KT, Rusu SD, Satish L et al. Aging-related attenuation of EGF receptor signaling is mediated in part by increased protein tyrosine phosphatase activity. *Exp Cell Res* 2003; 289(2):359–367.
88. Schouest JM, Luu TK, Moy RL. Improved texture and appearance of human facial skin after daily topical application of barley produced, synthetic, human-like epidermal growth factor (EGF) serum. *J Drugs Dermatol* 2012; 11(5):613–620.
89. Krueger N, Weber L, Kaess A, Buntrock H, Kerscher M. Biophysical and clinical evaluation of a topical treatment with 5% vitamin C and 0.1% madecassoside on skin physiology after 12 weeks. *18th Congress of the European Academy of Dermatology and Venereology*, EADV 2009, Berlin, Germany (Poster).
90. Fu JJJ, Hillebrand GG, Raleigh P et al. A randomized, controlled comparative study of the wrinkle reduction benefits of a cosmetic niacinamide/peptide/retinyl propionate product regimen vs. a prescription 0.02% tretinoin product regimen. *Br J Dermatol* 2010; 162(3):647–654.
91. Krueger N, Luebberding S, Streker M, Buntrock H, Kerscher M. Randomisierte, kontrollierte Untersuchung der Effekte eines dermatokosmetischen Pflegeregimes mit Niacinamide, Peptiden und einem Retinylester auf die Hautqualität im Gesicht. *46th Tagung der Deutschen Dermatologischen Gesellschaft*, DDG 2011, Dresden, Germany (Poster).
92. Krueger N, Moebius N, Kerscher M. Evaluation of skin physiology with biophysical measurements using four skin aging stages. *68th Annual Meeting of the American Academy of Dermatology*, AAD 2010, Miami Beach, FL (Poster).

Photoprotection

Brian L. Diffey

WHEN DO WE NEED PHOTOPROTECTION?

Cosmetic dermatologists need no persuasion that the ultraviolet (UV) component of sunlight, which comprises approximately 5% of terrestrial solar radiation, is largely responsible for the deleterious effects on the skin that are associated with sun exposure. Ubiquitous acceptance of this belief has formed the basis of sun protection campaigns hosted by public health agencies in many countries populated principally by people with white skin, as well as the continued development and improvement of topical sunscreens.

For most people, their greatest source of exposure to UV radiation is the sun. In people with white skins living in the tropics (30°N–30°S), sun protection is necessary all year to reduce the likelihood of sunburn (erythema), whereas for those living in temperate latitudes (40°N–70°N), sun awareness is generally limited to the 6-month period, that is, April to September, if sunburn is to be avoided.

It is popularly assumed that the hotter the sun, the greater the risk of sunburn, when in fact the main determinant of sunburn risk is the height of the sun in the sky. As a simple rule of thumb, when your shadow is shorter than your height, there is a risk of sunburn and sun protection measures are advised.

Several methods of personal protection against solar UV are available. These include

- Avoiding exposure to direct sunlight during the period around noon in summer
- Seeking shade
- Clothing designed to provide a high level of absorption of UV
- Hats that provide shade to the face and neck
- Topical sunscreens

When these measures are used in combination, it is possible to reduce exposure to solar UV to within acceptable levels without seriously limiting the range of outdoor activities that can be safely pursued.

Exposure to solar UV radiation is believed to be an important contributor to facial photoaging and daily application of a topical suncare product is thought to mitigate this process. The importance of a number of independent factors in reducing the lifetime UV exposure of facial skin, including the daily use of topical sunscreens all year round, is examined in "The UV Age" section.

SOLAR ULTRAVIOLET INDEX

The solar UV index (UVI) is a measure of the level of solar UV at the Earth's surface [1]. The values range from zero upward—the higher the value, the greater is the potential for damage to the skin and the less time it takes for harm to occur. In recent years, the UVI appears on TV weather forecasts and Internet websites to provide the public with a guide to the maximum intensity of the sun's UV rays.

In summer in Europe, the UVI typically peaks at values from 5 at high latitudes (~60°N, e.g., Scandinavia) to around 7 in central regions (~50°N, e.g., southern United Kingdom, Belgium, northern France) and up to 9 or 10 in southern Europe (~40°N, e.g., southern Spain). In the United States, the maximum UVI ranges from 11 in the southern continental United States to 5 in Alaska. For southern cities in Australia, such as Melbourne and Sydney, the measured UVI is maximal during summer (December–February), with UVI regularly reaching values of 12. In more northerly Australian cities, the maximum UVI can reach 16 [2].

The UVI measured on a summer's day across Europe is illustrated in Figure 10.1. Note the low values of 1–4 observed over Scandinavia and the United Kingdom, which are more the result of cloud cover than latitude, and contrast these values with the high values of 8 and 9 over the cloudless skies of southern Europe.

Table 10.1 shows how the numerical values of the UVI should be interpreted for different skin types.

PHYSICAL STRATEGIES FOR SUN PROTECTION

Avoiding Sunlight

The sun's UV rays are strongest in the 3-hour period around local noon when around one-half of a summer's day UV is received (see Figure 10.2). Simply keeping out of the sun by seeking shade, particularly around the middle of the day in tropical latitudes, is a powerful way of controlling personal exposure to solar UV radiation.

Shade

The UV radiation intensity at ground level comprises a direct component from the sun and a scattered, or diffuse, component from the sky (Figure 10.3a). When we seek shade and are in shadow, we remove the direct component and attenuate the diffuse component to a degree depending upon the fraction of the sky that is occluded (Figure 10.3b and c).

The impact of shade on UV intensity is such that when 60% of the sky is occluded, as well as direct sunlight, the intensity of UV on our skin is reduced to about one-fifth of that under an open sky. Another way of expressing this is to say that this degree of shade is equivalent to using a sunscreen delivering a sun protection factor (SPF) of about 5. Similarly, 80% and 90% occlusion of the sky, together with complete shading of direct sunlight, are equivalent to SPFs of about 10 and 20, respectively.

Shade can be provided naturally by trees, by utilizing canopies and semipermanent structures, or by constructed shade in areas where large numbers of people may gather.

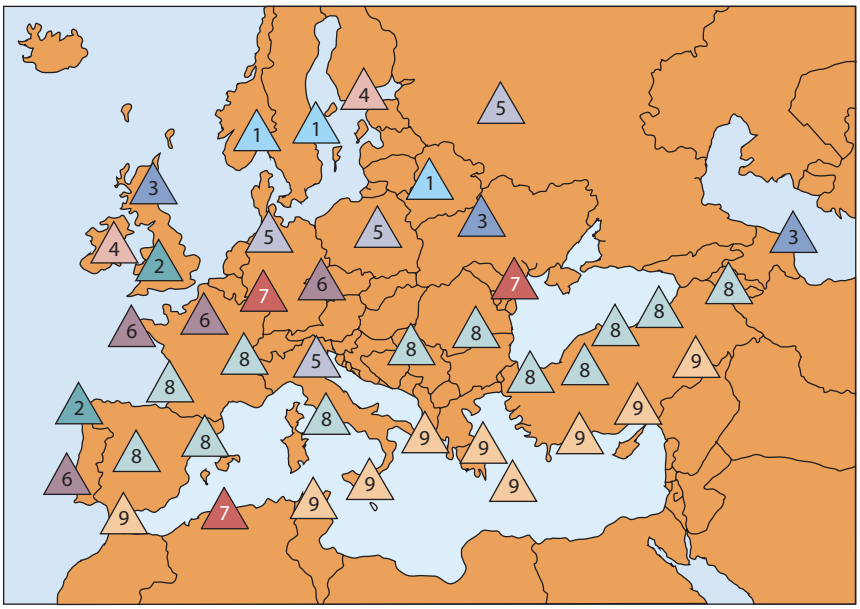


Figure 10.1 The solar UVI observed on a summer's day over Europe.

Table 10.1 Solar Ultraviolet Index and the Risk of Burning

	Skin type		
UV index	Burn easily, tends not to tan	Tans easily	Brown/black skin
1–2	Low	Low	Low
3–4	Medium	Low	Low
5	High	Medium	Low
6	Very high	Medium	Low
7–10	Very high	High	Medium
Low	The sun will not harm you.		
Medium	Avoid being in direct sunlight for more than 2 hours.		
High	It could burn in 30–60 minutes (cover up; use sunscreen).		
Very high	It could burn in 15–30 minutes (stay out of direct sunlight; use SPF30+).		

Small shade structures, such as parasols, can leave large amounts of sky visible to the occupant and may provide only low UV protection, typically protection factors (PFs) up to about 10. Trees provide a natural means of shade, but the diversity of genus and tree canopy dimensions can make it difficult to generalize the degree of protection afforded [3,4]. PFs for single trees can range from around 3 to greater than 50, depending on foliage and proximity to the periphery of the shadow cast by the tree (Figure 10.4).

Clothing and Hats

One consequence of the increasing concern about sun exposure has resulted in methods to determine the UV protection afforded by clothing fabrics and the introduction of the so-called ultraviolet protection factor (UPF), which is analogous to the SPF associated with sunscreens. The common method of determining the UPF is to use an *in vitro* method. Briefly, this method utilizes a source of UV radiation and a photodetector to measure the UV intensity, before and after passing through the fabric sample. The ratio of these two measurements is numerically equal to the UPF.

Clothing does not suffer from the uncertainties of sunscreen application (see "Factors Affecting the Protection Provided by Sunscreens" section), and a fabric whose UPF is 15, for example, really does provide this level of sun protection. National radiation laboratories in Australia and the United Kingdom have determined UPFs on several thousand summer-weight clothing fabrics with the following results [5,6]:

- Almost 90% of summer clothing has UPFs > 10 and, in practice, provides equivalent protection to sunscreens of SPF 30 or higher.
- Eighty percent of summer clothing has UPFs > 15 and under normal exposure, patterns will offer virtually complete protection.

A number of factors affect the protection offered by fabrics against solar UV radiation; these include weave, color, weight, stretch, and wetness (Figure 10.5).

Clothing is an effective and reliable source of protection against solar UV radiation, provided the garment exhibits good coverage of the skin, and the fabric prevents most of the incident UV radiation from reaching the skin beneath it. There are a number of commercial companies who market sun protective clothing claiming high UPFs (30+). While these claims are perfectly justified, it should be borne in mind that such high photoprotection may not be necessary except for highly sun-sensitive individuals with a pathological photosensitivity.

Wide-brimmed hats provide protection equivalent to a factor 4 or so over much of the face. A baseball-style hat

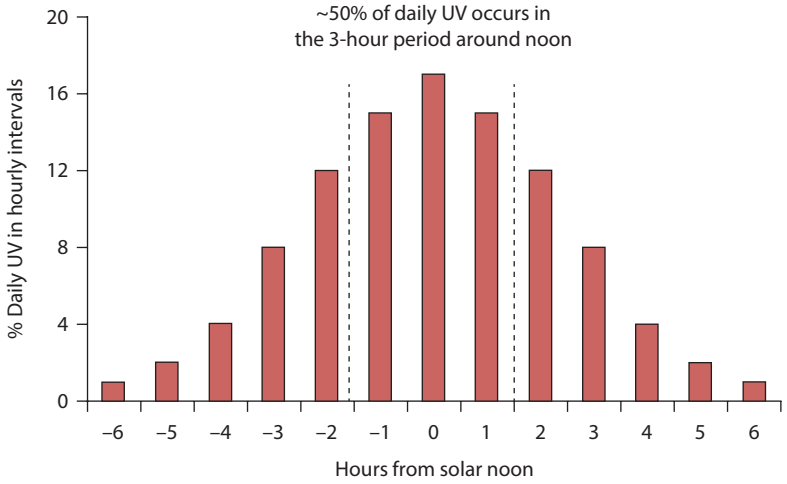


Figure 10.2 How ultraviolet varies during a summer day across temperate and tropical latitudes.

Figure 10.3 (a) When we are outside, we receive ultraviolet (UV) both directly from the sun and scattered from the sky. (b) Blocking only direct sunlight by shade still leaves us exposed to scattered UV from the sky. (c) But shielding our skin from both direct sunlight and much of the sky can reduce the UV intensity on our skin substantially.

provides good protection to the nose but leaves the cheeks and neck unprotected [7,8]. Legionnaire style hats, with a flap of fabric covering the neck and ears, are particularly effective.

Optical Filters

Materials that are visibly clear will absorb UV radiation to varying extents. For example, window glass transmits radiation down to 310 nm (within the UVB) [9], whereas plastics such as Perspex® and polycarbonate do not transmit below 370 nm. In general, windscreens on cars transmit some UVA but block UVB [10], unlike cockpit windscreens on airplanes, which block UVB and UVA [11].

SUNSCREENS

Topical sunscreens act by absorbing or scattering UV radiation and are widely available for general public use as a consumer product.

The first use of sunscreens was reported in 1928 [12] and, since then, they have become increasingly popular, particularly during outdoor recreation in which as little clothing as possible is worn, such as at the seaside [13,14]. When their application is commensurate with exposure, sunscreens undoubtedly protect against sunburn, although it is a truism that many people who apply sunscreen in the belief that they are protected will develop subsequent sunburn [15].

The core ingredient of a sunscreen is, of course, the UV absorber(s), but other factors such as the vehicle for the UV filters and optimization of the sunscreen in terms of attributes such as water resistance and photostability will also affect the efficacy and performance of the product [12].

Sun Protection Factor

The concept of the SPF was popularized by the Austrian scientist Franz Greiter in the 1970s and subsequently adopted by many regulatory authorities and the cosmetic and pharmaceutical industries. It is commonly interpreted as how much longer skin covered with sunscreen takes to burn compared with unprotected skin. So if you burn after 10 minutes in the sun, then using a sunscreen labeled with, say, SPF15, is taken to mean that you can safely remain in the sun for $10 \times 15 = 150$ minutes, or 2½ hours, before burning.

Figure 10.4 Protection provided by different types of tree.

This definition focuses on extending time in the sun, but a better way of thinking about the SPF is that if you spend a certain time in the sun, then wearing a sunscreen with a given SPF reduces the UV exposure to the skin to 1/SPF of that you would have received by spending the same time in the sun but with no sunscreen applied—so applying an SPF15 sunscreen results in an UV exposure to the skin of 1/15th of that you would have received if you had not applied any sunscreen. However, this statement is *only* true if the sunscreen is providing protection equivalent to the SPF, but as we shall see in "Factors Affecting the Protection Provided by Sunscreens" section, this rarely happens and most people who apply sunscreen are protected to a much lesser extent than they realize.

There is commonly held, but fallacious, belief that applying an SPF30 sunscreen confers little additional benefit to using an SFP15 sunscreen. The basis of the argument is that SPF15 means that 1–1/15 = 93.3% of solar UV is absorbed by the sunscreen and that SPF30 means that 1–1/30 = 96.6% is absorbed—apparently a difference so small that it is of little benefit. But what is important to skin health is not what is absorbed by the sunscreen but how much UV reaches the skin. So in the case of an SPF15 product, the skin exposure relative to unprotected skin for a given time in the sun is 1/15 = 6.7%, whereas for an SPF30 product, the relative exposure is 1/30 = 3.3%. In other words, twice as much UV reaches the skin when an SPF15 product is applied than when the same quantity of SPF30 is applied.

Thirty years ago, most commercially available sunscreen products had SPFs less than 10, but by 2000, most manufacturers produced products with factors of 15–30 and it is not uncommon to find products today claiming an SPF of 50 or higher.

Figure 10.5 Factors affecting sun protection properties of clothing.

What Wavelengths Should Sunscreens Protect Against?

We do not yet fully understand the importance of different wavelengths of UV radiation with regard to long-term effects of sun on the skin such as aging and skin cancer. It would seem sensible, therefore, to use sunscreens that absorb more or less uniformly throughout the UV spectrum: that is, absorb both UVB and UVA to much the same extent.

The rationale behind this thinking is that our skin has evolved to exist in harmony with the mix of wavelengths that make up the spectrum of sunlight here on the Earth's surface. Nature understands the importance of this so that when we seek natural shade or wear clothing to protect our skin from UV, the consequence is that we reduce the intensity, or power, of sunlight on our skin but change only minimally the spectrum or the relative mixture of different wavelengths [16].

The benefit of using a broad-spectrum sunscreen, that is, one that exhibits more or less equal absorption across the UV spectrum, is that for a given time in the sun, the total UV dose absorbed by the skin is much less than if, say, a sunscreen of the same SPF but absorbing mainly UVB radiation is used.

This concept can be illustrated by Figure 10.6, which shows the spectral profile—or the extent to which a particular product absorbs different wavelengths of UV—of three sunscreens all possessing exactly the same SPF.

Product A contains active ingredients that absorb mainly UVB radiation and is typical of sunscreens used in the 1980s and 1990s. Product B combines active filters that absorb both UVB and, to a lesser extent, UVA and typifies many products that have been on the market for the past 10 years or so. And product C is a modern, broad-spectrum sunscreen marketed by some of the larger sunscreen manufacturers in the past year or two.

Suppose that Ann uses product A, Betsy uses product B, and Clare uses product C. Each girl sunbathes for the same time, but do they all receive the same UV dose? The answer is *No*. Betsy will receive a UV dose to her skin that is 50% more than Clare's, while Ann receives three times the UV dose compared with Clare. Yet because each girl uses a sunscreen with the same SPF and we assume each girl applies the same quantity of product to her skin, they are protected equally against sunburn. So the moral is always use a sunscreen offering broad-spectrum protection in order to minimize the overall UV exposure of your skin.

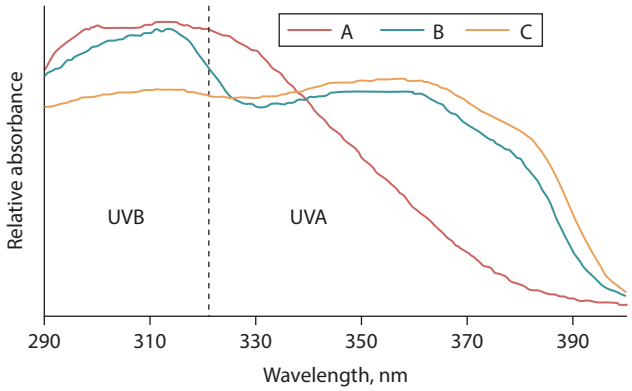


Figure 10.6 The spectral absorbance profile of three different sunscreens, each having the same sun protection factor but containing a different mix of active ultraviolet absorbers.

This example is the reason that it is now widely accepted that sunscreens should provide balanced, broad-spectrum protection and so manufacturers have sought to develop products with spectral profiles that approach this ideal. There has been considerable success in this regard, and today, we have available products that virtually meet this criterion. For example, a modern high-SPF (30+) broad-spectrum sunscreen might contain the following five active UV filters: octocrylene, bis-ethylhexyloxyphenol methoxyphenyl triazine, butyl methoxydibenzoylmethane, ethylhexyl salicylate, and diethylhexyl butamido triazone.

Sunscreen–Sunburn Paradox

A paradoxical result of many observational studies is the high prevalence of sunburn in subjects using sunscreen [17–21]. So why might this be given that the prevention of sunburn is by far the most common reason for using sunscreens and laboratory testing confirms unequivocally that sunscreens will prevent erythema?

How large the SPF should be to prevent sunburn can easily be determined if we know the local solar UV levels, the time spent and the behavior of someone using sunscreen in outdoors, and their personal susceptibility to sunburn. Maximum daily UV levels (called ambient UV), which occur on the ground, under a completely open (i.e., no shade), cloudless summer sky are about 60–70 SED in Australia and 40–50 SED for Europe. The SED, which is the acronym for standard erythema dose [22], is a measure of the UV dose of sunlight that results in sunburn; it requires an exposure of about 2 SED to produce a very mild sunburn in sun-sensitive individuals who burn easily and never tan, rising to about 4–5 SED in people with naturally white skin but who tan easily [23].

These maximum ambient exposures will not be received by people simply because it would be unrealistic to lie flat in the unshaded sun all day without moving. An extreme sunbather might spend half the time lying on their back and half the time supine, resulting in a maximum exposure on much of the body surface of about 50% of ambient. For people who are upright and mobile engaging in an outdoor pursuit such as gardening, walking, or sport, the exposure relative to ambient on commonly exposed sites, e.g., chest, shoulder, face, forearms, and lower legs, ranges from about 5% to 60%, depending on the particular body site and the presence of nearby shade, such as buildings.

So someone in southern Europe who spends all-day long sunbathing on a clear summer's day would receive a daily skin exposure of no more than 50 SED × 50% = 25 SED. If they have skin that responds typically to sunlight, they would need to use a sunscreen that reduces this exposure to, say, 3 SED or less if they are to avoid any erythema (sunburn) that evening. In other words, the sunscreen should provide 25 SED divided by 3 SED = eightfold protection, or put another way, have an SPF of 8. And if you are walking around in an urban environment, where you may receive about 20% of ambient on exposed sites such as the arms and face, sunburn should theoretically be avoided if you are wearing a product providing an SPF of [50 SED × 20%]/3 SED = SPF 3.

So then, why do people who use high factor (SPF > 15) sunscreen experience sunburn so frequently? That the protection achieved is often less than that expected is explained by a number of reasons, as discussed in the following.

Factors Affecting the Protection Provided by Sunscreens

There are several factors that determine why most people who use sunscreens will receive less protection than they are expecting from the labeled SPF.

Application Thickness

The protection offered by a sunscreen—defined by its SPF—is assessed after testing a panel of volunteers in the laboratory at an internationally agreed application thickness of 2 mg/cm^2. Yet there are many studies [15] that show that consumers in real-life situations apply much less than this—typically between 0.5 and 1.5 mg/cm^2.

The relationship between application thickness and resulting SPF has been investigated by a number of authors [24–27]. The results have been variable ranging from an exponential relationship between SPF and applied thickness [26] through to an approximately linear relationship [27], with others showing a relationship somewhere between exponential and linear [24,25]. In a theoretical analysis [28], it was shown that depending on the spectral absorption profile of the product, the relationship would vary but for sunscreens with spectral profiles typical of those currently available, a linear relationship is closest to the best descriptor.

So, if sunscreen was applied uniformly, most sunscreen users would only achieve a level of protection of around one-half of that expected from the SPF on the product label. But as we shall see in the next section, application is rarely uniform and as a consequence, the average protection delivered can be considerably less than this [29].

Application Technique

When sunscreens are tested on a panel of volunteers in the laboratory to determine their SPF, great care is taken to achieve a uniform layer of sunscreen over the test area by spreading with a gloved finger. In practice, of course, nothing like this care is taken when sunscreen is applied to the skin. Sunscreen is normally spread haphazardly and nonuniformly with the result that patchy sunburn may appear after sun exposure, as illustrated in Figure 10.7.

Spray-on sunscreens have become popular in recent years, but, as Figure 10.8 illustrates, unexpected sunburn can occur if they are not spread carefully over the skin after application [30].

Sunscreen Formulation

The formulation of the sunscreen can be an important factor influencing an individual's willingness to use and reapply a sunscreen. In terms of formulation, creams have lost popularity

Figure 10.7 The consequence of nonuniform sunscreen application (Photo courtesy of http://www.philip.greenspun.com).

Figure 10.8 Protected skin within the diameter of the sunscreen spray's mist with surrounding sunburn. (From Diffey BL, *J Am Acad Dermatol*, 45, 882, 2001. Reproduced with permission.)

due to the fact that they are less easy to rub into the skin and can leave a white film, which many consumers find unacceptable. High-SPF products, which could previously be found only in cream formulations, now include lotions, milks, gels, sticks, and sprays.

In one comparative study of formulations designed for facial use, including lotions, creams, gels, and sprays, an alcohol-based spray formulation of sunscreen was rated the most favorable as this sunscreen was said to be less greasy and less likely to leave a film than at least two of the other sunscreens evaluated [31].

Sunscreens containing inorganic chemicals, such as zinc oxide or titanium dioxide, as the sole active ingredient can leave a white film on the skin, and as a consequence, people may compensate for this by applying less quantity than products incorporating organic filters [32]. This can reduce the protection achieved, which is especially unfortunate, because inorganic sunscreens are sometimes marketed as total sunblocks and will tend to be used by sun-sensitive individuals, including those with sensitive skin or eczema.

The importance of good formulation, resulting in a cosmetically appealing product, is increasingly being recognized by manufacturers. It is all very well making a sunscreen with a very high SPF, but if consumers do not like the feel or look of it, they will not bother using it or may apply so little that the real protection they are getting leaves them vulnerable to sunburn and skin damage. Figure 10.9 compares two sunscreens, one with a formulation that results in a colorless film on the skin and the other that tends to leave a white residue. Remember, it is not all about the SPF.

Reapplication

The reasons for reapplying sunscreen during sun exposure are to compensate for initial underapplication so as to achieve an SPF more in line with the rated value and to replace sunscreen that may have been removed by water, vigorous toweling, or friction with clothing or sand. Inadequate application is the primary purpose for reapplication since modern water-resistant sunscreens adhere well to the surface of the skin even after immersion in water.

Guidance on sunscreen packs about reapplication is generally to "reapply frequently" or "reapply regularly" and a common recommendation by many public health agencies is to reapply sunscreen every 2–3 hours. Given considerations of cost, convenience, and human nature, it is unlikely many users will reapply sunscreens frequently or regularly.

If you use a sunscreen that is easily removed from the skin, then you will achieve little in the way of sun protection, no matter when it is reapplied. For sunscreens that bind well to skin, found in water-resistant products, the lowest skin exposure results from early reapplication into the sun exposure period and not at 2–3 hours, after initial application. Typically, reapplication of sunscreen at 20 minutes into a 4-hour exposure period to strong summer sunshine results in one-half to three-quarters

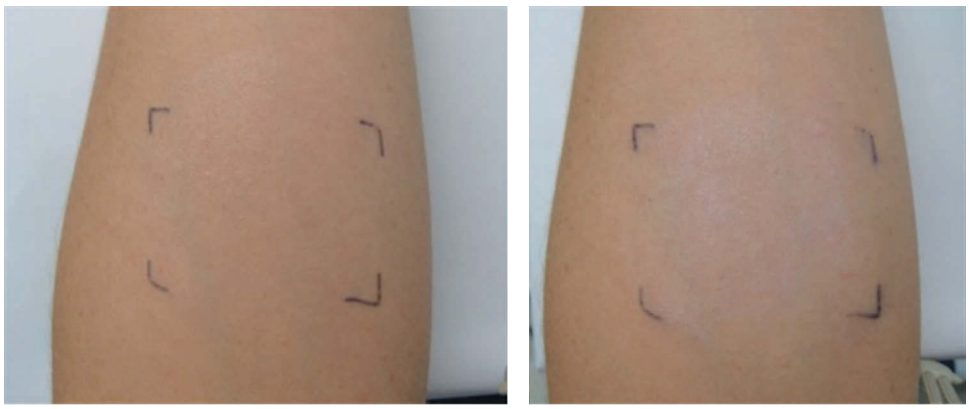


Figure 10.9 The sunscreen on the left leaves an invisible film on the skin, while that on the right leaves a white residue.

of the UV exposure that would be received compared with waiting 2 hours before the sunscreen is reapplied [33].

Consumers are advised to apply sunscreen liberally or generously. However, many studies have shown that users feel uncomfortable with application at 2 mg/cm^2—the thickness used by manufacturers during the testing process to determine the SPF—and prefer to apply quantities averaging at around one-half this thickness. That people generally apply less than 2 mg/cm^2 has led many commentators into the trap of believing that consumers use inadequate amounts of sunscreen for protection. The reality is the reverse. People use the quantity they feel comfortable with and in this sense are using the "correct" amount; it is the labeled SPFs that are misleading.

It is likely, therefore, that campaigns to encourage people to apply a greater quantity of sunscreen at a single application will fail. An important factor in sunscreen performance is the uneven nature of the skin surface. If an opaque sunscreen is applied to the skin, the surface markings become visible as the grooves on the skin surface are filled. With further application, the intervening ridges are also covered and the surface becomes more featureless. The situation is analogous to painting a wall with a textured surface (see Figure 10.10) when two coats of paint are almost always required for satisfactory coverage. In the same way, two "coats of sunscreen" may be required for adequate protection.

So advising people to reapply sunscreen early into their sun exposure period may well be more successful than at 2–3 hours when the reasons they have for being in the sun are more likely to make them forget. Here are the tips for applying sunscreen:

- Apply sunscreen liberally to exposed sites 15–30 minutes before going out into the sun.
- Do not rub the sunscreen into your skin, but spread the sunscreen as uniformly as possible over the surface of the skin and allow to dry.
- Reapply sunscreen to exposed sites 15–30 minutes after sun exposure begins.
- Further reapplication of sunscreen is necessary after vigorous activity that could remove sunscreen, such as swimming, toweling, or excessive sweating and rubbing.

Figure 10.10 Like painting a wall with a textured surface, when two coats of paint are almost always required for satisfactory coverage, two "coats of sunscreen" may be required for adequate protection to the textured skin surface.

All of the factors described in "Application Thickness" through "Reapplication" sections mean that, as a rule of thumb, the protection achieved from applying a sunscreen is estimated as typically about one-third of the rated SPF [15]. So in order to be confident that tenfold protection is being achieved, a sunscreen labeled SPF30 needs to be applied.

Finally, do not forget that people will tend to apply sunscreen more frequently on those summer days when the weather is fine and they intend spending recreational time outdoors. And it is on days such as these that they are most vulnerable to sunburn if sunscreen application is less than ideal.

ULTRAVIOLET AGE

When we look at Figure 10.11a, we see skin that is wrinkled and sagging with pigmentary changes, whereas the skin in Figure 10.11b is smooth and elastic. We might conclude that the person in Figure 10.11a is much older than in Figure 10.11b, but we would be wrong as they are one and the same person—a 64-year-old female.

So while both areas of skin have the same chronological age, their exposure to the sun's UV rays over the course of the subject's lifetime has been vastly different. The facial skin shown in Figure 10.11a has been exposed to solar UV radiation on a daily basis, the magnitude of exposure varying considerably over the course of a year reflecting, among other things,

(a)

(b)

Figure 10.11 The face (a) and lower back (b) of a 64-year-old woman.

seasonal variations in ambient UV radiation and time spent outdoors each day. On the other hand, the skin of the lower back in Figure 10.11b has been protected from solar UV on the large majority of days throughout life and has been exposed only during outdoor recreational activities such as swimming or sunbathing.

One way of reflecting this difference in exposure is to assign both areas of skin a *UV age*. This can be thought of as the age when chronically exposed skin with no photoprotection would have experienced the same UV exposure as areas of skin that are regularly protected throughout life, either by clothing or topical sunscreens. So, for example, the UV age of the facial skin of the 64-year-old woman shown in Figure 10.11a would be 64 years, whereas the UV age of the same woman's skin shown in Figure 10.11b might be only 20 years; over the course of the subject's lifetime of 64 years to date, this area of lower back skin has received the same cumulative UV exposure as the facial skin area shown in Figure 10.11a had received by the time the woman was aged 20 years.

Figure 10.11 is a graphic example of why it is widely accepted that exposure to solar UV radiation is an important factor in the aging of facial skin. While the precise action spectrum for photoaging in human skin is unknown, there are ample biochemical and histological data to implicate both UVA and UVB wavebands [34–36].

As a consequence, the cosmetics industry has responded by introducing topical products intended for daily use that incorporate UV filters. A recent analysis [37] examined the influence of a number of independent factors to determine which are most important in minimizing the UV age of facial skin.

Most importantly, regular use should begin early in life as this factor is the largest contribution toward the overall variance. Even if regular use begins later in life, the age at which this begins remains important.

Of lesser importance but still contributing appreciably toward the overall variance, is to choose a product offering state-of-the-art broad-spectrum protection in favor of a product that provides largely UVB protection. For example, a person who only begins using daily suncare at age 40 years could reduce the UV age of his or her skin by a further 10–14 years by choosing a good broad-spectrum product rather than a product absorbing principally in the UVB region, even though both may be delivering the same SPF, as illustrated in Figure 10.12.

And of least importance is to apply the product liberally (so as to approximate the labeled SPF) and to apply facial photoprotection on a daily basis throughout year. This last requirement only achieves a minimal benefit in terms of UV age compared with limiting facial photoprotection to the spring and summer months. Also, it does increase the possibility that vitamin D levels may be compromised during the winter months owing to attenuation of solar UV exposure by the facial photoprotectant during the early autumn.

The choice of a daily suncare product that exhibits good broad-spectrum protection would not in itself be enough to provide consumers with sustainable sun protection. To be sustainable, a product should not only be safe and deliver effective UV protection, it should also have a sensory and tactile profile that can enhance the user's experience and encourage regular use. So while it remains unproven and speculative, there is good reason to suppose that regular use of facial topical products containing UV filters that deliver broad-spectrum protection and are formulated so as to be pleasurable to use will be translated into fewer visible signs of aging later in life.

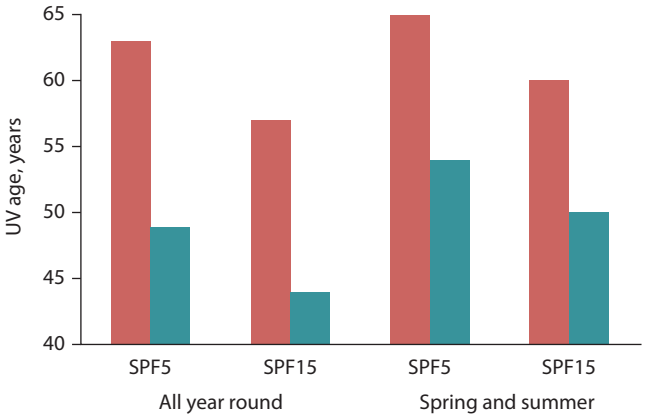


Figure 10.12 The ultraviolet (UV) age for use of two suncare products starting at age 40 years by someone living in temperate latitudes. The pink blocks refer to a broad-spectrum product with a spectral profile similar to that shown by curve C in Figure 10.6, and the blue blocks relate to a product absorbing principally in the UVB region, typical of that shown by curve A in Figure 10.6. Products are delivering an SPF of either 5 or 15 and are used on a daily basis either all year round or just in the spring and summer (March to August).

CONCLUSION

Applying sunscreen is just one element of a strategy aimed at controlling sun exposure, which includes seeking shade around the middle of the day and wearing clothing and wide-brimmed hats. Sunscreen application can be problematic, however. Insufficient cream is normally applied to achieve the rated SPF, and that which is applied is often spread nonuniformly, resulting in some exposed skin sites achieving little or no protection. In addition, sunscreen is removed to a greater or lesser extent due to activities such as swimming and toweling and reapplication often takes place when the skin has already been exposed to sufficient sunlight to result in sunburn.

These factors, coupled with other factors discussed in "Factors Affecting the Protection Provided by Sunscreens" section, provide ample evidence that the numerical measure of protection indicated on the product pack by the SPF is generally higher than achieved in practice. This mismatch between expectation and realization may be one contributing factor why sunscreens have not yet been conclusively confirmed to prevent skin cancer [38]. On the other hand, this apparent lack of efficacy of sunscreens should not prevent their use, alongside other sun protective measures, during recreational summer sun exposure. The corollary to this advice is, of course, that their use does not deliberately lead to excessive sun exposure as inadequate and nonuniform application, coupled with extended times in the sun, could result in unacceptably high exposure of "sunscreen-protected" skin.

In conclusion, the hierarchy of sun protection can be summed up as follows:

- *Shade*—can provide very high protection if a large part of the sky, as well as direct sunlight, is obscured. It is not difficult to achieve effective shade with PFs > 20.
- *Clothing*—generally good to high protection (usually PF > 10), although, of course, there is no protection to non-clothed areas.

- *Sunscreens*—low to moderate protection (mostly PF < 10) for commonly used labeled SPFs (15–30) because of the mismatch between typical application thicknesses and that used by manufacturers. Unlike clothing, there is uncertainty about the sites protected once the sunscreen has been rubbed into the skin.

REFERENCES

1. World Health Organization. *Global Solar UV Index: A Practical Guide*. Geneva, Switzerland: WHO, 2002.
2. Gies P, Roy C, Javorniczky J, Henderson S, Lemus-Deschamps L, Driscoll C. Global Solar UV Index: Australian measurements, forecasts and comparison with the UK. *Photochem Photobiol* 2004; 79:32–39.
3. Diffey BL, Diffey JL. Sun protection with trees. *Br J Dermatol* 2002; 147:397–399.
4. Parisi AV, Kimlin MG, Wong JCF, Wilson M. Personal exposure distribution of solar erythemal ultraviolet radiation in tree shade over summer. *Phys Med Biol* 2000; 45:349–356.
5. Gies HP, Roy CR, McLennan A. Textiles and sun protection. In: Volkmer B, and Heller H, eds. *Environmental UV-Radiation, Risk of Skin Cancer and Primary Prevention*. Stuttgart, Germany: Gustav Fischer, 1996, pp. 213–234.
6. Driscoll CMH. Artificial protection against solar radiation—Fabrics. In: Giacomoni PU, ed. *Sun Protection in Man*, Amsterdam, the Netherlands: Elsevier Science BV, 2001, pp. 457–486.
7. Diffey BL, Cheeseman J. Sun protection with hats. *Br J Dermatol* 1992; 127:10–12.
8. Wong JCF, Airey DK, Fleming RA. Annual reduction of solar UV exposure to the facial area of outdoor workers in Southeast Queensland by wearing a hat. *Photodermatol Photoimmunol Photomed* 1996; 12:131–135.
9. Almutawa F, Vandal R, Wang SQ, Lim HW. Current status of photoprotection by window glass, automobile glass, window films, and sunglasses. *Photodermatol Photoimmunol Photomed* 2013; 29:65–72.
10. Hampton PJ, Lloyd JJ, Diffey BL, Farr PM. Protection from UVA by car window glass. *Br J Dermatol* 2002; 147:17–18.
11. Diffey BL, Roscoe AH. Exposure to solar ultraviolet radiation in flight. *Aviat Space Environ Med* 1990; 61:1032–1035.
12. Shaath NA. Sunscreen evolution. In: Shaath NA, ed. *Sunscreens: Regulations and Commercial Development*, 3rd ed. Boca Raton, FL: Taylor & Francis Group, 2005, pp. 3–17.
13. Koh HK, Bak SM, Geller AC et al. Sunbathing habits and sunscreen use among white adults: Results of a national survey. *Am J Public Health* 1997; 87:1214–1217.
14. Robinson JK, Rademaker AW. Sun protection by families at the beach. *Arch Pediatr Adolesc Med* 1998; 152:466–470.
15. Diffey BL. Sunscreens: Expectation and realisation. *Photoderm Photomed Photoimmunol* 2009; 25:233–236.
16. Diffey BL, Brown MW. The ideal spectral profile of topical sunscreens. *Photochem Photobiol* 2012; 88:744–747.
17. Autier P, Boniol M, Doré J-F. Sunscreen use and increased duration of intentional sun exposure: Still a burning issue. *Int J Cancer* 2007; 121:1–5.
18. Wright MA, Wright ST, Wagner RF. Mechanisms of sunscreen failure. *J Am Acad Dermatol* 2001; 44:781–784.
19. Diffey BL, Norridge Z. Reported sun exposure, attitudes to sun protection and perceptions of skin cancer risk: a survey of visitors to Cancer Research UK's SunSmart campaign website. *Br J Dermatol* 2009; 160:1292–1298.
20. Dixon H, Shatten R, Borland R. Reaction to the 1995/1996 SunSmart Campaign: Results from a representative household survey of Victorians. In: *SunSmart Evaluation Studies No 5*. Melbourne, Australia: Anti-Cancer Council of Victoria, 1997, pp. 70–96.
21. Ling T-C, Faulkner C, Rhodes LE. A questionnaire survey of attitudes to and usage of sunscreens in northwest England. *Photodermatol Photoimmunol Photomed* 2003; 19:98–101.
22. CIE Standard. Erythema reference action spectrum and standard erythema dose. CIE S 007/E-1998. Vienna, Austria: Commission Internationale de l'Éclairage 1998.
23. Harrison GI, Young AR. Ultraviolet radiation-induced erythema in human skin. *Methods* 2002; 28:14–19.
24. Brown S, Diffey BL. The effect of applied thickness on sunscreen protection: In vivo and in vitro studies. *Photochem Photobiol* 1986; 44:509–513.
25. Stokes RP, Diffey L. How well are sunscreen users protected? *Photodermatol Photoimmunol Photomed* 1997; 13:186–188.
26. Faurschou A, Wulf HC. The relation between sun protection factor and amount of sunscreen applied in vivo. *Br J Dermatol* 2007; 156:716–719.
27. Bimczok R, Gers-Barlag H, Mundt C et al. Influence of applied quantity of sunscreen products on the sun protection factor—A multicenter study organized by the DGK Task Force Sun Protection. *Skin Pharmacol Physiol* 2007; 20:57–64.
28. Herzog B, Mueller S, Osterwalder U. Understanding sunscreens—Influence of amount of application on performance determined by in vivo and in silico experiments. *Poster P420 presented at 65th Annual Meeting of the American Academy of Dermatology*, Washington, DC, February 2–6, 2007.
29. Pissavini M, Diffey B. The likelihood of sunburn in sunscreen users is disproportionate to the SPF. *Photodermatol Photoimmunol Photomed* 2013; 29:111–115.
30. Barr J. Spray-on sunscreens need a good rub. *J Am Acad Dermatol* 2005; 52:180–181.
31. Solky BA, Phillips PK, Christenson LJ, Weaver AL, Roenigk RK, Otley CC. Patient preferences for facial sunscreens: A split-face, randomized, blinded trial. *J Am Acad Dermatol* 2007; 57:67–72.
32. Diffey BL, Grice J. The influence of sunscreen type on photoprotection. *Br J Dermatol* 1997; 137:103–105.
33. Diffey BL. When should sunscreen be reapplied? *J Am Acad Dermatol* 2001; 45:882–885.
34. Yaar M, Gilchrest BA. Photoageing: Mechanism, prevention and therapy. *Br J Dermatol* 2007; 157:874–87.
35. Kligman LH, Sayre RM. An action spectrum for ultraviolet induced elastosis in hairless mice: Quantification of elastosis by image analysis. *Photochem Photobiol* 1991; 53:237–242.
36. Bissett DL, Hannon DP, Orr TV. Wavelength dependence of histological, physical, and visible changes in chronically UV-irradiated hairless mouse skin. *Photochem Photobiol* 1989; 50:763–769.
37. Diffey BL. The impact of topical photoprotectants intended for daily use on lifetime ultraviolet exposure. *J Cosmet Dermatol* 2011; 10:245–250.
38. Anon. Do sunscreens have a role in preventing skin cancer? *Drug Therapeut Bull* 2011; 49:69–72.

Allergic risks to cosmetics and hypersensitive skin

An E. Goossens and Martine Vigan

INTRODUCTION

The assessment and detection of the number of contact allergic reactions to cosmetics are not simple. Generally, a consumer who has a problem with cosmetics will consult a doctor only if he or she does not recognize the cause to be a particular cosmetic product or if the dermatitis persists when the suspected product has been replaced by another, determined by trial and error. Consequently, only a small proportion of the population with cosmetic intolerance problems is ever seen by a dermatologist. Moreover, cosmetic reactions may present in unusual clinical forms, which may evoke an erroneous diagnosis.

In general, adverse effects are underreported [1], certainly to the cosmetics industry, which obtains its most reliable information in this regard mainly from the relatively few dermatologists who concentrate on cosmetic intolerance problems and from reports in the literature that are, almost by definition, out of date. Sometimes beauticians and consumers report adverse reactions, but in most cases, this kind of information is difficult to objectify unless it is verified by a dermatologist.

Application of cosmetic products to the skin may cause irritant, phototoxic, contact allergic, and photocontact allergic reactions, as well as contact urticaria. It is generally agreed that most skin-adverse reactions to cosmetic products are irritant in nature and that people with *sensitive skin* are particularly liable to develop such reactions. However, contact allergic reactions attract much more attention and thus tend to be overestimated, although recently such reactions are increasingly seen in dermatological practice. The identification of the cosmetic allergen is by no means a simple task. It demands special skills and interest on the part of the dermatologist, although labeling of all cosmetic ingredients is facilitating that task. Moreover, there are many factors involved in the sensitization to a specific cosmetic product, all of which have to be taken into account when one seeks an allergen.

FACTORS CONTRIBUTING TO CONTACT ALLERGIC REACTIONS TO A COSMETIC PRODUCT

Frequency of Use

One may expect frequently used products to cause more skin reactions than more exclusive products simply because more people are exposed to them. This alone does not imply anything about the quality of these products (the same thing may be said about individual cosmetic ingredients).

Composition

The complexity of a formula can be either positive or negative as far as its allergenic capacity is concerned. One of the principles of creating *hypoallergenic* cosmetics and perfumes is simplicity of formula: the fewer the constituents, the easier it is to identify the offending substance should difficulties arise, and the less danger there is of synergism. Some investigators recommend placing upper limits on concentrations rather than advising against the use of any particular ingredient. However, the more ingredients there are, the more chance there is of sensitization by one of them.

Preservatives are needed in water-based or other easily contaminated products and have recently become as important cosmetic allergens as fragrances. It seems that it is very difficult to combine potent antimicrobial and antifungal properties with low allergenic capacity: indeed, it is very difficult to restrict the biological activity of a substance to a single domain. Therefore, some cosmetic manufacturers have developed new packaging devices in order to prevent the introduction of air and microorganisms into the containers during usage, thus avoiding the addition of preservatives into the formulation.

Concentration of Ingredients

Although the use of low concentrations does not assure complete safety, the incidence of sensitization induction is, indeed, a function of the concentration of the allergen, at least to some extent. But once a patient has become sensitized, even low concentrations can trigger a reaction. Cases of allergy to the preservative mixture of methylchloro- and methylisothiazolinone (MCI/MI) illustrate this problem very well (Figure 11.1). At first, when a 30 ppm concentration of this mixture was allowed for use in cosmetic products in the European community and when this concentration was actually used in some products, there were *epidemics* of contact allergic reactions to it. Later on, the frequency of positive reactions had diminished considerably, not only because its use was declining, particularly in *leave-on* cosmetics (remaining on the skin for several hours), but also because its usage concentration had been reduced to 15 and 7.5 ppm in *rinse-off* (being removed almost immediately) and *leave-on* products, respectively. However, many problems are actually being seen again with the less sensitizing MI alone that, because of lower antimicrobial activity, is allowed up to 100 ppm in cosmetics (see Figure 11.2).

Purity of Ingredients

It is impossible to refine raw materials to absolute purity. More or less strict quality control of raw materials and finished

(a) (b)

Figure 11.1 (a and b) Methylisothiazolinone as the allergenic culprit, producing sharply demarcated infiltrated lesions.

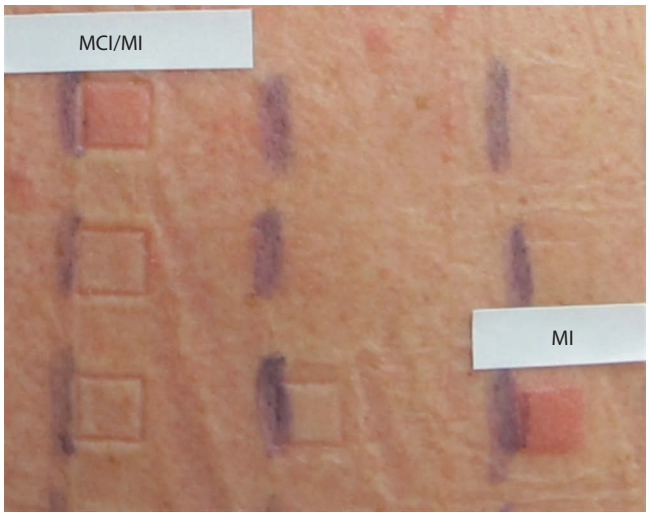


Figure 11.2 Positive patch-test reactions to methylchloroisothiazolinone/methylisothiazolinone and methylisothiazolinone, with the stronger reaction to the latter indicating it as the primary sensitizer.

products has long been general practice in modern cosmetic manufacturing. However, one can never rule out the sensitizing potential of impurities in these materials, such as has been the case, for example, with the amphoteric surface-active agent cocamidopropyl betaine, in which amides and amines originating from the synthesis were the allergenic culprits.

Common Use of Cosmetic Ingredients in Pharmaceuticals

Patients easily become sensitized to topical pharmaceutical products, which, unlike cosmetics, are most often applied to diseased skin. Once sensitization has occurred, however, they may react to cosmetics containing the same ingredients.

Role of Cross Sensitivity

Chemically related substances are likely to induce cross-reactions and contact eczematous lesions may be maintained in this way. This is especially the case with fragrance ingredients, which often cross-react with each other, as well as with natural ingredients, among which are botanically derived extracts. Cross-reactions may, however, occur with many other cosmetic ingredients as well.

Penetration-Enhancing Substances

The chemical environment can substantially affect the sensitizing potential of individual chemicals. For example, emulsifiers and solvents enhance skin penetration and thereby contact sensitization. Penetration-enhancing agents can also be the cause of false-negative patch-test reactions: the cosmetic product itself may be clearly allergenic, while the individual ingredients, abstracted from the environment of the product and tested separately, may not cause a reaction.

Condition of the Skin

Application on damaged skin, where the skin barrier is impaired, enhances the penetration of substances and thus increases the risk of an allergic reaction. This is the case with body-care products used to alleviate dry, atopic skin and with barrier creams for protecting the hands, which often suffer from irritant problems (dryness, cracking). The skin reaction may also be limited to certain areas that have been previously affected, since these react more readily to subsequent application of the same allergen. Sometimes, an already existing dermatitis or another eczematous skin condition such as atopic or seborrhoeic dermatitis may be aggravated or even mimicked, and also a noneczematous clinical picture may sometimes point

to a cosmetic allergy, for example, with preservative agents that may present as a lymphocytic infiltrate or even have a lupus erythematosus-like picture [2].

Contact Time

A said previously, a distinction is being made between leave-on products, such as face- and body-care products and makeup, and rinse-off products, such as soaps and shampoos. Particular attention needs to be paid to wipes (moist toilet tissues), with mainly preservatives as the allergenic culprits, since a thin film remains on the skin, sufficient to allow ingredients to penetrate.

Frequency of Application and Cumulative Effects

Daily use or use several times a day of cosmetics may cause ingredients to accumulate in the skin and thus increase the risk of adverse reactions. In fact, the concentration of an ingredient may be too low to induce sensitivity in a single product but may reach critical levels in the skin if several products containing it are used consecutively. This may be the case for people who are loyal to the same brand of, for example, day and night creams, foundations, and cleansing products, because a manufacturer will often use the same preservative system for all of its products. This should be taken into consideration by companies that use biologically active ingredients such as preservative agents, emulsifiers, antioxidants, and fragrances, because it might well account for many of the adverse reactions to these particular substances. In our experience, intense users of cosmetics are more prone to cosmetic dermatitis than others.

CORRELATIONS WITH THE LOCATION OF THE LESIONS

Like many other contact allergens, cosmetics can reach the skin in several different ways: by direct application; by airborne exposure to vapors, droplets, or particles that are released into the atmosphere and then settle on the skin (e.g., *volatile* fragrance components) causing *airborne* dermatitis; by contact with people (partners, friends, coworkers) who transmit allergens to cause *connubial* or *consort* dermatitis; by transfer from other sites on the body, often the hands, to more sensitive areas such as the mouth or the eyelids, in particular (this is called "ectopic" dermatitis, for example, due to resins in nail polish); and by exposure to the sun with photoallergens. In case of a severe allergic reaction, eczematous lesions may spread to body parts other than the application site or even become generalized.

Furthermore, the penetration potential of cosmetics is heightened in certain *occluded* areas, such as the body folds (axillae) and anogenital region, which also increases the risk of contact sensitization. The allergic reactions often tend to persist for weeks following the initial contact with the allergen. This may be partly attributable to residual contamination of clothing, but the increased penetration of the allergen, assisted by occlusion and friction, may lead to the formation of a reservoir from which the allergen is subsequently again released.

NATURE OF COSMETIC CONTACT ALLERGENS

In cosmetics, fragrances and preservative agents are the most important culprits, but reactions also occur to ingredients of category-specific products such as hair dyes, resins used in nail cosmetics, and sunscreens, as well as to antioxidants, vehicle components, emulsifiers, etc.

Fragrance components most often produce allergic reactions when present in toilet waters, after-shave lotions, and deodorants, but also skin-care and other cosmetic products may be involved. The main skin sites affected are the face, neck, axillae, and hands.

The literature confirms that fragrance mix (I), which contains eight components (amyl cinnamal, cinnamal, cinnamyl alcohol, hydroxycitronellal, eugenol, isoeugenol, geraniol, and *Evernia prunastri* [oak moss] extract, all diluted 1% in petrolatum and emulsified with sorbitan sesquioleate) and which is tested routinely in the baseline series, remains a good screening agent for contact allergy to fragrances because it is said to detect some 70%–80% of all perfume allergies [3,4]. However, this also depends on how many and which fragrances are tested in order to detect contact allergy and the literature insists on the need to test with additional compounds. Indeed, additional markers such as other mixes and individual components, as well as complex natural mixtures [5–8], increase the sensitivity of the testing. This is the reason why a second fragrance mix (II) consisting of hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral®), farnesol, citral, citronellol, coumarin, and alpha-hexyl cinnamal, as well as hydroxyisohexyl 3-cyclohexene carboxaldehyde itself has been introduced into the baseline series as well [9]. Nowadays, the relevance for positive patch tests can be more readily determined and sensitized consumers are better informed since 26 fragrance components are (since March 2005) labeled as cosmetic ingredients on the packaging (Annex 3 of the Cosmetic Directive 2003/15/EC).

Most fragrance-sensitive subjects present with multiple positive patch-test reactions, which indicate the presence of common or cross-reacting ingredients in natural products, the occurrence of cross-reactions between simple fragrance chemicals, or concomitant sensitization. Moreover, fragrance components may be allergenic by themselves but may also contain strongly sensitizing oxidation products [10,11], as is the case with, for example, the terpenic components limonene and linalool, or they may be contaminated by allergenic impurities. For example, this has been shown for resin acids and their oxidation products; the main allergens in colophonium are also detected in *Evernia prunastri* (oak moss), which was contaminated with or substituted by the cheaper *Evernia furfuracea* (tree moss), which, as colophonium, is also derived from pine trees [12].

Preservatives have recently become more important cosmetic allergens, particularly in water-based cosmetic products. However, within this class, important shifts have occurred over the years [13,14].

Methyldibromo glutaronitrile—which was used in a mixture with phenoxyethanol, better known as Euxyl K400®—became such an important cosmetic allergen that, in March 2007, the EU did not longer permit its further use in cosmetic products.

The mixture of MCI and MI, commonly in use since the 1980s, did cause an epidemic of contact allergies after which it has been recommended by the manufacturer to be used only in rinse-off products (up to a maximum of 15 ppm); however, it was still found in several leave-on products on the market such as moisturizers and (baby) wipes, the latter often producing allergic contact dermatitis [15], even in those who took care of babies. In cosmetics, MCI/MI is now largely replaced by MI, which is a weaker sensitizer than the chlorinated derivative, but also less efficient as a preservative; hence, larger use concentrations (up to 100 ppm) are required. MCI-/MI-sensitive

patients not only often react to this nonhalogenated derivative [16], but MI reveals to be an important primary sensitizer itself. Most cases are caused by the use of wipes (moist toilet paper) for intimate hygiene; however, also other cosmetic products may be the sensitization source [17]. The numerous cases and prevalence studies (e.g., [18]) recently reported in the literature point to a new epidemic of MI contact allergy all over Europe.

The incidence of positive reactions to formaldehyde and its releasers is slightly increasing again [14]. Besides releasing formaldehyde, imidazolidinyl urea and diazolidinyl urea do contain allergenic degradation products [19,20].

Parabens are rare causes of cosmetic dermatitis and when allergy does occur, the sensitization source is most often a topical pharmaceutical product. Its withdrawal from cosmetics (but neither from pharmaceuticals nor food) is merely a consumer, publicity, and political issue [21].

Exceptional cosmetic allergens are chlorphenesin that may cross-react with mephenesin, a rubefacient in topical pharmaceutical products [22], and iodopropynyl butylcarbamate, also present in baby and makeup cleansing wipes [23] and reported as a cosmetic allergen by Pazzaglia and Tosti in 1999 [24]. Its presence in cosmetics is being discussed, not because of its potentially allergenic properties but because of its iodine content.

Antioxidants are only a minor group of cosmetic allergens. Examples are propyl and octyl gallate [25], which may cross-react with other gallates that are also used as food additives. Some antioxidants are used more specifically in sunscreen products and also in moisturizing products to prevent aging but are rare causes of allergic contact dermatitis in such preparations, for example, tocoferol (vitamin E) acetate and retinol palmitate [26], ascorbic acid (vitamin C) [27], and idebenone or hydroxydecyl ubiquinone (a synthetic analog of Coenzyme Q10 (CoQ10) [28]. Also (meta)bisulfites are potential allergens in cosmetic creams and hair dyes [29]. More recently, we have observed six cases of contact allergy to tetrahydroxypropyl ethylenediamine, a chelating compound, due to its presence in skin-care products; no cross-reactions to ethylenediamine or edetate were observed [30].

With regard to *category-specific ingredients*, the number of reactions to oxidative-type hair dyes (para-phenylenediamine [PPD] and related compounds) increases in some centers and decreases in others (e.g., [31]). Active sensitization to PPD and related compounds from temporary tattoos has been encountered (e.g., [32]); however, hair dyes are the main culprits both in clients, in whom they often cause severe reactions, and hairdressers. Moreover, also immediate-type reactions or the contact urticaria syndrome may occur to it (see below), as well as to persulfates in hair bleaches.

In nail varnish, tosylamide/formaldehyde (= toluenesulfonamide formaldehyde) resin and also epoxy resin and copolymers may be the cause of *ectopic* dermatitis, which often gives rise to confusing clinical pictures, even mimicking occupational dermatitis. (Meth)acrylates are important causes of reactions to artificial nail adhesives and gel formulations, being the newest development in this regard, both generally in clients and particularly in manicurists [33].

As to sunscreens, because of media attention being given to the carcinogenic and accelerated skin-aging effects of sunlight, they are increasingly used, not only in sunscreen products but also in other cosmetics including moisturizers, and this in rather high concentrations. They are also used to protect cosmetic products from degradation. Sunscreen agents may be responsible for irritant, allergic, and photoallergic reactions (e.g., [34]) and also contact urticaria (see below). Octocrylene, in particular, has become a frequently reported contact allergen, also in children [35]. Moreover, it also often causes photocontact allergy (see below). The contribution of sunscreens to cosmetic allergy has been considered to be relatively small despite the increase in their use; however, the low rate of allergic reactions observed may be well because a contact allergy or a photoallergy to sunscreen products is often not recognized, since a differential diagnosis with a primary sun intolerance is not always obvious. Furthermore, the patch-test concentrations generally used might be too low, in part because of the risk of irritant reaction. Last but not least, photopatch testing is not routinely performed in a dermatological practice, which might be the most obvious reason for underreporting.

Excipients, emulsifiers, and humectants are common ingredients to topical pharmaceutical and cosmetic products, the former being likely to induce sensitization. The classical examples are wool alcohols, fatty alcohols (e.g., cetyl alcohol), and propylene glycol, but these are really rare allergens in cosmetics. Emulsifiers in particular have long been regarded as irritants, but their sensitization capacities should not be overlooked. It is imperative, of course, that patch testing be properly performed to avoid irritant reactions and that the relevance of the positive reactions be determined. A large number of newer emulsifiers, emollients, or excipients have been reported as cosmetic allergens, for example, sodium stearoyl lactate [36], polyglyceryl laurate [37], dicaprylyl maleate [38], isononyl isononanoate, and trioleyl phosphate [39], as well as ascorbyl tetraisopalmitate [40]. Some humectants are also, because of their low irritant properties and *skin mildness*, often incorporated in skin-care products *recommended by dermatologists*, *for use on intolerant* or *for sensitive skin* that have become very popular in recent years. A low irritant potential, however, does not preclude the occurrence of, albeit rarely, allergic contact dermatitis from such cosmetics. Examples are butylene glycol [41] (Figure 11.3) and pentylene glycol [42], i.e., aliphatic alcohols with similar uses (solvent,

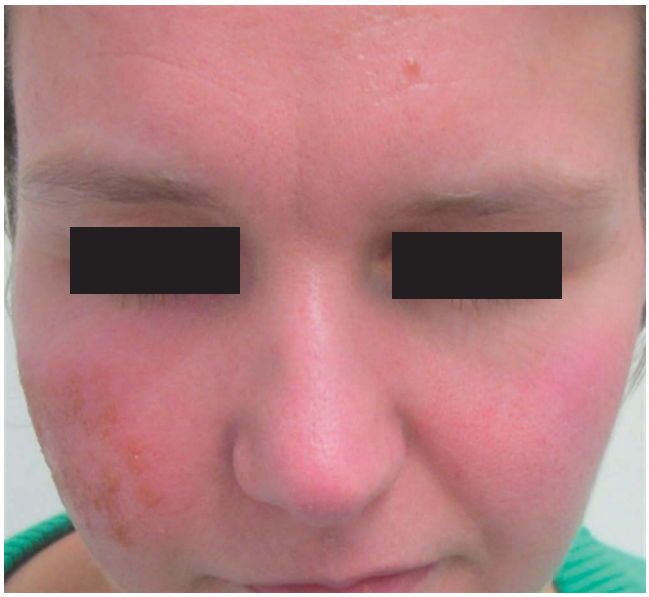


Figure 11.3 Allergic contact dermatitis from pentylene and butylene glycols.

humectants, and antibacterial) to propylene glycol that is considered to be more irritant and allergenic, and ethylhexylglycerin (syn. octoxyglycerin), a skin conditioning agent [43]. Other occasional contact allergens are alkyl glucosides, i.e., coco and lauryl glucosides [44], which are also used as mild surfactants and cleansing agents in *biological* cosmetics; decyl glucoside is a hidden allergen in sunscreen products [45].

Copolymers are potential allergens as well, for example, methoxy PEG-17 and PEG-22/dodecyl glycol copolymers and PVP/hexadecene copolymer (see [46] for a review), with the most recent one described being C30–38 olefin/isopropyl maleate/Ma copolymer in a sunscreen [47] and moisturizer [48]. In view of their rather high molecular weight, the exact nature of the allergens involved is not known, and impurities or degradation products might well be the actual culprits, such as has been shown, for example, for hydroxyethyl acrylate in hydroxyethyl acrylate/sodium acryloyldimethyl-taurate copolymer [49].

Natural ingredients: Botanically derived materials have become very popular in recent years and may give rise to (sometimes severe) contact dermatitis problems [50,51] in aroma therapists, beauticians, and clients. Patients found allergic to fragrance components should be advised to avoid such cosmetics, since these may cross-react.

Proteins and protein-derived ingredients, such as hydrolysates, are often used in skin-care products intended to be used for the treatment of the dry skin in atopic subjects (often children). Allergic contact dermatitis (sometimes located mainly on the eyelids [52]) may occasionally develop, for example, oat or *Avena* extract—of which the allergenic proteins may be removed though—[53], hydrolyzed wheat protein [54], and soy bean extract [55]. However, not only contact dermatitis but also immediate-type reactions [56] to such products may occur [57], particularly in atopic subjects; hence, their use has given rise to controversies since subjects may perhaps get sensitized through topical preparations and develop food allergies afterward, or vice versa [58,59].

Photocontact Allergens

In the 1960s, most photoallergic reactions resulted from the use of deodorant soaps containing halogenated salicylanilides and related compounds, while in the 1980s, they were most often due to musk ambrette and 6-methylcoumarin, present in, for example, after shaves, thus affecting men. This sometimes resulted in the development of persistent light reactions. Later on, sunscreens, particularly benzophenones (its presence needs to be labeled on the packaging) and dibenzoylmethane derivatives, became important photoallergens, while methylbenzylidene camphor, cinnamates, phenylbenzimidazole sulfonic acid, and octyl triazone were only occasionally reported in this regard (e.g., [34] for a review). The reactions to benzophenones and particularly octocrylene [35] are, in most cases, actually related to photocontact allergy to ketoprofen, a nonsteroidal anti-inflammatory drug widely used to treat muscle pain. The reason is not clear yet and needs to be further elucidated, since cross-reactivity as in the case between ketoprofen and benzophenones is not that obvious. Beside, most ketoprofen-sensitized subjects also react to the fragrance component cinnamyl alcohol.

Allergens Causing Immunologic Contact Urticaria

IgE-mediated or immediate-type allergic reactions may be caused both by low-molecular weight chemicals and large molecules, such as proteins and derivatives. Cosmetic examples of substances to which severe reactions (even anaphylaxis) also have been reported are permanent hair dyes, e.g., PPD [60–62], and also direct hair dyes, for example, basic blue 99 (e.g., [63]), persulfates in hair-bleaching products [64], the sunscreen agents benzophenones [65–67], and protein-derived, i.e., hydrolyzed products used in skin and hair-care products [68,69].

DIAGNOSING COSMETIC ALLERGY

We can only find the allergens we look for; hence, all ingredients in cosmetic products should be regarded as potential contact allergens [70–72]. Beside taking a careful history of the patient and noting the clinical symptoms and localization of the lesions, allergen identification for a patient with a possible contact allergy to cosmetics is performed by means of patch testing with the baseline (standard) series, specific cosmetic-test series, the used products themselves, and all their ingredients. Late readings up to 7 days are advised. If suspected, photopatch tests should be performed as well. However, when a cosmetic dermatitis is suspected and the results of patch testing are doubtful or false-negative, usage tests and/or repeated open application tests are additional test procedures to obtain a correct diagnosis. Moreover, if immunologic contact urticaria is suspected, prick tests with the cosmetic product and its ingredients, with immediate test readings, are necessary.

PRODUCTS FOR SENSITIVE SKIN

Most of the cosmetic industry is making a great effort to commercialize products that are the safest possible. The latest trend is target marketing to people with *hypersensitive* or *intolerant* skin, an often used term for the shadowy zone between normal and pathological skin. These would be people with increased neurosensitivity, heightened immune responsiveness, or a defective skin barrier, i.e., people with irritable skin such as atopic subjects or those suffering from seborrhoeic dermatitis or rosacea. This means that part of the cosmetic industry is moving more into the area of pathological skin and that certain products are in fact becoming drugs, often called "cosmeceuticals" in the United States. In Japan, however, these products fall in the category of *quasidrugs*.

The meaning of most such claims used nowadays is unclear both for the dermatologist and for the consumer; the latter is convinced that hypersensitive skin is allergic skin. It is the dermatologist's task to diagnose the skin condition and to provide specific advice about the products that can safely be used. All such problems must be approached individually, not least the contact allergic types, because people sensitive to specific ingredients must avoid products containing them. Therefore, ingredient labeling can be of tremendous help. Moreover, providing the allergic patient with a limited list of cosmetics that can be used is practical and effective [73].

COSMETOVIGILANCE: THE POSTMARKETING SURVEY

As the cosmetics products can have undesirable effects, mainly allergic effects, and as these side effects of them may lead to acute or chronic health impairment, their safety has to be regulated. This is taken care of in European Union by the Cosmetics Products Directive (76/768/EEC) [74], which is planned to be replaced on July 2013 by the new Cosmetic Products Regulation (EC N°1223/2009) [75]. This new regulation requires

manufacturers to ensure the safety of their products in normal use and under reasonable foreseeable conditions, as well as national market surveillance authorities to monitor compliance with the regulation. For surveillance authorities, there are three steps: monitoring activities, corrective actions, and exchange of information via the RAPEX [76], which is a general and horizontal early warning and monitoring system. It is designed for handling urgent situations caused by products that present a serious and immediate risk to the health and safety of consumers. Its essential aim is to provide information in order to allow authorities of all member states to take immediate and appropriate action when a serious risk arising from a product has been detected.

In 2006, the Council of Europe adopted a resolution [77] recommending that each member state implements a system for registering undesirable effects of cosmetics products (cosmetovigilance) directed at protecting public health. This cosmetovigilance system is based on reported cases, as has been put in place in France since 2004, the results of which are on the website of the "Agence Nationale de Sécurité des Médicaments" [78]. Other cosmetovigilance systems seem to have been created in Belgium, Norway, Sweden, Denmark, Germany, and Italy (1) [79–82], collecting the reports from the health professionals; a pilot study in the Netherlands showed the interest to collect also consumers' reports [83]. Before the existence of public cosmetovigilance systems, the French Group of Dermato-Allergologists (the GERDA) had already in 1996 created a confraternal structure "REVIDAL GERDA," collecting case reports on allergic reactions to cosmetic products observed by dermatologists [83]. REVIDAL GERDA has worked in collaboration with the industry, and its members have often been able to test ingredients provided by the respective companies in order to also detect new allergens [84]. All cosmetovigilance systems have been shown to provide valuable information on the symptoms (Figure 11.4) and the localization of undesirable effects of cosmetics products, and the French one, in particular, has shown that the occurrence of immediate reactions to cosmetics products is not so rare and that testing ought to include open and also prick tests, with immediate readings [68,69]. It has also been shown to be an important tool for detecting new emerging ingredients, such as vitamin K, wheat hydrolyzed proteins [57], octocrylene [35], or alkyl glucosides [44]. When a problem emerges, certain measures need to be taken, for example, informing and advising the respective producers, such as in the case of hydrolyzed (wheat) proteins, or informing the general public via the media as for the so-called temporary henna tattoos [32] (Figure 11.5). The cosmetovigilance system is indeed a way to obtain information on the safety of cosmetics ingredients and can be used by the member states to assess whether new EU regulation provides adequate security.

Figure 11.4 Induction of sensitization to para-phenylenediamine by a so-called temporary henna tattoo.

Figure 11.5 Information for the general public via the media for the so-called temporary henna tattoos (Reproduced with permission from ASSAPS).

CONCLUSION

The identification of cosmetic allergens is challenging because of the extreme complexity of the problem. This applies not only for the dermatologist who is trying to identify the culprit and advise his or her patient but certainly also for cosmetic manufacturers, who are extremely concerned about assuring the innocuousness of their products. Precise, current, and rapid information about adverse reactions to cosmetic products is critical in product design. Apparently, premarketing studies are unable to identify all the pitfalls. Therefore, the fruitful communication that is developing between dermatologists

and cosmetic manufacturers must be encouraged. Sensitivity to cosmetics can never be totally avoided, but its incidence can be substantially reduced.

REFERENCES

1. Berne B, Boström A, Grahnén AF et al. Adverse effects of cosmetics and toiletries reported to the Swedish medical products agency 1989–1994. *Contact Dermatitis* 1996; 34:359–362.
2. Morren MA, Dooms-Goossens A, Delabie J et al. Contact allergy to isothiazolinone derivatives. *Dermatologica* 1992; 198:260–264.
3. Johansen JD, Menné T. The fragrance mix and its constituents: A 14-year material. *Contact Dermatitis* 1995; 32:18–23.
4. Frosch PJ, Pilz B, Andersen KE et al. Patch testing with fragrances: Results of a multi-center study of the European Environmental and Contact Dermatitis Research Group with 48 frequently used constituents of perfumes. *Contact Dermatitis* 1995; 33:333–342.
5. Larsen W, Nakayama H, Fischer T et al. A study of new fragrance mixtures. *Am J Contact Dermatitis* 1998; 9:202–206.
6. Frosch PJ, Johansen JD, Menné T et al. Lyral is an important sensitizer in patients sensitive to fragrances. *Br J Dermatol* 1999; 141:1076–1083.
7. Frosch PJ, Johansen JD, Menné T et al. Further important sensitizers in patients sensitive to fragrances. I. Reactivity to 14 frequently used chemicals. *Contact Dermatitis* 2002; 47:78–85.
8. Frosch PJ, Johansen JD, Menné T et al. Further important sensitizers in patients sensitive to fragrances. II. Reactivity to essential oils. *Contact Dermatitis* 2002; 47:279–287.
9. Bruze M, Andersen KE, Goossens A. Recommendation to include fragrance mix 2 and hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral) in the European Baseline patch test series. *Contact Dermatitis* 2008; 58:129–133.
10. Karlberg A-T, Goossens A. Contact allergy to oxidized d-limonene among dermatitis patients. *Contact Dermatitis* 1997; 36:201–206.
11. Christensson JB, Andersen KE, Bruze M. Air-oxidized linalool-a frequent cause of fragrance contact allergy. *Contact Dermatitis* 2012; 67:247–250.
12. Lepoittevin JP, Meschkat E, Huygens S, Goossens A. Presence of resin acids in "oakmoss" patch test material: A source of misdiagnosis? Letter to the Editor. *J Invest Dermatol* 2000; 115:129–130.
13. Wilkinson JD, Shaw S, Andersen KE et al. Monitoring levels of preservative sensitivity in Europe: A 10-year overview (1991–2000). *Contact Dermatitis* 2002; 46:207–210.
14. Svedman C, Andersen KE, Brandão FM. Follow-up of the monitored levels of preservative sensitivity in Europe: Overview of the years 2001–2008. *Contact Dermatitis* 2012; 67:312–314.
15. Timmermans A, De Hertog S, Gladys K et al. Dermatologically tested baby toilet tissues: A cause of contact dermatitis in adults. *Contact Dermatitis* 2007; 57:97–99.
16. Gruvberger B, Lecoz C, Gonçalo M et al. Repeated open application testing with methylisothiazolinone: Multicentre study within the EECDRG. *Dermatitis* 2007; 18:111.
17. Garcia-Gavín J, Vansina S, Kerre S, Naert A, Goossens A. Methylsiothiazolinone: An emerging allergen in cosmetics? *Contact Dermatitis* 2010; 63:96–101.
18. Lundov MD, Krongaard T, Menné T et al. Methylisothiazolinone contact allergy—A review. *Br J Dermatol* 2011; 165:1178–1182.
19. Doi T, Kajimura K, Taguchi S. The different decomposition properties of diazolidinyl urea in cosmetics and patch test materials. *Contact Dermatitis* 2011; 65:81–91.
20. Doi T, Takeda A, Asada A et al. Characterization of the decomposition of compounds derived from imidazolidinyl urea in cosmetics and patch test materials. *Contact Dermatitis* 2012; 67: 284–292.
21. Revuz J. Vivent les parabènes. Long live parabens. *Ann Dermatol Vénéréol* 2009; 136:403–404.
22. Wakelin SH, White IR. Dermatitis from chlorphenesin in a facial cosmetic. *Contact Dermatitis* 1997; 37:138–139.
23. Natkunarajah J, Osborne V, Holden C. Allergic contact dermatitis to iodopropynyl butylcarbamate found in a cosmetic cleansing wipe. *Contact Dermatitis* 2008; 58:316–317.
24. Pazzaglia M, Tosti A. Allergic contact dermatitis from 3-iodo-2-propynyl-butylcarbamate in a cosmetic cream. *Contact Dermatitis* 1999; 41:290.
25. Giordano-Labadie F, Schwarze HP, Bazex J. Allergic contact dermatitis from octylgallate in lipstick. *Contact Dermatitis* 2000; 42:51.
26. Manzano D, Aguirre A, Gardeazabal J et al. Allergic contact dermatitis from tocopheryl acetate (vitamin E) and retinol palmitate (vitamin A) in a moisturizing cream. *Contact Dermatitis* 1994; 31:324.
27. Belhadjali H, Giordano-Labadie F et al. Contact dermatitis from Vitamin C in a cosmetic anti-aging cream. *Contact Dermatitis* 2001; 45:317.
28. Sasseville, D, Moreau, L, Al-Sowaidi, M. Allergic contact dermatitis to idebenone used as an antioxidant in an anti-wrinkle cream. *Contact Dermatitis* 2007; 56:117.
29. Garcia-Gavín J, Parente J, Goossens A. Allergic contact dermatitis caused by sodium metabisulfite, a challenging allergen. A case series and literature review. *Contact Dermatitis* 2012; 67:62–69.
30. Goossens A, Baret I, Swevers A. Allergic contact dermatitis from tetrahydroxypropyl ethylenediamine in cosmetic products. *Contact Dermatitis* 2011; 64:161–164.
31. Thyssen JP, Andersen KE, Bruze M et al. Para-Phenylenediamine sensitization is more prevalent in central and southern European patch test centres than in Scandinavian: Results from a multicentre study. *Contact Dermatitis* 2009; 60:314–319.
32. Lecoz CJ, Lefebvre C, Keller F et al. Allergic contact dermatitis caused by skin painting (pseudo tattooing) with black henna, a mixture of henna and para-phenylenediamine and its derivatives. *Arch Dermatol* 2000; 136:1515–1517.
33. Constandt L, Van Hecke E, Naeyaert J-M et al. Screening for contact allergy to artificial nails. *Contact Dermatitis* 2005; 52:73–77.
34. Goossens A. Photoallergic contact dermatitis. *Photodermatol Photoimmunol Photomed* 2004; 20:121–125.
35. Avenel-Audran M, Dutartre H, Goossens A et al. Octocrylene, an emerging photoallergen. *Arch Dermatol* 2010; 146:753–757.
36. Jensen CD, Charlotte D, Andersen, KE. Allergic contact dermatitis from sodium stearoyl lactylate, an emulsifier commonly used in food products. *Contact Dermatitis* 2005; 53:116.
37. Washizaki K, Kanto H, Yazaki S et al. A case of allergic contact dermatitis to polyglyceryl laurate. *Contact Dermatitis* 2008; 58:187–188.
38. Lotery H, Kirk S, Beck M et al. Dicaprylyl maleate—An emerging cosmetic allergen. *Contact Dermatitis* 2007; 57:169–172.
39. Goossens A, Verbruggen K, Cattaert N et al. New cosmetic allergens: Isononyl isononanoate and trioleyl phosphate. *Contact Dermatitis* 2008; 59:320–321.
40. Swinnen I, Goossens A. Allergic contact dermatitis from ascorbyl tetraisopalmitate. *Contact Dermatitis* 2011; 64:241–242.
41. Sugiura M, Hayakawa R, Kato Y et al. Results of patch testing with 1, 3-butylene glycol from 1994 to 1999. *Environ Dermatol* 2001; 8:1–5.
42. Gallo R, Viglizzo G, Vecchio F et al. Allergic contact dermatitis from pentylene glycol in an emollient cream, with possible cosensitization to resveratrol. *Contact Dermatitis* 2003; 48:176–177.
43. Linsen G, Goossens A. Allergic contact dermatitis from ethylhexylglycerin. *Contact Dermatitis* 2002; 47:169.
44. Goossens A, Decraene T, Platteaux N et al. Glucosides as unexpected allergens in cosmetics? *Contact Dermatitis* 2003; 48:164–166.
45. Blondeel A. Contact allergy to the mild surfactant decylglucoside. *Contact Dermatitis* 2003; 49:304–305.
46. Quartier S, Garmyn M, Becart S et al. Allergic contact dermatitis to copolymers in cosmetics—Case report and review of the literature. *Contact Dermatitis* 2006; 55:257–267.
47. Kai AC, White J, White I et al. Contact dermatitis caused by C30–38 olefin/isopropyl maleate/MA copolymer in a sunscreen. *Contact Dermatitis* 2011; 64:353–354.

48. Swinnen I, Goossens A, Rustemeyer T. Allergic contact dermatitis caused by C30–38 olefin/isopropyl maleate/MA copolymer in cosmetics. *Contact Dermatitis* 2012; 67:318–320.
49. Lucidarme N, Aerts O, Roelandts R et al. Hydroxyethyl acrylate: A potential allergen in cosmetic creams? *Contact Dermatitis* 2008; 59:321–322.
50. Kiken DA, Cohen DE. Contact dermatitis to botanical extracts. *Am J Contact Dermatitis* 2002; 13:148–152.
51. Thomson KF, Wilkinson SM. Allergic contact dermatitis to plant extracts in patients with cosmetic dermatitis. *Br J Dermatol* 2003; 142:84–88.
52. Pazzaglia M, Jorizzo M, Parente G et al. Allergic contact dermatitis due to avena extract. *Contact Dermatitis* 2000; 42:364.
53. Vansina S, Debilde D, Morren M-A, Goossens A. Sensitizing oat extracts in cosmetic creams: Is there an alternative? *Contact Dermatitis* 2010; 63:169–171.
54. Sanchez-Pérez J, Sanz T, García- Díez A. Allergic contact dermatitis from hydrolyzed wheat protein in a cosmetic cream. *Contact Dermatitis* 2000; 42:360.
55. Shaffrali FCG, Gawkrodger DJ. Contact dermatitis from soybean extract in a cosmetic cream. *Contact Dermatitis* 2001; 44:51–52.
56. Varjonen E, Petman L, Mäkinen-Kiljunen S. Immediate contact allergy from hydrolyzed wheat in a cosmetic cream. *Allergy* 2000; 55:294–296.
57. Pecquet C, Lauriere M, Huet S et al. Is the application of cosmetics containing protein-derived products safe? *Contact Dermatitis* 2002; 46:123.
58. Boussault P, Léauté-Labrèze C. Saubusse E et al. Oat sensitization in children with atopic dermatitis. *Allergy* 2007; 62:1251–1256.
59. Goujon-Henry C, Hennino A, Nicolas JF. Letter to the editor. *Allergy* 2008; 63:781–782 (former paper discussed).
60. Sahoo B, Handa S, Penchallaiah K et al. Contact anaphylaxis due to hair dye. *Contact Dermatitis* 2000; 43:244.
61. Wong GAE, King CM. Immediate-type hypersensitivity and allergic contact dermatitis due to para-phenylenediamine in hair-dye. *Contact Dermatitis* 2003; 48:166.
62. Sösted H, Agner T, Menné T et al. 55 cases of allergic reactions to hair dye: a descriptive, consumer complaint-based study. *Contact Dermatitis* 2002; 47:299–303.
63. Wigger-Alberti W, Elsner P, Wüthrich B. Immediate-type allergy to the hair dye basic blue 99 in a hairdresser. *Allergy* 1996; 51:64.
64. Alto-Korte K, Mäkinen-Kiljunen S. Specific immunoglobulin E in patients with immediate persulfate hypersensitivity. *Contact Dermatitis* 2003; 49:22–25.
65. Bourrain JL, Amblard P, Béani JC. Contact urticaria photoinduced by benzophenones. *Contact Dermatitis* 2003; 48:45–47.
66. Emonet S, Pasche-Koo F, Perin-Minisini MJ et al. Anaphylaxis to oxybenzone, a frequent constituent of sunscreens. *J Allergy Clin Immunol* 2001; 107:556–557.
67. Yésudian PD, King CM. Severe contact urticaria and anaphylaxis from benzophenone-3 (2-hydroxy 4-methoxy benzophenone). *Contact Dermatitis* 2002; 46:55–56.
68. Varjonen E, Petman L, Mäkinen-Kiljunen S. Immediate contact allergy from hydrolyzed wheat in a cosmetic cream. *Allergy* 2000; 55:294–296.
69. Vansina S, Debilde D, Morren M-A, Goossens A. Sensitizing oat extracts in cosmetic creams: Is there an alternative? *Contact Dermatitis* 2010; 63:169–171.
70. Goossens A. Allergy and hypoallergenic products. In: André O Barel, Marc Paye, Howard I Maibach, eds. *Chapter 53 in Handbook of Cosmetic Science and Technology*, 3rd ed. New York: Informa Healthcare 2009, pp. 553–562.
71. Nardelli A, Carbonez A, Ottoy W et al. Frequency of and trends in fragrance allergy over a 15-year period. *Contact Dermatitis* 2008; 58:134–141.
72. Travassos AR, Claes L, Boey L, Drieghe J, Goossens A. Non-fragrance allergens in specific cosmetic products. *Contact Dermatitis* 2011; 65:276–285.
73. Goossens A, Drieghe J. Computer applications in contact allergy. *Contact Dermatitis* 1998; 38:51–52.
74. European Commission. Council Directive 76/768/EEC. July 1976. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31976L0768:EN:HTML. Last accessed May 31, 2013.
75. European Commission. Regulation (EC) N° 1223:2009 of the parliament and of the council of 30 November 2009. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:342:0059:01:EN:HTML. Last accessed May 31, 2013.
76. Directive 2001/95/EC of the European Parliament and of the Council of 3 December 2001 on general product safety. http://eur-lex.europa.eu/Notice.do?val=272287:cs&lang=en&list=272287:cs,258366:cs,258142:cs,&pos=1&page=1&nbl=3&pgs=10&hwords=&checktexte=checkbox&visu=#texte. Last accessed May 31, 2013.
77. Council of Europe. Resolution ResAP. 2006. 1 on a vigilance system for undesirable effects of cosmetics products ('cosmetovigilance') in Europe in order to protect public health. https://wcd.coe.int/ViewDoc.jsp?id=1061283&Site=CM. Last accessed May 31, 2013.
78. http://www.ansm.sante.fr. Last accessed May 31, 2013.
79. cosmétovigilance. http://www.health.belgium.be/eportal/SearchResults/index.htm. Last accessed May 31, 2013.
80. Folkehelseinstituttet. National register of adverse effects from cosmetic products. 2008–2010. 2011. http://www.fhi.no/dokumenter/df751a6d55.pdf. Last accessed May 31, 2013.
81. Sautebin L. A cosmetovigilance survey in Europe. *Pharmacol Rev* 2007; 55:455–460.
82. Sportiello L, Cammarota S, de Porto S, Sautebin L. Notification of undesirable effects of cosmetics and toiletries. *Pharmacol Res* 2009; 59:101–106.
83. Salverda JGW, Bragt PJC, de Wit-Bos L et al. Results of a cosmetovigilance survey in The Netherlands. *Contact Dermatitis* 2013; 68:139–148.
84. Le Coz CJ, Leclere JM, Arnoult E et al. Allergic contact dermatitis from shellac in mascara. *Contact Dermatitis* 2002; 46:149–152.

Hormones and the skin

Gérald E. Piérard, Claudine Piérard-Franchimont, and Trinh Hermanns-Lê

INTRODUCTION

Hormones play an important role in the life span of each individual. In particular, skin is recognized as a hormone-dependent organ [1–3]. Metabolic effects related to the amounts of hormones reaching the skin and the intrinsic cutaneous neuroendocrine activity are important to consider. In addition, like any other organ, the hormonal system is influenced by the global aging process. This leads to various deteriorations possibly responsible for functional deficiencies. Such involution in turn influences the multifaceted global aging machinery operative in the skin. Quite distinct are the skin manifestations of some endocrinopathies mimicking or interfering with skin aging [4,5]. Endocrine treatments and endocrine disruptors interfere with the natural endocrine status.

SKIN AS A TARGET FOR HORMONES AND NEUROENDOCRINE SIGNALS

The various endocrine functions are modulated with age. Changes occurring in three distinct hormonal systems are intricately linked to skin aging process, namely, (1) the hypothalamo–pituitary–gonadal axis affecting gonadal function, (2) the adrenals producing the dehydroepiandrosterone (DHEA) sex hormone precursor, and (3) the growth hormone (GH)/insulin-like growth factor (IGF)-1 axis affecting GH production and the IGF-I release by the liver [3]. In addition, other endocrine compounds including thyroid hormones and insulin play important roles in the skin.

The endocrine and neuroendocrine signals affecting the skin are numerous [1–3]. Their main receptors present in the skin are listed in Table 12.1. The diversity and complexity of the expected effects are sizeable.

SKIN AS A SOURCE OF HORMONES AND NEUROENDOCRINE COMPOUNDS

Irrespective of age, most of the skin components are under the physiological control of endocrine and neuroendocrine factors produced at distance or locally by some cutaneous cells. Some hormones and neurotransmitters are in fact synthesized by nerves, as well as by epithelial and dermal cells in the skin [1]. They are listed in Table 12.2. They modulate many aspects of skin physiology.

A number of environmental and intrinsic factors regulate the levels of activity of the cutaneous neuroendocrine systems [6]. Solar radiation, particularly the ultraviolet (UV)-A and UV-B spectrum, is the most prominent environmental factor affecting the cutaneous neuroendocrine systems [7–9]. The ambient temperature, moisture, and dew point, as well as diverse chemicals and biological xenobiotics, represent other important intercurrent factors. Some internal mechanisms affecting the neuroendocrine system of the skin are generated in reaction to a series of environmental signals or result from local biological rhythms and from local or general diseases [1,10].

The most important endocrine compound produced by the skin is vitamin D. It regulates calcium metabolism and exhibits other systemic effects as well. For example, epidemiological evidence suggests that skylight deprivation associated with a reduction in circulating levels of vitamin D_3 results in an increased incidence of carcinomas of the breast, colon, and prostate [11]. In addition, vitamin D_3, its analogues, and vitamin A modulate *in vivo* the biology of keratinocytes and melanocytes of the skin [12,13].

GENDER-INDEPENDENT ENDOCRINE AGING

Any endocrine gland responds to the global aging process. A few direct consequences interfere with skin aging. They are mostly related to the declined activities of the pituitary gland, adrenal glands, ovaries, and testes [3].

GH is secreted by the pituitary gland under the control of several hypothalamic and peripheral modulators exerting either positive or negative influences. The controlled balance among the modulating factors determines the pulsatile and circadian secretion of GH. Moreover, physiological changes, occurring during puberty, pregnancy, aging, and severe acute illness, affect the GH secretion. The peripheral GH effects are mainly exerted by the IGF-1, produced by the liver upon GH stimulation. The circulating IGF-1 is bioavailable and functionally active depending upon its binding with the IGF-binding proteins (IGF-BPs). Hypothalamic secretion of GH-releasing hormone and the response to this hormone are attenuated during somatopause. During that period, GH released by the pituitary gland slows with concomitant declines in release of IGF-1 by the liver and other organs. A complex interplay exists between these endocrine changes and other hormonal systems affected by aging, such as production of melatonin and leptin.

Skin is a target of the GH-IGF axis that exerts a significant influence on the dermal and epidermal physiology [14,15]. GH, IGF-1, IGF-2, and IGF-BPs are present in the skin, and they are involved in its physiological homeostasis, including

Table 12.1 Endocrine and Neuroendocrine Receptors Active in the Skin

1. Adrenergic receptors
2. Androgen and estrogen receptors
3. Calcitonin gene–related peptide receptors
4. Cholinergic receptors
5. Corticotropin-releasing hormone and urocortin receptors
6. Glucocorticoid and mineralocorticoid receptors
7. Glutamate receptors
8. Growth hormone receptors
9. Histamine receptors
10. Melanocortin receptors
11. Miscellaneous neuropeptide receptors
12. Miscellaneous receptors
13. Neurokinin receptors
14. Neutrophin receptors
15. Opioid receptors
16. Parathormone (PTH) and PTH-related protein (PTHrP) receptors
17. PRL and LH-CG receptors
18. Serotonin receptors
19. Thyroid hormone receptors
20. Vasoactive intestinal peptide receptors
21. Vitamin D receptors

Table 12.2 Hormones and Neuroendocrine Compounds Produced in Part by the Skin

1. Hypothalamic and pituitary hormones
2. Neuropeptides and neurotrophins
3. Neurotransmitters/neurohormones
4. PTHrP
5. Sex steroid hormones
6. Thyroid hormones
7. Various steroid hormones

the dermoepidermal cross talking. Not only the systemic but also the paracrine and/or autocrine cutaneous activity of the GH-IGF axis contribute to the skin homeostasis [14–17]. GH supplementation modifies the skin presentation [18–21], in part corresponding to some improvement or corrective effects on aging skin [22].

Adrenopause is defined as the age-related declines in both genders in adrenal production of the sex steroid precursors, DHEA and its sulfate conjugate (DHEAS). The progressive decline in DHEA serum concentration with age and, conversely, its supplementation have not demonstrated evidence for a causal effect on the aging facets of skin [23,24], except on increased sebum production.

The paradigm of deleterious hormonal effects is presented by the impact of corticosteroids on skin atrophy. Iatrogenic effects of topical and systemic corticotherapies are equally involved. Corticosteroids regulate the expression of genes encoding collagens I, III, IV, V; decorin; elastin; matrix metalloproteinases (MMPs) 1, 2, and 3; tenascin; and tissue inhibitors of MMPs 1 and 2. However, the precise molecular mechanisms of skin atrophy induced by corticosteroids are not yet elucidated. The corticosteroid-induced atrophy can be one of the most severe models for skin aging corresponding to dermatoporosis [25].

GENDER-INFLUENCED ENDOCRINE AGING

Alterations in the hypothalamo–pituitary–ovarian axis initiate the menopause process representing a seminal transition in woman's aging. Menopause, corresponding to the cessation of ovarian function and menstrual cycling, is associated with vasomotor symptoms ("hot flushes"), osteoporosis [26], cardiovascular and immune system effects, changes in mood and sleep patterns, impairments in sexual and cognitive functions, and disturbances in skin and urogenital epithelia. In the aging man, functional changes in the hypothalamo–pituitary–testicular axis are more subtle and the concept of andropause is questioned. Although the sudden arrest of testicular activity similar to menopause does not occur during aging, testicular function slows down progressively with a concurrent decline in circulating androgens. Conceptually, this was described as partial androgen decline in the aging male (PADAM). Coincident with this phenomenon, men experience clinical alterations including changes in lean body mass and muscle strength; declines in bone mineral density; cardiovascular changes; altered cognition, mood, and sleep patterns; urogenital effects (e.g., benign prostatic hypertrophy); changes in sexual function (low libido, erectile dysfunction); and various disturbances in skin and hair.

Alterations in gonadal, adrenal, and peripheral production of sex hormones impact various aspects of skin physiology. Estrogens (estradiol) and androgens (testosterone and 5a-dihydrotestosterone) mediate their effects by stimulating a series of specific cell receptors [27–30]. The role of estrogen in the skin has been largely elucidated by comparing skin physiology in premenopausal and postmenopausal women [31–34]. Sex hormones express a variety of biological and immunological effects in the skin [3]. Estrogen, alone or in combination with progesterone, prevents or reverses some aspects of skin atrophy, dryness, and wrinkles associated with chronological aging or photoaging. Estrogen and progesterone stimulate the keratinocyte proliferation, while estrogen downregulates apoptosis, thereby preventing epidermal atrophy. In addition, estrogens possibly enhance collagen synthesis, and the combination of estrogens and progesterone reduces collagenolysis through the inhibition of MMP activity in fibroblasts, thereby maintaining skin thickness. Estrogens maintain skin moisture by increasing the dermal amount of hyaluronic acid. Progesterone apparently amplifies sebum excretion.

Phytoestrogens present in the environment are occasionally incorporated in topical products [35]. Under regular conditions, no specific changes have been ascribed in the skin to these compounds.

Pregnancy is another typical period of life affecting the skin in women [36]. Indeed, the hormonal changes are prominent and exert their effects particularly on skin pigmentation, hair cycling, and dermal compliance to mechanical stress leading to striae distensae.

Pigmentary changes are common during pregnancy. Hyperpigmentation of the areola, axillae, and genitalia commonly develops. Linea nigra refers to the typically reversible darkening of the linea alba, a hypopigmented line extending from the pubis symphysis to the xiphoid process of the sternum. Melasma is a related finding comprising irregular, blotchy, facial hyperpigmentation that occurs in up to 70% of pregnant women. This disorder is aggravated by sun exposure and by oral contraceptive intake by nonpregnant women. Melasma commonly regresses during the postpartum but occasionally persists, posing a therapeutic challenge.

The most common structural change during pregnancy is striae distensae. Sites of predilection include those areas prone to stretch including the abdomen, hips, buttocks, and breasts. Genetic factors as well as family history, personal history, and ethnicity are strong predictors of an individual risk of developing striae distensae, surpassing pregnancy weight gain or changes in body mass index. These findings support a genetic predisposition to this condition.

Much of the research on the role of androgens in skin aging has been conducted in men and male animal models. However, the signaling pathways of estrogens and androgens are interrelated and their serum concentration profiles in men and women are affected differently by age [3,37].

ENDOCRINOPATHIES AND THE SKIN

Several endocrinopathies, through excess or deficiency in hormone production, alter specific cutaneous functions and structures leading in some instances to the acceleration of the skin aging process [4,5]. Diabetes mellitus [38–41] and acromegaly [42–45] are two typical examples. However, all aspects of skin aging are not boosted by these diseases.

Acromegaly results from a pathological excess in GH. Bone overgrowth is combined with dermal and subcutaneous tissue hypertrophies [42–45]. The hands and feet become particularly enlarged. Epidermal cells are enlarged and the rate of keratinocyte production is increased. The rates of sebum and sweat production are similarly increased. In some patients, skin pigmentation is enhanced. Conversely, dermal thinning, decreased skin elasticity, and, less frequently, easy ulcerations have been described in GH deficiency [43]. In both pathological conditions, the normalization of altered circulating GH levels only determines a partial reversibility of the skin alterations [44].

In diabetes, a generalized abnormality of the small blood vessels is due to deposition of glycoprotein in the vessel walls. This condition results in narrowing the lumina and decreasing the blood flow through them. Xerosis, particularly of the legs, is quite common [39,40]. Skin stiffness and decreased joint mobility has been noted more frequently in diabetics [38,40] and seems to be associated glycation of collagen and other macromolecules of the dermis.

Thyroid disorders have some impact on the skin aspect [46,47]. The epidermis is indeed quite responsive to thyroid hormones, and this reactivity accounts for most of the changes noted clinically. The roughness and dryness of the skin in myxoedema and the smoothness in hyperthyroidism is tentatively explained in this way [4,5]. In hypothyroidism, the faint yellowish tinge to the skin is probably due to the deposition of carotene in the skin. A common reddish blush high on the cheeks gives the appropriately termed "peaches and cream appearance." In myxoedema, the skin looks dry and roughened, and the hair tends to be coarse and thinner than normal in myxoedema. In thyrotoxicosis, the skin feels warm and moist because of the hyperdynamic circulation and increase in sweating. The hair is fine. In addition, some patients complain of persistent generalized itch. Onycholysis occurs in some cases of hyperthyroidism and a diffuse pigmentation develops in a few patients.

The adrenal glands are occasionally subject to pathological changes resulting in hyperactivity (Cushing syndrome) or hypoactivity (Addison disease). In Cushing syndrome, the glucocorticoids in excess affect both the epidermis and the dermis. They slow down the keratinocyte production and provoke the thinning of the epidermis and shrinking of individual keratinocytes. In addition, glucocorticoids thin the dermis owing to the metabolic inhibition on fibroblasts. The net result of glucocorticoid action is skin thinning, closely resembling dermoporosis. The livid facial appearance, especially marked on the cheeks, is due to the skin thinning at a site where the subpapillary venous plexus is nearer the surface than in most other body sites. Striae distensae are the results of loosening structure of the dermis at sites of maximal stress and appear to represent elastic fiber failure owing to the stress [48]. These lesions are normally evident to some degree in adolescence and pregnant women but are more prominent in Cushing syndrome. In addition, the skin appears thin and the subcutaneous veins are obvious, there is skin fragility to minor trauma, and purpuric patches occur after trivial knocks.

Hyperpigmentation is the major skin manifestation of Addison disease. The melanoderma is generalized but especially noticeable in areas that are normally not or only slightly pigmented, particularly the palmar creases and the oral mucosa.

HORMONE REPLENISHMENT THERAPY AT MENOPAUSE

For years, hormone replacement therapy (HRT) for menopausal women was globally presented as beneficial for the recipients. It markedly improved climacteric changes in many organs including skin. The bulk of recent studies confirmed that estrogens or estroprogestins effectively suppress the climacteric syndrome and genital atrophy, while significantly decreasing the risk of osteoporotic fractures. In the skin of good responders to HRT, both the epidermis and the dermis appear influenced by the supplementary therapy [49–52]. By contrast, poor responders take no or limited benefits to this management at the level of the skin [50,53].

Both the climacteric period characteristic for the perimenopause and the PADAM phase commonly affect negatively the regular skin biology [32,54]. HRT in postmenopausal women aims at limiting the adverse changes [32,55–59]. However, a limitation in such a claim exists because good and poor responders were distinctly identified [32,50]. In addition, smoking habit possibly interferes with the HRT effect [56].

ENDOCRINE DISRUPTORS

Some chemical compounds exhibit endocrine disruptive effects [60]. The number of identified chemicals of emerging concern is steadily increasing. Their nature varies among world regions. Some of them are deliberately dispersed in the environment, others are industrial pollutants, and still others originate from casual compounds including skin care products (titanium dioxide, zinc oxide, etc.) [35,61–66].

CONCLUSION

Skin produces and reacts to hormones, neuroendocrine mediators, and endocrine disruptors. The physiological declines in hormone production with age affect skin physiology. Clearly, some endocrinopathies interfere with skin biology and possibly influence its aging machinery.

REFERENCES

1. Slominski A, Wortsman JN. Neuroendocrinology of the skin. *Endocrine Rev* 2000; 21:457–487.
2. Quatresooz P, Piérard-Franchimont C, Kharfi M et al. Skin in maturity. The endocrine and neuroendocrine pathways. *Int J Cosmet Sci* 2007; 29:1–6.
3. Farage M, Miller KW, Zouboulis CC et al. Gender differences in skin aging and the changing profile of the sex hormones with age. *J Steroids Hormon Sci* 2012; 3:1000109.
4. Jabbour SA, Miller JL. Endocrinopathies and the skin. *Int J Dermatol* 2000; 39:88–99.
5. Quatresooz P, Thirion L, Piérard-Franchimont C et al. Cutaneous manifestations of endocrine disorders. *Rev Med Liège* 2006; 61:104–108.
6. Paus R, Arck P, Tiede S. Neuro-endocrinology of epithelial hair follicle stem cells. *Molec Cell Endocrinol* 2008; 288:38–51.
7. Schiller M, Brzoska T, Böhm M et al. Solar-simulated ultraviolet radiation-induced upregulation of the melanocortin-1 receptor, proopiomelanocortin, and α-melanocyte-stimulating hormone in human epidermis in vivo. *J Invest Dermatol* 2004; 122:468–476.
8. De Rigal J, Des Mazis I, Diridollou S et al. The effect of age on skin color and color heterogeneity in four ethnic groups. *Skin Res Technol* 2010; 16:168–178.
9. Piérard GE, Piérard-Franchimont C, Quatresooz P. Field melanin mapping of the hairless scalp. *Skin Res Technol* 2012; 18; 431–435.
10. Henry F, Arrese JE, Claessens N et al. The skin and its chronobiological clock in everyday life. *Rev Med Liège* 2002; 57:661–665.
11. Giovannucci E, Liu Y, Rimm EB et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *J Natl Cancer Inst* 2006; 98:451–459.
12. Uhoda E, Petit L, Piérard-Franchimont C et al. Ultraviolet light-enhanced visualization of cutaneous signs of carotene and vitamin A dietary deficiency. *Acta Clin Belg* 2004; 59:97–101.
13. Piérard-Franchimont C, Paquet P, Quatresooz P et al. Smoothing the mosaic subclinical melanoderma by calcipotriol. *J Eur Acad Dermatol Venereol* 2007; 21:657–661.
14. Edmondson SR, Thumiger SP, Werther GA et al. Epidermal homeostasis: The role of the growth hormone and insulin-like growth factor systems. *Endocrinol Rev* 2003; 24:737–764.
15. Kumar KV, Shaikh A, Sharma R et al. Palmoplantar keratoderma with growth hormone deficiency. *J Pediatr Endocrinol Metab* 2012; 25:327–329.
16. Hyde C, Hollier B, Anderson A et al. Insulin-like growth factors (IGF) and IGF-binding proteins bound to vitronectin enhance keratinocyte protein synthesis and migration. *J Invest Dermatol* 2004; 122:1198–1206.
17. Sharp LL, Jameson JM, Cauvi G et al. Dendritic epidermal T cells regulate skin homeostasis through local production of insulin-like growth factor 1. *Nat Immunol* 2005; 6:73–79.
18. Piérard GE, Piérard-Franchimont C, Nikkels AF et al. Naevocyte triggering by recombinant human growth hormone. *J Pathol* 1996; 180:74–79.
19. Conte F, Diridollou S, Jouret B et al. Evaluation of cutaneous modifications in seventy-seven growth hormone-deficient children. *Horm Res* 2000; 54:92–97.
20. Monafo V, Marseglia GL, Maghnie M et al. Transient beneficial effect of GH replacement therapy and topical GH application on skin ulcers in a boy with prolidase deficiency. *Pediatr Dermatol* 2000; 17:227–230.
21. Cimaz R, Rusconi R, Fossali E et al. Unexpected healing of cutaneous ulcers in a short child. *Lancet* 2001; 358:211–212.
22. Rudman D, Feller AG, Nagraj HS et al. Effects of human growth hormone in men over 60 years old. *N Engl J Med* 1990; 323:52–54.
23. Bourguignon R, Uhoda I, Henry F et al. DHEA and rejuvenating intracrinology? Between reason and magic. *Rev Med Liège* 2002; 57:438–442.
24. Calvo E, Luu-The V, Morissette J et al. Pangenomic changes induced by DHEA in the skin of postmenopausal women. *J Steroid Biochem Mol Biol* 2008; 112:186–193.
25. Kaya G, Saurat JH. Dermatoporosis: A chronic cutaneous insufficiency/fragility syndrome. Clinicopathological features, mechanisms, prevention and potential treatments. *Dermatology* 2007; 215:284–294.
26. Piérard GE, Piérard-Franchimont C, Vanderplaetsen S et al. Relationships between bone mass density and tensile strength of the skin in women. *Eur J Clin Invest* 2001; 31:731–735.
27. Shah MG, Maibach HI. Estrogen and skin: An overview. *Am J Clin Dermatol* 2001; 2:143–150.
28. Haag M, Hamann T, Kulle AE et al. Age and skin site related differences in steroid metabolism in male skin point to a key role of sebocytes in cutaneous hormone metabolism. *Dermatoendocrinology* 2012; 4:58–64.
29. Lai JJ, Chang P, Lai KP et al. The role of androgen and androgen receptor in skin-related disorders. *Arch Dermatol Res* 2012; 304:499–510.
30. de Giorgi V, Gori A, Gandini S et al. Estrogen receptor beta and melanoma. A comparative study. *Br J Dermatol* 2013; 168:513–519.
31. Wines N, Willsteed E. Menopause and the skin. *Austr J Dermatol* 2001; 42:149–160.
32. Raine-Fenning NJ, Brincat M, Muscat-Baron Y. Skin ageing and menopause: Implications for treatment. *Am J Clin Dermatol* 2003; 4:371–378.
33. Archer DF. Postmenopausal skin and estrogen. *Gynecol Endocrinol* 2012; 28:S2–S6.
34. Blume-Peytavi U, Atkin S, Gieler U et al. Skin academy: Hair, skin, hormones and menopause—Current status/knowledge on the management of hair disorders in menopausal women. *Eur J Dermatol* 2012; 22:310–318.
35. Patisaul HB. Effects of environmental endocrine disruptors and phytoestrogens on the kisspeptin system. *Adv Exp Med Biol* 2013; 784:455–479.
36. Henry F, Quatresooz P, Valverde-Lopez JC et al. Blood vessel changes during pregnancy. A review. *J Cosmet Dermatol* 2006; 7:65–69.
37. Zouboulis CC, Makrantonaki E. Hormonal therapy of intrinsic aging. *Rejuvenation Res* 2012; 15:302–312.
38. Flagothier C, Quatresooz P, Bourguignon R et al. Cutaneous stigmata of diabetes. *Rev Med Liège* 2005; 60:553–559.
39. Uhoda E, Debatisse B, Paquet P et al. The so-called dry skin of the diabetic patient. *Rev Med Liège* 2005; 60:560–563.
40. Piérard GE, Piérard-Franchmont C, Scheen A. Critical assessment of diabetic xerosis. *Expert Opin Med Diagn* 2013; 7:201–207.
41. Piérard GE, Seité S, Hermanns-Lê T et al. The skin landscape in diabetes mellitus. Focus on dermocosmetic management. *Clin Cosmet Investig Dermatol* 2013; 6:27–35.
42. Billon C, Beylot-Barry M, Doutre MS et al. Cutaneous manifestations of acromegaly: 4 cases. *Ann Dermatol Venereol* 1996; 123:821–823.
43. Lange M, Thulesen J, Feldt-Rasmussen U et al. Skin morphological changes in growth hormone deficiency and acromegaly. *Eur J Endocrinol* 2001; 145:147–153.
44. Braham C, Betea D, Piérard-Franchimont C et al. Skin tensile properties in patients treated for acromegaly. *Dermatology* 2002; 204:325–329.
45. Quatresooz P, Hermanns-Lê T, Ciccarelli A et al. Tensegrity and type I dermal dendrocytes in acromegaly. *Eur J Clin Invest* 2005; 35:133–139.
46. Szepetiuk G, Piérard GE, Betea D et al. Biometrology of physical properties of skin in thyroid dysfunction. *J Eur Acad Dermatol Venereol* 2008; 22:1173–1177.
47. Safer JD. Thyroid hormone action on skin. *Curr Opin Endocrinol Diabetes Obes* 2012; 19; 388–393.
48. Piérard-Franchimont C, Hermanns JF, Hermanns-Lê T et al. Striae distensae in darker skin types: The influence of melanocyte mechanobiology. *J Cosmet Dermatol* 2005; 4:174–178.
49. Sauerbronn AV, Fonseca AM, Bagnoli VR et al. The effect of systemic hormonal replacement therapy on the skin of postmenopausal women. *Int J Cynaecol Obstet* 2000; 68:35–41.

50. Piérard-Franchimont C, Piérard GE. Post-menopausal aging of the sebaceous follicle. A comparison between women receiving hormone replacement therapy or not. *Dermatology* 2002; 204:17–22.
51. Guinot C, Malvy D, Ambroisine L et al. Effect of hormonal replacement therapy on skin biophysical properties of menopausal women. *Skin Res Technol* 2005; 11:201–204.
52. Quatresooz P, Piérard GE. Downgrading skin climacteric aging by hormone replacement therapy. *Exp Rev Dermatol* 2007; 2:373–376.
53. Oikarinen A. Systemic estrogens have no conclusive beneficial effect on human skin connective tissue. *Acta Obstet Gynecol Scand* 2000; 79:250–254.
54. Paquet F, Piérard-Franchimont C, Fumal I et al. skin at menopause; dew point and electrometric properties of the stratum corneum. *Maturitas* 1998; 28:221–227.
55. Piérard GE, Letawe C, Dowlati A et al. Effect of hormone replacement therapy for menopause on the mechanical properties of skin. *J Am Geriat Soc* 1995; 42:662–665.
56. Castelo-Branco C, Figueras F, Martinez de Osaba MJ et al. Facial wrinkling in postmenopausal women effects of smoking status and hormone replacement therapy. *Maturitas* 1998; 29:75–86.
57. Piérard-Franchimont C, Cornil F, Dehavay J et al. Climacteric skin ageing of the face. A prospective longitudinal intent-to-treat trial on the effect of oral hormone replacement therapy. *Maturitas* 1999; 32:87–93.
58. Piérard GE, Vanderplaetsen S, Piérard-Franchimont C. Comparative effect of hormone replacement therapy on bone mass density and skin tensile properties. *Maturitas* 2001; 40:221–227.
59. Quatresooz P, Piérard-Franchimont C, Gaspard U et al. Skin climacteric aging and hormone replacement therapy. *J Cosmet Dermatol* 2006; 5:3–8.
60. Birnbaum LS. State of the science of endocrine disruptors. *Environ Health Perspect* 2013; 121:a107.
61. Dhanirama D, Gronow J, Voulvoulis N. Cosmetics as a potential source of environmental contamination in the UK. *Environ Technol* 2012; 33:1597–1608.
62. Krause M, Klit A, Blomberg Jensen M et al. Sunscreens: Are they beneficial for health? An overview of endocrine disrupting properties of UV-filters. *Int J Androl* 2012; 35:424–436.
63. Duri S, Tran CD. Supramolecular composite materials from cellulose, chitosan and cyclodextrin: Facile preparation and their selective inclusion complex formation with endocrine disruptors. *Langmuir* 2013; 29:5037–5049.
64. Grassi M, Rizzo L, Farina A. Endocrine disruptors compounds, pharmaceuticals and personal care products in urban wastewater: Implications for agricultural reuse and their removal by adsorption process. *Environ Sci Pollut Res Int* 2013; 20:3616–3628.
65. Rylander L, Rignell-Hydbom A, Tinnerberg H et al. Trends in human concentrations of endocrine disruptors: Possible reasons and consequences. *J Epidemiol Community Health* 2014; 68:4–5.
66. Teng C, Goodwin B, Shockley K et al. Bisphenol A affects androgen receptor function via multiple mechanisms. *Chem Biol Interact* 2013; 203:556–564.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Diet and the skin

Alessandra Marini

INTRODUCTION

Beauty comes from the inside. The relationship between nutrition and the effect on skin aging has become an interesting topic that excites researchers and clinicians worldwide (current overview in [1,2]). Skin functions and healthy appearance depend on a sufficient supply of essential nutrients [3]. Vitamins, carotenoids, tocopherols, flavonoids, minerals, fatty acids, and a variety of plant extracts have been reported to possess potent antioxidant properties and have been widely used in the skin care industry in an attempt to prolong youthful skin appearance. New insight into the effect of orally applied, biologically active molecules on skin functions has stimulated a continuously growing interest in the development of nutritional supplements and, most importantly, functional food products to benefit human skin. Intervention studies indicate that it is in fact possible to manipulate and to delay skin aging and to improve skin conditions through supplementation with selected nutritional supplements.

Skin aging results from two independent distinct factors that can be clearly distinguished at a clinical, histological, and molecular level: intrinsic (genetic, endocrinologic) and extrinsic (environmental) factors. The intrinsic skin aging is referred to as chronological skin aging and is an ineluctable process due to genetically determined loss of cell function with age [4]. The extrinsic skin aging is the result of external factors and environmental influence. As the exterior barrier of the body, skin is in direct contact with the environment. Among all environmental factors, ultraviolet (UV) radiation is most important for extrinsic skin aging [5]. Other factors include infrared (IR) radiation, exposure to tobacco smoke, and exposure to traffic-related, airborne particulate matter [5]. Kligmann coined the term photoaging to describe the modifications occur after years of exposure to UV radiation [6]. In sun-exposed skin, the aging process is accompanied by enhanced cumulative oxidative damage; as a consequence, collagen fibrils become disorganized, their synthesis decreases, while skin levels of type I and III collagen precursors and cross-links are reduced, and there is an abnormal accumulation of elastin-containing material [7]. Photooxidative stress is involved in processes of photoaging and photocarcinogenesis and plays a major role in the pathogenesis of photodermatoses [8]. Repair of UV-dependent damage may be supported by molecules that are capable to induce suitable repair systems: the antioxidants. Antioxidants are substances that prevent oxidative damage to cells and tissue. They act as scavengers of reactive oxygen species (ROS) generated in primary or secondary reactions following UV irradiation. Naturally, human skin has endogenous enzymatic and nonenzymatic antioxidants. However, with ongoing aging and environmental influences, the body's endogenous antioxidative system attenuates and the production of ROS increases [9]. Based on their structural features, promising candidates for endogenous photoprotection in humans are found among the antioxidant micronutrients including carotenoids, tocopherols, flavonoids, and other polyphenols as well as vitamin C and E, essential omega-3-fatty acids, some proteins, and lactobacilli [10], which have been referred as agents capable of promoting skin health and beauty.

The changes in personal lifestyles over the years have led to a significant increase to sunlight exposure, and this had led to a surge in the incidence of skin cancer and photoaging.

Prevention of skin aging is of constantly increasing importance to the general population; therefore, in recent years, the concept of photoprotection has gained attention as mainstay of skin protective strategies and a viable approach to reduce the occurrence of skin cancer and photoaging. It has already been shown that nutrition-based anti-skin-aging strategies are most effective if they are directed against extrinsic skin aging [3,11].

Human studies have underlined the possibility of preventing or at least minimizing photoaging by external use of efficient sunscreens or by the internal use of nutraceuticals (current overview in [1,7]).

Moreover, numerous studies have focused on the possible role of diet in the capacity of the skin to resist damage induced by UV radiation [10]. Modern sunscreen products therefore frequently combine UV filters with one or more biologically active molecules that provide photoprotection through mechanisms that are not based on absorption or reflection of UV rays and thus are completely different from UV filters [12]. The protective capacity of actives relies instead on their capacity to prevent some of the biochemical and molecular consequences that occur in the skin after UV radiation. The development of novel actives for skin photoprotection is a highly innovative and dynamic field [12]. The group of molecules that are being used as actives with quite diverse target points for photoprotection is heterogeneous and constantly growing. There are an increasing number of products marketed in the community as foods containing concentrated sources of nutrients and presented for supplementing the intake of those nutrients from the normal diet. According to the European Directive 2002/46/EC, "food supplements means foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities" [13]. Today, the nutricosmetic

ingredient market includes four principal segments: carotenoids, vitamins, polyunsaturated fatty acid (PUFA), and others [7]. Some interesting antioxidants and their properties, which have drawn attention for their unique antiaging effects, are discussed next.

VITAMIN C

L-ascorbic acid is the most widely known vitamin and an essential micronutrient, required for multiple biological functions. Vitamin C is included in nutraceutical supplements to reduce skin photodamages, rebalance free radical-mediated pathologic process, and prevent photoaging [7].

Vitamin C is not naturally synthesized by the human body, and therefore, an adequate dietary intake is required and essential for a healthy human diet. The richest natural sources are fresh fruits and vegetables such as citrus fruits, kiwi, black currant, tomatoes, rose hip, guava, chili pepper, or parsley [14].

Vitamin C plays an important role in skin biology, contributing to the formation of efficient skin barrier and fibroblast proliferation and therefore essential for the maintenance of normal connective tissue as well as for wound healing [15]. By stimulating collagen synthesis, it improves the elasticity of the skin, thereby reducing wrinkles [16].

Vitamin C is considered to be one of the most powerful, least toxic natural antioxidants; it can scavenge deleterious free radicals that contribute to the process of skin aging; therefore, it is used in cosmetic and dermatological products [17]. Vitamin C is efficient in the protection against ultraviolet B (UVB). It reduces the sunburn reaction and prevents the formation of thymine dimers, thus preventing DNA damage [18].

Furthermore, its ability to suppress skin pigmentation via the inhibition of tyrosinase activity in melanocytes makes it a useful whitening agent [16]. However, the use of vitamin C in cosmetic products is difficult. Ascorbic acid is an unstable compound in water solution; thus, its oral administration could represent an alternative to topical application, benefiting from increased stability and less dependence on the vehicle [16].

VITAMIN E

The term vitamin E is a generic description for all tocopherol and tocotrienol derivatives [19]. This group of compounds is highly lipophilic, operative in membranes or lipoproteins. Their most important antioxidant function appears to be the inhibition of lipid peroxidation, scavenging lipid peroxyl radicals to yield lipid hydroperoxides and a tocopheroxyl radical [20,21]. Vitamin E stabilizes cell membranes and protects the tissue more sensitive to oxidation such as the skin. Moreover, it helps in the preservation of vitamin A and prevents the oxidation of some hormones [22]. Natural sources of vitamin E include vegetables, oils, seeds, nuts, corn, soy, whole wheat flour, margarine, some sorts of meat, and dairy products [9]. The intake of natural vitamin E products helps against collagen cross-linking and lipid peroxidation, which are both linked to aging of the skin [14].

Vitamin E has been used in the healing of wounds of skin, photoprotection such as sunburn, photocarcinogenesis, photoimmunoinhibition, and changes in the dermal immunostimulation [23]. Many clinical trials demonstrated the effects of tocopherol. The data seem to be controversial, but high doses of oral vitamin E may affect the response to UVB in humans [24]. Cesarini demonstrated that alpha-tocopherol together with beta-carotene, lycopene, and selenium significantly reduced lipoperoxide levels, UV-induced erythema, and sunburnt cells [25].

Alpha-tocopherol is the predominantly isoform of vitamin E in humans and animals, it removes free radical intermediates and prevents oxidation reactions [9]. However, tocotrienol has been shown to have higher antioxidant, anticancer, and neuroprotective properties. Yamada et al. observed that dietary tocotrienols protect the skin against damage produced by UVB in hairless mice [26].

Oral combination treatments of vitamins C and E increase the photoprotective effects compared with monotherapies. In a study with 12 volunteers, vitamin C was supplemented at 500 mg/day over a period of 8 weeks, and the erythemal response following UV exposure was followed [27]. Supplementation with only vitamin C had no effect on minimal erythemal dose (MED). In a study investigating the cooperative activity of both compounds, vitamin E and vitamin C, against UV-induced erythema [28], four treatment groups were followed over a period of 50 days. RRR-alfa-tocopherol and ascorbate were supplemented as single components at dose levels of 2 and 3 g/day, respectively. With the combination, 2 g/day of alfa-tocopherol and 3 g/day of ascorbate were administered; controls remained without treatment. After treatment with the combination of both the vitamins, the "sunburn threshold" or MED was significantly increased from about 100 mJ/cm² before to about 180 mJ/m² after supplementation. Treatment with the single compounds provided only moderate protection, which was not statistically significant.

Short-time intervention with high doses of vitamin E and vitamin C provides some protection. When vitamin E was ingested at 1000 IU together with 2 g ascorbic acid/day over a period of 8 days, a minor increase in MED was determined [29]. Vitamins E and C prevent phototoxic damage like UV-dependent erythema, formation of sunburn cells, lipid peroxidation, and DNA damage, as shown in several studies [30,31].

VITAMIN B6

The recent discovery of potential functions of vitamin B6 as antioxidant awakened interest in the protective roles of vitamin B6. On the other hand, recent growing evidence has suggested that its excessive dose can cause phototoxicity and adverse effects [32].

CAROTENOIDS

The carotenoids are examples of dietary constituents with beneficial effects on skin health. Carotenoids are vitamin A derivates like β-carotene, astaxanthin, lycopene, and retinol, which are all highly effective antioxidants and neutralize singlet oxygen and peroxyradicals and have been documented to possess photoprotective properties [3,12]. Fruits and vegetables provide most of the carotenoids in the human diet with a mean daily intake of about 5 mg total carotenoids per day, as measured in Germany [33]. Carotenoids represent a class of lipophilic secondary plant components and are among the most widespread natural colorants, with beta-carotene as the most frequently applied endogenous sun protectants. Based

on epidemiological observations, fruits and vegetables, which are rich in sources of carotenoids, are thought to provide health benefits by decreasing the risk of various diseases [34]. Among the carotenoids, lycopene is the most efficient singlet oxygen quencher. When skin is exposed to UV light stress, more skin lycopene is destroyed compared to β-carotene, suggesting that lycopene has a role in mitigating oxidative damage [35]. All tomato products are the major source of lycopene for the human organism. Further sources are watermelon, guava, rosehips, and pink grapefruit. A number of recent studies in humans have shown that oral uptake of carotenoids has photoprotective effects. In an intervention study with beta-carotene, it was shown that protection against UV-induced erythema can be achieved [36]. The efficacy of beta-carotene in systemic photoprotection depends on the duration of treatment and on the dose. In healthy volunteers, a 12-week oral administration of at least a total of 12 mg of carotenoids per day results in a reduction of UV-induced erythema for at least 7 weeks [36]. Similar effects have been described in volunteers receiving a lycopene-rich diet [37]. Carrots, pumpkin, sweet potatoes, mangos, and papaya are some examples of β-carotene-containing fruits and vegetables. Upon dietary supplementation, β-carotene can be further enriched in skin, in which it is already a major carotenoid [38]. β-carotene is an endogenous photoprotector, and its efficacy has been demonstrated in various trials [10,39]. In order to investigate whether a diet rich in carotenoids is useful for photoprotection, tomato paste was selected as a dietary source containing high amounts of lycopene [40]. To improve absorption, olive oil was coingested with the paste (20 g/day), providing 16 mg lycopene per day. Dietary intervention was performed over a period of 10 weeks, after which increased lycopene levels in serum and skin were determined. After 10 weeks of intervention, erythema formation was significantly lower in the group consuming the tomato paste compared to control [41], but no significant protection was found at week 4 of treatment. The data show that protection against UV-induced erythema can be achieved by a modulation of the diet.

Astaxanthin is found in microalgae, yeast, salmon, trout, krill, shrimp, crayfish, and crustacean [14]. It prevents UVA-induced alterations in cellular superoxide dismutase activity [42]. Camera et al. showed significant photoprotection of a combination of astaxanthin, canthaxanthin, and β-carotene [43]. The uptake of astaxanthin by fibroblasts was higher than that of canthaxanthin and β-carotene, which leads to the assumption that the effect of astaxanthin toward photooxidative changes was stronger than that of the other substances [43]. Suganuma et al. showed that astaxanthin could interfere with UVA-induced matrix-metalloproteinase-1 and skin fibroblast elastase/neutral endopeptidase expression [44].

Retinol is a fat-soluble unsaturated isoprenoid essential for growth, differentiation, and maintenance of epithelial tissues. Natural retinol and retinol ester are contained in liver, milk, egg yolk, cheese, and fatty fish. Topical retinoid inhibits the UV-induced, MMP-mediated breakdown of collagen and protects against UV-induced decreases in procollagen expression [45,46]. Oral treatment with retinol or retinal derivatives has not yet been proposed as a possible antiaging treatment. It should be noted that the large CARET trial mentioned the lung cancer–promoting effects of 25,000 IU retinyl palmitate combined with 30 mg β-carotene intake [47]. Thus, the belief that chemical quenching of free radicals by natural compounds exerts always beneficial effects has been challenged, and it is important to know that the systemic increase of antioxidants by dietary supplementation may also lead to adverse effects.

VITAMIN D

Vitamin D acts as a prohormone and the human body can synthesize it through sun exposure; therefore, the skin is the major source of vitamin D. Smaller amounts of vitamins D2 and D3 come from the dietary intake of animal-based foods such as fatty fish or egg yolk. Some products like milk, cereals, and margarine can be enriched with vitamin D [14].

Numerous functions of the skin are regulated by vitamin D, such as inhibition of proliferation, stimulation of differentiation including formation of the permeability barrier, promotion of innate immunity, regulation of the hair follicle cycle, and suppression of tumor formation [48]. Several *in vitro* and *in vivo* studies have documented the protective effects of 1,25(OH)2D3 against UVB-induced skin damage and carcinogenesis [49,50]. It should be mentioned that the long-term intakes of vitamin D above the upper intake levels can result in adverse health effects [14].

POLYPHENOLS AND FLAVONOIDS

Because of their antioxidant properties and the increasing studies showing their probable role in the prevention of various diseases associated with oxidative stress, polyphenols have drawn the attention of the antiaging researchers over the last decade. Polyphenols are mostly found in fruits, vegetables, cereals, chocolate, dry legumes, and plant-derived beverages such as fruit juices, tea, coffee, and red wine [14]. Polyphenols such as green tea polyphenols (GTPs), grape seed proanthocyanidins, resveratrol, silymarin, and genistein, combined with sunscreen protection, have the ability to protect the skin from the adverse effects of UV radiation [51]. Among the agents that have received attention for their photoprotective qualities, green tea has recently gained prominence for health benefits observed in some, though not all, epidemiological studies. GTPs are made from unfermented leaves of the plant *Camellia sinensis*. GTPs act as potent antioxidants and offer protection against UVB-induced stress [9]. Treatment of cultured cells with EGCG, a major polyphenolic constituent of green tea, directly inhibits the baseline expression of metalloproteinases (MMPs), such as MMP-2, MMP-9, and neutrophil elastase even in the absence of UV exposure [52]. Oral administration of GTP to mouse as a sole source of liquid remarkably inhibited UV-induced expression of MMPs in mouse skin, suggesting that GTP has a potential antiphotoaging effect [53]. Treatment of EGCG diminishes UVA-induced skin damage (roughness and sagginess), protects against the loss of dermal collagen in hairless mouse skin, and also blocks the UV-induced increase of collagen secretion and collagenase mRNA level in cultured human epidermal fibroblasts and the promoter-binding activities of AP-1 and NF-kB [54].

Polyphenols can be divided into many different functional groups such as the phenolic acids, flavonoids, stilbenes, and lignans [55]. Flavonoids comprise a group of secondary plant pigments that are used in cosmetics and dermatology. In addition to antioxidant properties, they exhibit other biological activities that likely contribute to their cutaneous effects. Flavonoids and flavonoid-rich products can protect skin against UV-induced damage

at the molecular and cellular level and may as well improve overall skin quality. Regular intake confers significantly to photoprotection and helps in maintaining skin health by improving skin structure and function [56]. Phlorizin belongs to the group of dihydrochalcones, a type of flavonoid, and it could be found in the bark of pear (*Pyrus communis*), apple, cherry, and other fruit trees. It has been used for more than 150 years but its antiaging effects have only been reported in the last few years [14].

Other polyphenols have been described to have potent antioxidant properties. Among them, silymarin, resveratrol, curcumin, and genistein have been demonstrated to have beneficial effects on skin aging parameters.

Silymarin is a naturally polyphenolic flavonoid isolated from the milk thistle plant (*Silybum marianum L. Gaertn*) and is a mixture of several flavonolignans, which includes silybin, silibinin, silidianin, silychristin, and isosylibin [57]. The antioxidant effects of silymarin in mouse models have been established, and silybin is the main constituent responsible for these effects [57]. Silymarin is effective against burn-induced oxidative damage and morphological alterations in rat skin [58].

Resveratrol (trans-3,4′,5-trihydroxystilbene) is a polyphenolic phytoalexin found largely in the skin and seeds of grapes, nuts, fruits, and red wine. It has been the subject of intense interest in recent years due to a range of unique antiaging properties [14]. Resveratrol is a potent antioxidant with anti-inflammatory and antiproliferative properties [59]. Moreover, it has been suggested to protect skin from UV-induced photodamage and photoaging [23]. Resveratrol imparts its protective effects against multiple UVB exposure via modulations in the cki–cyclin–cdk network and MAPK pathway [60].

Curcumin is a dietary pigment from the plant *Curcuma longa* and has been shown to protect against the deleterious effects of injury by attenuating oxidative stress and suppressing inflammation (reviewed in [61]).

Genistein and daidzein are isoflavones that have antioxidative and photoprotective effects [9]. Soybeans are a rich source of isoflavones, but they can also be found in *Ginkgo biloba* extract, Greek oregano, and Greek sage. Genistein preserves cutaneous proliferation and repair mechanism; it has photoprotective efficacy on reconstituted skin induced by acute UVB irradiation [62].

POLYUNSATURATED FATTY ACIDS

PUFAs are categorized into omega-3, omega-6, and omega-9 families [7]. ω-3 is derived from linolenic acid, and ω-6 is derived from linoleic acid [14]. They are present in multiple food sources such as fish and shellfish, flaxseed, hemp oil, soya oil, canola oil, chia seeds, pumpkin seeds, sunflower seeds, leafy vegetables, walnuts, sesame seeds, avocados, salmon, and albacore tuna [14]. Using nutrients such as omega-3 PUFAs for the promotion of skin health and treatment of skin disorders is a novel concept [3]. Scientific studies have drawn attention to the antiaging properties of alpha-linolenic acid, showing a link between inflammation and skin aging [7,63] and their protective activity [64].

The fatty acids show an antioxidant, free radical scavenging effect. It could thereby be demonstrated that eicosapentaenoic acid may provide a significant protection against UV radiation–induced erythema [24].

PRE- AND PROBIOTICS

Thanks to the recent advances in microbiology and immunology, immense progress has been made in our understanding of the cutaneous microflora (overview in [65]). Preservation of the microflora is a way to maintain a healthy skin functions, and because of its role in skin health and disease, the maintenance or restoration of healthy skin microbiota has become the aim of modern therapies [65]. Pre- and probiotics have been suggested as important applications of such therapies and in the last few years have reached scientific popularity as safe and effective agents to regulate the body's microenvironment and the skin health [66]. A constantly growing body of literature exists about their relevance in cosmetic and dermatology (overview in [66]). Most of these examples deal with the orally administration of food grade, but recently, their use in cosmetic applications direct to the skin has been proposed. Prebiotics rebalance the skin microflora, while probiotic concepts consist of applying an inactivated microbial biomass [66].

Gibson and Roberfroid in 1995 introduced the concept and defined the prebiotics as "nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one, or a limiting number of, bacteria in the colon [67]." Traditional dietary sources of prebiotics include soybeans, inulin sources (such as Jerusalem artichoke and chicory root), raw oats, unrefined wheat, unrefined barley, and yacon [66]. Some of the oligosaccharides that naturally occur in breast milk are believed to play an important role in the development of a healthy immune system in infants [66].

Probiotics are defined as "live organisms which upon administration in adequate amounts confer a health benefit to the host" by improving the characteristics of the intestinal microflora [65]. Probiotics can be consumed in various forms of fermented or nonfermented food products. Food vehicles include live yoghurts, fermented dairy drinks, freeze-dried supplements (capsules, pills, liquid suspensions, and sprays), cheese, fromage frais, and fruit juices [66]. Over the years, a wide range of bacteria have been proposed and used as probiotic [66]. However, only those classified as lactic acid bacteria have received major considerations in regard to food and nutrition [66]. Most probiotics currently used are microbes typical of healthy gastrointestinal microbiota aimed at promotion of gut health and improvement of immune system function. They include *Lactobacillus* (*L. casei*, *L. rhamnosus*, *L. johnsonii*) and *Bifidobacterium* species (*B. breve*, *B. longum*, *B. bifidum*), which belong to the lactic acid bacteria group, as well as *Enterococcus*, *Escherichia coli*, *Propionibacterium*, *Bacillus*, and some yeasts [66]. Nutritional supplementation of hairless mice with *Lactobacillus johnsonii* provided protection of the skin immune system against UVB radiation–induced immunosuppressive effects [68]. Similar effects have recently been described in a human *in vivo* study, and it has been proposed that oral consumption of probiotic bacteria may represent a novel approach to protect the skin immune system against UV radiation [69]. Probiotics improve gut barrier function, restore healthier gut microecology, stimulate the host immune system, and antagonize the inflammatory alterations [66]. A regular consumption of fermented dairy products is likely to improve the natural skin barrier function and improved its cosmetic appearance. In the case of diseases with some imbalance in microorganisms, such as impure skin/mild acne or dry skin/mild atopic dermatitis, pre- and probiotic concepts represent an effective alternative to strictly antibacterial products [66].

Although carotenoids, vitamins, polyphenols, flavonoids, and PUFAs are used in different cosmeceutical products, many other emerging ingredients are gaining in popularity [70] such as ectoin [71], melatonin [72], coenzyme Q10 [73], glucosamine and pomegranate [70], vitamin K2 [74], polyglucosides such as chitin and chitosan [75], ferulic acid [9], glutathione [9], and pycnogenol [76].

CONCLUSIONS

To conclude, a promising strategy for enhancing skin protection from oxidative stress is to support the endogenous system, with antioxidants containing products capable of promoting skin health and beauty, which are normally present in the skin. However, it is important to note that this should not be confused with the permanent intake of nonphysiological high dosages of isolated antioxidants. We briefly illustrated the beneficial effects of some interesting substances used as functional food; however, further researches are essential to confirm their benefits and their use in clinical practice. Certainly, a diversified and well-balanced healthy diet rich in fruit and vegetables definitely helps to preserve the healthy and youthful appearance of the skin. It is important to note that endogenous photoprotection is complementary to topical photoprotection and that these two forms of prevention clearly should not be considered mutually exclusive.

ABBREVIATIONS

GTP Green tea polyphenol
PUFA Polyunsaturated fatty acid
ROS Reactive oxygen species

REFERENCES

1. Krutmann J, Humbert P. *Nutrition for Healthy Skin*. Berlin, Germany: Springer, 2011.
2. Preedy VR. *Handbook of Diet, Nutrition and the Skin*. Wageningen, the Netherlands: Wageningen Academic Publishers, 2012.
3. Marini A. Beauty from the inside. Does it really work? *Hautarzt* 2011; 62:614–617.
4. Malvy J, Guinot C, Preziosi P et al. Epidemiologic determinants of skin photoaging: Baseline data of the SU.VI.- MAX. cohort. *J Am Acad Dermatol* 2000; 42:47–55.
5. Schroeder P, Schieke S, Morita A. Premature skin aging by infrared radiation, tobacco smoke and ozone. In: Gilchrest BA, Krutmann J, eds. *Skin Aging*. New York: Springer, 2006, pp. 45–54.
6. Kligmann LH, Kligmann AM. The nature of photoaging: Its prevention and repair. *Photodermatology* 1986; 3:215–227.
7. Morganti P. Skin photoprotection and nutraceuticals: An overview. In: Preedy VR, ed. *Handbook of Diet, Nutrition and the Skin*. Wageningen, the Netherlands: Wageningen Academic Publishers, 2012, pp. 217–231.
8. Krutmann J. Ultraviolet A radiation-induced biological effects in human skin: Relevance for photoaging and photodermatosis. *J Dermatol Sci* 2000; 23 (Suppl 1):22–26.
9. Wu Y, Chen HD, Li YH et al. Antioxidant and skin: An overview. In Preedy VR, ed. *Handbook of Diet, Nutrition and the Skin*. Wageningen, the Netherlands: Wageningen Academic Publishers, 2012, pp. 69–90.
10. Sies H, Stahl W. Nutritional protection against skin damage from sunlight. *Annu Rev Nutr* 2004; 24:173–200.
11. Krutmann J. Skin aging. In: Krutmann J, Humbert P, eds. *Nutrition for Healthy Skin*. Berlin, Germany: Springer, 2011, pp. 15–24.
12. Krutmann J, Yarosh D. Modern photoprotection of human skin. In: Gilchrest BA, Krutmann J, eds. *Skin Aging*. New York: Springer, 2006, pp. 103–112.
13. Karajiannis H, Fish C. Legal aspects. In: Krutmann J, Humbert P, eds. *Nutrition for Healthy Skin*. Berlin, Germany: Springer, 2011, pp. 167–180.
14. Schagen SK, Zampeli VA, Evgenia Makrantonaki E et al. Discovering the link between nutrition and skin aging. *Dermatoendocrinology* 2012; 4:298–307.
15. Marini A. Nahrungsergänzungspräparate in der Dermatologie. *Dermatologie Praxis* 2012; 4:14–18.
16. Duarte TL, Almeida IF. Vitamin C, gene expression and skin health. In: Preedy VR, ed. *Handbook of Diet, Nutrition and the Skin*. Wageningen, the Netherlands: Wageningen Academic Publishers, 2012, pp. 115–127.
17. Humbert P, Binda D, Robin S et al. Beauty from Inside: Nutrition-Based strategies in cosmetic dermatology. In: Krutmann J, Humbert P, eds. *Nutrition for healthy skin*. Berlin, Germany: Springer, 2011, pp. 189–196.
18. Placzek M, Gaube S, Kerkmann U et al. Ultraviolet B-induced DNA damage in human epidermis is modified by the antioxidants ascorbic acid and D-alpha-tocopherol. *J Invest Dermatol* 2005; 124:304–307.
19. Traber MG, Sies H. Vitamin E in humans: Demand and delivery. *Annu Rev Nutr* 1996; 16:321–347.
20. Brigelius-Flohe R, Traber MG. Vitamin E: Function and metabolism. *J FASEB* 1999; 13:1145–1155.
21. Liebler DC. The role of metabolism in the antioxidant function of vitamin E. *Crit Rev Toxicol* 1993; 23:147–169.
22. Cassano R. Vitamin E chemistry, biological activity and benefits on the skin. In: Preedy VR, ed. *Handbook of Diet, Nutrition and the Skin*. Wageningen, the Netherlands: Wageningen Academic Publishers, 2012, pp. 145–163.
23. Baumann L. *Cosmetic Dermatology: Principles and Practice*, 2nd ed. New York: McGraw-Hill Medical Publishers, 2009.
24. Boelsma E, Hendriks HF, Roza L. Nutritional skin care: Health effects of micronutrients and fatty acids. *Am J Clin Nutr* 2001; 73:853–864.
25. Cesarini JP, Michel L, Maurette JM et al. Immediate effects of UV radiation on the skin: Modification by an antioxidant complex containing carotenoids. *Photodermatol Photoimmunol Photomed* 2003; 19:182–189.
26. Yamada Y, Obayashi M, Ishikawa T et al. Dietary tocotrienol reduces UVB-induced skin damage and sesamin enhances tocotrienol effects in hairless mice. *J Nutr Sci Vitaminol* 2008; 54:117–123.
27. McArdle F, Rhodes LE, Parslew R et al. UVR-induced oxidative stress in human skin in vivo: Effects of oral vitamin C supplementation. *Free Radic Biol Med* 2002; 33:1355–1362.
28. Fuchs J, Kern H. Modulation of UV-light-induced skin inflammation by D-alpha-tocopherol and L-ascorbic acid: A clinical study using solar simulated radiation. *Free Radic Biol Med* 1998; 25:1006–1012.
29. Eberlein-König B, Placzek M. Protective effect against sunburn of combined systemic ascorbic acid (vitamin C) and d-alpha-tocopherol (vitamin E). *J Am Acad Dermatol* 1998; 38:45–48.
30. Fuchs J. Potentials and limitations of the natural antioxidants RRR-alpha-tocopherol, L-ascorbic acid and beta-carotene in cutaneous photoprotection. *Free Radic Biol Med* 1998; 25:848–873.
31. McVean M, Liebler DC. Prevention of DNA photodamage by vitamin E compounds and sunscreens: Roles of ultraviolet absorbance and cellular uptake. *Mol Carcinog* 1999; 24:169–176.
32. Kato N. Role of vitamin B6 in skin health and diseases. In: Preedy VR, ed. *Handbook of Diet, Nutrition and the Skin*. Wageningen, the Netherlands: Wageningen Academic Publishers, 2012, pp. 59–66.
33. Pelz R, Schmidt-Faber B, Heseker H. Carotenoid intake in the German National Food Consumption Survey. *Z Ernährungswiss* 1998; 37:319–327.

34. Stahl W. Systemic photoprotection by carotenoids. In: Krutmann J, Humbert P, eds. *Nutrition for Healthy Skin*. Berlin, Germany: Springer, 2011, pp. 65–70.
35. Ribaya-Mercado JD, Garmyn M, Gilchrest BA, Russell RM. Skin lycopene is destroyed preferentially over beta-carotene during ultraviolet irradiation in humans. *J Nutr* 1995; 125:1854–1859.
36. Stahl W, Heinrich U, Jungmann H et al. Carotenoids and carotenoids plus vitamin E protect against ultraviolet light-induced erythema in humans. *Am J Clin Nutr* 2000; 71:795–798.
37. Stahl W, Sies H. Carotenoids and protection against solar UV radiation. *Skin Pharmacol Appl Skin Physiol* 2002; 15:291–296.
38. Alaluf S, Heinrich U, Stahl W et al. Dietary carotenoids contribute to normal human skin color and UV photosensitivity. *J Nutr* 2002; 132:399–403.
39. Köpcke W, Krutmann J. Protection from sunburn with beta-Carotene—A meta-analysis. *Photochem Photobiol* 2008; 84:284–288.
40. Gärtner C, Stahl W, Sies H. Lycopene is more bioavailable from tomato paste than from fresh tomatoes. *Am J Clin Nutr* 66:116–122.
41. Stahl W, Heinrich U, Wiseman S et al. Dietary tomato paste protects against ultraviolet light-induced erythema in humans. *J Nutr* 2001; 131:1449–1451.
42. Lyons NM, O'Brien NM. Modulatory effects of an algal extract containing astaxanthin on UVA-irradiated cells in culture. *J Dermatol Sci* 2002; 30:73–84.
43. Camera E, Mastrofrancesco A, Fabbri C et al. Astaxanthin, canthaxanthin and beta-carotene differently affect UVA-induced oxidative damage and expression of oxidative stress-responsive enzymes. *Exp Dermatol* 2009; 18:222–231.
44. Suganuma K, Nakajima H, Ohtsuki M et al. Astaxanthin attenuates the UVA-induced up-regulation of matrix-metalloproteinase-1 and skin fibroblast elastase in human dermal fibroblasts. *J Dermatol Sci* 2010; 58:136–142.
45. Fisher GJ, Wang ZQ, Datta SC et al. Pathophysiology of premature skin aging induced by ultraviolet light. *N Engl J Med* 1997; 337:1419–1428.
46. Fisher GJ, Datta S, Wang Z et al. c-Jun-dependent inhibition of cutaneous procollagen transcription following ultraviolet irradiation is reversed by all-trans retinoic acid. *J Clin Invest* 2000; 106:663–670.
47. Omenn GS, Goodman GE, Thornquist MD et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* 1996; 334:1150–1155.
48. Bikle DD. The skin and vitamin D. In: Preedy VR, ed. *Handbook of Diet, Nutrition and the Skin*. Wageningen, the Netherlands: Wageningen Academic Publishers, 2012, pp. 93–113.
49. De Haes P, Garmyn M, Verstuyf A et al. 1,25-Dihydroxyvitamin D3 and analogues protect primary human keratinocytes against UVB-induced DNA damage. *J Photochem Photobiol B* 2005; 78:141–148.
50. Dixon KM, Deo SS, Wong G et al. Skin cancer prevention: A possible role of 1,25dihydroxyvitamin D3 and its analogs. *J Steroid Biochem Mol Biol* 2005; 97:137–143.
51. Nichols JA, Katiyar SK. Skin photoprotection by natural polyphenols: Anti-inflammatory, antioxidant and DNA repair mechanisms. *Arch Dermatol Res* 2010; 302:71–83.
52. Stahl W, Mukhtar H. Vitamins and Polyphenols in systemic photoprotection. In: Gilchrest BA, Krutmann J, eds. *Skin Aging*, New York: Springer, 2006, pp. 113–121.
53. Vayalil PK, Mittal A. Green tea polyphenols prevent ultraviolet light-induced oxidative damage and matrix metalloproteinases expression in mouse skin. *J Invest Dermatol* 2004; 122:1480–1487.
54. Kim J, Hwang JS. Protective effects of (-)-epigallocatechin-3-gallate on UVA- and UVB-induced skin damage. *Skin Pharmacol Appl Skin Physiol* 2001; 14:11–19.
55. Manach C, Scalbert A, Morand C et al. Polyphenols: Food sources and bioavailability. *Am J Clin Nutr* 2004; 79:727–747.
56. Stahl W. Flavonoid-rich nutrients for the skin. In: Krutmann J, Humbert P, eds. *Nutrition for Healthy Skin*. Berlin, Germany: Springer, 2011, pp. 85–90.
57. Wagner H, Diesel P, Seitz M. The chemistry and analysis of silymarin from Silybum marianum Gaertn. *Arzneimittelforschung* 1974; 24:466–471.
58. Toklu HZ, Tunali-Akbay T, Erkanli G et al. Silymarin, the antioxidant component of Silybum marianum, protects against burn-induced oxidative skin injury. *Burns* 2007; 33:908–916.
59. Tsai SH, Lin-Shiau SY, Lin JK. Suppression of nitric oxide synthase and the down-regulation of the activation of NFkappaB in macrophages by resveratrol. *Br J Pharmacol* 1999; 126:673–680.
60. Reagan-Shaw S, Afaq F, Aziz MH et al. Modulations of critical cell cycle regulatory events during chemoprevention of ultraviolet B-mediated responses by resveratrol in SKH-1 hairless mouse skin. *Oncogene* 2004; 23:5151–5160.
61. Heng MC. Curcumin targeted signaling pathways: Basis for anti-photoaging and anti-carcinogenic therapy. *Int J Dermatol* 2010; 49:608–622.
62. Moore JO, Wang Y, Stebbins WG et al. Photoprotective effect of isoflavone genistein on ultraviolet B-induced pyrimidine dimer formation and PCNA expression in human reconstituted skin and its implications in dermatology and prevention of cutaneous carcinogenesis. *Carcinogenesis* 2006; 27:1627–1635.
63. Giacomoni PU. Aging science and the cosmetics industry. The micro-inflammatory model serves as a basis for developing effective anti-aging products for the skin. EMBU report 2005; 6:545–548.
64. Kim HH, Cho S, Lee S et al. Photoprotective and anti-skin-aging effects of eicosapentaenoic acid in human skin in vivo. *J Lipid Res* 2006; 47:921–930.
65. Krutmann J. Pre- and Probiotics for human skin. *J Dermatol Sci* 2009; 54:1–5.
66. Marini A, Krutmann J. Pre- and probiotics for human skin. In: Preedy VR, ed. *Handbook of Diet, Nutrition and the Skin*. Wageningen, the Netherlands: Wageningen Academic Publishers, 2012, pp. 319–331.
67. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: Introducing the concept of prebiotics. *J Nutr* 1995; 125:1401–1412.
68. Guéniche A, Benyacoub J, Buetler TM et al. Supplementation with oral probiotic bacteria maintains cutaneous immune homeostasis after UV exposure. *Eur J Dermatol* 2006; 16:511–517.
69. Bouilly-Gauthier D, Jeannes C, Maubert Y et al. Clinical evidence of benefits of a dietary supplement containing probiotic and carotenoids on ultraviolet-induced skin damage. *Br J Dermatol* 2010; 163:536–543.
70. Chaudary R. Good nutrition for healthy skin. *Nutraceut Business Technol* 2010; 6:12–17.
71. Buenger J, Driller H. Ectoin: An effective natural substance to prevent UVA-induced premature photoaging. *Skin Pharmacol Physiol* 2004; 17:232–237.
72. Biagini G, Gabbanelli F, Lucarini G et al. The green chemistry. Activity of an antioxidant network melatonin rich. *SOFW-J* 2006; 132:16–26.
73. Puizina-Ivic N, Miric L, Carija A et al. Modern approach to topical treatment of aging skin. *Collegium Antropologicum* 2010; 34:1145–1153.
74. Geleijnse JM, Vermeer C, Grobbee DE et al. Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: The Rotterdam study. *ASN* 2004; 34:3100–3108.
75. Janak K, Vidanarachchi JK, Maheshika S et al. Chitin, chitosan and their oligosaccharides in food industry. In: Se-Kwon K, ed. *Chitin, Chitosan and Their Oligosaccharides and Their Derivatives*. New York: CRC Press, 2011, pp. 543–560.
76. Marini A, Grether-Beck S, Jaenicke T et al. Pycnogenol® effects on skin elasticity and hydration coincide with increased gene expressions of collagen type I and hyaluronic acid synthase in women. *Skin Pharmacol Physiol* 2012; 25:86–92.

The red face

Tamara Griffiths

INTRODUCTION

Facial redness is a common problem encountered in the clinic with varying impacts, depending on disease severity and patient perception. It may be a minor nuisance in some patients but completely socially debilitating in others. Negative social stigmata associated with facial redness, such as the perception of excessive alcohol intake, or that of a heightened emotional state, such as embarrassment, overexcitement, or anger, motivate sufferers to seek treatment. Furthermore, unpleasant symptoms such as stinging, burning, tightness, or itching can also occur. The causes of facial redness are often multifactorial; therefore, the dermatologist's approach must be systematic and thorough in order to maximize therapeutic success.

SKIN BARRIER

The primary function of the skin is to act as an effective barrier between the body and the external environment. It prevents loss of fluids and electrolytes, regulates temperature, and protects from environmental assaults such as UV radiation and infection. Key to its permeability or moisture barrier function is the outermost cutaneous layer, the stratum corneum (SC).

The SC is a highly complex and specialized structure. Corneocytes are embedded in a lipid matrix of parallel lamellar membranes (bilayer) containing cholesterol, free fatty acids, and glucosylceramides. Together they form an effective biological membrane likened to "bricks and mortar" where the corneocytes form the cohesive bricks and lipid matrix represents the mortar essential for barrier repair [1]. A number of compounds collectively known as natural moisturizing factors (NMFs) enable the SC to retain moisture and remain hydrated [2]. NMFs have humectant properties and consist of urea, lactic acid, and amino acids derived from the hydrolysis of the protein filaggrin.

Desquamation of the SC is orchestrated by a complex series of tightly controlled events. Hydrolytic enzymatic reactions disrupt corneocyte adhesion, and signaling mechanisms can be affected by pH, water content, and the inflammatory cytokine milieu. For example, dehydration of the SC below a critical level will result in impaired desquamation. The skin appears flaky and dry due to the accumulation of adhesive corneocytes and subsequent scaling. Exogenous factors such as UV radiation, aging, diet, ambient humidity, and underlying disease and therapy can affect SC desquamation, barrier function, and repair, as can underlying endogenous and genetic factors.

SENSITIVE SKIN

Sensitive skin was first described by Thiers in 1960 [3], and it has been a controversial concept within the dermatological community over the years. However, it is now generally accepted that the syndrome of sensitive skin exists as an entity whereby a patient perceives their own skin to be less tolerant and more reactive compared to that of the general population [4,5]. The condition is self-diagnosed and may affect as much as 50% of women and 40% of men, though estimates are variable.

Subjective symptoms include facial discomfort, stinging, burning, tightness, and itching with or without clinical signs of redness and inflammation. Triggers include water with high mineral content, i.e., hard water, cosmetics, and other topical products. Other exogenous factors include exposure to wind, sun, extremes or rapid changes in temperature, hormonal influences, as well as psychological stress and ingestion of hot or spicy (capsaicin-rich) foods, among others [6]. Symptoms may occur immediately, within minutes or after days. Highly reactive skin can deteriorate into a state of perpetual sensitivity lasting for days to weeks, known as "status cosmeticus" (Figure 14.1). All topically applied products become intolerable, even those which were not problematic previously [7].

The pathophysiology of sensitive skin is poorly understood but is not felt to be directly related to immunologic or allergic mechanisms. Impaired barrier function may have an etiological role, a hypothesis supported by incitement of symptoms with chemical and physical triggers. Increased transepidermal water loss has been reported in those with sensitive skin [8], as well as those with a positive response to the lactic acid sting test [9]. Impairment of barrier function may result in abnormal penetration of skin irritants, which subsequently induce inflammatory cascades and/or neurosensorial dysfunction, resulting in a pathologic response to otherwise innocuous cutaneous stimuli [10]. The prominence of neurosensory symptoms suggests the role of neurogenic factors, both within the epidermis [11] and central nervous system [12]. Patients may have altered nerve endings or chronic nerve end trauma, increased levels or slow removal of neurotransmitter, or altered central information processing [13].

Counseling the patient with sensitive skin requires sympathy and patience. Explaining the pathomechanistic theories is often helpful as an educated patient may feel more empowered and compliant. A "washout" period of 2 weeks using only a sensitive skin syndet bar and nonalkaline, ceramide-based moisturizer may help normalize the skin barrier. Slow introduction of products free from common allergens and irritants

Figure 14.1 Status cosmeticus.

Figure 14.2 Papulopustular rosacea.

can then be considered. Powdered cosmetics and those easily removed with water are preferred, as are those with fewer ingredients (less than 10). Suitable antioxidants can be considered as well as physical sunscreens [13]. Novel therapies using agents that inhibit capsaicin-induced activators or other agents that reduce neuron reactivity may prove helpful in the future [14,15].

ROSACEA

Rosacea is a chronic inflammatory condition characterized by facial flushing and erythema, telangiectasias, edema, papules and pustules, ocular manifestations, and rhinophyma (Figure 14.2). Patients may exhibit few or all of the signs ranging over a broad spectrum of severity, as well as variable symptoms of burning, stinging, and skin sensitivity. The clinical picture is varied, but patients often have a history of facial "flushing and blushing" possibly arising in childhood or adolescence. Rosacea has a negative impact on quality of life, and studies suggest up to 76% of patients have lowered self-esteem and 41% avoided social gatherings due to the disease [16]. Prevalence rates vary and range from less than 1% to greater than 20% of the population. It occurs more commonly in northern Europeans and those of Celtic heritage [17], but the granulomatous variant may occur more commonly in those of African or Asian origin.

In 2002, rosacea was defined and classified into four subtypes [18]: (1) erythematotelangiectatic rosacea, (2) papular rosacea, (3) phymatous rosacea, and (4) ocular rosacea. It is still unclear as to whether there is a progressive developmental march from one type to the next or whether the condition exists as a syndrome with clinical overlap.

Central facial flushing and erythema with periocular sparing is a characteristic of erythematotelangiectatic rosacea. The neck and upper chest may also be affected and associated facial stinging or burning may occur. Triggers include emotional stress, exercise, sun exposure and heat, temperature changes, ingestion of alcohol, and spicy foods. Transient flushing can progress leading to permanent redness and telangiectatic vessels. Patients with papulopustular disease go on to develop inflammatory papules and pinpoint pustules. Microbes including *Demodex folliculorum*, *Helicobacter pylori*, *Staphylococcus epidermidis*, and *Chlamydia pneumoniae* have been implicated [19]. The absence of comedones may help distinguish papular rosacea from *acne vulgaris.*

Phymatous rosacea characteristically occurs on the nose with enlargement, skin thickening, and surface nodularity, but these changes can occur on other areas of the face and on the ears. Severe rhinophyma can result in functional impairment, for example, nasal airway obstruction or even difficulty eating, and requires surgical intervention [20]. Ocular disease may precede cutaneous signs or occur simultaneously. Common ocular manifestations include blepharitis, conjunctivitis, chalazion, conjunctival hyperemia, and telangiectasias. Stinging, dryness, photosensitivity, and grittiness may also occur. Corneal complications can present as decreased visual acuity and warrant ophthalmologic attention.

The complex pathophysiology of rosacea remains poorly understood. There is clearly a genetic component, and a positive family history is not unusual, but as of yet, the condition cannot be attributed to a single gene. Vascular [21,22], nervous, and immune dysregulation are involved and interrelated, with end-stage fibrosis resulting from chronic inflammation. Reactive oxygen species are postulated to play a role in the inflammatory process [23] as well as a helper-inducer T-cell response to *Demodex* mites, for example. Proinflammatory genes involved in vasoregulation and neurogenic inflammation have been shown to be upregulated in the very early stages of rosacea, along with marked inflammatory infiltrates (Th1 cells, macrophages, mast cells). Their presence prior to any clinical signs of inflammatory disease, i.e., papules and pustules, suggests

rosacea is primarily an inflammatory disease characterized by neuroimmune and neurovascular dysfunctions [24].

There are a large number of treatments for rosacea depending on the type of disease. Lifestyle modification to avoid triggers should be discussed, including broad-spectrum UVA and UVB photoprotection—physical blocking agents are preferred. As SC impairment and high reactivity can play a role in the pathogenesis of rosacea, advice tailored to the patient with sensitive skin is recommended. Some suggest that "priming the skin" using only mild cleansers and moisturizers for several days will correct SC impairment and improve tolerance to subsequent topical treatments [25]. Topical antibiotics may be appropriate in inflammatory disease, and other agents such as tretinoin, benzoyl peroxide, and azalaic acid can be considered depending on skin reactivity. Oral antibiotics can be used in papulopustular rosacea: it is their anti-inflammatory properties that are now felt to be more relevant than their antimicrobial effects. Laser and light-based treatments may be useful for static erythema and telangiectasias, and surgical treatment may be indicated in cases of rhinophyma.

SEBORRHEIC DERMATITIS

Seborrheic dermatitis is a common cause of facial redness, also frequently affecting the scalp and chest. Typically, the nasolabial folds, ears, eyebrows, scalp, and chest are affected, though other sites include the intertriginous zones (Figure 14.3). Erythema, flaking, and a greasy appearance are typical, though the skin of patients with seborrheic dermatitis is not necessarily more oily than those who are disease-free [26]. Seborrheic dermatitis affects 1%–3% of the population and is common in adolescents and young adults, though it can also occur on the scalp in infants as "cradle cap" or diaper area as "napkin dermatitis." There is a predilection for seborrheic dermatitis in patients with comorbidities such as HIV/AIDS [27,28] and Parkinson's disease [29].

Many factors play a role in the etiology of seborrheic dermatitis, including endogenous host factors as well as external influences. There appears to be some correlation between seborrheic dermatitis and sebum levels. The disease not only commonly affects areas of sebaceous gland distribution but also develops at puberty (with the exception of infantile disease) and is more common in men, which suggests an androgenic influence on the pilosebaceous unit.

The lipophilic yeast *Malassezia*, which is a skin commensal, has been long associated with the disease. Correlation between the density of *Malassezia* and severity of disease has been demonstrated [30], but it is unclear whether patients with seborrheic dermatitis have higher *Malassezia* counts than normal controls [31]. Some have suggested that *Malassezia* may produce a toxin or lipase that triggers the disease [32]. The subsequent classification of the genus *Malassezia* into seven species has not been helpful, as association of disease with any particular species has been inconclusive. Some suggest disease is caused by an abnormal immune reaction to the yeast [33], and the prevalence of disease in HIV-positive patients supports the role of some form of immune dysregulation. Although the precise contribution of *Malassezia* is not entirely clear, the efficacy of antifungal agents in the treatment of the disease supports positive association.

In addition to antimycotic shampoos, creams, and lotions, topical corticosteroids and calcineurin inhibitors have also been demonstrated to be effective. The condition also appears to photoresponsive, as the disease tends to abate in the summer months.

(a) (b)

Figure 14.3 (a and b) Seborrheic dermatitis.

OTHER CAUSES OF THE RED FACE

Psoriasis: Psoriasis is a common, chronic inflammatory dermatosis affecting up to 2% of the population. Facial psoriasis affects 17%–46% of those with psoriasis and is a poor prognostic indicator. Patients with facial psoriasis have more progressive and treatment-resistant disease compared to psoriatics with facial sparing. There are three suggested variants of facial psoriasis: hairline psoriasis, sebopsoriasis, and true facial psoriasis [34]. The seborrheic variant, as with seborrheic dermatitis, affects the face and scalp, axillae, inframammary creases, and flexures. Yellow, greasy scales are noted, unlike the usual white micaceous scale seen in chronic plaque psoriasis. A careful history, including family history, and examination to check for other signs of psoriasis will help in the diagnosis. It has been postulated facial psoriasis is triggered by microbial overgrowth. No positive correlation has been demonstrated with *Candida* growth, though *Malassezia* may play a role [35]. This may be particularly relevant in HIV-positive patients as extensive forms of facial psoriasis have been observed in this population [36].

Atopic dermatitis: Atopic dermatitis (AD) or eczema is a chronic, relapsing, intensely pruritic inflammatory dermatosis, common in both children and adults. Complex interactions between genetic, immunologic, and environmental factors are involved. Disease can have a variety of presentations, but facial disease is not uncommon, and there is a predilection for this site particularly in infants. AD can occur as a relatively limited disease localized to the face, but in most cases, there will be other foci of disease such as the flexures or hands. There may be a positive personal or family history of atopy, and after a thorough physical examination, a clinical diagnosis can be reached. Complicating factors such as contact or irritant dermatitis must also be considered. Epidermal barrier dysfunction plays a role in the pathophysiology of the disease, resulting in dry, sensitive skin even when the inflammatory component is relatively well controlled.

Contact dermatitis: Allergic contact dermatitis is caused when an allergen comes into contact with previously sensitized skin, resulting in a cell-mediated delayed hypersensitivity response. Uneventful exposure may occur over years, but once sensitization occurs, outbreaks can develop from even minor exposure. Disease can affect the face as a result of hypersensitivity to allergens in hair dye, hair spray, permanent wave solutions, or other hair dressing products. Nail varnish, false nail and false eyelash adhesives, fragrances, preservatives, and cosmetics can all result in facial disease. Medicaments, sunscreens, flavoring agents, nickel, and other allergens must also be considered, as well as photocontact dermatitis if the distribution is suggestive. If contact dermatitis is suspected, relevant patch testing should be performed. Allergen avoidance should result in disease resolution.

SUMMARY

Facial redness can be a debilitating and complex condition, often blurring the lines between cosmesis and disease. Resolution is dependent on the correct diagnosis, understanding of the underlying pathomechanisms and effective treatments that are ideally evidence based. The physician should bear in mind that facial redness may not be due to a single disease entity, and clinical overlap should be considered particularly in recalcitrant cases. Careful attention should be given to the integrity of the barrier membrane as patients with hyperreactive skin may be intolerant of potentially effective topical treatments. Lifestyle issues may also play a role in improving the condition, and a supportive doctor–patient relationship is required for optimum patient satisfaction.

REFERENCES

1. Elias PM. Epidermal lipids, barrier function and desquamation. *J Invest Dermatol* 1983; 80 (Suppl. 1):44–49.
2. Blank IH. Factors which influence the water content of the SC. *J Invest Dermatol* 1952; 13:430–433.
3. Thiers H. Pequ sensible. In: Thiers H, *Les Cosmetiques*, 2nd ed. Paris, France: Masson, 1986, pp. 266–268.
4. Maibach HI, Lammintausta K, Beradesca E, Freeman S. Tendency to irritation: Sensitive skin. *J Am Acad Dermatol* 1989; 21:833–835.
5. Willis CM, Shaw S, De Lacharriere O et al. Sensitive skin: An epidemiological study. *Br J Dermatol* 2001; 145:258–263.
6. De Lacharriere O. Self-perceived sensitive skin. In: Draelos ZD, eds. *Cosmetic Dermatology Products and Procedures*. Oxford, U.K.: Wiley-Blackwell, 2010, pp. 22–26.
7. Fischer AA. 1990. Part I: "Status cosmeticus": A cosmetic intolerance syndrome. *Cutis* 1990; 46:109–110.
8. Morizot E, Le Fur I, Numagami K et al., eds. Self-reported sensitive skin: A study o 120 healthy Japanese women. *22nd IFSCC*, Edinburgh, Scotland, September 2002.
9. Seidenari S, Francomano M, Mantovani L. Baseline biophysical parameters in subjects with sensitive skin. *Contact Dermatitis* 1998; 38:311–315.
10. Pedro P, Catarina R, Catarina P, Monteiro RL. Is there any barrier impairment in sensitive skin: A quantitative analysis of sensitive skin by athematica modelling of transepidermal water loss desorption curves. *Skin Res Technol* 2011; 17:181–185.
11. Denda M, Nakatani M, Ikeyama K, Tsutsumi M, Denda S. Epidermal keratinocytes as the forefront of the sensory system. *Exp Dermatol* 2007; 16:157–161.
12. Querleux B, Dauchot K, Jourdain R et al. Neural basis of sensitive skin: An fRMI study. *Skin Res Technol* 2008; 1:1–3.
13. Draelos ZD. Sensitive skin: Perceptions, evaluation and treatment. *Contact Dermatitis* 1997; 8:67–78.
14. Kueper T, Krohn M, Haustedt lo et al. Inhibition of TRPV1 for the treatment of sensitive skin. *Exp Dermatol* 2010; 19:980–988.
15. Gueniche A, Bastien P, Ovigne JH et al. Bifidobacterium longum lysate: A new ingredient for reactive skin. *Exp Dermatol* 2010; 19:31–38.
16. Asksoy B, Altaykan-Hap A, Egemen D et al. The impact of rosacea on quality of life: Effects of demographic and clinical characteristics and various treatment modalities. *Br J Dermatol* 2010; 163(4):719–725.
17. Webster GF. Rosacea. *Med Clin North Am* 2009; 93:1183–1194.
18. Wilkin JK, Dahl M, Detmar M et al. Standard classification of rosacea: Report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. *J Am Acad Dermatol* 2002; 56:584–587.
19. Lazaridou E, Giannopoulou C, Fotiadou C et al. The potential role of microorganisms in the development of rosacea. *J Dtsch Dermatol Ges* 2011; 9(1):21–25.
20. Sadick H, Riedel F, Bran G. Rhinophyma in rosacea: What does surgery achieve? *Hautarzt* 2011; 62(11):834–841.
21. Wilkin J. A role for vascular pathogenic mechanisms in rosacea: Implications for patient care. *Cutis* 2008; 82(21):100–102.
22. Huggenburger R, Detmar M. The cutaneous vascular system in chronic skin inflammation. *J Investig Dermatol Symp Proc* 2011; 15:24–32.
23. Jones DA. Rosacea, reactive oxygen species, and azelaic acid. *J Clin Aesthet Dermatol* 2009; 2(1):26–30.

24. Steinhoff M, Buddenkotte J, Aubert J et al. Clinical, cellular and molecular aspects in the pathophysiology of rosacea. *J Invest Dermatol Symp Proc* 2011; 15:2–11.
25. James Q. Del Rosso, DO. *October 2010: Priming the Skin Concept First Presented at Fall Clinical Dermatology*, Las Vegas, NV, November 13, 2010. Personal communication.
26. Burton JJ, Pye RJ. Seborrhoea is not a feature of seborrheic dermatitis. *Br Med J (Clin Res Ed)* 1983; 286:1169–1110.
27. Marino CT, McDonald E, Romano JF. Seborrheic dermatitis in acquired immunodeficiency syndrome. *Cutis* 1991; 50:217–218.
28. Mathes BM, Douglass MC. Seborrheic dermatitis in patients with acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1985; 13:947–951.
29. Binder RL, Jonelis FJ. Seborrheic dermatitis in neuroleptic-induced Parkinsonism. *Arch Dermatol* 1983; 119:473–475.
30. Heng MCY, Henderson CL, Barker DC et al. Correlation of Pityrosporum ovale density with clinical severity of seborrheic dermatitis as assessed by a simplified technique. *J Am Acad Dermatol* 1990; 23:82–86.
31. McGinley KJ, Leyden JJ, Marples RR et al. Quantitative microbiology of the scalp in non-dandruff, dandruff and seborrheic dermatitis. *J Invest Dermatol* 1975; 64:401–405.
32. Parry ME, Sharpe GR. Seborrheic dermatitis is not caused by an altered immune response to Malassezia yeast. *Br J Dermatol* 1998; 139:254–263.
33. Bergbrandt I-M, Faergemann J. Seborrhoeic dermatitis and Pityrosporum ovale: A cultural and immunological study. *Acta Derm Venereol* 1989; 69:332–335.
34. Van de Kerkhof PCM, Murphy GM et al. Psoriasis of the face and flexures. *J Dermatol Treatment* 2007; 13:351–360.
35. Rosenburg EW, Noah PW, Skinner RB et al. Microbial association of 167 patients with psoriasis. *Act Derm Venereol* 1989; 69:72–75.
36. Minsue Chen T, Cockerell CJ. Cutaneous manifestations of HIV infections and HIV-related disorders. In: Bolognia JL, Jorizzo JL, and Rapini RP, eds. *Dermatology*. London, U.K.: Mosby, 2003, pp. 1199–1216.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Pigmentation of the face

Lara Tripo, Alice Garzitto, and Ilaria Ghersetich

INTRODUCTION

Hyperpigmentary disorders of the face are increasing in dermatological practice. This is due to modern lifestyle with overexposure to UV and wide usage of hormones for contraception or in replacement therapy. In addition, some inflammatory diseases, such as acne, and new cosmetic procedures lead to a higher risk of developing facial postinflammatory pigmentations.

Human skin color can vary from a dark brown to a nearly colorless pigmentation, mainly determined by its content (amount and type) of melanin. Variation in skin color is largely due to genetic factors.

For practical convenience, six skin types are distinguished according to Fitzpatrick, listed on the basis of increasing pigmentation from I to VI.

Pigment formation is involved in many cutaneous physiological processes, such as inflammation and skin protection from sun exposure. Melanocytes and tyrosinase enzyme produce and convert DOPA into melanin; the keratinocytes then ingest the melanosomes, which contain the pigment, and eventually melanin is shed with the stratum corneum cells. Therefore, the highly peculiar condition of each patient, the resistance of some lesions to treatment, and the high prevalence of reappearance make hyperpigmentation disorders a therapeutic challenge for dermatologists, even for very experienced ones. Many topical agents, technical devices, and cosmetic procedures are available with different outcomes, not always predictable, depending on the underlying disease. Independent of cause and clinical type though, the therapy of hyperpigmented lesions can be based on accelerated epidermal turnover with removal of melanin in superficial layer (glycolic, salicylic, and lactic acids), increase in melanosome transfer and downregulation of tyrosinase enzyme (tretinoin), delay in melanocyte proliferation, secretory function, and inhibition of inflammation (steroids), and decrease in melanogenesis with inhibition of the tyrosinase enzyme (hydroquinone [HQ], kojic acid [KA], arbutin, and 4-butylresorcinol).

Based on histology or Wood's light examination (320–400 nm), hyperpigmentations can be classified as epidermal, dermal, or mixed type, according to the level of melanin deposition in the skin.

In epidermal melanosis, the skin shows only an excessive quantity of melanin with a normal number of melanocytes. The lesions appear sharply demarcated under Wood's light examination and have a dark-brown color. This kind of pigmentation is the most responsive to local treatment.

In dermal melanosis, the melanin pigment is localized in the dermis, among bundles of collagen or within the melanophages. The epidermis is normal. The lesions are not sharply demarcated under Wood's light and tend to have a brown-gray color. This type of hyperpigmentation is less responsive to local treatment.

In the mixed type, which represents the most common one, there is increased melanin in the epidermis and melanophages in the dermis. Wood's light examination and treatment outcomes show clinical aspect of both epidermal and dermal pigmentation types.

Pigmentations of the face can also be seen in many genetic syndromes (Leopard syndrome, centrofacial lentiginosis, neurofibromatosis), but more often they are acquired [1].

ACQUIRED PIGMENTATIONS

Acquired pigmentations of the face can recognize many possible causes, but the most frequent are certainly represented by postinflammatory hyperpigmentation (PIH) and melasma.

PIH is a very common and rather persistent condition in Asians and dark-skinned populations. It can be a consequence of cutaneous inflammation from a wide range of etiologies, such as inflammatory dermatoses (one for all acne), infections, trauma, reactions to medications, and medical procedures (i.e., laser therapy) [2].

The lesions have the same pattern and distribution of the initial dermatoses, but the intensity of the dyschromia is not related to the degree of the previous inflammation. Superficial epidermal pigmentation is usually brown and fades out in several months; dermal pigmentation instead is gray-brown and usually lasts for years.

PIH develops because the inflammation of the epidermis induces keratinocyte production and release of many mediators (prostaglandins, leukotrienes, and cytokines) that affect melanocyte proliferation and melanin production. Pigmentary incontinence or melanin dropping can cause dermal hyperpigmentation, with the presence of melanophages in the dermis [3,4].

Treatment of PIH may be very difficult and the primary goal for therapy is to treat the etiology. Many topical therapies, such as depigmenting agents, can be used, but particularly important is the combination of these therapies with the frequent and constant use of sunscreens. Indeed, it is well known that sunlight often worsens the spots [5].

Melasma (Figures 15.1 and 15.2) is a commonly acquired, localized disorder of the pigmentation that is characterized by irregular brown or grayish-brown macules and patches with well-defined margins, usually occurring symmetrically on sun-exposed areas of the body, most commonly not only

Figure 15.1 Melasma in a young Asian woman.

Figure 15.2 Melasma in a young Hispanic woman.

on the face and in particular on the forehead, malar eminence and cheeks but also on upper lip and chin and rarely on upper limbs. This typical disease mostly affects women of reproductive age with darker skin tones (Fitzpatrick skin type IV–VI), but people of all ages, races, and skin colors may be affected. Female sex hormones (endogenous and exogenous), genetic influence, and most of all solar and in general UV exposure along with phototoxic drugs (anticonvulsants) and cosmetics are the most known etiological factors [6].

The exact prevalence of melasma is unknown, but some small-scale studies have suggested a prevalence of 4%–10% in Latin America, as high as 40% in Southeast Asian populations, increasing to 20%–50% in pregnant women and up to 10% of men [7].

Basing upon Wood's light examination of the skin, melasma can be classified into four major clinical types and patterns, with good correlation with histology (in accordance with depth of melanin pigment):

1. Epidermal (light brown; with an enhancement of pigmentation under Wood's light; histologically, it is characterized by a melanin increase in the basal, suprabasal, and corneum layers)
2. Dermal (ashen or bluish-gray; no enhancement of pigmentation under Wood's light; histologically, there is a preponderance of melanophages in superficial and deep dermis)
3. Mixed (dark brown; enhancement of pigmentation under Wood's light in some areas and not in others)
4. Indeterminate (not visible under Wood's light)

Pathogenesis of melasma is complex and it appears not to be restricted only to melanocytes.

UV light is a commonly reported initiating or exacerbating factor for melasma, most likely because of its effects on melanocytes and on cytokine production. UV radiation induces melanocyte proliferation, migration, and melanogenesis. In addition, UV radiation can lead to the production of multiple cytokines, including interleukin-1, endothelin-1, alpha-melanocyte-stimulating hormone, and adrenocorticotropic hormone from keratinocytes, which upregulate melanocyte proliferation and melanogenesis.

The hormonal link to melasma has not been clearly elucidated yet. Many patients though notice onset or worsening of the disease with pregnancy or under oral contraceptive pills.

Emerging data have also shed some light on the role of the stem cell factor in the pathogenesis of melasma, with a greater expression of the stem cell factor around dermal fibroblasts, a greater expression of c-kit in the basal layer, and an increased number of melanocytes and epidermal melanin in the affected skin [8,9].

It has also been demonstrated that, especially after UV exposure, the activation of the inducible nitric oxide synthase (iNOS) within keratinocytes has an important role in the process of melanogenesis, with activation of the AKT/NFkB pathway. iNOS is able to stimulate the tyrosinase enzyme of melanocytes with an increased production of melanin in the affected skin, thus emphasizing the role of keratinocytes in the pathophysiology of melasma.

Finally, melasma seems to have also a vascular pathogenetic component. In fact, lesional skin shows a significant increase of vascular endothelial growth factor expression in keratinocytes and numerous and larger blood vessels compared to uninvolved skin. The exact role of the vascularization in the genesis of hyperpigmentation still has to be clarified [10].

Melasma severity can be assessed using the melasma area and severity index.

Currently, many options are available such us bleaching agents and chemical peels but most of all the frequent use of sunscreens.

HYPERPIGMENTATION TREATMENT OPTIONS

Treatment of facial skin pigmentations is still challenging and the best results are normally seen in epidermal forms. The goal is to decrease melanin production. For this reason, different therapeutic options have been used during the years to treat melasma and PIHs, which represent a major cosmetic and social concern for many patients.

Schematically, they can be distinguished into

1. Topical and cosmetic treatments
2. Physical treatments
3. Chemical peelings
4. Injection treatments

Topical and Cosmetic Treatments

Bleaching agents have to be used for several months and they are much more effective in epidermal types.

Hydroquinone

HQ is a hydroxyphenolic compound that inhibits the conversion of DOPA to melanin by inhibition of the tyrosinase enzyme. It has been the gold standard for hyperpigmentation treatment for many decades. It is also supposed to inhibit DNA and RNA syntheses and to induce degradation of melanosomes and destruction of melanocytes. HQ preparations are the most extensively used to treat melasma in concentrations varying from 2% (over the counter) to 4% (by prescription). HQ can also be used in combination with other agents. HQ adverse reactions (which are dose and time related) are erythema, stinging, colloid milium, irritation and allergic contact dermatitis, nail discoloration, and paradoxical postinflammatory hypermelanosis [7]. In some European countries, the use of HQ is forbidden.

Tretinoin (retinoic acid)

Retinoic acid (RA) is a vitamin A derivative. Topical RA 0.05%–0.1% reduces pigmentation by inhibition of tyrosinase transcription, reduction in melanosome transfer, and stimulation of keratinocyte turnover. RA has to be applied for a long time: significant lightening becomes evident after 24 weeks, with better results obtained in combination with other compounds. The most common side effects are erythema, peeling, burning, and stinging. It should be emphasized that the use of total sunscreens is mandatory during RA treatment [7].

Arbutin

Arbutin or arbutoside is a glycosylated HQ, present at high concentrations in certain plants. It is a very-water-soluble compound; the optimal pH may be 5 or 7 (neutral). Its mechanism of action seems to be related to the inhibition of tyrosine hydroxylase and DOPA oxidase. So arbutin inhibits, with a competitive mechanism, the enzyme activity, not its production. Even though arbutin is a precursor of HQ, different studies show that it is a more effective and less toxic skin lightener than HQ and it can also be added to several topical compounds [7].

Azelaic acid

Azelaic acid (AA) is a natural, saturated straight-chain dicarboxylic acid that has a selective effect on hyperactive and abnormal melanocytes (inhibition of tyrosinase, cell membrane–associated enzyme thioredoxin reductase, specific mitochondrial dehydrogenases, and DNA synthesis). The reported preparations are 10%, 15%, 20%, and 35%, with the 20% one being most commonly used. AA has to be applied twice daily for several months—up to 8 months, even though lightening starts after 1–2 months. Generally speaking, early cases respond better than long-standing ones, and epidermal pigmentation responds faster than the mixed type. There are no significant adverse effects, apart from an initial and transitory irritation [7].

Steroids

Several types of topical corticosteroids have been used in the treatment of melasma and other hyperpigmentary disorders. Mild steroids (1% hydrocortisone) have been used with poor results, while potent (2% betamethasone) and very potent steroids (0.05% clobetasol propionate) gave better results. They have better efficacy when combined with tretinoin or HQ. The adverse effects of topical steroids are those typical of their long-term use: atrophy, itching, acne, and telangiectasia, especially frequent in areas more susceptible to local steroid damage (i.e., the face) [7].

Kojic acid

KA is one of the last used bleaching agents to treat melasma. Chemically (5-hydroxymethyl-4H-pyrin-4one), it is an antibiotic produced by many species of *Aspergillus* and *Penicillium*, with anti-inflammatory and pain-relief activities. Its whitening activity is due to its slow-binding inhibition of tyrosinase. KA is normally used in 1% preparations, twice daily for two months; higher concentrations do not improve its depigmenting activity. Its most important side effect is contact allergy; it has been observed with a higher frequency in Japan, where the compound is widely used [7].

4-n-butylresorcinol

4-*n*-butylresorcinol has been characterized as a strong tyrosinase and TRP-1 inhibitor among all resorcinol derivates. The improvement onset with this topical treatment is fast with a good lightening degree after 12 weeks of treatment. It is useful to keep up the bleaching result of a therapy with HQ and it is indicated for long-term use, because no side effects have been reported so far [11].

COMBINATION TREATMENTS

Different combined preparations have been used during time, with the intent to increase efficacy and reduce side effects of depigmenting drugs. The most widely association used is HQ + RA + steroid, the so-called Kligman and Willis' formula (5% HQ, 0.1% RA, and 0.1% dexamethasone). Recently, Pigmentary Disorders Academy's (PDA) expert opinions were that topical fixed triple combinations with 0.01% fluocinolone acetonide (FA), a low-potency (class IV) corticosteroid, plus 4% HQ and 0.05% tretinoin (RA), should be used as first-line therapy for melasma, and it proved to be superior to both HQ and RA alone. An innovative product containing microencapsulated HQ 4% and retinol 0.15% with antioxidants has improved hyperpigmentation disorders of the face. Another important association is that of HQ 5%, RA 0.1%, and hydrocortisone 1% [12–14].

Physical Treatments

Lasers have to be selectively chosen and have to be used in those cases in which there is a proven resistance to the most common topical therapies.

In the past, attempts to treat melasma with lasers that targeted melanin, such as Q-switched ruby laser (694 nm), the short-pulsed green dye laser (504–510 nm), the Q-switched neodymium laser (1064 nm), and the argon laser (514 nm), yielded disappointing results. Better results are obtained with Er:YAG laser resurfacing and with the combination of pulsed CO_2 laser and Q-switched alexandrite laser, because the CO_2 laser would destroy melanocytes, while alexandrite laser would remove the pigment left in the dermis [15].

Intense pulsed light (IPL) is a noncoherent, broad-spectrum light source that emits a continuous spectrum in the range of 500–1200 nm; regarding wavelengths, IPL sources can be used with lower cutoff filters to treat superficial face pigmentation and higher cutoff filters for deeper lesions. The therapeutic efficacy is relatively higher in patients with epidermal-type of PIH and melasma than those with the mixed type. Side effects are very limited with IPL treatment: generally, a transient erythema and a paradoxical hyperpigmentation are observed and usually resolve few days after the procedure. However, IPL achieves only temporary and transient results with a new appearance of hyperpigmentation after several weeks or months [15].

Fractional resurfacing (FR) is a novel concept of skin rejuvenation that has the potential to treat a variety of epidermal and dermal conditions. In fact, it can produce a unique thermal damage pattern. FR may be helpful in the treatment of epidermal melasma and has been used to treat PIH with variable success due to the risk of developing pigmented lesions associated with the device [16].

Chemical Peelings

Chemical peelings are performed through the application of chemical agents on the face to induce the progressive exfoliation of the superficial layers of the skin. Peels are currently divided into superficial, medium, and deep. Superficial peeling with trichloroacetic acid (TCA) is still widely used in concentrations of 15, 25, 50. At the highest concentration, i.e., 75%, destruction of the epidermis and superficial dermis occurs. Patients have to be carefully selected, avoiding subjects with skin types of III or more (IV–VI), those with clinical history of herpes simplex, and those without a good psychological compliance (because of burning and possible pain during TCA applications). TCA should be used by experienced physicians only, because of its possible severe side effects: instantaneous epidermal necrosis, postinflammatory pigmentation, and hypertrophic scars.

Alpha-hydroxy acids (AHAs) are a group of organic acids widely represented in fruits and vegetables. They act by reducing the cohesiveness of corneocytes and stimulate the biosynthesis of glycosoaminoglycans. Glycolic acid (GA) is the most widely used one at a 50%–80% concentration. The application of GA should last few minutes and should be immediately followed by rinsing with plane water or sodium bicarbonate 1%. Following these guidelines, the treatment can be repeated at 3–4-week intervals, minimizing the common side effects (erythema, desquamation) [17].

Lactic acid, a member of AHA similar to GA, is a new therapeutic peeling agent used in melasma. Another possible peeling is 30% salicylic acid. With both peelings, no significant side effects have been observed so far [18].

Tretinoin 10% mask peeling is another available treatment option: one week before the peel, a 0.025% tretinoin cream is applied on a daily basis (at night), followed by 4 tretinoin peels (once every three weeks) using total sunscreen during all the treatment; the skin becomes reddish the first two days, while the exfoliation starts on the third–fourth day, and it lasts approximately one week. Good results can be achieved with this technique also in dark phototypes [19,20].

New Injection Treatments

Topical trans-4-aminomethylcyclohexanecarboxylic acid (tranexamic acid [TA]), a plasmin inhibitor, has shown to prevent UV-induced pigmentation. The experimental technique consists of intradermal or subcutaneous microinjection of 0.05–0.1 mL of a highly diluted drug mixture in the desired area. By injecting TA intradermally, it may be possible to treat the dermal-type melasma in addition to the mixed type. It has also been demonstrated that the use of topical and oral TA together leads to a decrease of hyperpigmentation in melasma lesions [21].

CONCLUSIONS

Pigmentations of the face can be a social problem for the affected patients. Treatment of melasma and PIH can be extremely difficult. Many treatment procedures, technical devices, and topical agents are available today, with different outcomes, since the final result is not always predictable, varying from patient to patient (skin complexion, type of skin lesions).

Furthermore, it has been clearly pointed out that the use of broad-spectrum sunscreens is mandatory during and after therapy, regardless of the kind of treatment performed. The careful avoidance of other exacerbating factors—contraceptives, cosmetics, phototoxic drugs—should also be recommended.

REFERENCES

1. Nieuweboer-Krobotova L. Hyperpigmentation: Types, diagnostics and targeted treatment options. *J Eur Acad Dermatol Venereol* 2013; 27:2–4.
2. Eimpunth S, Wanitphadeedecha R, Manuskiatti W. A focused review on acne-induced and aesthetic procedure-related postinflammatory hyperpigmentation in Asians. *J Eur Acad Dermatol Venereol* 2013; 27:7–18.
3. Callender VD, St. Surin-Lord S, Davis EC, Maclin M. Postinflammatory hyperpigmentation: Etiologic and therapeutic considerations. *Am J Clin Dermatol* 2011; 12:87–99.
4. Davis EC, Callender VD. Postinflammatory hyperpigmentation: A review of the epidemiology, clinical features, and treatment options in skin of color. *J Clin Aesthet Dermatol* 2010; 3:20–31.
5. Lacz NL, Vafaie J, Kihiczak NI, Schwartz RA. Postinflammatory hyperpigmentation: A common but troubling condition. *Int J Dermatol* 2004; 43:362–365.
6. Prignano F, Ortonne JP, Buggiani G, Lotti T. Therapeutical approaches in melasma. *Dermatol Clin* 2007; 25:337–342.
7. Ball Arefiev KL, Hantash BM. Advances in the treatment of melasma: A review of the recent literature. *Dermatol Surg* 2012; 38:971–984.
8. Sheth VM, Pandya AG. Melasma: A comprehensive update: Part I. *J Am Acad Dermatol* 2011 October; 65:689–697.
9. Young Kang H, Ortonne JP. Melasma update. *Actas Dermosifiliogr* 2009; 100:110–113.
10. Passeron T. Melasma pathogenesis and influencing factors—An overview of the latest research. *J Eur Acad Dermatol Venereol* 2013; 27:5–6.
11. Kolbe L, Mann T, Gerwat W et al. 4-*n*-butylresorcinol, a highly effective tyrosinase inhibitor for the topical treatment of hyperpigmentation. *J Eur Acad Dermatol Venereol* 2013; 27:19–23.

12. Rendom M, Cardona LM, Bussear EW et al. Successful treatment of moderate to severe melasma with triple-combination cream and glycolic acid peels: A pilot study. *Cutis* 2008; 82:372–378.
13. Chan R, Park KC, Lee MH et al. A randomized controlled trial of the efficacy and safety of a fixed triple combination (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) compared with hydroquinone 4% cream in Asian patients with moderate to severe melasma. *Br J Dermatol* 2008; 159:697–703.
14. Cook-Bolden FE, Hamilton SF. An open label study of the efficacy and tolerability of microencapsulated hydroquinone 4% and retinol 0,15% with antioxidants for the treatment of hyperpigmentation. *Cutis* 2008; 81:365–371.
15. Li Y-H, Chen JZS, Wei H-C et al. Efficacy and safety of intense pulsed light in treatment of melasma in Chinese patients. *Dermatol Surg* 2008; 34:693–701.
16. Tannous ZS, Astner S. Utilizing fractional resurfacing in the treatment of therapy-resistant melasma. *J Cosmet Laser Therapy* 2005; 7:39–43.
17. Ghersetich I, Brazzini B, Lotti T. Chemical peeling. In: Lotti TM, Katsambas AD, eds. *European Handbook of Dermatological Treatments*, 2nd ed. Berlin, Germany: Springer, 2003.
18. Sharque KE, Al-Tikreety MM, Al-Mashhadani SA. Lactic acid chemical peels as a new therapeutic modality in melasma in comparison to Jessner's solution chemical peels. *Dermatol Surg* 2006; 32:1429–1436.
19. Ghersetich I, Troiano M, Brazzini B et al. Melasma: Treatment with 10% tretinoin peeling mask. *J Cosmet Dermatol* 2010; 9:117–121.
20. Sheth VM, Pandya AG. Melasma: A comprehensive update: Part II. *J Am Acad Dermatol* 2011; 65:699–714.
21. Tse TW, Hui E. Tranexamic acid: An important adjuvant in the treatment of melasma. *J Cosmet Dermatol* 2013; 12:57–66.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

16

Makeup techniques in dermatology

Zoe Diana Draelos

INTRODUCTION: VALUE OF COSMETICS

Dermatology is a branch of medicine that focuses on health and appearance more thoroughly than any other. While healthy skin is a prerequisite for an attractive appearance, dermatologic treatments go beyond medications to enter the world of cosmetics. This creates a challenge for the dermatologist because knowledge mastery of prescription and extensive OTC formulations is unique. This chapter examines one specific area of OTC formulations known as cosmetics. Cosmetics are products designed to color, scent, and adorn the body through the use of color, texture, and fragrance. They do not physiologically alter the skin or treat bodily disease. However, cosmetics address important diseases of the psyche including low self-esteem, depression, and poor self-image. It is interesting to note that these diseases of psyche will eventuate in diseases of the body if not appropriately treated. Thus, most physicians may underappreciate the value of cosmetics in dermatology.

Cosmetics, also known as makeup, can be artistically applied to the face and body to camouflage underlying disease, improve upon undesirable contours, restore proportions, mask pigmentation issues, add color, create the illusion of youth, and complement prescription therapies. This chapter examines makeup from a medical viewpoint examining makeup techniques in dermatology for the lip, eyelid, eyebrow, eyelash, and face. The cosmetics used in each of these areas will be discussed both from a formulation and appropriate use standpoint. Incorporation of cosmetics into the dermatologic armamentarium for the prevention and treatment of disease, as well as for camouflaging purposes, will provide the dermatologist with the necessary information to master this challenging area.

LIP COSMETICS

The lips are important for speaking, eating, and kissing. The lips express emotion but unfortunately develop diminishing cosmetic value with aging as fat is lost from the lips, creating architectural loss of the vermilion. A popular site for filler injection is the lip, necessary for reestablishment of this important facial landmark. However, the simplest way to restore lip appearance is through the use of lip cosmetics. Modern lip cosmetics, including lipsticks, polymer lipsticks, lip stains, and lip liners, can be used to reconstruct the lip shape, restore lip color, and redefine lip shape. This discussion focuses on the use of lip makeup in dermatology to enhance lip appearance and complement other lip procedures.

Lipstick

Lipstick is an extruded rod of color dispersed in a blend of oils, waxes, and fats packaged in a roll-up tube (Figure 16.1). The colored cosmetic is removed from the rod by stroking over the lips. This creates a film that can moisturize dry lips, add color to aging lips, camouflage lip contour abnormalities, and provide sun protection.

Altering the ratio of oils to waxes creates the various lipstick formulations. Waxes, such as white beeswax, candelilla wax, carnauba wax, ozokerite wax, lanolin wax, ceresin wax, and other synthetic waxes, allow the lipstick to adhere to the transitional lip tissue. Oils are then added to soften the wax and add shine to the lips. Commonly used oils include castor oil, white mineral oil, lanolin oil, hydrogenated vegetable oils, or oleyl alcohol. The oils also allow the dispersion of pigment to color the lip. Only certain coloring agents are allowed in lipsticks due to the frequent ingestion of the cosmetic. In the United States and the European Union, authorities regulate these colors to ensure the safety of the customers. The United States classifies the coloring agents used in cosmetics into three groups: food, drug, and cosmetic (FD&C) colors; drug and cosmetic (D&C) colors; and external drug and cosmetic colors. Only the first two groups can be used in lipsticks. The external drug and cosmetic colors can only be used in locations where they are not likely to enter the mouth. Recently, there has been concern regarding the presence of lead in red lipsticks. Indeed, there may be small traces of lead in the coloring agents used in red lipsticks, but it is not considered to be a health issue at present. It is for this reason that coloring agents are tightly regulated for consumer safety.

Lipsticks and Sun Protection

Lipsticks provide excellent sun protection for persons with actinic cheilitis or prior history of squamous cell carcinoma of the lip. Opaque lipsticks that completely block the underlying lip mucosa from vision provide complete sun protection [1]. This is achieved through incorporation of titanium dioxide into the formulation. Titanium dioxide is on the U.S. Sunscreen Monograph and functions as an inorganic sunscreen. These opaque lipsticks will not be labeled with a sun protection factor (SPF), however, because the manufacturer wishes for the product to maintain its cosmetic status. If the titanium dioxide is called out as a sunscreen ingredient and SPF testing is undertaken, the product then becomes an OTC drug and must be labeled with an expiry date and follow other packaging requirements. For this reason, it is best to advise the patient to put some of the lipsticks on the back of their hand at the cosmetic counter to see if the underlying skin is visible. These lipsticks will not be identified by any sun protection claims.

Lip sun protection can also be achieved by adding sunscreen ingredients to either pigmented lipsticks or unpigmented lip balms and lip glosses. The SPF of these products usually stops at 30 because the taste of the organic sunscreens

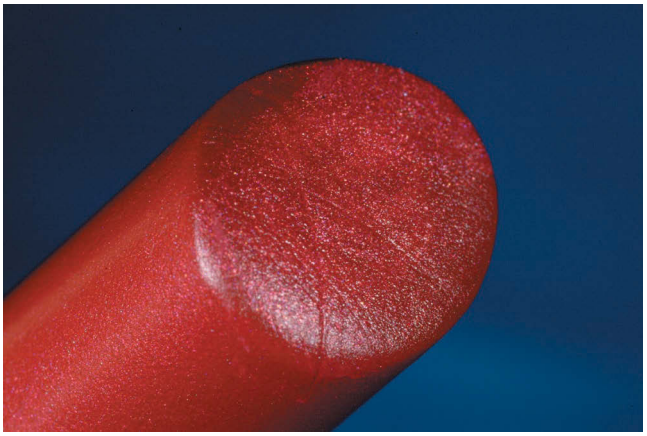


Figure 16.1 Opaque lipstick. Opaque lipsticks contain titanium dioxide and pigments to completely conceal the underlying lip tissue providing excellent sun protection and optimal camouflaging. (From Cosmetics and Dermatological Problems and Solutions 3E, Informa Healthcare, 2011. With permission.)

Figure 16.2 Polymer lipstick. Polymer lipsticks are stroked across the lip with a sponge applicator to create a pigmented film, but the film is dull and drying to the lips. (From Cosmetics and Dermatological Problems and Solutions 3E, Informa Healthcare, 2011. With permission.)

is bitter and unacceptable to the consumer. Most lip products currently marketed are in the SPF 15 range for this reason. Lip balms have a high wax content that allows the sunscreen to stay on the lips even through licking. Lip glosses, primarily used to add shine to the lips, do not stay on the lips well with licking and are not the best choice for lip protection. Some lip glosses may incorporate pigment for a transparent shiny lip appearance, but again adhere poorly to the lip and provide only short photoprotection.

Lip Camouflaging

Lip camouflaging may be necessary for females who have undergone cryosurgery of the lip for actinic keratoses, Mohs surgery for lip squamous cell carcinoma, or reconstruction following an upper lip basal cell carcinoma. Any procedure that deforms the lip in the female may require camouflaging to restore an attractive appearance and improve self-esteem. Polymer film lipsticks are useful for this purpose because a long-lasting water and rub-resistant pigmented film is deposited on the lip. These lip products are packaged as two-tube products where one end contains the colored lip polymer and the opposite end contains a lip gloss (Figure 16.2). The pigmented polymer is applied first with a sponge brush and allowed to dry. The product polymerizes on the lip and is difficult to remove with rubbing, providing 4–8 hour camouflage.

One of the problems with these polymer lipsticks is that they are very drying to the lips and lack shine. It is for this reason that the accompanying lip gloss is provided. The shorter wearing lip gloss prevents water loss from the lips and gives the lips a moist appearance desired by most women. The lip gloss must be frequently reapplied, however, as it does not adhere to the lip mucosa. Products that do not adhere well to the skin are said have a low substantivity. The ability of the lip color to last through eating, speaking, and rubbing can be improved by covering the polymer lipstick with an opaque lipstick. This combination is attractive while providing optimal camouflaging of underlying lip defects.

If the shape of the lip has been distorted, the lip polymer or lipstick should be combined with a lip liner. Lip liners are thin extruded pigmented rods encased in wood or placed in an automatic pencil-type holder (Figure 16.3). Their formulation is similar to lipsticks, except that stiffer waxes with higher melting points are used with minimal oil. This creates an extremely hard rod that applies a thick layer of pigment to the lips. Lip liners are used to define the outer edge of the lips and are valuable in reconstructing a normal lip contour. For example, the patient can be taught to artistically draw symmetrical lips or larger lips with the lip liner and then filler inside the line with an opaque lipstick.

Lip liners can also meet other cosmetic needs in the mature female. A common cosmetic problem is the bleeding of lipstick into the fine lines on the upper and lower lips. The thick

Figure 16.3 Lip liner. Lip liners are thin pencils that can be used to artistically draw the vermilion border. (From Cosmetics and Dermatological Problems and Solutions 3E, Informa Healthcare, 2011. With permission.)

wax lip liner layer applied around the lips can prevent lip products from migrating into these lines, maintaining the lipstick film on the lips [2]. Lip liner can also add definition to the lips since the vermilion border can become obscured with sun exposure. If the lip liner is selected one to two shades darker than the lipstick, improved lip definition can be achieved. Finally, lip liner can be used to temporarily draw lip proportions prior to lip filler injections to be sure that the patient is comfortable with the proposed lip size. This will help with planning of the procedure. The dermatologist should remember, however, lip liners can be a source of allergic contact dermatitis [3].

Lip Color Correction

With advancing age, the lips tend to lose their burgundy color, necessitating the need to wear a lip cosmetic to add facial color. A special type of long-wearing lipstick is a lip stain containing indelible coloring agents known as bromo acids. These bromo acids include fluoresceins, halogenated fluoresceins, and related water-insoluble dyes. The most commonly used indelible coloring agent is acid eosin, a tetrabromo derivative of fluorescein. Acid eosin, also known as bromo acid or D&C Red No. 21, is naturally colored orange but changes to a red salt at a pH of 4. Conditions present on the lip change the orange lipstick to a vivid red indelible stain that is long lasting. This pigment stains the lips red and cannot be removed until worn away by licking or eating. The long-lasting color eliminates the need to frequently reapply lip cosmetics. These products can also dry the lips and should be combined with a moisturizing lipstick in patients with cheilitis.

EYE COSMETICS

The lips are the focal point of the lower face and the eyes are the focal point of the upper face. Some might say that the eyes are the major focal point of the face due to their ability to express emotion, interest, health, and attention. Eye adornment is firmly rooted in antiquity for both men and women, recorded as early as 4000 BC. Archeologists have identified a variety of eye cosmetics, including green malachite powder for application to both the upper and lower eyelids accompanied by eyeliner paste made of powdered antimony, burnt almonds, black copper oxide, and brown clay ocher. The eyeliner paste was stored in a pot and moistened with saliva for application to the lid margin with a thin stick. The eyes were further adorned with glitter composed of ground beetle shells [4].

Eye cosmetics can be divided into the eye regions where they are applied: eyelid, eyelash, and eyebrow. Each of these cosmetics serves to highlight a facial structure important to female beauty. This section examines these cosmetics, highlighting information important to the dermatologist.

Eyelid Cosmetics

The eyelid skin is the thinnest on the body because it accommodates eyeball movement. This thin skin is fragile and easily damaged by UV radiation, accounting for the rapid aging of this tissue. The primary cosmetic applied to the eyelid is eye shadow available as a pressed powder, anhydrous cream, and emulsion. Eye shadow is available in tremendous color variety, but coal tar derivative colors are prohibited from use in the eye area (Figure 16.4). Only certain purified, natural colors or inorganic pigments can be used in the United States as a result of the Food, Drug, and Cosmetic Act of 1938 [5]. These pigments include iron oxides, titanium dioxide, ultramarine blue or violet or pink, manganese violet, carmine, chrome oxide and hydrate, iron blue, bismuth oxychloride, and mica. These pigments can be mixed to create a variety of colors designed to draw attention to the eye and enhance appearance.

Figure 16.4 Eye shadow. Eye shadows are applied to the upper eyelid to create heightened interest in the eye area. Many different colors are available to complement and contrast with the iris color. (From Cosmetics and Dermatological Problems and Solutions 3E, Informa Healthcare, 2011. With permission.)

In addition, various texture-modifying agents are added to eye shadow. A dull or matte appearance is created by adding titanium dioxide, which also increases the opacity of the eye shadow, making it useful for camouflaging eyelid pigmentation irregularities. An iridescent pearled eye shadow appearance is created by adding bismuth oxychloride (BiOCl), mica, and/or fish-scale essence. This pearled shine enhances upper eyelid wrinkles and folds making this texture a poor choice for camouflaging. Similarly, metallic iridescent finishes provided by copper, brass, aluminum, gold, or silver powders are also not appropriate for camouflaging. These iridescent finishes are better worn as a fashion statement.

Eye shadows are available in powder and cream formulations. The powder is the most popular applied to the eyelid by lightly stroking a soft sponge-tipped applicator or a brush across the skin. The powders are composed of talc with pigments and zinc or magnesium stearate used as a binder. To increase the wear of the eye shadow powder, kaolin or chalk may be added to improve oil and perspiration absorption. Sometimes mineral oil, beeswax, or dimethicone is added to create a creamy powder. These creamy powders are better for camouflaging in persons with mature dry skin.

Cream eye shadows are preferred over the powders when waterproof properties are important or the eye shadow must stay in place for a long time. These products are packaged in a jar and applied with the finger or withdrawn from a cylindrical tube and stroked across the eyelid with a sponge-tipped applicator. Cream eye shadows may contain waxes, cyclomethicone, and pigments in a volatile petroleum distillate vehicle.

Eye cosmetics become more important with aging to add color to a sallow face, but proper selection is important because eye shadows can easily migrate into the folds of redundant upper eyelid skin accentuating their appearance. The dermatologist can pass a few important cosmetic tips to the aging

patient who may have undergone blepharoplasty surgery or botulinum toxin injections to decrease periorbital rhytids. For the mature patient, pressed powder eye shadows are recommended, even though patients may think rich creamy eye shadows might aid in moisturizing dry eyelids. The creamy eye shadows should be avoided as they migrate quickly into the upper eyelid folds. Frosted finish and iridescent eye shadows also draw attention to the crepey texture of redundant eyelid skin. Instead, matte finish eye shadows are recommended. Finally, there are eye shadow setting creams available that will increase the ability of the eye shadow to stay in place and not migrate into the folds. The cream is applied first followed by the powdered eye shadow.

Eye shadows can also be used to camouflage upper eyelid dyspigmentation from lentigines or telangiectasias. Mature patients may be tempted to select vivid, dark eye shadow colors to cover the undesirable eyelid skin color. However, vivid colors draw attention to the upper eyelid and should be avoided in favor of pastels and muted colors, such as pink, bluish gray, mauve, tan, or peach. Upper eyelid dyspigmentation is best camouflaged by applying facial foundation to the upper eyelid followed by pressed powder eye shadow. Applying facial foundation to the upper eyelid also improves eye shadow wearability, which is the technical term used in the cosmetics industry for the ability of a cosmetic to remain in place. Facial foundations are discussed later in this chapter.

Eyelash Cosmetics

Another eye area for adornment is the eyelash, which can be enhanced with mascara and eyeliner. Since the eyelashes form a frame for the eye, luxuriant eyelashes can attract attention to this expressive facial feature.

Mascara

The most popular facial cosmetic is mascara intended to darken, thicken, and lengthen the eyelashes. Most women consider long eyelashes a prerequisite to being attractive, as evidenced by the popularity of prescription bimatoprost for eyelash growth. Mascaras must be carefully formulated to allow easy and even application without smudging, irritancy, or toxicity on the sensitive eye tissues. The U.S. Food, Drug, and Cosmetic Act prohibits coal tar colors in the eye area; thus, mascara pigments must be selected from vegetable colors or inorganic pigments and lakes. Commonly used mascara pigments include iron oxide to produce black, ultramarine blue to create navy, and umber (brown ochre) or burnt sienna (a mixture of hydrated ferric oxide with manganic oxide) or synthetic brown oxide to create brown [6].

The most popular mascara formulations are liquids dispensed from an automatic mascara tube, consisting of a tube into which a round brush is inserted through a small aperture to remove a metered amount of product [7]. Mascaras can be dispensed from this tube in two formulations: water based and solvent based. The water-based products can be removed from the lashes with soap and water, while the solvent-based products require a special removal fluid. Both of these formulations and their relevant dermatologic issues are discussed.

Water-based mascaras contain waxes (beeswax, carnauba wax, synthetic waxes), pigments (iron oxides, chrome oxides, ultramarine blue, carmine, titanium dioxide), and resins. They are classified as oil-in-water emulsions with the oily materials dissolved in water, which constitutes the majority of the formulation. The water evaporates quickly creating a fast-drying pigmented film that thickens and darkens the lashes. These mascaras are water soluble, allowing for easy removal with soap and water, but unfortunately, smudges with perspiration and tearing are common.

Solvent-based mascaras are formulated with petroleum distillates to which pigments (iron oxides, chrome oxides, ultramarine blue, carmine, titanium dioxide) and waxes (candelilla wax, carnauba wax, ozokerite, hydrogenated castor oil) are added. They represent a water-in-oil emulsion where the water is dissolved in the oil, which is the major ingredient. This formulation yields a waterproof product that performs well with perspiration and tearing, but removal is difficult and requires an oil-based lotion or cream. These products have a prolonged drying time and care must be taken to avoid smudging the product immediately after application.

There are a variety of claims made regarding mascaras in the popular press. It is worthwhile for the dermatologist to analyze the ingredients that support these claims. A common claim for mascaras is lash lengthening. Lash lengthening is achieved by adding nylon or rayon fibers to the mascara, which stick to the eyelashes via the mascara and add length. The eyelashes can also appear longer when they are curled upward. Thus, some mascaras contain a polymer, such as polyvinylpyrrolidone (PVP), that shrinks as it dries, curling the eyelash hair and making the eyelashes appear longer. Other mascaras claim that they condition the eyelash hairs. These formulations may contain hydrolyzed animal protein, which is also used in instant hair conditioners. Lash-thickening mascaras may contain talc or kaolin.

Mascara Safety Issues

The most popular packaging for mascara is in a tube with a multitufted applicator brush. The applicator is inserted into the tube between uses, providing numerous opportunities to inoculate bacteria into the mascara. The most dangerous of these bacteria is *Pseudomonas aeruginosa* [8,9]. *Staphylococcus epidermidis* and *Staphylococcus aureus* organisms may also proliferate in contaminated mascaras [10]. Even though mascaras contain antibacterial preservatives, it is still wise to discard all mascara tubes after 3 months and not allow multiple persons to use the same mascara tube [11]. Persons susceptible to infection or known bacterial carriers should select solvent-based mascaras, providing less water for bacterial growth.

Eyeliner

Eyeliner is used on the upper and lower lid margins to define the eye and is available in cake, liquid, and pencil forms. Cake eyeliner has the same composition as eye shadow, except for the addition of surfactants, promoting formation of a paste when the powder is mixed with water. Liquid eyeliner may contain water, cellulose gum, thickeners (magnesium aluminum silicate), and styrene-butadiene latex. These products are packaged as marking pens or in the same form as mascaras, with a cylindrical tube and unitufted applicator brush. Some of the newer liquid eyeliners are based on polymers, such as ammonium acrylate copolymer, leaving a pigmented film after drying [12].

Pencil-type eyeliners are the most popular due to their application ease (Figure 16.5). They contain natural and synthetic waxes combined with pigments, mineral or vegetable oils, and lanolin derivatives that are extruded into rods and

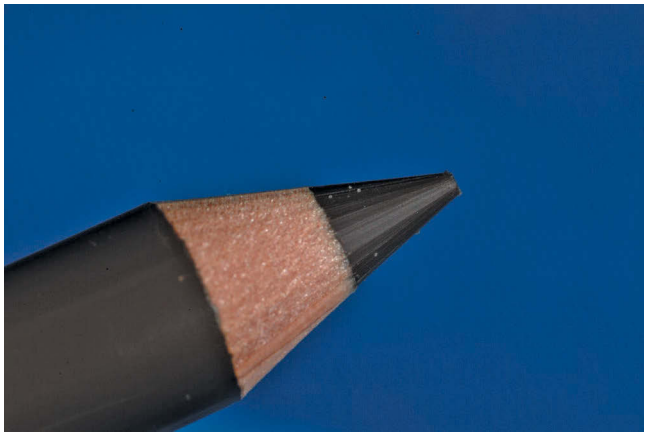


Figure 16.5 Eyeliner. Pencil eyeliners are used to draw a pigmented accent line along the upper and lower eyelashes to provide a frame for the eyes. (From Cosmetics and Dermatological Problems and Solutions 3E, Informa Healthcare, 2011. With permission.)

Figure 16.6 Eyebrow cosmetics. Eyebrow cosmetics are used to darken graying eyebrows or create the illusion of fuller eyebrows by placing a pigmented film on the hairs and the underlying skin. (From Cosmetics and Dermatological Problems and Solutions 3E, Informa Healthcare, 2011. With permission.)

encased in wood. The pencil is then sharpened to the desired tip, which can be thin or broad, depending on consumer preference. Resharpening also removes exposed eyeliner, thus decreasing contamination.

Camouflaging Eyelash Cosmetics

Eyelashes function cosmetically as a frame for the eye. Unfortunately, they may thin due to age, alopecia areata, or eyelid scarring secondary to surgery. Thinned or absent eyelashes result in nondescript eyes and loss of the main focal point for the face.

Eyeliner, mascara, and loose transparent face powder can be used to cosmetically compensate for thinned eyelashes. The first step is to use a liquid eyeliner to dot the upper and lower eyelids, creating the illusion of eyelashes. A light application of dark brown or black fibered mascara should then be applied to the remaining lashes. A powder brush is then dipped in loose powder and dusted on the wet mascara with the eye closed to prevent powder from entering the eye. Another layer of mascara is then applied and the process is repeated until the remaining lashes have been thickened to the desired degree. This technique is useful only in patients who have generalized eyelash thinning or focal areas of complete loss.

It is more difficult to reconstruct the lash line in patients who have large areas of eyelash loss or total eyelash loss. In these female patients, a brown or black liquid or pencil eyeliner should be used to rim the entire eye, except for one-quarter inch around the inner canthus on the upper and lower eyelids. On the normal eye, terminal hairs do not grow around the inner canthus. For female patients with more extensive loss, artificial demilashes can be applied; in the patient with total eyelash loss, complete artificial eyelashes can be applied.

Eyebrow Cosmetics

The accepted shape and width of the eyebrows is subject to fashion trends. Eyebrows were almost completely plucked in the 1950s with a thin pencil line drawn to connect the few remaining hairs. Unfortunately, many women who are now in their 60s and 70s can no longer grow eyebrow hairs as a result of overplucking during their younger years. This is in direct contrast to the eyebrow look of the 1960s, which was totally natural and ungroomed. At the time of this writing, thick eyebrows are desirable, but stray hairs beneath the brow line are plucked to give a groomed appearance. To obtain the eyebrow appearance of the moment, eyebrow cosmetics, such as eyebrow pencil and eyebrow sealer, are used, constituting our next topic of discussion.

Eyebrow pencils are used to darken light or gray eyebrows, fill in sparse or absent eyebrow hairs, and reconstruct malformed or misshapen eyebrows. Eyebrow pencils are formed by mixing pigments, petrolatum, lanolin, and synthetic or natural waxes (Figure 16.6). This formulation is similar to lipstick products; however, this differs in that higher melting point waxes are used to yield a firmer product. Formulations may be encased in wood to form a pencil or extruded into rods placed in a plastic holder. Inert, mainly inorganic pigments are used since the Federal Food, Drug, and Cosmetic Act prohibits the use of coal tar colors in the eye area. They are stroked over the skin in the eyebrow region to actually color the skin and eyebrow hairs [13].

Eyebrow sealers are intended as a grooming agent for unruly eyebrows and a glossening agent to add shine to eyebrow hairs. Originally, white petroleum jelly was used for this purpose, but now, cosmetic companies market a more elegant product. The sealer is essentially a liquid hair spray containing polymer-holding agents packaged in a mascara-type tube. A brush is used to stroke the product over the eyebrow hairs. Eyebrow sealers can be used by persons with bushy eyebrows to hold the hairs closer to the orbital ridge or by those with multidirectional eyebrow hairs who wish to hold the hairs in a more cosmetically acceptable line. Sometimes the eyebrow sealer is pigmented to function both to darken and groom eyebrows.

Camouflaging Eyebrow Cosmetics

The structure of the eyebrows can be abnormal due to congenital deformity, surgical procedures, or acquired loss from

alopecia universalis, hypothyroidism, leprosy, traumatic scarring, and other conditions. Before cosmetic reconstruction can begin, it is important to identify the proper location of the eyebrow on the face. The medial aspect of the eyebrow should begin at a point defined by a straight line drawn from the lateral nose upward. The eyebrow should maximally arch at a point defined by a line drawn from the lateral nose through the pupil. The eyebrow should end at a point defined by a line drawn from the lateral nose through the lateral aspect of the eyeball. Eyebrow pencil can be used to draw absent hairs. A more natural appearance is created if the pencil is used in short strokes rather than to draw one straight line [14].

FACIAL FOUNDATION

Facial foundation is a pigmented cream, powder, or lotion designed to add color to the face and camouflage underlying color or contour defects (Figure 16.7). It may also provide other skin benefits, such as photoprotection, moisturization, or oil control based on the formulation. For the dermatologist, the most important role of facial foundation is for camouflaging purposes. Cream facial foundations are squeezed from a tube and have a creamy texture due to the incorporation of low-viscosity oils in addition to waxes in the anhydrous preparation. They usually contain a high proportion of titanium dioxide to provide superior coverage [15]. Powder foundations are removed from a compact by stroking with a wet sponge. They are composed of talc, kaolin, zinc oxide, precipitated chalk, titanium dioxide, and iron oxide [16]. This product dries quickly and possesses a matte, or dull, finish. Finally, liquid facial foundations can be oil-in-water or water-in-oil formulations. Those used for camouflaging purposes are usually water-in-oil emulsions containing pigments suspended in oil, such as mineral oil or lanolin alcohol. Vegetable oils (coconut, sesame, safflower) and synthetic esters (isopropyl myristate, octyl palmitate, isopropyl palmitate) may also be incorporated. The water evaporates from the foundation following application, leaving the pigment in oil on the face.

Figure 16.7 Facial foundation. Camouflaging facial foundations can be packaged in many forms. This is a cream facial foundation formed into a stick for stroking over the face. (From Cosmetics and Dermatological Problems and Solutions 3E, Informa Healthcare, 2011. With permission.)

Facial Foundation Application for Camouflaging

The most popular facial foundations for camouflaging are liquids or creams. These products are the easiest to use as they possess good blending characteristics, require minimal application skill, provide excellent skin coverage, and wear long enough for most individuals [17]. The remainder of this chapter focuses on the use of facial foundations for camouflaging purposes.

The first step in using facial foundation for camouflaging is to select a makeup closest to the patient's natural skin color. Blending usually is necessary, but no more than three colors should be combined. If the patient has an underlying pigmentation problem, this counts as one color. Pigmentation abnormalities may be due to increased melanin, producing a brown color, or increased hemosiderin, producing a rust color, or degenerated facial elastin, producing a yellow color, etc. Once the closest foundation color has been selected, it may necessary to blend in yellow, if the individual has a sallow complexion, or reds, if the patient has a ruddy complexion.

All facial tones should be represented in the final foundation blend if a good color match is to be obtained. Blending is usually done by applying a small amount of the makeup to the back of the hand. This provides a good surface for blending that can be easily held up to the face to evaluate the color match and also warms the product, which allows easier mixing and application. The final foundation color mix is then dabbed, not rubbed, over the scarred area and then applied from the central face outward into the hairline for approximately 1/4 in. and blended over the ears and beneath the chin. It is necessary to feather the cosmetic where application ends to achieve a more natural appearance.

Following a brief drying period, the facial cosmetic must be set with an unpigmented talc-based powder to prevent smudging, provide waterproof characteristics, and impart a matte finish. The powder should be pressed into the facial foundation by the fingers. Additionally, the powder also increases the ability of the facial foundation to stay on the skin resisting removal with rubbing. Camouflaging makeups are designed to be worn with this powder and do not function properly without it.

Camouflaging facial foundations usually require more than soap and water washing due to the waterproof nature of the product. Most companies provide an oily cleanser for cosmetic removal and then recommend soap and water cleansing of the skin. The cosmetic should only be worn when needed and definitely thoroughly removed at bedtime [18].

Color and Camouflaging Principles

Camouflaging cosmetics can be used to correct defects of contour, pigmentation, or a combination of both [19]. Defects of contour are defined as areas where the scar tissue devoid of appendageal structures is hypertrophied or atrophied [20]. Pigmentation defects are abnormalities solely in the color of the skin with no texture abnormalities [21,22].

Contour abnormalities can be corrected by artistically shading the defect. The basic concept of facial scar recontouring is predicated on the fact that dark colors make surfaces recede, while light colors make surfaces appear to project [23]. Thus, lighter colors will minimize depressed areas of scarring, while darker colors will minimize protuberant areas of the scar. Pigmented facial powders can be dusted over contour abnormalities to achieve the correction.

Pigmentation defects can be camouflaged by either applying an opaque facial foundation that allows none of the abnormal underlying skin tones to be appreciated or by applying foundations of complementary colors [24]. For example, red pigmentation defects can be camouflaged by applying a green foundation, which is the complementary color to red. The blending of the red skin with the green foundation yields a brown tone, which can be readily covered by a more conventional facial foundation. Furthermore, yellow skin tones can be blended with a complementary colored purple foundation to also yield brown tones. Skin areas that are lighter or darker than desired can be camouflaged by applying facial foundations with the appropriate amount of brown pigment to hide the defect [25].

SUMMARY: EMOTIONAL NEED FOR COSMETICS

Cosmetics fulfill a very basic human need, which is the need to be considered attractive [26]. Individuals who are perceived as attractive by others have a more positive life outlook and higher self-esteem [27]. Colored facial cosmetics can be effectively used not only to enhance appearance but also for camouflaging purposes [28]. This chapter has examined makeup techniques in dermatology. It has divided cosmetics into those used on the lips, eyelids, eyelashes, eyebrows, and face, presenting basic ingredient formulation, application information, and camouflaging ideas. It is hoped that the dermatologist can use this information to assist patients in their quest for life fulfillment through an attractive appearance.

REFERENCES

1. Schena D, FAntuzzi F, Girolomoni G. Contact allergy in chronic eczematous lip dermatitis. *Eur J Dermatol* 2008 November/December; 18(6):688–692.
2. Ryu JS, Park SG, Kwak TJ et al. Improving lip wrinkles: Lipstick-related image analysis. *Skin Res Technol* 2005 August; 11(3):157–164.
3. Angelini E, Marinaro C, Carrozzo AM, Bianchi L, Delogu A, Giannelo G, Nini G. Allergic contact dermatitis of the lip margins from para-tertiary-butylphenol in a lip liner. *Contact Dermatitis* 1993 March; 28(3):146–148.
4. Panati C. *Extraordinary Origins of Everyday Things*. New York: Harper & Row Publishers, 1987, p. 223.
5. Lanzet M. Modern formulations of coloring agents: Facial and eye. In: Frost P, Horowitz SN, eds. *Principles of Cosmetics for the Dermatologist*. St. Louis, MO: CV Mosby Company, 1982, pp. 138–139.
6. Wilkinson JB, Moore RJ. *Harry's Cosmeticology*, 7th ed. New York: Chemical Publishing, 1982, pp. 341–347.
7. Lanzet M. Modern formulations of coloring agents: Facial and eye. In: Frost P, Horwitz SN, eds. *Principles of Cosmetics for the Dermatologist*. St. Louis, MO: CV Mosby, 1982.
8. Wilson LA, Ahern DG. Pseudomonas-induced corneal ulcer associated with contaminated eye mascaras. *Am J Ophthalmol* 1977; 84:112–119.
9. MMWR Reports. Pseudomonas aeruginosa corneal infection related to mascara applicator trauma. *Arch Dermatol* 1990; 126:734.
10. Ahearn DG, Wilson LA. Microflora of the outer eye and eye area cosmetics. *Dev Ind Microiol* 1976; 17:23–28.
11. Bhadauria B, Ahearn DG. Loss of effectiveness of preservative systems of mascaras with age. *Appl Environ Microbiol* 1980; 39:665–667.
12. Lanzet M. Modern formulations of coloring agents: Facial and eye. In: Frost P, Horwitz SN, eds. *Principles of Cosmetics for the Dermatologist*. St. Louis, MO: CV Mosby, 1982, pp. 143–144.
13. Klarmann EG. *Cosmetic Chemistry for the Dermatologist*. Springfield, IL: Charles C Thomas, 1962, pp. 53–54.
14. Allsworth J. *Skin Camouflage*. Cheltenham, England: Stanley Thornes Ltd, 1985, pp. 41–42.
15. Schlossman ML, Feldman AJ. Fluid foundation and blush makeup. In: deNavarre MG, ed. *The Chemistry and Manufacture of Cosmetics*. Wheaton, IL: Allured Publishing Company, 1988, pp. 748–751.
16. Wilkinson JB, Moore RJ. *Harry's Cosmeticology*, 7th ed. New York: Chemical Publishing, 1982, pp. 304–307.
17. Reisch M. Masking agents as adjunct therapy in cutaneous disorders. *Clin Med* 1961; 8(5).
18. Thomas RJ, Bluestein JL. Cosmetics and hairstyling as adjuvants to scar camouflage. In: Thomas RJ, Richard G, eds. *Facial Scars*. St. Louis, MO: CV Mosby, 1989, pp. 349–351.
19. Antoniou C, Stefanaki C. Cosmetic camouflage. *J Cosmet Dermatol* 2006 December; 5(4):297–301.
20. Aydogdu E, Misirlioglu A, Eker G, Akoz T. Postoperative camouflage therapy in facial aesthetic surgery. *Aesthetic Plast Surg* 2005 May–June; 29(3):190–194.
21. Draelos ZK. Cosmetic camouflaging techniques. *Cutis* 1993; 52:362–364.
22. Benmaman O, Sanchez JL. Treatment and camouflaging of pigmentary disorders. *Clin Dermatol* 1988; 6:50–61.
23. Helland JR, Schneider MF. *Special Features*. New York: M Evans and Company, 1985, pp. 41–46.
24. Balkrishnan R, McMichael AJ, Hu JY, Camacho FT, Kaur M, Bouloc A, Rapp SR, Feldman SR. Corrective cosmetics are effective for women with facial pigmentary disorders. *Cutis* 2005 March; 75(3):181–187.
25. Draelos ZD. Use of cover cosmetics for pigmentation abnormalities. *Cosmet Dermatol* 1989; 2:14–16.
26. Korichi R, Pelle-de-Queral D, Gazano G, Aubert A. Why women use makeup: Implication of psychological traits in makeup functions. *J Cosmet Sci* 2008 March–April; 59(2):127–137.
27. Holme SA, Beattie PE, Fleming CJ. Cosmetic camouflage advice improves quality of life. *Br J Dermatol* 2002 November; 147(5):946–949.
28. Boehncke WH, Ochsendorf F, Paeslack I, Kaufmann R, Zollner TM. Decorative cosmetics improve the quality of life in patients with disfiguring skin diseases. *Eur J Dermatol* 2002 November–December; 12(6):577–580.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Nail care, nail modification techniques, and camouflaging strategies

Bertrand Richert, Christel Scheers, and Josette André

NAIL MANICURE

Nail Polish Remover

Classically, nail manicure begins with the removal of any nail polish remaining on the nail plate. Nail polish removers cleanse and prepare the nail for manicure. Varnish removers principally contain not only organic solvents to dissolve nitrocellulose but also small amounts of oils to lessen the drying effect of solvents. Due to its drying effect, a nail polish remover should be used only once weekly. Specific removers for brittle nails, which contain alpha-butyrolactone in the place of acetone and are odorless, can be found in the market [1].

Typical formulation for nail polish remover [2]:

- Solvents: Acetone, butyl or ethyl acetate, ethoxy ethanol
- Lipids: Castor oil, lanolin oil
- Additives: Fragrances, preservatives, vitamins, UV absorbers, dyes

Cutting and Filing

It is better to perform trimming after bathing in order to decrease mechanical trauma [3]. The nail is first cut with nail clippers and then filed with fine sandpaper or a diamond dust file. This defines the length of the nail and shapes it. Filing should always be performed horizontally as a vertical motion promotes lamellar nail splitting. Filing seems to be less traumatic than cutting. The nail plate may be pumiced to smooth the surface, erase the ridging, or eliminate varnish staining and keratin granulations. Afterward, fingertips should be bathed in lukewarm soapy water to soften the cuticles.

Cuticle Removers

Cuticle removers are most often alkaline agents (potassium or sodium hydroxide) but can sometimes be 1%–5% concentration of alpha-hydroxyacids (lactic acid). These agents destroy keratin by attacking the disulfide bonds of cystine. They are rinsed off after an application of a few minutes. Cuticle removers soften the cuticle and lessen its adherence to the nail plate. Cuticles are then gently pushed back with the pulp of another finger or with a cotton-covered orange wood stick. Hyponychium and periungual grooves are cleaned the same way. Cuticles should not be cut with either nippers or V-shaped curettes. Hangnails are cut with special nippers. Cuticle removers should not be left on the nail for too long in individuals prone to paronychia [4].

Typical formulation for cuticle removers [2]:

- Water
- Softening agent: Potassium or sodium hydroxide, or alpha-hydroxyacids
- Emollients (lanolin) or humectants (propylene glycol, glycerin)
- Thickening agent: Sorbitol, magnesium, or aluminum silicate
- Perfume

Buffing

Some women may choose buffing instead of nail lacquer. An abrasive powder (kaolin, stannic oxide, talc) is applied to the nail surface and then polished with a chamois-covered buffer. This gives a shiny aspect to the nail plate. The free edge of the nail may be colored with a white pencil (white clay) (original French manicure).

Creams for Daily Care

Cuticle softeners are emollient creams used between manicures to favor softening of the cuticle and avoid the formation of hangnails. They may contain quaternary ammonium compounds or urea.

Creams for brittle nails have to be applied after moistening of the nail plate by soaking it in lukewarm water for 15 minutes [5]. They should contain phospholipids to improve nail hydration and flexibility. Usually, they are ordinary water-in-oil moisturizing creams with low water and high lipid content [2]. They may also contain urea 5%–20% and lactic acid [5].

It is claimed that nail oils containing jojoba oil, bisabolol, panthenol, vitamins, and amino acids penetrate the nail plate; however, it is not clear what effects vitamins have on the nails. It is possible that some oils may help to retain humidity. In general, oils, as well as creams and ointments, make the nail more elastic and thus prevents nail splitting [6].

Typical formulation for creams for brittle nails [2] (De Groot):

- Water
- Lipids: Beeswax, lanolin, jojoba oil, propolis
- Emulsifier: Sodium laurylsulfate
- Preservative, perfume, etc.

Benefits of Manicure

Manicure gives a nice, clean, and healthy look to the hands (Figure 17.1).

Pitfalls of Manicure

Mechanical Hazards

- Excessive buffing may be responsible for thinning of the nail plate.
- A vigorous pushing back of the cuticles may induce transverse leukonychia or Beau's lines.
- Overzealous cleaning of the distal groove can cause onycholysis.
- Disruption of the cuticles may lead to the opening of the cul-de-sac with subsequent chronic paronychia (Figure 17.2).
- Overuse of polish and cuticle removers may lead to skin irritation and nail fragility.

Figure 17.1 Manicure gives a nice, clean, and healthy look to the hands.

Figure 17.2 Chronic paronychia resulting from cutting off the cuticles.

- Recent studies have emphasized that nail polish does not influence pulse oximetry to a clinically relevant dimension [7]. Nevertheless, available studies have been performed in stable or mildly hypoxic subjects; some authors advise to remove nail polish—mainly dark colored—or nail decorations in critically ill patients [8,9].

Infectious Hazards

- Microtraumatisms to the folds favor bacterial (acute paronychia), viral (warts, herpes, hepatitis C), and mycotic infections (*Candida*) [10].
- Several publications relate epidemic mycobacterial furonculosis from footbath spas [10,11]. Studies incriminate professional, but also intrafamilial, transmission of hepatitis C [12].
- A dramatic fatal case was secondary to infective endocarditis [13].
- Precise standards of disinfection are mandatory in nail salons [14–16].

Allergic Hazards

- As far as nail polishes and cuticle removers are concerned, irritant contact dermatitis is much more common than allergic contact dermatitis. This mainly derives from an improper use of the product. Allergic contact dermatitis to cuticle softeners and hand creams may be related to the classic allergens contained in the products.

Nail Lacquers

Composition

Typical formulation of a nail lacquer [4]:

- Solvents—thinners 70%
- Nitrocellulose 15%
- Film modifier (resin) 7%
- Plasticizers 7%
- Thixotropic agents 1%
- Pigments 0.1%

Nail lacquers are composed of the following:

1. *Film formers*: The main constituent of the film that remains on the nail after drying is *nitrocellulose*. It creates a hard, mat, waterproof, and resistant film that adheres poorly to the plate and is not flexible.
2. *Film modifiers*: To improve adherence and gloss of the film former, a film modifier, which is in fact composed of resins, has to be added. The most commonly used film modifier is toluene sulfonamide/formaldehyde resin (TSFR), which is also called Santolite®. Nowadays, it tends to be replaced by other film modifiers, especially in hypoallergenic varnishes: alkyd resins, acrylates, vinyls, polyester resins, and phthalic anhydride/trimellitic anhydride/glycols copolymer (PTGC) [17,18].
3. *Plasticizers*: The principal aim of these products is to increase the flexibility of the entire film. Dibutyl phtalate and camphor were the most frequently used. Manufacturers are tending toward eliminating dibutyl phthalate, even though it has been declared "safe" by the Cosmetic Ingredient Review Expert Panel (United States), because it is classified as carcinogenic, mutagenic, or toxic

for reproduction (CMR) Category 2 on the EU Dangerous Substance List and is no longer used in European cosmetics [4]. In some U.S. states such as California, dibutyl phtalate–containing products are not allowed. Other examples are castor oil, tricresyl phosphate, and glyceryl tribenzoate [4,17].

4. *Solvents, thinners*: Solvents regulate the drying time and also lower viscosity, thus improving brushability. High viscosity leads to a thick and streaky film; low viscosity results in poor coverage. Ideal viscosity should permit easy application and leave a homogenous film. The most commonly used are alkyl esters (i.e., ethyl, *n*-butyl acetate) and glycol ethers (propylene glycol monomethyl ether). Thinners also regulate the evaporation time and the viscosity, but their main goal is to reduce the cost of the nail lacquer. Thinners are essentially aliphatic alcohols (ethanol, isopropanol, butanol) and aromatic hydrocarbons such as toluene. In the United States, toluene is now suspected to be oncogenic, teratogenous, and air contaminant and therefore tends to be replaced. In Europe, toluene is considered as "safe from a general toxicological view" in nail cosmetics, up to an amount of 25% for adults (CMR cat 3). It is recommended to keep it out of children's reach.
5. *Pigments and colorants*: They provide color to the nail lacquer. Manufacturers use mineral pigments (ferric ferrocyanide, titanium dioxide) and organic pigments (D&C red 6, 7, 34, FD&C Yellow 5, etc.). Precipitating a particular pigment with aluminum hydroxide to form a salt complex can stabilize colorants [4]. Pearlescent nail varnishes contain guanine crystals, derived from Atlantic herring and other fish scales, bismuth oxychloride, or mica coated with TiO_2. All are used to enhance light reflection. Thermochrome pigments, which induce color changes depending on the temperature and photochrome pigments, the shades of which vary according to the light, offer new possibilities [19]. Coloring agents such as organic colors may be selected from a list of certified colors approved by the FDA. Inorganic colors and pigments may also be used but must conform to low heavy metal content standards [20].
6. *Thixotropic agents*: These agents, also called suspending agents, allow homogeneous dissolution of the pigment within the lacquer. The most frequently used thixotropic agent is stearalkonium hectorite. Thixotropic agents increase nail enamel viscosity at rest, thus preventing pigment precipitation. However, they become fluid as soon as a mechanical constraint is exerted, by shaking either the brush or the bottle. To promote fluidification of the varnish, small metallic (nickel) or preferably plastic beads are added to it in the bottle [19].
7. *Additives*: Sunscreens (i.e., benzophenone-1, octocrylene) are often added to preserve the color. Other additives may be added for specific purposes (see the "Categories of Nail Lacquers" section). Fragrances can now be added to nail polishes, as well as metal or plastic glitters to give special effects. Newly advertised "magnetic nail polishes" contain iron powder. Prior to solvent evaporation of the applied magnetic nail lacquer, a magnet (delivered along with the nail polish) can be held over the nail, causing the iron powder in the formulation to gravitate toward the magnet and form a desired pattern. Any polish containing magnetic material must be removed prior to magnetic resonance imaging [16,21].

Categories of Nail Lacquers

Base *Base coats* contain more resin in order to increase the adherence of the varnish to the nail. They do not contain colorants, in order to act as a protective antistain barrier between the nail plate and the shaded varnish [4].

Top Coat *Top coats* contain more nitrocellulose and plasticizers because they must be tough and flexible to improve nail varnish resistance. Often, they also contain special UV-absorbing materials like benzophenone 1 and 3, to help protect the underlying colored coats. Cobalt may be added to the top coat to give a glitter color but may be responsible for contact dermatitis [22].

Hypoallergenic The aim of these polishes is to allow women who are allergic to TSFR to wear nail polish. TSFR is replaced by phthalic polyester resin, epoxy resin, and PTGC [20]. The durability, gloss, and abrasion resistance of these other resins are said to be less than TSFR. However, they may also induce allergic contact dermatitis [18,23–25].

Hardeners These are base coats containing formaldehyde. The latter is believed to cross-link protein of the nail plate, thus not only increasing the surface hardness but also decreasing flexibility. It should be applied only to the distal 1/5 of the nail plate. Long-term use may induce nail rigidity and cracks. Concentration should be no higher than 5%. New nail hardeners have been marketed. They may contain silicium—which is thought to penetrate the nail plate and reinforce the disulfide bonds within the keratin—or short nylon fibers or even diamond powder or Kevlar.

Ridge Fillers Badly ridged nails impede the adherence of nail polish. A ridge filler evens out the ridges of the nail plate and gives a uniform and smooth nail surface, perfect for polish to adhere to, and thereby enabling it to last longer. These products are opaque and have a thicker viscosity. Ridge fillers may also be used as the base of choice for acrylics, gels, and wraps. The filling ingredient is usually an impalpable powder such as talc. They may also contain silica, silk fibers, or even algae extract to fill in the ridges.

UV-Curing Nail Lacquers (Gel Polish) Gel polish is a novel manicure system gaining popularity especially because it is odorless and offers a large span of glossy colors. It is claimed to give a 2-week perfect manicure and is easily removed without damaging the natural nail plate (Figure 17.3). Shellac®, launched in 2010, is the leading brand. Other brands have appeared since then. The gel polish is generally applied in a salon by a nail technician. The application involves a base coat that is cured under a UV lamp, two layers of a proprietary color coat, and a top coat. During the curing process under the UV lamp, the manufacturer states that the solvents evaporate and tiny tunnels form in the layer of polish, connected by acetone-dissolvable polymers. Theoretically, the removal solvent is advertised as easily penetrating the polish because of these tiny tunnels, thereby dissolving the polymers, with remaining polish easily wiped away. In practice, the nails are covered with gauze dipped in acetone and wrapped with aluminum foil. After 2 minutes, the lacquer is rubbed away and the remnants are ground out. The three different

Figure 17.3 Shellac® gel after 4 weeks. Note that the lacquer is neither chipped off nor scratched and still very glossy. The proximal part of the nail is devoid of lacquer and shows the growth of the nail since the application of the light-cured gel.

Figure 17.4 Orange discoloration of the nails induced by a nail lacquer.

coats of polish contain numerous chemicals in addition to the proprietary formula, especially the top coat that contains acrylates [16,26].

Nail Care Lacquers Nail lacquers containing 10% urea improve the cosmetic appearance of the nail. Nevertheless, no relevant changes have been detected in nail thickness or water loss [27]. Many nail lacquers claiming that they improve the aspect or the growth of the nail by adding vitamins, alpha-hydroxyacids, herbal extracts, etc. may be found in the market. However, it has never been proved that any of them have been efficacious. A recent study developed a lexicon for sensory properties of nail polish [28].

Benefits of Nail Lacquers

Cosmetic: Refinement, elegance, and a wide range of personal expression.

Camouflaging: Nail lacquers hide chromonychia, onycholysis, and splinter hemorrhages. They can also mask a subungual melanoma and delay its diagnosis [29]. Ridge fillers may even nail diseases with plate surface alterations (ridges from aging, nail lichen planus, pitting, trachyonychia, etc.) and be covered with colored nail varnish.

Protection: The tough and flexible film on the nail surface increases the resistance of the plate to microtraumatisms and maintains a more constant degree of nail hydration. It is said that a layer of nail lacquer could add 5% to the strength of a nail.

Pitfalls of Nail Lacquers

Technical and Mechanical Hazards

- *Yellow-orange staining* (Figure 17.4) of the distal end may be observed with some colored nail polishes. This may be limited with the use of a base coat.

Figure 17.5 Keratin granules resulting from new layers of varnish applied over old ones for long periods.

- *Keratin granulations* (Figure 17.5) are superficial friability of nail keratin. They appear when new layers of varnish are applied over old ones for long periods. This can be avoided by wearing nail varnish only 5 days a week.
- In nail hardeners, formaldehyde may be responsible for *severe nail damages* (paronychia, subungual hyperkeratosis, onycholysis, or hemorrhages) and *lip hemorrhages*. Formaldehyde is irritant and could favor TSFR sensitization.
- *Nail brittleness* and thinning linked to the new popular light-cured gel polish have recently been reported (Figure 17.6) [26].

Allergic Hazards Nail varnish may be responsible for *allergic contact dermatitis* and rarely contact urticaria. Allergic patients typically develop dermatitis at sites distant from the

Figure 17.6 Nail brittleness resulting from light-cured gel. (Courtesy of Tosti, A., Miami, FL.)

fingers (handborne dermatitis): eyelids, lower half of the face, sides of the neck, upper chest, and also genitalia. Symmetrical allergic airborne dermatitis of the face has also been described. Tosylamide formaldehyde resin is responsible for the majority of allergic cases. In a recent study by Warshaw et al. [30], TSFR was responsible for more than 6% of cosmetic allergies in females and more than half of the women allergic to nail products reacted to TSFR. Allergy to TSFR may be suspected not only in case of nonelucidated lip and tongue swelling mimicking angioedema but also in cases of eczema worsening in atopic children [31,32]. Contact allergy to polyester resin, epoxy resin, methyl acrylate, nitrocellulose, and PTGC may also be observed, even if they are components of so-called hypoallergenic lacquers [18,23]. Allergy to nickel or cobalt contained in varnishes is described [22]. The increasing use of UV curable nail lacquers led to new cases of allergic contact dermatitis to (meth)acrylates (see the "Pitfalls of Acrylic Nails (Sculptured Nails and Gel Nails)" section). Reports of cheilitis or swelling of the lips caused by gel polish were recently described [34].

NAIL REPAIR

Composition

Wraps are small thin pieces of silk, fiberglass, paper, or linen.

Mending the Nail

The purpose of nail mending is to create a splint for partially fractured nails or for a longitudinal split. To begin, a small piece of material is cut to the size and shape of the fingernail. The fissure is first bonded with cyanoacrylic glue. The nail is then painted with clear nail polish and the patterned wrap is embedded in it. Several coats of lacquer are then applied. Wraps are not durable because they are made of very soft material. Silk wrap nails are often preferred to other artificial nail reinforcements because they are sheer and flexible and are often considered as looking most like a natural nail. Linen is thicker and offers increased strength but inhibits cyanoacrylate penetration to the nail, thus lowering adhesion. Fiberglass is a wrap, which combines the benefits of both silk and linen [34].

ARTIFICIAL NAILS

Artificial nails are resistant and offer a wide range of refinement and fantasy. Polishes and airbrushes are used to create "nail art." Many adornments may be associated to perfect the artificial nail (Figures 17.7 and 17.8).

They may be used for short, brittle, or broken nails. They also permit to hide nail surface abnormalities.

Preformed Artificial Nails

Composition

Preformed plastic nails (plastic tips, press-on nails) are made of thermoplastic resin acrylonitrile butadiene styrene (ABS) and are available in various shapes and sizes (Figure 17.9). They are stuck onto the nail surface with cyanoacrylate glue [35].

Figure 17.7 Nail art. The nails are matching the shoes.

Figure 17.8 Nail art with glued-on crystals.

Figure 17.9 Nail tips come in different shapes and sizes.

Figure 17.10 Nail tip covering the distal half of the nail.

Two types of tips exist:

1. Those that are stuck on the distal half nail to elongate the length of the plate, used as a template to support an artificial coating (light-cured gel). They are thinner on the nail plate and thicker at the free edge of the nail. This enhances a better interlocking of the nail to the tip (Figure 17.10).
2. Those that cover the whole nail surface and are used for special occasions (Figure 17.11). They can be lacquered (Figure 17.12) or decorated or may even come already ornamented. However, they should not be worn for more than 2 days. The whole length of the tip is homogenously thick.

Procedure

In the first type, the nail surface is first filed (Figure 17.13) and the tips are fixed with cyanoacrylate glue at the extremity of the nail (Figure 17.14a and b). If the artificial nail is too long, it may

Figure 17.11 Nail tip covering the whole length of the nail.

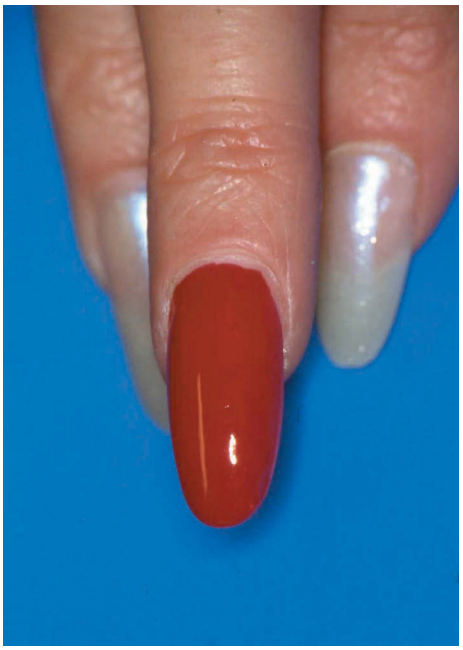
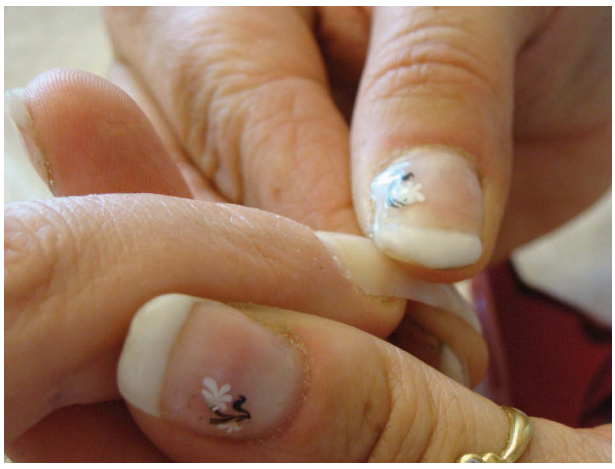


Figure 17.12 Same patient as in Figure 17.11 with the tip lacquered.

be shortened with a "guillotine clipper" (Figure 17.15) and then shaped as per one's desire (rounded or squared corners) with a file (Figure 17.16). The difference in height between the proximal natural nail and the distal artificial nail is corrected by using artificial acrylic nail coatings (Figure 17.17), each of them being light cured (Figure 17.18). The newly formed nail may be painted or decorated afterward (Figure 17.19). These tips may

Figure 17.13 Preformed artificial nails. The nail surface is first filed.

(a)



(b)

Figure 17.14 Preformed artificial nails. (a) The tip, covered with cyanoacrylic glue, is first locked to the free edge of the nail. (b) Then, it is pressed onto the nail surface firmly to avoid any entrapment of air.

Figure 17.15 Preformed artificial nails. The tip is shortened to the desired length with a "guillotine."

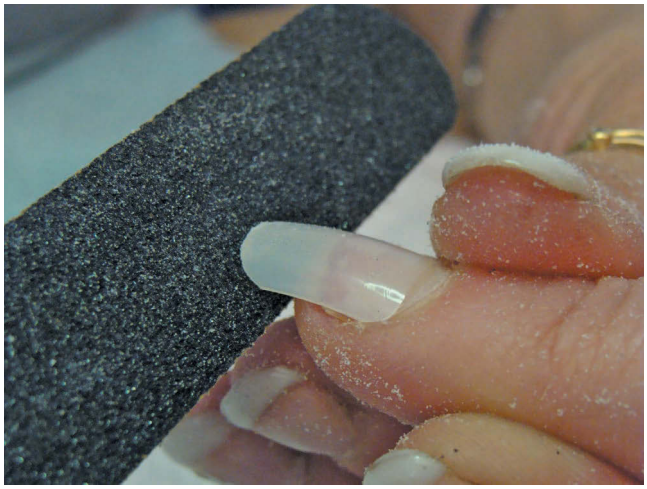


Figure 17.16 Preformed artificial nails. The tip is then filed to the desired shape (rounded or squared corners).

be easily detached from the distal nail, but not the proximal part that has to be ground out.

In the second type, the tips cover the whole surface of the nail plate. They have simply to be glued onto the whole nail surface that has previously been slightly filed. As they are unfinished and colorless, they need to be polished. These tips can be easily removed with acetone. They may be applied onto a broken nail and thus have a repair function [36]. Some tips are becoming popular in young people: already colored or ornamented tips sold as a "kit" and containing 10 nail tips, glue, and a cleaning agent. They do not need further finishing.

Benefits of Preformed Artificial Nails

This technique is trendy, cheap, easy to use, and sold as a "do-it-yourself kit." Plastic tips are easier to use than the sculptured nail technique. They do, however, need a normal nail to be properly fixed.

Figure 17.17 Preformed artificial nails. The difference in height between the proximal natural nail and the distal artificial nail is corrected by using artificial acrylic nail coatings.

Figure 17.18 Preformed artificial nails. Each coating is light cured.

Pitfalls of Preformed Artificial Nails

Mechanical hazards:

- They may cause onycholysis and nail surface damage.
- Technical errors and low adherence can favor bacterial, mycotic, or mycobacterial infection.

Contact allergy:

Allergy may be responsible not only for severe dystrophy of the nails, paronychia, or eczema of fingertips but also for ectopic eczema on the dorsal hand, face, eyelids, or trunk. Persistence of the dermatitis, until the nail has grown out, is frequent and probably due to remains of the adhesive glue.

Cyanoacrylate does not usually cross with the (meth) acrylate monomers used in sculptured or gel nails.

Figure 17.19 Preformed artificial nails. The newly formed nail is painted and decorated afterward.

The most frequent allergens of preformed artificial nails are [35,36]

- Ethyl cyanocrylate (glue)
- Seldom: Tricresyl ethyl phthalate (tips), p-t-butyl phenol resin (adhesive)

Sculptured Artificial Nails

Composition

Typical formulation for sculptured artificial nails [2]:

- Liquid: Acryl-type monomer (99%) + stabilizer (1%)
- Powder: Acryl-type polymer (97%) + polymerization initiator (3%)

An artificial nail is made of an acrylic resin obtained by blending a liquid containing acrylate monomer (methyl, ethyl, or isobutyl methacrylate) with a powder containing the polymer (polymethyl or ethyl methacrylate).

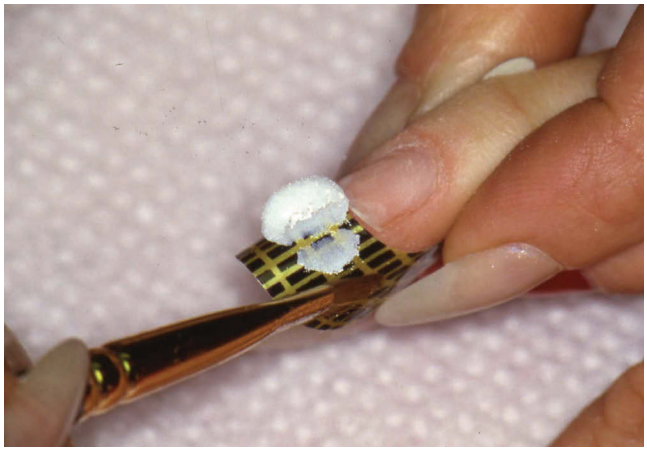
The monomer contains a stabilizer (hydroquinone) and a catalyst (*N,N*-dimethyl-p-toluidine). The polymer contains a polymerization initiator (benzoylperoxide) [2,35].

Other components such as plasticizers, solvents, accelerators, pigments, sunscreens, and titanium dioxide may be included [17].

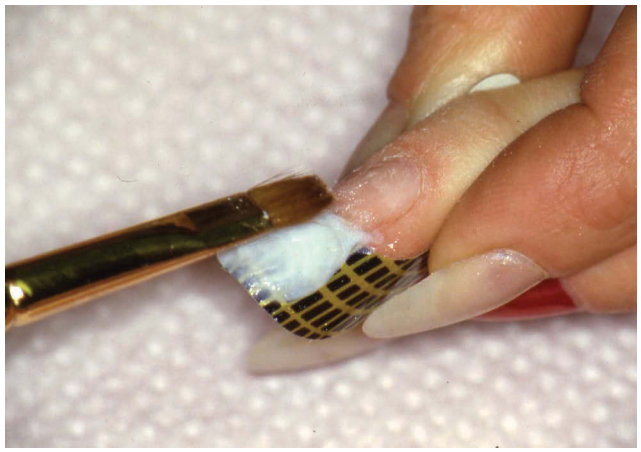
Procedure

The nail plate surface is pumiced and disinfected. A metalized paperboard template is placed on and around the natural nail to frame the new nail (Figure 17.20). A primer (methacrylic acid) is painted onto the natural nail. The *primer* acts as a double-sided tape, as it sticks both to the nail and the acrylic. To avoid its toxicity, new acid-free noncorrosive primers have appeared, as well as newer artificial nail formulations, which no longer require a nail primer [37]. Following this, several layers of the acrylic paste that has just been blended are applied (Figure 17.21a and b). After hardening at room temperature, which occurs rapidly, the template is removed and the artificial nail is shaped, pumiced, and buffed, resulting in a real nail extension (Figure 17.22). This procedure is rather difficult to perform and requires good skills from the nail sculptor. Sculptured nails can be dissolved in acetone.

Figure 17.20 Sculptured artificial nails. A metalized paperboard template is placed on and around the natural nail to frame the new nail.



(a)



(b)

Figure 17.21 Sculptured artificial nails. (a) A ball made from the powder (monomer) and the liquid (polymer) is put on the nail. (b) Several layers of the acrylic paste are applied to shape the artificial nail.

Figure 17.22 Sculptured artificial nails. After hardening at room temperature, this results in a real nail extension.

Benefits of Sculptured Artificial Nails

Sculptured artificial nails offer real customized nail extensions. They are resistant and attractive.

Pitfalls of Sculptured Artificial Nails

They are similar to those of light-cured gel. See the "Pitfalls of Acrylic Nails (Sculptured Nails and Gel Nails)" section.

Nail Gels

Composition

They are made up of a mixture of acrylic monomers and polymers directly provided by the manufacturer. There are mainly two types of gels:

1. *Acrylic light-cured gels*: The compounds are similar to those found in acrylic nails, except for 2-hydroxyethyl methacrylate (2-HEMA) that is not present in all acrylic nails [36,37]. Nail gels may contain frequently urethane acrylates.
2. *Ethyl cyanoacrylate gels*: Here, the polymerization is obtained by spraying or brushing an activator (N, N-dimethylparatoluidine).

Procedure

In acrylic light-cured gel, polymerization is obtained by exposure to UV light. Successive layers of gel (base, 2 coats of gel, and a top coat) are applied on the nail surface, each layer being hardened by a short exposure to UV light. Gels may already be colored and have different textures. Nail extensions may be obtained by applying several layers of gel on a template (Figure 17.23a through f) or by gluing a plastic tip on the distal half of the nail plate (Figures 17.14 through 17.16). The gap between the tip and the cuticle is filled with gel that is UV cured. Two to three layers of gel (including topcoat) are then applied on top of this. They may be already colored gel. Stickers may be added and secured with a last layer of translucent gel (Figure 17.24a and b).

The technique is similar to restorative dental bonding used by dentists. Acetone has no effect on UV gel nails, so grinding them or waiting for complete nail growth are the only two solutions to remove them. Therefore, with regular touch-ups (Figure 17.25), they often become permanent artificial nails with unfortunately a progressive unsightly thickening of the artificial nail.

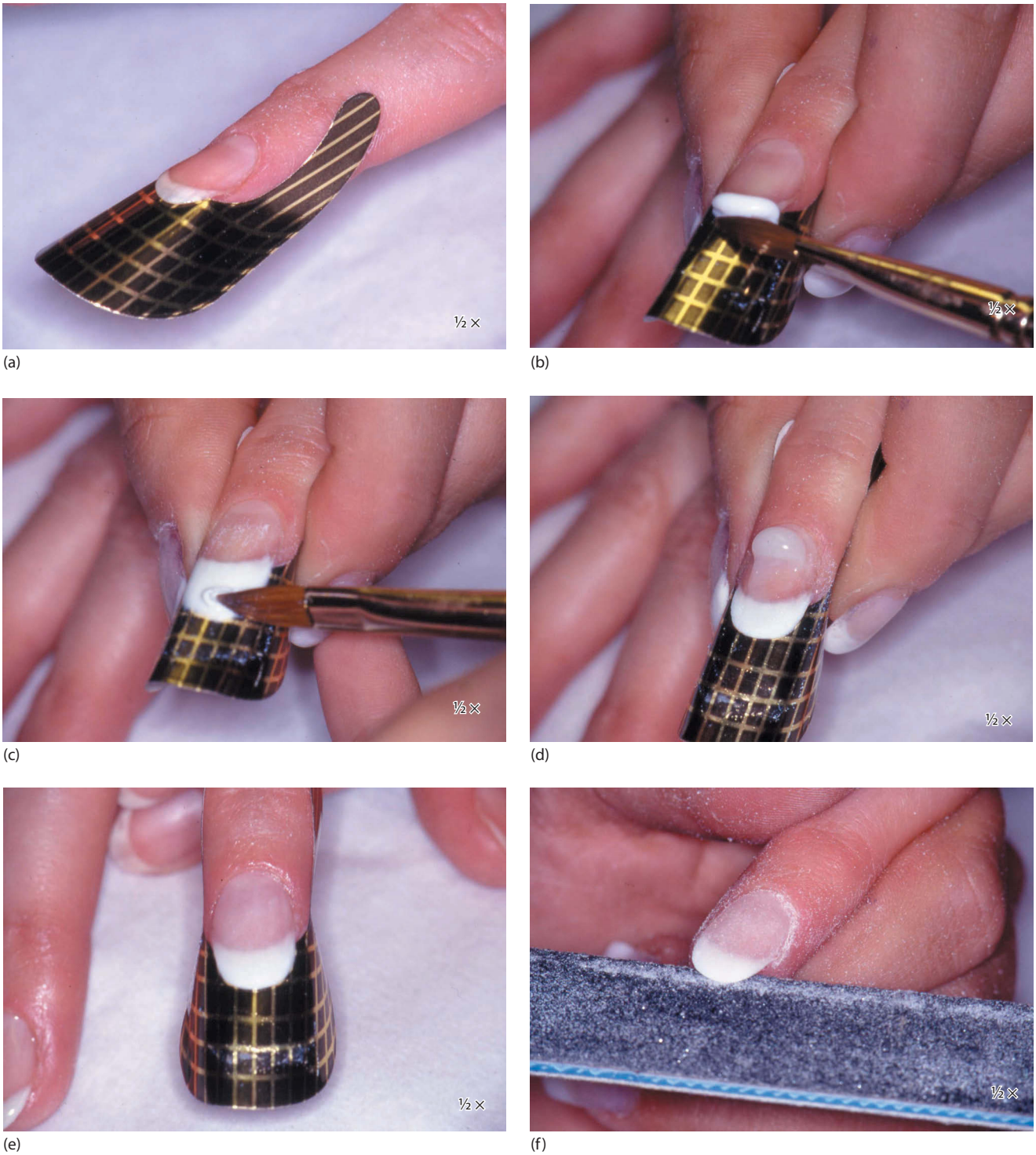
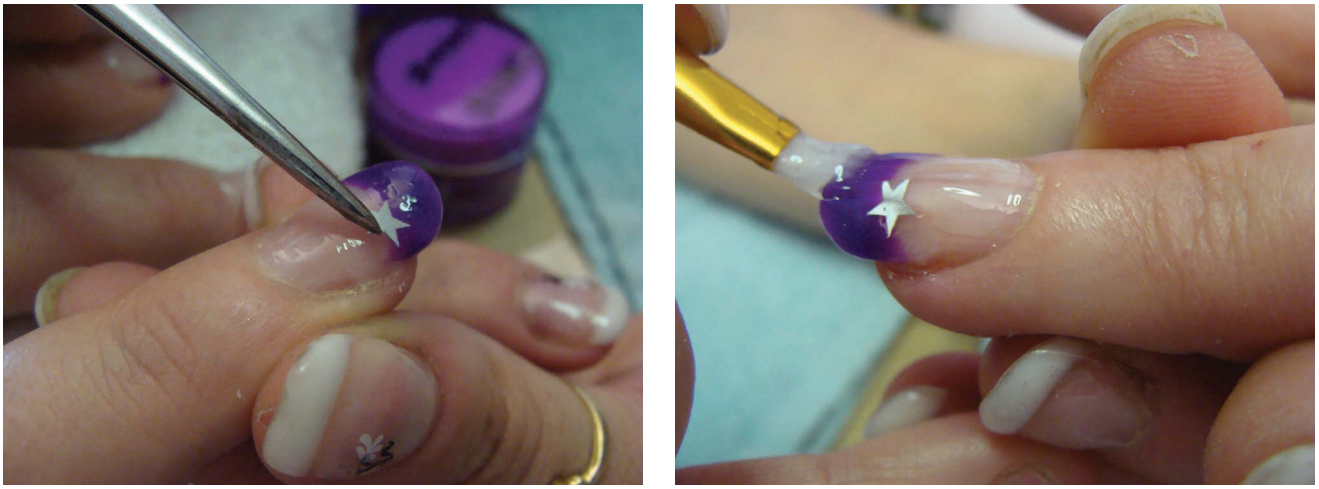


Figure 17.23 (a–f) Light-cured gel. Nail extensions may be obtained by applying several layers of gel on a template. The nail is then filed and shaped.



(a) (b)

Figure 17.24 (a) Stickers may be added. (b) Then they are secured with a last layer of translucent gel.

Figure 17.25 With the growth of the nail, regular touch-ups become necessary. With time, these *permanent* artificial nails will unfortunately give a progressive unsightly thickening of the artificial nail.

Figure 17.26 Onycholysis and thinning of the nail after removal of acrylic nails. Note the remains of gel following the curve of the cuticle just ahead of the lunula.

Benefits of Gel Nails

They are popular because they do not require the use of methacrylic acid as primer and are odorless, easy to apply, and give the nails a glamorous appearance. Gel nails may help to improve the appearance of disfigured nails (trachyonychia, onychoschizia, pitting, etc.) [38].

Shellac and similar brands offer a "light-cured" nail lacquer. They contain acrylates that are polymerized with UV light, which make the nail lacquer highly resistant.

Pitfalls of Acrylic Nails (Sculptured Nails and Gel Nails)

Technical and mechanical hazards:

- Their realization is time consuming (10 nails = 2 hours) and touch-ups are needed every three weeks.
- Excessive length of artificial nails can favor onycholysis (lever effect) (Figure 17.26) or nail fracture and impairs finger performance [39].
- Excessive filing, pumicing, and inadequate use of the primer can cause brittleness or thinning of the nail.
- Monomers can be irritant and lead to subungual hyperkeratosis or onycholysis or severe nail dystrophy.
- Excessive shrinkage of gel enhancement products may cause a sensation of nail bed tightness.
- Recently, nail UV lights were suspected to favor nonmelanoma skin cancers on the hands [40]. Nevertheless, the risk seems very low, regarding the safety of the devices [41,42]. Physical blocking sunscreens or UVA protective gloves are, however, recommended to limit the risk of carcinogenesis and photoaging [43].

Figure 17.27 Poor adherence allows penetration of water between the artificial and natural nails and contamination with *Pseudomonas*.

Infectious hazards:

- Poor adherence allows penetration of water between the artificial and the natural nail and potential contamination with *Pseudomonas* (Figure 17.27).
- Wearing overlong nails favors onycholysis, allowing penetration of water between the nail plate and the bed, leading to contamination with germs like *Pseudomonas*.
- Infections may be transmitted (*Pseudomonas aeruginosa, Serratia marcescens*) more easily by people wearing artificial nails, especially health-care workers (nosocomial infectious outbreaks) [44–47] or even from the patient himself [48].

Nail care for health workers:

- Fingernails should be no longer than 2mm.
- Nail polish may be allowed [49].
- All artificial nails are forbidden.

Allergic hazards:

- Contact dermatitis usually starts 2–4 months after the first application but may appear as long as 16 months after. It may affect not only the customer but also the manicurist.
- The first symptom is itching of the nail bed, followed by painful paronychia and/or paresthesia. Onycholysis and subungual dermatitis are frequently observed. Eyelids, face, or more distant areas may be affected. Cases of occupational allergic asthma [50] and rhinitis [51] have also been described.
- The most frequent allergen is the (meth) acrylate monomer, whereas the polymer is a weak sensitizer. Monomers may remain unpolymerized in the final sculptured nail and in the filing dust. This is due to the fact that the successive gel layers are insufficiently exposed to UV light. The methyl methacrylate monomer (banned by the FDA in the United States since 1974) is the most incriminated, but also ethyl- and butylmethacrylates. Cross-reactions can occur.
- Some cases of allergy to dental or orthopedic acrylates may be explained because of previous sensitization to acrylates in artificial nails and have to be mentioned prior to surgery.

Screening patch tests to detect allergy to (meth)acrylates are:

- 2-HEMA, ethyl-2-cyanoacrylates (ECA) [36]
- 2-HEMA, ethylene glycol dimethacrylate (EGDMA), triethylene glycol diacrylate (TREGDA) [52]

Toxic hazards:

Severe *paresthesia*, associated with a Raynaud's-like syndrome and permanent nail loss, may result from a direct toxicity of acrylics on cutaneous nerves [53–55]. In these cases, patch testing remains negative.

Methacrylic acid–containing primers may be associated with accidental poisoning in children, dermal burns and burns of the airways, and the gastrointestinal tract [56,57].

NAIL ADORNMENT

Stick-on nail dressings (press-on polish, nail wraps) are the new way to adorn fingers and toes (Figure 17.28a and b). Unlike nail polish, they will not chip or stain the nail and are quicker to

(a)

(b)

Figure 17.28 (a) A lacquered nail resting on a sheet with stick-on nail dressings. (b) The same nail with a stick-on dressing on.

apply, as no drying time is required. They are made of a thin colored or decorated synthetic film with an adhesive backing containing acrylates. Their adherence to the plate is faster if heat is used (hair dryer). The nail wrap range is designed to last up to 7 days on nails and 8 weeks on the toes, with each nail wrapping treatment taking just 15 minutes to apply at home. Designs may include metallic gold, silver, crystals, dots, stickers, decals, and animal print [58].

The ultimate refinement is to stick a gold tip on a fifth fingernail (Figure 17.29). Some fashion victims also wear a piercing in a long nail (Figure 17.30).

Figure 17.29 The ultimate refinement: gold tip with real diamonds on a fifth fingernail. (Courtesy of Baran, R., Cannes, France.)

Figure 17.30 A nail piercing seen from here. (Courtesy of Baran, R., Cannes, France.)

(a)

(b)

Figure 17.31 (a) Permanent toe dystrophy from a trauma in a young lady. (b) A thimble-shaped digital fixation, molded from the contralateral great toe, brings esthetic and functional comfort to the patient.

NAIL PROSTHESIS

For all nail dystrophies where medical or surgical attempts would be vain, as well as in distal partial or total digital amputation, a thimble-shaped digital fixation brings esthetic and functional comfort to the patient. The prosthesis may be easily fitted on a finger stump (Figure 17.31a and b). The artificial nail on the fixation takes nail varnish and lacquer removal well. Molding is made from the contralateral digit if possible, and the color of the fixation is matched perfectly to the skin color. Pillet Hand Prosthesis (France and United States) and American Hand Prosthetics (United States) are two major manufacturers of these fixations [37,59,60].

REFERENCES

1. Savage T, Khan A, Loftus BG. Acetone-free nail polish remover pads: Toxicity in a 9-month old. *Arch Dis Child* 2007; 92(4):371.
2. de Groot AC, Weylandt JW, Nater JP. Nail cosmetics. *Unwanted Effects of Cosmetics and Drugs Used in Dermatology*, 3rd ed. Amsterdam, the Netherlands: Elsevier Science, 1994, pp. 524–529.
3. Dahdah MJ, Scher RK. Nail diseases related to nail cosmetics. *Dermatol Clin* 2006; 24(2):233–239, vii.

4. Baran R, Schoon D. Cosmetology for normal nails. In: Baran R, Maibach HI, eds. *Textbook of Cosmetic Dermatology*. London, U.K.: Informa Healthcare, 2010, pp. 247–258.
5. Dimitris R, Ralph D. Management of simple brittle nails. *Dermatol Ther* 2012; 25(6):569–573.
6. Haneke E. Onychocosmeceuticals. *J Cosmet Dermatol* 2006; 5(1):95–100.
7. Rodden AM, Spicer L, Diaz VA, Steyer TE. Does fingernail polish affect pulse oximeter readings? *Intensive Crit Care Nurs* 2007; 23(1):51–55.
8. Hinkelbein J, Koehler H, Genzwuerker HV, Fiedler F. Artificial acrylic finger nails may alter pulse oximetry measurement. *Resuscitation* 2007; 74(1):75–82.
9. Yamamoto LG, Yamamoto JA, Yamamoto JB, Yamamoto BE, Yamamoto PP. Nail polish does not significantly affect pulse oximetry measurements in mildly hypoxic subjects. *Respir Care* 2008; 53(11):1470–1474.
10. Chang RM, Hare AQ, Rich P. Treating cosmetically induced nail problems. *Dermatol Ther* 2007; 20(1):54–59.
11. Winthrop KL, Abrams M, Yakrus M et al. An outbreak of mycobacterial furunculosis associated with footbaths at a nail salon. *N Engl J Med* 2002; 346(18):1366–1371.
12. Karmochkine M, Carrat F, Dos Santos O, Cacoub P, Raguin G. A case-control study of risk factors for hepatitis C infection in patients with unexplained routes of infection. *J Viral Hepat* 2006; 13(11):775–782.
13. Turgut F, Kanbay M, Uz B et al. A forgotten but important risk factor for infective endocarditis in patients with prosthetic valve: Pedicure. *Scand J Infect Dis* 2007; 39(3):274–276.
14. Rich P, Daniel C. Nail cosmetics: The benefits and pitfalls. In: Scher RK, Daniel CR, eds. *Nails: Diagnosis, Therapy, Surgery*. Philadelphia, PA: Elsevier Saunders, 2005, pp. 221–227.
15. Rich P. Nail cosmetics. *Dermatol Clin* 2006; 24(3):393–399.
16. Jefferson J, Rich P. Update on nail cosmetics. *Dermatol Ther* 2012; 25(6):481–490.
17. Rietschel RL, Fowler JF Jr. Preservatives and vehicles in cosmetics and toiletries. *Fisher's Contact Dermatitis*. 6th edn. Hamilton, Ontario, Canada: BC Decker, 2008, pp. 266–318.
18. Nassif AS, Le Coz CJ, Collet E. A rare nail polish allergen: Phthalic anhydride, trimellitic anhydride and glycols copolymer. *Contact Dermatitis* 2007; 56(3):172–173.
19. André J, Scheers Ch, Baran R. The normal nail and use of nail cosmetics and treatments. In: Barel AO, Paye M, Maibach HI, eds. *Handbook of Cosmetic Science and Technology*, 4th ed. Boca Raton, FL: CRC Press, 2014, pp. 597–607.
20. Baran R, André J. Side effects of nail cosmetics. *J Cosmet Dermatol* 2005; 4(3):204–209.
21. Guarneri F, Borgia F, Cannavò SP. Novitas in antiquo: Magnetic nails. *Contact Dermatitis* 2013; 68(6):376–377.
22. Guarneri F, Guarneri C, Cannavò SP. Nail-art and cobalt allergy. *Contact Dermatitis*. 2010; 62(5):320–321.
23. Shaw S. A case of contact dermatitis from « hypoallergenic » nail varnish. *Contact Dermatitis* 1989; 20(5):385.
24. Castelain M, Veyrat S, Laine G, Montastier C. Contact dermatitis from nitrocellulose in a nail varnish. *Contact Dermatitis* 1997; 36(5):266–267.
25. Gach JE, Stone NM, Finch TM. A series of four cases of allergic contact dermatitis to phthalic anhydride/trimellitic anhydride/glycols copolymer in nail varnish. *Contact Dermatitis* 2005; 53(1):63–64.
26. Chen AF, Chimento SM, Hu S, Sanchez M, Zaiac M, Tosti A. Nail damage from gel polish manicure. *J Cosmet Dermatol* 2012; 11(1):27–29.
27. Krüger N, Reuther T, Williams S, Kerscher M. Effect of urea nail lacquer on nail quality. Clinical evaluation and biophysical measurements. *Hautarzt* 2006; 57(12):1089–1094.
28. Sun C, Koppel K, Chambers E. An initial lexicon of sensory properties for nail polish. *Int J Cosmet Sci* 2014; 36(3):262–272.
29. Goldman BD, Rich P. Subungual melanoma obscured by nail polish. *J Am Acad Dermatol* 2001; 44(5):875.
30. Warshaw EM, Buchholz HJ, Belsito DV et al. Allergic patch test reactions associated with cosmetics: Retrospective analysis of cross-sectional data from the North American Contact Dermatitis Group, 2001–2004. *J Am Acad Dermatol* 2009; 60(1):23–38.
31. Moran B, Murphy GM. Recurrent tongue swelling: An unusual manifestation of allergic contact dermatitis. *Contact Dermatitis* 2009; 60(2):114–115.
32. Jacob SE, Stechschulte SA. Tosylamide/formaldehyde resin allergy—A consideration in the atopic toddler. *Contact Dermatitis* 2008; 58(5):312–313.
33. Scheers C, André J, Negulescu M, Blondeel A, Kolivras A. Recurrent cheilitis and lip oedema caused by (meth)acrylates present in ultraviolet-curable nail lacquer. *Contact Dermatitis* 2015; 72(5):341–342.
34. Baran R, Rigopoulos, D. Nail cosmetics and real nail prostheses. *Nail Therapies*. London, U.K.: Informa Healthcare, 2012, pp. 102–109.
35. Kanerva L, Lauerma A, Estlander T, Alanko K, Henriks-Eckerman ML, Jolanki R. Occupational allergic contact dermatitis caused by photobonded sculptured nails and a review of (meth) acrylates in nail cosmetics. *Am J Contact Dermatitis* 1996; 7(2):109–115.
36. Constandt L, Hecke EV, Naeyaert J-M, Goossens A. Screening for contact allergy to artificial nails. *Contact Dermatitis* 2005; 52(2):73–77.
37. Schoon D, Baran R. Cosmetics for abnormal and pathological nails. In: Robert B, Howard IM, eds. *Textbook of Cosmetic Dermatology*. London, U.K.: Informa Healthcare, 2010, pp. 259–268.
38. Nanda S, Grover C. Utility of gel nails in improving the appearance of cosmetically disfigured nails: Experience with 25 cases. *J Cutan Aesthet Surg* 2014 December; 7(4):240–241.
39. Jansen CW, Patterson R, Viegas SF. Effects of fingernail length on finger and hand performance. *J Hand Ther* 2000; 13(3):211–217.
40. MacFarlane DF, Alonso CA. Occurrence of nonmelanoma skin cancers on the hands after UV nail light exposure. *Arch Dermatol* 2009; 145(4):447–449.
41. Diffey BL. The risk of squamous cell carcinoma in women from exposure to UVA lamps used in cosmetic nail treatment. *Br J Dermatol* 2012; 167(5):1175–1178.
42. Markova A, Weinstock MA. Risk of skin cancer associated with the use of UV nail lamp. *J Invest Dermatol* 2013; 133(4):1097–1099.
43. Shipp LR, Warner CA, Rueggeberg FA, Davis LS. Further investigation into the risk of skin cancer associated with the use of UV nail lamps. *JAMA Dermatol* 2014; 150(7):775–776.
44. Pottinger J, Burns S, Manske C. Bacterial carriage by artificial versus natural nails. *Am J Infect Control* 1989; 17(6):340–344.
45. Passaro DJ, Waring L, Armstrong R et al. Postoperative Serratia marcescens wound infections traced to an out-of-hospital source. *J Infect Dis* 1997; 175(4):992–995.
46. Gordin FM, Schultz ME, Huber R, Zubairi S, Stock F, Kariyil J. A cluster of hemodialysis-related bacteremia linked to artificial fingernails. *Infect Control Hosp Epidemiol* 2007; 28(6):743–744.
47. Moolenaar RL, Crutcher JM, San Joaquin VH et al. A prolonged outbreak of *Pseudomonas aeruginosa* in a neonatal intensive care unit: Did staff fingernails play a role in disease transmission? *Infect Control Hosp Epidemiol* 2000; 21(2):80–85.
48. Parker AV, Cohen EJ, Arentsen JJ. Pseudomonas corneal ulcers after artificial fingernail injuries. *Am J Ophthalmol* 1989; 107(5):548–549.
49. Fagernes M, Lingaas E. Factors interfering with the microflora on hands: A regression analysis of samples from 465 healthcare workers. *J Adv Nurs* 2011; 67(2):297–307.
50. Baran R. Nail beauty therapy: An attractive enhancement or a potential hazard? *J Cosmet Dermatol* 2002; 1(1):24–29.
51. Torres MC, Linares T, Hernandez MD. Acrylates induced rhinitis and contact dermatitis. *Contact Dermatitis* 2005; 53(2):114.
52. Teik-Jin Goon A, Bruze M, Zimerson E, Goh C-L, Isaksson M. Contact allergy to acrylates/methacrylates in the acrylate and nail acrylics series in southern Sweden: Simultaneous positive patch test reaction patterns and possible screening allergens. *Contact Dermatitis* 2007; 57(1):21–27.

53. Slodownik D, Williams JD, Tate BJ. Prolonged paresthesia due to sculptured acrylic nails. *Contact Dermatitis* 2007; 56(5):298–299.
54. Baran RL, Schibli H. Permanent paresthesia to sculptured nails. A distressing problem. *Dermatol Clin* 1990; 8(1):139–141.
55. Fisher AA. Permanent loss of fingernails due to allergic reaction to an acrylic nail preparation: A sixteen-year follow-up study. *Cutis* 1989; 43(5):404–406.
56. Linden CH, Scudder DW, Dowsett RP, Liebelt EL, Woolf AD. Corrosive injury from methacrylic acid in artificial nail primers: Another hazard fingernail products. *Pediatrics* 1998; 102(4 Pt 1):979–984.
57. Woolf A, Shaw J. Childhood injuries from artificial nail primer cosmetic products. *Arch Pediatr Adolesc Med* 1998; 152(1):41–46.
58. Draelos ZD. Cosmetic treatment of nails. *Clin Dermatol*. 2013 October; 31(5):573–577.
59. Richert B, Baran R. Soins podologiques—Camouflage—Cosmétologie unguéale. In: Richert B, Baran R, eds. L'ongle: de la clinique au traitement. Paris, France: Med'Com, 2009, pp. 133–138.
60. Pillet J, Didierjean A. Ungual prostheses. *J Dermatol Treat* 2000; 12:41–46.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Focal hyperhidrosis: Diagnosis, treatment, and follow-up

Oliver Kreyden

PRIMARY AND SECONDARY HYPERHIDROSIS: FORMS, DIAGNOSIS, AND TREATMENT

The autonomic nervous system coordinates all functions essential for survival: heartbeat, blood pressure, digestion, night and day rhythm, sexuality, and body temperature, among others. As a warm-blooded or homoeothermic species, the human being must maintain the very same body temperature regardless of external influence. Only a slightly increased body temperature leads to fever, and an elevated temperature over 5°C is hardly compatible with life. Our body has mainly two different systems to cool down body temperature, both coordinated by the autonomic nervous system:

- Vasodilation with opening the superficial vessels to allow heat exchange through radiation (similar to a radiator)
- Sweating leading to lower body temperature due to evaporation

Therefore, sweating is an important mechanism in the regulation of body temperature. This fact is often misrepresented by saying that sweating is healthy. Sweating is neither healthy nor unhealthy. It is simply necessary, like other functions of the autonomic nervous system. The latter has two parts: the sympathetic part that increases and the parasympathetic branch that decreases action of the nervous system. In patients with hyperhidrosis, there is an overactivation of the autonomic nervous system in total and of the sympathetic branch in particular. Therefore, hyperhidrosis patients often suffer from other vegetative disorders such as flushing, colon irritability, tremor, and sleeping disorders. Taking exact anamnesis helps in finding exact diagnosis and distinguishes primary hyperhidrosis from the secondary form in most cases due to endocrinopathy. Besides, it could be shown that patients with primary hyperhidrosis show perceptual abnormalities and exaggerated sudomotor reactions to thermoalgesic stimulation, consistent with central sensitization of sympathetic circuits. Interestingly, the reduced sympathetic outflow after thoracoscopic sympathectomy induced normalization of this sensory perception, but it did not modify the abnormal control of efferent sudomotor activity [1]. Further, it could be demonstrated that when patients suffering from focal hyperhidrosis were exposed to mental stress, there was more than 10-fold activity of sudomotor fibers compared to the nonhyperhidrotic control group exposed to the same stress level [2]. However, exact definition of hyperhidrosis is difficult as the border between normal sweating and pathophysiological sweating is fluent. An accepted definition could be the production of excess sweat beyond the amount required to return elevated body temperature to normal and/or paradoxical sweating without any reason to correct elevated body temperature (i.e., sweating in cold winter without any exercising) [3].

As mentioned, we distinguish primary from secondary hyperhidrosis. We will not find any underlying reason in primary, mostly localized (focal) hyperhidrosis (idiopathic primary hyperhidrosis), whereas the secondary form is due to an underlying disease, mainly endocrinological or neurologic diseases (Table 18.1) [4].

Secondary Hyperhidrosis

In general, secondary hyperhidrosis is rare. Most hyperhidrosis patients are suffering from a primary form where we do not find any underlying disease as a cause of sweating. As a rule of thumb, in patients with generalized sweating, a secondary form should always be excluded. It is of most importance to point out that every patient with an abnormal form or history of sweating has to be checked for a possible secondary hyperhidrosis. As any secondary form of hyperhidrosis is connected with other symptoms of morbidity, anamnesis of the actual complaints and personal history as well as family history is very important. The following symptoms are suspects for secondary hyperhidrosis and should be referred for further examinations to the endocrinologist, neurologist, or in some cases family doctor to exclude the underlying disease:

- General sweating over the amount of focal (or multifocal) hyperhidrosis, e.g., chest, back, face, and limbs (Figure 18.1)
- Nocturnal sweating
- Paroxysmal sweating
- Associated symptoms, e.g., flushing, diarrhea, tremor, ravenousness, sleepless, and loss of weight
- Concomittant (personal anamnesis)
- Age of onset more than 30 years or duration of symptoms less than 1 year

On the other hand, there are symptoms that indicate a harmless primary hyperhidrosis:

- Bilateral and relatively symmetric sweating
- Age of onset less than 25 years
- Positive family history
- Nocturnal cessation of sweating
- Harmless concomitant vegetative symptoms such as flushing, colon irritability, and sleep disorders

Secondary hyperhidrosis is a severe illness, and dermatologists are often the first doctors to see these patients.

Table 18.1 Etiology of Secondary Hyperhidrosis

Causative disorder	Example
Physiologic hyperhidrosis	Acclimatization
	Exercising
Endocrinologic disorders	Menopause
Hormone disorders	Hyperpituitarism
	Hyperthyroidism
Elevated catecholamines	Hypoglycemia
	Shock
	Pheochromocytoma
Neurologic disorders	Cervical rib
	Carpal canal syndrome
	Auriculotemporal syndrome of Frey (gustatory sweating)
	Tabes dorsalis
	Syringomyelia
	Encephalitis
	Diabetic neuropathia
	Hemiplegia
	Plexus lesions
	Sympathetic chain lesions
Compensatory hyperhidrosis in association with widespread anhidrosis	Ross syndrome
	Diabetic neuropathia
	Miliaria
	After sympathectomy
	Sympathetic chain lesions
Axon reflex sweating	Inflammatory skin lesions
Nevoid disorder	Naevus sudoriferus
Idiopathic primary hyperhidrosis	Hyperhidrosis axillaris
	Hyperhidrosis manuum
	Hyperhidrosis pedum

Source: Adapted from Hölzle E, Pathophysiology of sweating, in Kreyden, O.P. et al., eds., *Hyperhidrosis and Botulinum Toxin in Dermatology*. *Current Problems in Dermatology*, Vol. 30, Karger, Basel, Switzerland, 2002, pp. 10–22.

Figure 18.1 Generalized hyperhidrosis with sweat marks beyond the margin of the axilla involving submammary region and the back. (Reproduced from Kreyden OP, Botulinum toxin in treatment of axillary, palmar and plantar hyperhidrosis, in Redaelli, A., ed., *Botulinum Toxin A in Aesthetic Medicine with Treatment for Hyperhidrosis and Odontostomatology*, Officina Editoriale Oltroarno, Firenze, Italy, 2010, pp. 199–219. With permission.)

Therefore, it is important that the symptoms are not underestimated and that patients get referred to colleagues of other specialties if ever there is a doubt. Collaboration with other specialists such as endocrinologists, gynecologists, neurologists, and in first line the general practitioner is of most importance when treating patients for hyperhidrosis (Table 18.1).

Primary Hyperhidrosis

The primary or essential form occurs typically in young patients experiencing mental stress (nervous sweating) without other pathogenic factors. This sweating is focal and located in most cases in the axilla (Figure 18.2a), on the palms (Figure 18.2b), or on the soles of the feet or the forehead (Figure 18.2c), respectively. It is estimated that about 3%–4% of the population are suffering from primary hyperhidrosis, whereas the estimated number of unreported cases is high, so that some authors estimate an overall percentage of 8%–10% [5]. This is due to the patients' lack of knowledge of effective treatment options and therefore patients' acceptance of the disease. On the other hand, still nowadays, many physicians recommend acceptance of the sweating because either they do not believe in the efficacy of the treatment options (botulinum doubter) or they simply underestimate the impact on the patient's life quality. The main reason for the ongoing skepticism against botulinum toxin (BTX) even after 20 years of its use in the treatment of focal hyperhidrosis is lack of information. This leads to rumors that are reported so many times that people (patients and doctors) believe in those untruths. Therefore, it is most important to take primary and particularly secondary hyperhidrosis seriously and to accept those conditions as a severe dermatological disease with a high impact factor for the patient's daily life. It is widely accepted that dermatologists are the specialists to care for hyperhidrosis patients [5].

In primary hyperhidrosis, the reported family history is 30%–65% [6], depending on the quality of the physician's anamnesis. The impact factor in quality of life is high. It could be shown in a survey on impairment of life quality before and after treatment of focal hyperhidrosis that 80% of the affected patients were limited in their daily activity before therapy and 75% of the treated patients felt no restriction anymore [5] (Figure 18.3).

Clinical Appearance of Primary Hyperhidrosis

In most cases, primary hyperhidrosis is focal, meaning restricted to certain areas. Sometimes, the sweating can be multifocal, e.g., the axillae, hands, and feet. If the sweating is even more diffuse involving also the chest and the back, we talk of a generalized constitutional primary hyperhidrosis (GCPH). This form sometimes leads to diagnostic problems as it is difficult to distinguish from secondary hyperhidrosis. Therefore, it is recommended to perform more diagnostic investigation in those cases to be sure not to overlook a secondary cause for the

Figure 18.2 (a) Sweat marks of a patient with severe axillary hyperhidrosis (grade IV). (b) Typical palmar sweating with confluent sweat pearls in a patient with hyperhidrosis IV. (c) Onset of a frontal hyperhidrosis is typically located at the receding hairline. This is important to know when treating patients with botulinum.

sweating. In general, we find the following four main types in primary hyperhidrosis:

1. Axillary hyperhidrosis
2. Palmar hyperhidrosis (mostly combined with plantar hyperhidrosis)
3. Frontal hyperhidrosis
4. Multifocal hyperhidrosis (a combination of the three types)

In general, we distinguish four types of severity of focal hyperhidrosis (Table 18.2).

Less frequently, we are faced with inter- or submammary (mainly female) (Figure 18.4), inguinal (Figure 18.5), or perianal hyperhidrosis. According to the extent of frontal hyperhidrosis, patients may suffer from hyperhidrosis of the neck and/or the whole scalp (Figure 18.6), respectively.

Diagnostic Procedures and Therapy Modality of Primary Hyperhidrosis

As mentioned before, the diagnosis of primary or idiopathic hyperhidrosis is based on the clinical appearance and the patient history. Early onset in (or in rare cases even before) puberty, focal sweating in typical areas, and positive family history for hyperhidrosis are the clues for diagnosis. In those cases, there is no need for further examinations such as laboratory tests or any imaging procedures. However, if patients suffer in addition from other endocrinological disorder symptoms or there are inconsistencies in the patient's history, further examination in collaboration with other specialists is highly recommended to exclude definitely secondary hyperhidrosis.

Depending on the affected area of the focal hyperhidrosis, the therapy modality may change. In any case, but particularly in axillary hyperhidrosis, Minor starch test should be performed. Minor starch test gives important information on the severity of the hyperhidrosis and is very helpful in the follow-up by demonstrating the efficacy of the therapy or in cases of unsatisfying results to detect the un- or undertreated areas. In principle, all focal primary hyperhidrosis cases can be treated most effectively with BTX-A. Since the introduction of this very effective and noninvasive treatment modality, surgical option is more or less abandoned. However, tap water iontophoresis (TWI) is still the therapy of choice in palmoplantar hyperhidrosis (see the "Tap Water Iontophoresis" section).

ANATOMY OF SWEAT GLANDS

Eccrine Sweat Glands [7,8]

We find sweat glands all over the body. The total number lies between 2 and 4 million. We know two types of sweat glands: eccrine sweat glands that form the majority and apocrine sweat glands that are present just in limited areas such as axilla, perianal region, areolae, periumbilical skin, prepuce, scrotum, mons pubis, and labia majora. Eccrine sweat glands are most numerous on the sole of the foot (620/cm^2) and the forehead (360/cm^2) followed by the palms and axillae (300/cm^2)

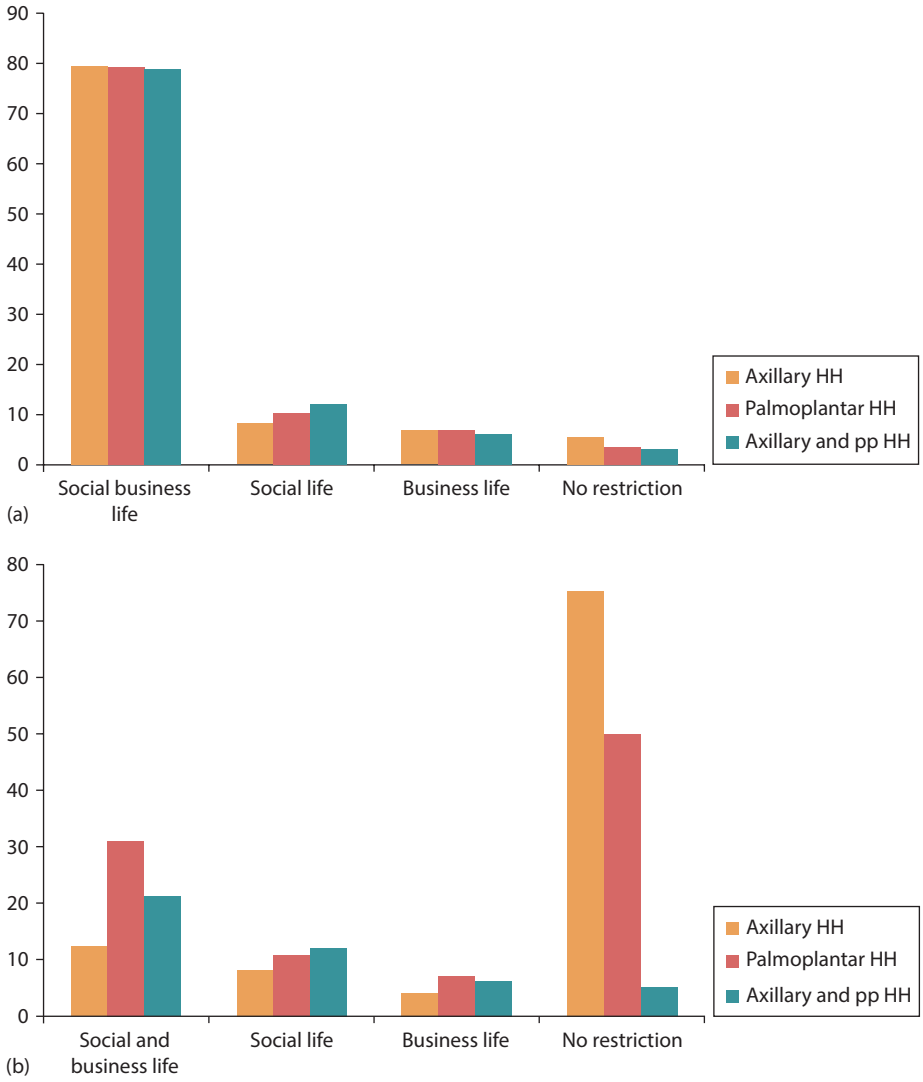


Figure 18.3 When do you feel limited in daily activity due to your primary hyperhidrosis? (a) Before treatment. (b) After treatment. (From Junker J and Kreyden OP, *Kosmetische Medizin*, 2, 32, 2008.)

Table 18.2 Graduation of Focal Hyperhidrosis

Grade of severity of focal hyperhidrosis	Axillary hyperhidrosis (Discoloration in Minor starch test)	Palmoplantar
I	None or poor	Slightly wet on the palms
II	Definable but slight	Important wet palms including volar digits with visible fine sweat pearls
III	Predominantly dark	Confluent sweat pearls on the palm and sides of the fingers
IV	Dripping	Confluent sweat pearls on the dorsum of the fingers and dripping hyperhidrosis of the hand

and are rare on the thigh (120/cm^2), the scrotum (80/cm^2), and the back (65/cm^2). They are absent from the margins of the lip, nail bed, nipple, inner preputial surface, labia majora, glans penis, and glans clitoris. The ratio between apocrine and eccrine sweat glands is 1:1 in the axilla but 1:10 in other regions.

Eccrine sweat glands are long-branched tubular structures with a coiled secretory portion and a straight ductular portion. The secretory coil is situated deep in the dermis, and we can distinguish it clearly from dark cells within its epithelium. Clear cells have a round, large, moderately euchromatic nucleus. The major part of sweat, in particular water and electrolytes, is formed by clear cells. Dark cells have a cuboidal shape and secrete PAS-positive glycoproteins from dense granules within its cytoplasm. These glycoproteins are the most prominent protein constituents in the sweat. The main function of dark cells remains unknown.

Eccrine sweat glands are innervated by sympathetic nerve fibers from the spinal cord. Nerve cells from the spinal

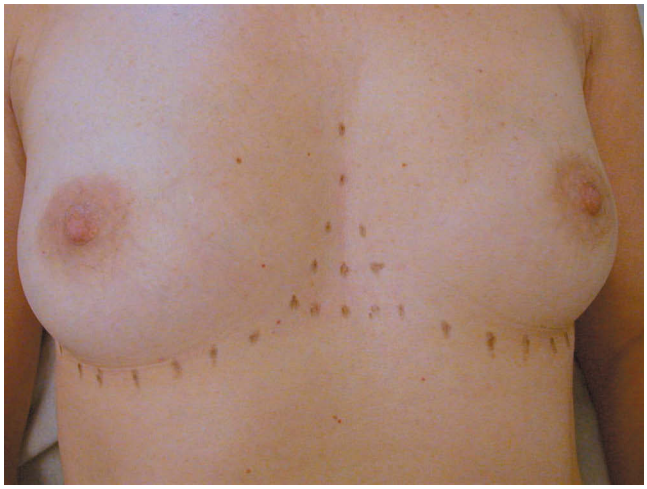


Figure 18.4 Sub- and intermammary hyperhidrosis is quite frequent and very often neglected by the treating physician. Botulinum injection is very effective in this particular indication. (Reproduced from Kreyden OP, Botulinum toxin in the management of focal hyperhidrosis. Anatomy of sweat glands, in: Benedetto, A.V., ed., *Botulinum Toxin in Clinical Dermatology*, Taylor & Francis Group, London, U.K., 2006, pp. 261–293. With permission.)

cord segments Th2 to Th8 supply the skin of the upper limbs, from Th1 to Th4 the face, from Th4 to Th12 the trunk, and from Th10 to L2 the lower limbs. This understanding is important for surgical treatment of hyperhidrosis with endoscopic thoracic sympathectomy (ETS).

Figure 18.5 Hyperhidrosis of the groin is relatively rare but can be very troublesome when severe. It can necessitate the of wearing napkins.

Figure 18.6 Whole scalp hyperhydrosis. In most cases, it is combined with frontal HH but can occur independently. A patient complains of wet hair, like after a shower, only occasioned by little physical stress. (Reproduced from Kreyden OP et al., *Hyperhidrosis and Botulinum Toxin in Dermatology. Current Problems in Dermatology*, Vol. 30, Karger Verlag, Basel, Switzerland, 2002. With permission.)

Apocrine Sweat Glands

Apocrine sweat glands consist of a basal secretory coil and a straight duct leading to the skin surface. The secretory region is situated in the deep dermis. The secretory cells are cuboidal but may be squamous when the gland is distended with a secretory product. The ducts of apocrine glands are morphologically similar to the eccrine ducts. The apocrine sweat glands are innervated by sympathetic nerve fibers coming from the same spinal segments as those of eccrine sweat glands. The secretory product of apocrine sweat glands is a sterile, thick, milky, and odorless fluid containing protein, carbohydrate, ammonia, lipids, ferric ions, and fatty acids. Only after bacterial decomposition, is the characteristic smell generated. We believe that apocrine sweat glands are a relic of human evolution. In animals, the secretory product with its pheromones is an important signal for potency and territorial behavior. However, the role for modern humans is not clear.

PHYSIOLOGY OF SWEAT GLANDS

Thermoregulation

Sweating is an important mechanism in the regulation of a constant body temperature and can be defined as a physiologic response to an increased body temperature due to elevated ambient temperature or to physical stress. Normal perspiration rate is estimated at about 0.5–1 mL/minute leading to 1–2 L/day. However, in stress situations, we can produce up to 10 L/day. Besides eccrine sweat glands, there are other effectors for thermoregulation such as changing the diameter of blood vessels of the skin or metabolic and muscular activity. Whereas through the increased blood circulation, heat loss is achieved with radiation like a radiator, sweating generates evaporative heat loss from the body surface. This very sensible regulation is controlled by the vegetative nerve system, which is located in the hypothalamus. Several factors modify thermoregulation in the hypothalamic center. These include hormones, pyrogens, physical activity, emotional stimuli, temperature changes and emotional stimuli such as temperature changes during the

menstrual cycle and thermoregulatory imbalances during the climacterium. Through the limbic system, emotional and physical activity influences the thermoregulatory center.

Mechanism of Sweat Secretion [4]

The secretory activity of the human eccrine sweat gland consists of the following two major functions:

1. Secretion of an ultrafiltrate of a plasma-like precursor fluid by the secretory coil in response to acetylcholine (ACh) that is released from the sympathetic nerve endings
2. Reabsorption of sodium in excess of water by the duct, thereby producing hypertonic skin surface sweat

Sato postulated the concept of the ionic mechanism of fluid secretion in exocrine glands by the clear cells of the eccrine acini [9] (Figure 18.7). ACh released from periglandular cholinergic nerve endings in response to nerve impulses binds to cholinergic receptors of the sweat gland. The activation of these receptors located on the clear cells stimulates an influx of extracellular Ca^{2+} into the cytoplasm. The increased intracellular Ca^{2+} stimulates

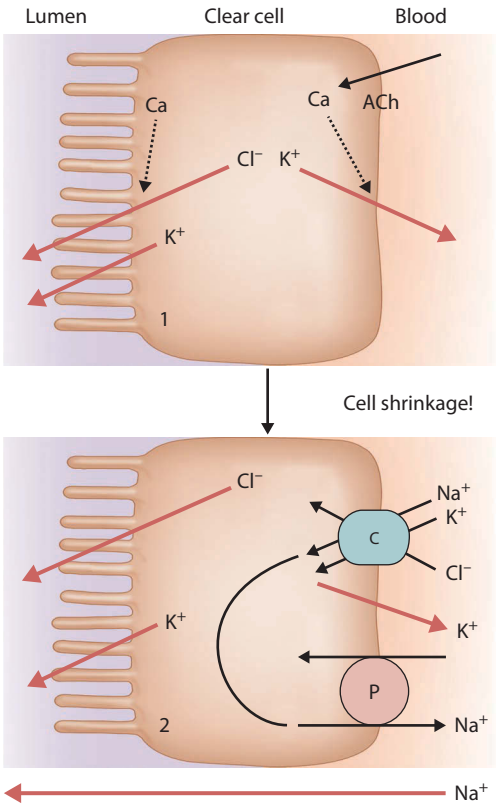


Figure 18.7 Mechanism of eccrine sweat secretion. C = Na^+–K^+–$2Cl^-$-cotransporter; P = Na^+–K^+–ATPase-dependent Na pump (Modified from Sato H. Biology of the eccrine sweat gland. In: Freedberg, I.M. et al., eds. *Dermatology in General Medicine*, Vol. 5. New York: McGraw-Hill, 1993, pp. 155–164; in Hölzle E, Pathophysiology of sweating, in Kreyden, O.P. et al., eds., *Hyperhidrosis and Botulinum Toxin in Dermatology. Current Problems in Dermatology*, Vol. 30, Karger, Basel, Switzerland, 2002, pp. 10–22; reproduced from Kreyden OP et al., *Hyperhidrosis and Botulinum Toxin in Dermatology. Current Problems in Dermatology*, Vol. 30, Karger Verlag, Basel, Switzerland, 2002. With permission.)

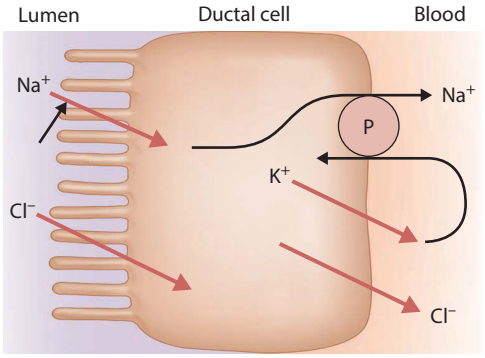


Figure 18.8 Mechanism of reabsorption of electrolytes from primary eccrine sweat. P = Na^+–K^+–ATPase-dependent Na pump. (Modified from Sato H. Biology of the eccrine sweat gland. In: Freedberg, I.M. et al., eds. *Dermatology in General Medicine*, Vol. 5. New York: McGraw-Hill, 1993, pp. 155–164; in Hölzle E, Pathophysiology of sweating, in Kreyden, O.P. et al., eds., *Hyperhidrosis and Botulinum Toxin in Dermatology. Current Problems in Dermatology*, Vol. 30, Karger, Basel, Switzerland, 2002, pp. 10–22.)

Cl channels in the luminal membrane and K-channels in the basolateral membrane, causing a net KCl efflux from the cell. Consequently, cell volume decreases because water follows the solutes to maintain isoosmolarity; the cell shrinks. The decrease in K^+ and Cl^- provides a favorable chemical potential gradient, probably the driving force, for Na–K–2Cl cotransporters located in the basolateral membrane. The cotransporter carries Na^+, K^+, and $2Cl^-$ into the cell in an electrically neutral fashion. In the steady state of secretion, K^+ and Na^+ recycle across the basolateral membrane without further loss. In contrast, Cl^- enters into the cell via Na–K–2Cl-cotransporters. The movement of Cl^- across the apical (luminal) membrane depolarizes the apical membrane and generates the negative luminal potential. This luminal negative potential then attracts Na^+ into the lumen across the Na-conductive intercellular junction. Thus, the Na^+ and the Cl^- that enter the lumen across the cell join into the lumen to form NaCl in the isotonic primary fluid.

In the coiled portion of the sweat duct, reabsorption of NaCl occurs to preserve electrolytes creating hypotonic sweat, which is secreted at the skin surface. The absorption of NaCl by the duct is due to the active transport of Na^+ ions by the Na pump located in the basal ductal cell membrane (Figure 18.8). Chloride is also transported against the chemical gradient but down a favorable electrical gradient. In cystic fibrosis, Cl channels in the luminal membrane are defective and those in the basal membrane are significantly decreased, resulting in excess Cl^- in the sweat secreted onto the surface.

NONBOTULINUM TREATMENT OF PRIMARY HYPERHIDROSIS

In principle, the eccrine sweat gland is innervated by the sympathetic nervous system. Like the motor end plate and the parasympathetic nervous system, the transmitter substance for the eccrine sweat gland is ACh. The nerve impulse leads from the limbic system of the brain to the end organ (i.e., the motor end plate or the eccrine sweat gland, respectively) via a switch position, the so-called ganglion. These switch positions have the very same transmitter and receptors, ACh, and nicotinic

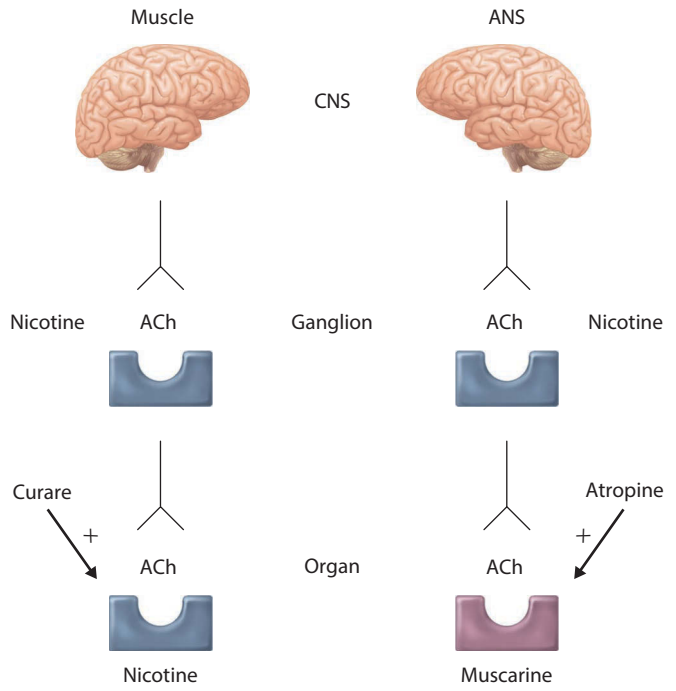


Figure 18.9 Diagram of the cholinergic pathway. Note that acetylcholine (ACh) acts as transmitter for the autonomic nerve system (ANS) and the muscle but the receptors are different. (Drawn by Dr. O. Ph. Kreyden, Dermatologie Praxis.)

receptors. At the level of the end organ, however, the receptors differ. Muscles (motor end plate) use nicotinic receptors, the parasympathetic nerve system and the sweat glands use muscarinic receptors, whereas the transmitter for motor end plate, parasympathetic nervous system, and eccrine sweat glands is always Ach (Figure 18.9).

In case of a postsynaptic block, this difference is of importance. While muscle activity has to be blocked with a nicotinic receptor blocker, i.e., curare, the parasympathetic nerve system and the eccrine sweat glands need a muscarinic receptor blocker, i.e., atropine.

In 1949, Burden showed that BTX-A acts as a presynaptic blocker and not as believed in those days as a postsynaptic blocker. Therefore, BTX-A can be used therapeutically for all conditions that are ACh dependent (muscle activity, parasympathetic nerve system impairment, and hyperhidrosis), whereas postsynaptic blockers are selective.

Antiperspirants

Whereas deodorants act with fragrance and antibiotics, antiperspirants reduce the sweat flow and therefore the body odor. In most of the deodorants, triclocarban or triclosan is added as an antimicrobial essence. Also, antiperspirants have a certain antibacterial activity due to their acidity. For a very long period, the mechanism of action of the antiperspirants was not clear at all and many theories were postulated. Papa and Kligman summarized the efforts of more than 20 years of research with the words: "Fact is that next to nothing is known concerning the way in which aluminum salts inhibit eccrine sweating!" [10]. The theory of Sulzberger that a periductal infiltrate of lymphocytes is the reason leading to a hypohidrosis was abandoned as well as the postulate of an increase of permeability of the acrosyringium due to aluminum salts leading to complete dermal reabsorption of the sweat. Quatrale et al. revealed in fluorescence microscopy studies a plug of electron-dense amorphous material in the stratum corneum [11]. Hölzle confirmed this by finding PAS-positive material in the upper part of the stratum corneum in the dilated lumen of the secretory glands with atrophy of the secretory cells and he concluded that the sweat glands show a tendency to atrophy after the long-term use of antiperspirants [12].

The most widely used ingredients for topical antiperspirants are aluminum salts. Aluminum chloride hexahydrate, introduced by Stillians in 1916, is one of the most effective antiperspirants. Unfortunately, it has a high capacity for causing either irritant or even contact dermatitis. Preparations containing zirconium salts have been abandoned mainly because of their role in producing rare cases of skin granulomas, probably due to a delayed-type allergic reaction. Aluminum (hydro-)chloride is therefore preferred because this is less toxic, causes less skin irritation and allergic dermatitis, and is less corrosive to different fabrics. However, it is less effective than aluminum chloride hexahydrate, and so aluminum chloride is used preferably in a concentration of 30%. Aluminum salts in concentrations less than 20% usually are remarkably less effective and are therefore only used in cosmetic products. Contrary to the manufacturer's recommendation, the solution or cream should be used every night before sleeping and not every second or third night. In addition, it is very important to use the cream or solution in sufficient quantities only before bedtime because for crystallization of the stratum corneum plug to occur, complete anhidrosis of the affected areas is absolutely necessary.

In recent years, aluminum has been discussed as causing breast cancer. This is mainly ascribed to a publication dating to 2005 where they found a higher concentration of aluminum concentrations in the tissue of breast cancer patients [13]. Since then, several further such studies were performed, but no study was able to confirm the correlation between aluminum uptake and increasing breast cancer incidence [14]. In the late 1980s, aluminum was suspected to cause Alzheimer disease as researchers found a higher concentration of aluminum in the tap water of the county of Kent in the south of England. The correlation was made as in Kent there was statistically increased Alzheimer disease in this period of time. However, the correlation between aluminum uptake and Alzheimer disease could never be confirmed scientifically. In summary, we can state that all the different commercially available aluminum-containing products are safe, and there is no scientific evidence for causing either breast cancer or Alzheimer disease.

Anticholinergic Drugs (Parasympatholytics)

Anticholinergic medications work through the inhibition of parasympathetic postsynaptic membrane receptors on sweat glands. The mainly used medications in Europe nowadays are bornaprine hydrochloride (Sormodren®) and methantheline bromide (Vagantin®). Because of their adverse effects profile, the use of anticholinergics is limited mostly to selected patients who manifest multifocal or generalized hyperhidrosis. Whereas bornaprine hydrochloride acts centrally, methantheline bromide has most of its action peripherally and therefore has fewer side effects. Systemic medication is best used in

cases of generalized hyperhidrosis because different sweating sites can be treated at the same time. The major indication for these antimuscarinic (not nicotinic; see in the preceding text) drugs is generally Parkinsonism. However, the list of side effects of these drugs is extensive and relatively severe. Most prominent side effects are mydriasis with sometimes blurred vision, dry mouth and eyes, dizziness and constipation, and urinary retention after long-term intake. Because of the danger of glaucoma, parasympatholytics should not be prescribed without a prior ophthalmologic consultation. Postsynaptic ganglia blockers have a relatively short half-life. This requires the consumption of medication by mouth three to four times a day, which easily and quickly becomes a compliance issue. In addition, owing to dose-dependent side effects, the dosage of the drug has to be titrated by increasing its strength slowly, until the desired degree of hypohidrosis is reached. The dosage can therefore differ between patients, and patients usually are encouraged to use their medication individually. Experience showed that parasympatholytics can be prescribed in cases where BTX or iontophoresis is not leading to complete satisfaction. Sometimes, anticholinergic drugs may be helpful as an additional treatment to the nonsurgical treatment such as BTX and/or iontophoresis. Experience showed that many times these medications are commonly discontinued by patients after a short course due to the need for frequent intake and due to the side effects. Therefore, it is recommended to prescribe these medications in reserve, meaning intake only in strongly selected situations.

Tap Water Iontophoresis

The principles of iontophoresis were first described by Ichihashi [15], but therapeutic administration of electricity has been known for over two centuries. Already in 1740, Pivati used iontophoresis in the treatment of arthritis. The mechanism of iontophoresis is based on the principles of electricity: elements with the same charge repel and contrarily charged ones attract each other. Therefore, the penetration of charged molecules to cross the epidermis is facilitated by the use of external current. For many years, iontophoresis was used only to facilitate transport of molecules (manly drugs), which otherwise would hardly penetrate into the skin. Levit was the first to introduce TWI into practical dermatotherapy [16]. The mechanism of production of anhidrosis has been studied by several investigators and remains unclear. The postulate that an obstruction high in the sweat duct leads to anhidrosis was rejected because there were no structural changes in the eccrine sweat glands by light and transmission electron microscopy before and after treatment with TWI and because the low current densities are well below the threshold of damage to the acrosyringium. Sato could demonstrate that anodal current has more of an inhibitory effect than cathodal current and that water is superior to saline. On the contrary, increased concentrations of electrolytes diminished the therapeutic effects. He also confirmed that the inhibitory effect is a function of the amperage used. He concluded that the strong acidity generated by hydrolysis of water in the anodal bath and the further accumulation of H^+ in the sweat duct by the anodal current may be responsible for the inhibition of sweating due to an unknown lesion in the duct of sweat pore [17]. The widely used direct current (DC) iontophoresis is more and more replaced by alternating current with direct current offset (AC/DC) iontophoresis. Using DC-TWI, an amperage of 8–25 mA at a voltage of 20–40 V is used, whereas with AC/DC-TWI, the same efficacy is achieved with a lower current (8–12 mA) and a fixed voltage of 16 V. In this mode, side effects such as burning and stinging sensations during performance, erythema along the water surface, and especially electric stings by abrupt change in voltage (getting out of the bath) are minimized.

To achieve ideal and optimized result, TWI treatment should be performed daily in an initial phase for about 10–14 days until anhidrosis is achieved. At every treatment session, one side of the extremity is bathed for 15 minutes in the anodal pan and the other one in the cathodal bath. Thereafter, sides are switched and the procedure is repeated for another 15 minutes. In summary, one entire treatment session takes 30 minutes. One of the advantages of TWI is that in case of palmoplantar hyperhidrosis, both hands and feet can be treated in the same session. In this specific case, the hands are bathed in one pan (anodal) and the feet in the other pan (cathodal). After 15 minutes, polarity has to be switched and the therapy is repeated for another 15 minutes as described earlier. For convenience, some authors recommend changing polarity only every second treatment. However, this can lead to unsatisfactory results, which is why we recommend changing the polarity of the current for each treatment after 15 minutes. Experience revealed that the most time-saving therapy is the following:

- Initial therapy session every day for 30 minutes. This therapy cycle takes 10–14 days. Each side of the extremity should be bathed at least 15 minutes in the anodal bath. Therefore, it is important to change polarity after half time of the procedure. The dosage has to be at least 25 V/mA (Figure 18.10).
- As soon as anhidrosis (or acceptable hypohidrosis) is reached, the therapy is interrupted until sweating of the palms recurs. This is noticed in most cases when the tips of the finger begin to sweat. The therapy-free intervals varies from 1 to 8 weeks, depending on the severity of the focal hyperhidrosis.
- After recurrence, iontophoresis has to be repeated until normhidrosis is reached (maintenance therapy). In general,

Figure 18.10 Tap water iontophoresis is most effective for palmoplantar hyperhidrosis when applied correctly.

four treatment sessions are enough for maintenance therapy, depending on the severity of the initial hyperhidrosis. Patients either perform the sessions every day as described earlier or twice a day at weekends (e.g., on weekends, morning and evening). Maintenance therapy has to be repeated every 4–6 weeks.

Although TWI is a physical therapy, there are side effects that should not be disregarded. It is important to explain each side effect to the patient beforehand and even more important to instruct patients how to avoid these side effects:

- Burning stinging pain during treatment depending on the voltage
- Painful therapy in erosive spots with the risk of burn marks
- Burn marks when in contact with metal (rings, bracelets, etc.)
- Increasing irritation of the dorsum of the hands/feet and wrist/ankle
- Dry and itchy hands with increasing therapy

Therefore, it is most important to instruct each patient to remove all metal items before therapy and to cover up each erosive spot with Vaseline before TWI treatment. Hands/feet should be creamed on a regular base during the whole treatment time to prevent irritation or cumulative irritant hand/feet eczema. Before and after each treatment, the wrist/ankle should be moisturized very carefully. Sometimes, topical corticosteroids are necessary during the treatment period. As a contraindication, cardiac pacemaker has to be noted. However, metal implants such as endoprosthesis are not a contraindication, the same for pregnancy or lactation.

Even TWI is most effective in over 90% of palmoplantar hyperhidrosis; there are nonresponders, mainly type IV palmoplantar hyperhidrosis patients (Table 18.2). Moreover, due to the time-consuming treatment plan, compliance to conduct the maintenance therapy may be hampered even if the therapy is successful. The advice to plan fixed treatment sessions can help to improve self-discipline (e.g., every Wednesday evening watching the news on television). Every nonresponder should be interrogated carefully before advising him to interrupt therapy because it is most important not to lose an excellent treatment modality only because of misunderstanding, wrong instructions, or compliance problems. Those questions should be asked before suspending iontophoresis therapy:

- Noncompliance?
  - If yes, why? Time lack? Pain? Laziness?
- Insufficient dosage?
  - If yes, why? Pain? Irritation?
- Application faults?
  - Water temperature?
  - Enough water?
  - Enough voltage?
  - Change of polarity in half-time therapy?
  - Enough time of therapy on each session?
  - Sufficient period of therapy in total?

The treatment of iontophoresis should only be abandoned if the therapy is insufficient after all these problems are solved. For nonresponders and patients who break off the treatment, alternative treatments such as BTX injections (see the preceding text), systemic anticholinergic drugs, or surgery should be provided.

Surgical Treatments

Axillary Sweat Gland Excision

Both eccrine and apocrine sweat glands are predominately located in the superficial subcutis and the dermal–subcutaneous interface. Excision of the axillary skin and subcutaneous tissue en bloc represents the only comprehensive solution for severe cases of axillary hyperhidrosis that do not respond to BTX (see in the succeeding text). With the era of BTX, this procedure was forgotten for a very long time. The disfiguring scars, which are difficult to avoid in the axillary area, were and still are the main complaint about this technique. Efficacy, however, depends on the technique that is applied. The radical elliptic resection gives the best long-term results [18]. In selected cases, this treatment has still his place, mainly in males wishing a safe and predictable excellent result, not bothering about any scars under the armpit.

Sweat Gland Suction and Curretage

Sweat gland suction and curettage have the advantage of not leaving unsightly scaring (Figure 18.11). This was the main reason why this technique was developed, after the open sweat gland excision presented excellent results with the disadvantage of leaving disfiguring scars in most of the cases. However, experience showed that this technique is less efficient than excision, unfortunately. The results in the first months after treatment are good to excellent depending on the technique and/or radicalness of the treatment. However, initial response rate of 80% and more decreases to 25% and less after 9–12 months. A study in 2001 revealed that only 10% of patients were satisfied after combined suction and curettage treatment, 70% were more or less satisfied, and 20% of patients were disappointed by this treatment [19]. These chastening long-term results have to do with the technique itself. It is important to appreciate the anatomy, since abrasive surgery such as curettage will not completely remove the dermal sweat glands. Even if most of the eccrine glands are situated directly under the epidermis, some

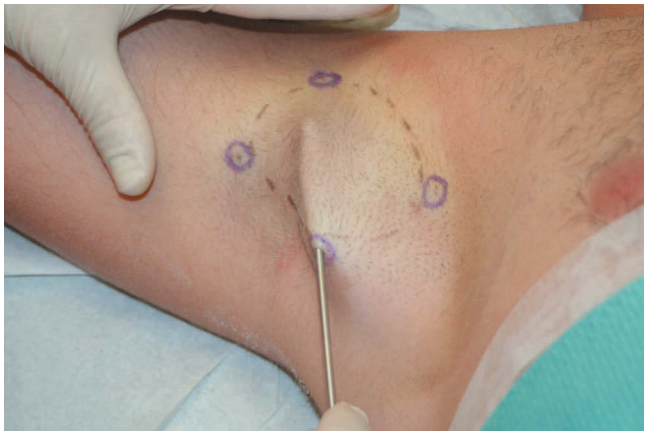


Figure 18.11 Axillary suction and curettage may be an alternative treatment option for patients who wish a definitive treatment. However, the success rate is limited and strongly depended on the technique.

eccrine glands are located entirely in the deep dermis, particularly in the center of the axilla. Remembering that the density of sweat glands in the axilla is 300/cm^2, it seems impossible to remove all the hidrotically active sweat glands by suction only. In summary, this technique is efficient in the first months because of physical damage to the fine superficial nerve plexi, which recover after months due to chemotaxis. Therefore, after several months, the nerve plexi recover and the hyperhidrosis recurs. However, recently published studies show truly better results as we learned to be more aggressive and to create more tissue damage during intervention leading to extensive subcutaneous scars, which prevent nerve recovery through chemotaxis. In summary, this technique can be recommended when all the noninvasive treatments here failed and the patient wishes for a scar-free procedure with a good but perhaps not maximal improvement of the hyperhidrosis. In any case, the patient has to be informed beforehand of a possibly moderate result. BTX injection (see in the succeeding text) can still be performed after this surgery.

Thoracic Endoscopic Sympathectomy [20]

In general, two different methods are applied for destroying the sympathetic ganglia. Either the sympathetic chain is excised or the area ablated with electrocautery or laser. Less frequently clipping of the chain is used. Patients are operated in general anesthesia intubated with a double-lumen endotracheal tube for selective one-lung ventilation during surgery in a semisitting position with insufflation of carbon dioxide to depress the lungs (Figure 18.12). The double-lumen endotracheal intubation is recommended to permit a selective total collapse of the lungs. The patient is positioned supine, and a 7 mm trocar for the camera, a 5 mm trocar for the electrocoagulation hook, and a 2 mm trocar for a grasper are inserted in the submammary fold in the fourth intercostal space. The T2 and T3 ganglion and, for axillary hyperhidrosis, additionally T4 ganglion are resected, and if present, the Kuntz nerve is coagulated. The procedure is done bilaterally. At the end, a pleural catheter is introduced for several hours through the 5 mm trocar to evacuate pneumothorax. The patient is discharged home the following day. The operation could be performed as a same-day procedure as well. The majority of surgeons prefer to resect the T2–T3 ganglia in palmar hyperhidrosis and additionally T4 in axillary hyperhidrosis. Leaving the stellate ganglion untouched, the risk of postoperative Horner's syndrome is negligible. The Kuntz nerve is present in approximately 10% of patients. Overlooking this nerve may lead to incomplete denervation of the hand and axilla, resulting in surgical failure and early recurrence.

The risk of side effects or direct complications after thoracic endoscopic sympathectomy (TES) is minimal. Since there is possibility of endoscopic surgery instead of open thoracic surgery, the direct complications such as Horner syndrome and pneumo- or hematothorax are minimal. The immediate effect of TES after successful surgery is phenomenal. Immediately after surgery, the hands turn from wet and cold to warm and dry. However, the indications for TES should be evaluated very carefully, owing to the technical difficulties of the procedure, its invasive nature, and the high complication rate of compensatory hyperhidrosis (84%) [21]. Further problem is that this complication is not predictable. Up to one-third of the patients suffer from moderate to severe sweating over their entire body, especially over the trunk and the proximal extremities. This compensatory sweating can be to such an extent that patients have to refrain from working. As the sweating is mostly generalized, the therapeutic options are limited (see in the preceding text) so that not rarely patients need to be put on parasympatholytics on a regular base (Figure 18.13).

The risk of compensatory hyperhidrosis increases with the location and extent of the area treated. The risk for compensatory hyperhidrosis is higher for TES for facial or axillary hyperhidrosis than for palmar hyperhidrosis as the extent of anhidrosis of the upper trunk is higher than for the hands only. Even though plantar hyperhidrosis cannot be treated by TES, many patients operated for palmar hyperhidrosis profit from an improvement of the feet sweating as well. In summary, because of the risk of severe postoperative complications, TES must be strictly reserved only for severe hyperhidrosis of the palms that does not respond to any other treatment, mainly TWI and BTX treatment (see in the succeeding text).

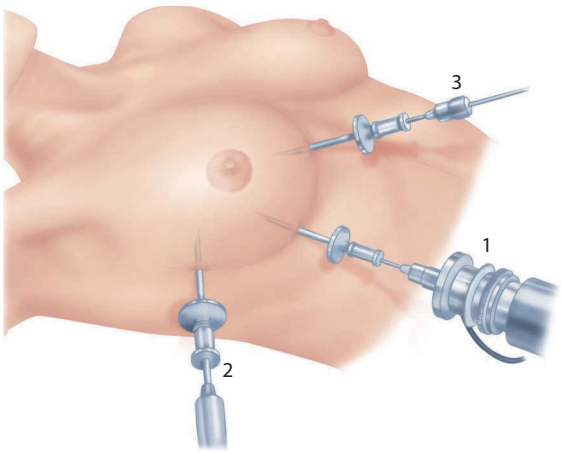


Figure 18.12 Surgical approach for thoracic endoscopic sympathectomy.

Figure 18.13 Minor starch test of a patient with compensatory hyperhidrosis after thoracic endoscopic sympathectomy. The patient is suffering from an extended hyperhidrosis of the chest and the back. Note the sharp demarcation of the hyperhidrosis.

BTX-A IN PRIMARY HYPERHIDROSIS

History of BTX-A

The first recorded case of food poisoning caused by the neurotoxin-producing bacterium *Clostridium botulinum* (botulism) is believed to have been in 1735. Dr. Justinus Christian Kerner (1786–1862) published a very precise description of the symptoms of patients suffering from botulism after eating uncooked, smoked sausages or ham in 1817 [22,23]. The prominent clinical features of botulism include widespread parasympathetic symptoms such as blurred vision, diplopia and dilated pupils, dry mouth with dysphagia, asthenia, constipation, nausea, vomiting, and abdominal cramps, followed by increasing muscle weakness descending from the head to feet and culminating in respiratory failure (Box 18.1). Because very little was known about infections at that time, Kerner believed a fatty acid to be responsible for the illness. Pierre Emile van Ermengem (1851–1932), professor of bacteriology in Ghent, Belgium, isolated the responsible bacterium and refuted the fatty acid theory of Kerner. Before the First World War, Tchitchikine discovered the neurotoxin of *C. botulinum*, and it was Dr. Hermann Sommer who first succeeded in purifying the exotoxin in 1920. During the Second World War, much research was done in the United States at Fort Detrick, Maryland, principally by Schantz [24] who was searching for an antidote to counter BTX, which was thought to be a potential biological weapon ready to be used by several other countries. In 1949, Burgen showed that the block of ACh release by BTX occurred in the presynaptic nerve endings and not, as previously believed, by postsynaptic blockage of receptors, like atropine. In the 1960s, an ophthalmologist Alan Scott [25,26] was searching for a nonsurgical alternative for the treatment of strabismus. His idea to weaken the extraocular muscles with BTX brought him in contact with Schantz. After several trials on monkeys, BTX, serotype A (BTX-A) was approved in 1989 by the Federal Drug Administration for the treatment of strabismus, blepharospasm, and hemifacial spasm. Other fields of medicine quickly became interested, and BTX-A was used for a wide variety of indications, in particular for the treatment of hyperkinetic muscles. Bushara [27] was the first to suggest a possible indication for BTX-A in the treatment of hyperhidrosis. Since 2002, BTX-A has been approved for the treatment of axillary hyperhidrosis in most countries.

BOX 18.1

"On the 12th of February 1815, a 44-year-old farmer, who was no stranger to alcohol, bought a liver sausage (Leberwurst) and ate it that evening with disgust because it was mouldy, acidic, and stank. On the following day, he felt dizzy and suffered from double vision. On the second day, he had difficulties in breathing, could no longer swallow, and was extremely hoarse. He called for the surgeon to let his blood. The patient said he "knew he would die and that it was all the fault of that miserable sausage." On the fifth day, the patient had great difficulties in speaking, despite the fact that he was fully conscious. When the doctor opened his closed eyelids, he found the pupils dilated and the eyes motionless and staring. The patient's face was reddish, his body hot, and the skin dry. His flow of urine had dried up, and the stool did not appear even after an enema. The patient could move his arms, but he said he felt like they were paralyzed. He stumbled when he tried to walk a few steps. In the afternoon of the seventh day, the patient turned pale. He gave a sign that those around him should pray, made some brisk, almost convulsive motions, became peaceful, and—stopped breathing! Six days and nineteen hours after eating that miserable sausage" [25].

Commercially Available BTX-A

BTX type-A-purified neurotoxin complex is presently available as three different toxins:

1. Onabotulinum toxin: Botox®/Vistabel® (Allergan, Irvine, CA, USA)
2. Abobotulinum toxin: Dysport®/Azzalure® (Ipsen Ltd, Wrexham, UK and Galderma, Lausanne, Switzerland)
3. Incobotulinum toxin: Xeomin®/Bocouture® (Merz Aesthetic, Frankfurt, Germany)

BTX type-B neurotoxin complex, distributed as Myobloc® in the United States or as Neurobloc® in Europe (Elan Pharmaceuticals, San Francisco, USA), plays only a marginal role in the use of these toxins for dermatological indications. Onabotulinum and incobotulinum are comparable in their efficacy, their duration of efficacy, and their onset of action. All toxins are distributed in the form of a dry, crystalline powder and must be reconstituted with 0.9% physiologic saline. The biological activity for all three products is defined in mouse units (MUs) or just units (Us): one MU is defined as the amount of neurotoxin that is lethal in 50% of 18–22 g Swiss Webster female mice (i.e., lethal dose $[LD]_{50}$) after an intraperitoneal injection (i.e., mouse LD50 equals 1 MU or U). It is very important to note that the equivalent U for abobotulinum is not the same as for onabotulinum and incobotulinum. This is due to different bacterial strains and manufacturing processes of each individual toxin. The dose conversion factor between onabotulinum/incobotulinum to abobotulinum is 1:2.5 (Table 18.3). Onabotulinum is the only toxin for the moment which offers a cell-based potency assay (CBPA) alternative to the known LD_{50}. Incobotulinum is absolutely free from complex proteins, which could be an advantage in secondary nonresponders due to antibody building. However, this effect is hardly seen in dermatological indications due to small injecting volumes. However, it could be very interesting in neurological indication with higher amounts of toxin need. It must be stated that on the World Wide Web, many other brands of BTX-A exist. Some of them are licensed copies of the original Botox, which have the higher amount of complex proteins; some of them are of doubtful or unknown origin. It is of importance to point out that the only toxins that should be used are those with enough clinical experience and safety and efficacy data. Further, the drugs should have approval for the indication used.

Minor Starch Test

It is essential to assess axillary hyperhidrosis objectively before treatment. A patient's medical history may not necessarily reflect the severity of the hyperhidrosis. It may be understated or overdrawn by the patient. It is the task of the treating physician to separate patients with moderate hyperhidrosis, manageable with aluminum salt solutions, from patients with severe hyperhidrosis, to be treated with iontophoresis, BTX, or even surgery. Each patient should undergo the Minor starch

Table 18.3 Different Dilution of the Different Botulinum Toxin Brands for Hyperhidrosis Treatment

	0.02 mL	0.04 mL	0.1 mL	0.2 mL	0.3 mL	0.4 mL
Onabotulinum 100 U **5.0 mL NaCl**	0.4 U	0.8 U	**2.0 U**	4.0 U	6.0 U	8.0 U
Incobotulinum 100 U **5.0 mL NaCl**	0.4 U	0.8 U	**2.0 U**	4.0 U	6.0 U	8.0 U
Abobotulinum 500 U **8.0 mL NaCl**	1.3 U	2.5 U	**6.3 U**	12.5 U	18.8 U	25.0 U

Note: Bold values show the correct dilution of the different botulinum toxin brands and the correct units per injection point when treating focal hyperhidrosis.

test before treatment with botulinum. The Minor starch test has many advantages:

- Severity of hyperhidrosis
- Area to be treated
- Prognosis indicator for duration of efficacy
- Identification of reason for unsatisfactory results
- Reveals patients with overwhelming expectations
- Indicator for retreatment

Minor starch test is very easy to perform and it is delegatable. This technique allows a semiquantitative measurement of focal hyperhidrosis, demonstrating the full extent of sweating in the affected area and, through the intensity of the purple coloration, the severity of sweating. Therefore, by performing a Minor starch test before each treatment, the treating physician can determine how many injection sites and how much BTX are needed prior to commencing therapy. It is advisable always to measure the affected area and document the colorimetric response with photographs and to retain them as part of the patient's permanent record. This will allow comparison of efficacy before and after treatment during follow-up visits and will allay any misgivings or feelings of dissatisfaction that the patient may fallaciously come to have. Further, it gives an excellent impression of professionalism to the treated patient. (This doctor cares. He is the first one who objectified my hyperhidrosis.) Performing the Minor starch test is also important for the personal learning curve. In case of an unsatisfactory result, this test helps in the management of the patient.

To perform Minor starch test correctly, first, the whole hyperhidrotic area has been covered with iodine solution (i.e., Lugol or Betadine solution; Video 18.1). Then, the whole area is sprinkled with starch (e.g., corn flour starch, Maizena®; Video 18.2). Only as little powder as possible is used to achieve a good colorimetric response (Figure 18.14a through c). If too much powder is used, the powder will absorb the moisture of the sweat and the intensity of the patient's sweating may not be assessed correctly. If performed correctly, Minor starch test gives better results. Even if the anamnesis of patients suffering from axillary hyperhidrosis are often uniform, the Minor Starch test reveals the proper intensity of the hyperhidrosis.

Therapy, Dilution, and Injection Technique of the Different Forms of Focal Hyperhidrosis

Axillary Hyperhidrosis

Axillary sweating is not a life-threatening disease, but nonetheless can have a substantial impact on the quality of the sufferer's life both professionally and socially. Most patients with axillary hyperhidrosis have consulted many physicians in the past, most of the time without finding any substantial, long-lasting solutions to their problem. In a cross-sectional longitudinal study, 251 patients were asked about the impact of their focal hyperhidrosis on their lives; 68.5% had to see more than two physicians (21.7% more than three) before a correct diagnosis was made; 78.9% suffered in their social and professional life due to their hyperhidrosis; 75% were limited in their daily activity; and 50% had to abstain from leisure activities [6]. Naumann et al. found similar data with 80% of patients with at least a moderate limitation in daily activities and 72% felt less confident or depressed (49%) [28]. In fact, the negative impact of hyperhidrosis on a patient's quality of life is comparable to conditions such as severe atopic dermatitis, cystic acne, or mild to moderate psoriasis. Focal hyperhidrosis should therefore be viewed as a substantive illness and not simply regarded as a lifestyle disorder [5].

Before each BTX treatment for axillary hyperhidrosis, the affected area has to be made visible using Minor starch test (see in the preceding text). After outlining the affected area with a marker, the axilla should be cleansed of all iodine and starch, and a final wipe down with denatured 70% isopropyl alcohol should be performed before initiating the BTX injections. In the first years of treatment, we marked the injection site and the injection points with gentian violet or a nonremovable surgical pen. The injection site was marked with a point. However, we had to learn that this specific scheme had disadvantages. The nonremovable pen was apparent for several days and particularly female patients complained that they were unable to show the axilla for several days after treatment. Therefore, we began to use mascara pens as a marker, which can easily be removed after treatment. Further, we realized that in some cases the effect of the therapy was altered due to the injection marks using points only at the injection site. As we know that the diffusion of the toxin is about 1 cm, the marks were made in a more or less regular distance of 1 cm. However, experience showed that the marks were sometimes in a bigger distance than the diffusion rate of BTX and therefore left a nontreated area, which resulted in an insufficient result. Therefore, we changed our marks from points to rings, a lot of attention is paid that the circles touch each other in order to achieves a complete distribution of the toxin without any gaps (Figure 18.15a and b; Video 18.3).

As the treatment itself is not very uncomfortable, we abstain from any anesthesia for treatment of the axilla. However, some authors recommend pretreatment with EMLA® cream with occlusion for half an hour before treatment. In Europe, the toxin is diluted in general with nonpreserved saline. Some authors recommend using preserved saline to reduce pain during injections [29]. However, experience showed that there is not much difference in patients' perception.

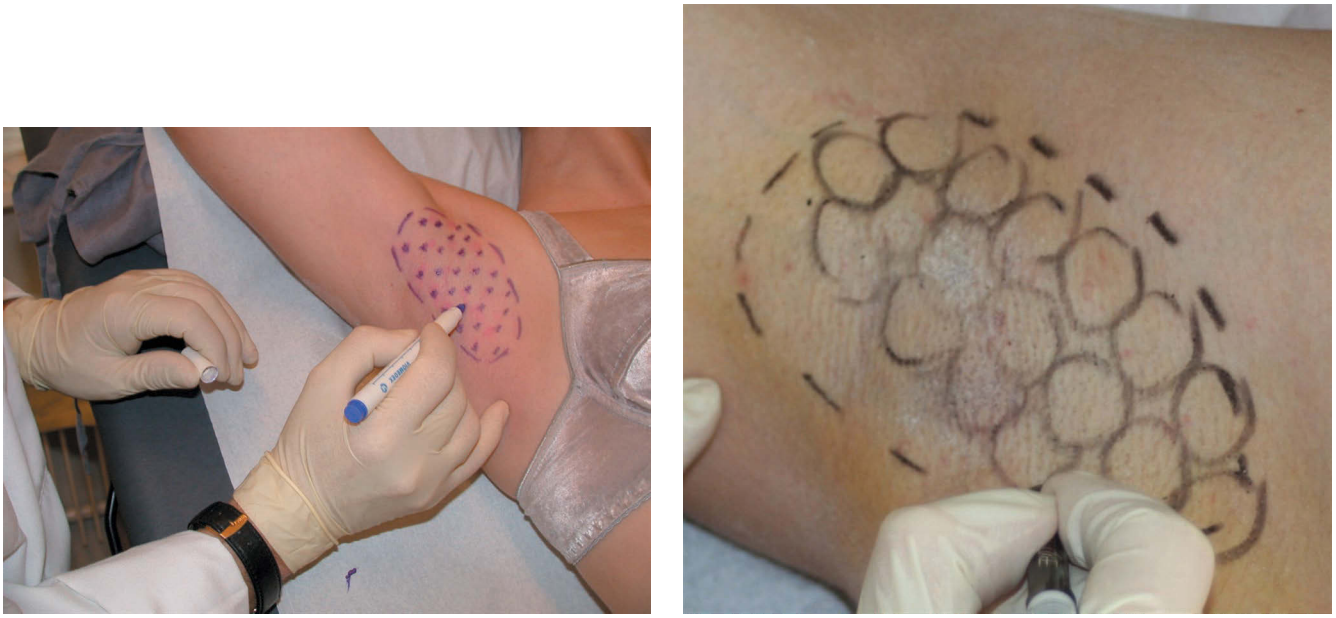
(a) (b) (c)

Figure 18.14 (a–c) How to perform Minor starch test. The sweating area is treated first with Lugol solution and then powdered with starch powder, leaving to a distinct purple discoloration (depending on the severity of the hyperhidrosis). Minor starch test is a perfect semiquantitative test showing exactly the affected area and giving information on the severity of focal hyperhidrosis. (Reproduced from Kreyden OP, Botulinum toxin in the management of focal hyperhidrosis. Anatomy of sweat glands, in Benedetto, A.V., ed., *Botulinum Toxin in Clinical Dermatology*, Taylor & Francis Group, London, U.K., 2006, pp. 261–293. With permission.)

Generally, a total dose of 50 U of onabotulinum or incobotulinum and 250 U of abobotulinum per axilla is required to adequately treat a moderately severe hyperhidrotic axilla. Therefore, no more than a total dose of 1 vial (100 U) of onabotulinum or incobotulinum and 2/3 of abobotulinum 500 U (1 vial) is needed per patient. However, in severe hyperhidrosis, grade IV patients sometimes need more than 100 U onabotulinum and incobotulinum or 1 vial of 500 U abobotulinum of the toxin. It is wise to define the total dosage needed to treat a patient sufficiently in the needed dose per injection point, e.g., 2 U per injection point (onabotulinum and incobotulinum) or 5 U per injection point (abotulinum, using a ratio 1:2.5). The total dose of toxin needed depends on the number of injection sites. It goes without saying that a grade I hyperhidrosis patient needs fewer injection sites than a patient with grade IV hyperhidrosis and therefore needs less toxin in a total dose. Consequently, the total dose of injected toxin should no longer be defined as a total recommended dose for a given anatomical site (i.e., 50 U of Botox per axilla) but by the amount of units used per injection site (i.e., 2 U Botox for each injection point).

In other words, the total dosage of BTX needed for axillary treatment depends on the size of the colorimetric response exhibited by the Minor starch test, which in most patients is a surface area of approximately 7 × 13 cm (90 cm^2). Since the diffusion capacity of BTX is about 1.0–1.5 cm in radius (~3 cm in diameter), 20–30 points injected at a distance of approximately 1.5 cm apart are sufficient to cover an area of 90 cm^2 (Video 18.4). Higher doses (≥800 U) of BTX have been used for therapeutic purposes [30], but the increased risk for antigenicity and immune resistance with the production of IgG-neutralizing antibodies is higher. Besides, the longer duration of effect of such a recommended high dose therapy has to be offset against the higher costs of treatment as the commercially available toxin is very costly. However, as the risk of immune response is minimized by using complex-free Incobotulinum, for future use, it is imaginable that we will recommend higher dose treatments for better results when treating for focal hyperhidrosis.

Manufacturer's guidelines recommend that a vial of BTX should be reconstituted with preservative-free isotonic saline. However, it could be shown that reconstitution with preserved saline has no impact on efficacy [29]. Consequently, once the vial of BTX is reconstituted without a preservative, it should be fully consumed within 4 hours, owing to the possibility that the solution may be unable to remain sterile for an extended period. However, no studies to date have been performed to document the presence or lack of sterility of a reconstituted vial of BTX after more than 4 hours. Every treating physician



(a) (b)

Figure 18.15 (a and b) Experience showed that results are more effective using rings instead of points when marking the injection points. ([a] Reproduced from Kreyden OP, Botulinum toxin in the management of focal hyperhidrosis. Anatomy of Sweat Glands, in Benedetto, A.V., ed., *Botulinum Toxin in Clinical Dermatology*, Taylor & Francis Group, London, U.K., 2006, pp. 261–293. With permission.)

therefore has become accustomed to use one whole vial of BTX per patient for obvious economic reasons. Over the years, however, we have learned that there are no adverse events or significant loss of potency resulting from the storage of reconstituted BTX for a few days and even a few weeks. Consequently, physicians should abandon this practice and use the exact amount of BTX each patient needs, predicated upon the size and severity of the affected area as defined by the Minor starch test.

The optimal dilution of onabotulinum and incobotulinum for the treatment of hyperhidrosis is still under discussion, but a reconstitution with 5 mL has been most effective in the indication of hyperhidrosis. Please note that for aesthetic indications, a dilution of 2.5 mL or even 1.0 mL is recommended. As the efficacy ratio of onabotulinum/incobotulinum and abobotulinum is 1:2.5, the dilution of abobotulinum is slightly higher to reach this specific ratio (Table 18.3). Although the reconstitution of onabotulinum/incobotulinum of 5 and 8 mL abobotulinum is widely accepted, Bigalke et al. [31] showed that the biological availability of BTX could be enhanced by lowering the concentration of BTX and increasing the dilution volume. However, a 1-year side-to-side study of 300 patients treated with abobotulinum in a dilution of 8 mL for one armpit and diluted with 10 mL abobotulinum for the other armpit could not show any differences in duration and total efficacy [32].

Palmoplantar Hyperhidrosis

The dilution of BTX (onabotulinum/incobotulinum and abobotulinum) for the treatment of hyperhidrosis of the palms or soles can be the same as that for the treatment of hyperhidrosis of the axillae (see earlier). However, to avoid attendant muscle weakness after BTX injections, especially in the hands, the reconstitution volume for both onabotulinum/incobotulinum and abobotulinum should not extend 5 or 8 mL, respectively (see in the preceding text). Again, as the radial diffusion distance of BTX is about 1.0–1.5 cm, the interval between two injection points should not exceed this diameter in centimeters. The technique with the circles is best. Minor starch test is not indicated in initial treatment as the area of interest is clear by anatomy. However, in cases of insufficient results, Minor starch test can provide particular information where to inject for correction treatment. Therefore, depending on the size of the hands or feet, approximately 20–25 injection points should be planned for the treatment of one palm, additionally 14 injections for the fingers (in each interarticular region and the finger tips), and four injections for the interdigital section. This leads summa summarum to approximately 40 injections per hand (80 injections per patient), making 80 U onabotulinum/incobotulinum or 240 U abobotulinum per hand (160 U onabotulinum/incobotulinum and 480 U abobotulinum, respectively, per patient). In other words, we need about 1.5 vial Botox, Xeomin, and 1 vial Dysport to treat a patient's hand for hyperhidrosis.

For treating the feet, more toxin is needed. It is important to note that, in general, the sole itself is not the most hyperhidrotic area. Therefore, it is most important to perform a Minor starch test to detect where the active hyperhidrotic areas are. In most cases, the medial part of the feet can be left out for treatment. Instead, the lateral parts of the feet, the area of the Achilles tendon, and the dorsum of the forefoot are usually the most hyperhidrotic areas. Without Minor starch test, those areas will not be detected and expensive treatment will go beyond the need of the patients. In general, approximately 80 injection points for one foot are needed, leading to a total dose of approximately 160 U of onabotulinum/incobotulinum (320 U of abobotulinum) per foot. Around three vials of Botox

or Xeomin summa summarum are needed to treat a patient with plantar hyperhidrosis. With Dysport, approximately 1½ vials is needed.

Economically speaking, the use of abobotulinum could be more interesting for physicians who treat hyperhidrosis patients frequently.

In distinct contrast to the painless BTX injections for hyperhidrosis of the axillae, BTX injections for hyperhidrosis of the palms and soles require regional anesthesia (see in the succeeding text).

Anesthesia of the Palms after Kreyden [33]

Because of the long list of side effects associated with nerve blocks, many different modalities for regional anesthesia have been tried by the author—including cooling sprays and EMLA cream under occlusion for 1 hour or more. The cooling spray technique produces an unpleasant frozen hand, for both the patient and the treating doctor. Furthermore, there is only a moderate anesthetic effect, particularly for the burning pain experienced during the injection of the solution (it is less for the needle stick). EMLA cream under occlusion for 1 hour or more gives an excellent anesthetic effect for the stinging of the needle but only minimal relief from the burning experienced during the injection of the fluid. Moreover, the topical application of an anesthetic cream with occlusion for 1 hour produces maceration and swelling of the hand, which makes it extremely difficult to find the correct depth to inject the BTX, which must be intradermal and not subdermal. It is imperative to remain intradermal with injections of BTX for palmar hyperhidrosis, especially as muscle weakness needs to be avoided. In cases of insufficient results, this particular issue of using EMLA cream before treatment is responsible for the lack of efficacy. But not—as was suggested by some authors—because of the EMLA itself but because of the imprecise injection by the physician due to maceration of the skin. Therefore, EMLA pretreatment for palmar injections is not recommended.

A report on topical dermal analgesia induced by iontophoretic administration of 2% lidocaine [34] leads the author to perform a new form of anesthesia for the treatment of palmoplantar hyperhidrosis with BTX [35]. This new technique achieves almost complete anesthesia with only slight stinging and burning, similar to what is felt during injections of BTX for axillary hyperhidrosis.

After a 30-minute iontophoresis with 2% lidocaine solution, each injection site is sprayed with a superficial frost of liquid nitrogen to reduce pain maximally. With this combined anesthesia, patients are almost completely free of pain. The technique is very easy to perform and has no major side effect (see in the succeeding text).

The lidocaine solution used for iontophoresis is ordered from a local pharmacy in large quantities (e.g., 5 L of lidocaine hydrochloride 100 g in aqua conservans 4900 g). The iontophoresis unit used is the Hidrex Med PSP 1000 (from Hidrex, Heiligenhaus, Germany). Patients undergo iontophoresis as described elsewhere (see section "Tap Water Iontophoresis") but with lidocaine 2% solution and not with tap water. The hand should be covered by the lidocaine solution until the back of the hand is submerged as is usually done for antihyperhidrotic iontophoretic therapy. This leads to superficial anesthesia, which is enhanced by the local cryotherapy immediately before injecting. Before injecting, liquid nitrogen is sprayed over the injection site by the assistant. Different nozzles and cones are available for cryotherapy (A–D), whereas A has the biggest and D has the smallest exit port. To achieve anesthesia, it is sufficient to create a frost just before injecting. Therefore, it is highly recommended to use the smallest available nozzle when treating patients with this technique. In other words, it is important to avoid freezing (as done in therapeutic cryotherapy such as treatment for actinic keratosis) to prevent blistering after treatment. In untrained hands, blistering leaving red spots for several days (sometimes weeks). This side effect led to the development of a new nozzle presenting 10 holes instead of only 1 hole. This has the essential advantage that physicians are capable of performing the recommended frost instead of a local freezing of the skin. Using the spray technique correctly, the 10-hole nozzle produces a defocused iced spray, leading to a superficial frosting of the skin that perfectly allows complete anesthesia without any blistering. Although this combined technique requires some training and an assistant to perform (assistant cools, physician injects), this technique is highly recommended owing to increased patient satisfaction (Video 18.5).

In an experimental group of 36 patients, this combined iontophoresis/cryotherapy anesthesia technique, after Kreyden, was used to produce anesthesia prior to injecting BTX in the palmoplantar surface. The technique resulted in an overall satisfaction rate in 92.3% of all patients compared to only 37.8% in a group treated with EMLA and 17.8% in a group treated with nerve blocks [35]. The low level of satisfaction after nerve block is due not to the poor anesthetic effect, but to the severe side-effect profile of this technique.

Summarizing, the anesthesia technique after Kreyden has the advantage of specifically dosing a focus of liquid nitrogen cryotherapy in such a manner that it does not cause the entire hand to freeze, which leads to an excellent anesthesia with highly satisfied patients without any major side effects.

Hyperhidrosis of the Forehead, Anogenital, and Submammary Region

Forehead

In most cases of hyperhidrosis of the forehead, patients sweat profusely at the hairline only (Figure 18.2c). This is important to note as the patient's complaint does not help in this particular situation as most patients state that they sweat over the whole face. In fact, they do not notice that the sweating area is at the hairline and the feeling of sweating over the whole face is due to the dripping of the sweat from the hairline. Knowing this, it is also important to mention that the affected hyperhidrotic area is at the hairline with approximately 2 cm beyond the hairline. This fact should be considered when treating patients for frontal hyperhidrosis to achieve satisfying results. Owing to the involvement of the underlying frontalis, BTX should not be injected within 1.5–2.0 cm of the eyebrows to prevent the occurrence of brow ptosis. For the same reason, the dilution of the BTX should be much less than that that is used for axillary hyperhidrosis. A dilution of 2.5 mL per vial of incobotulinum/incobotulinum or 4 mL of abobotulinum is recommended for the treatment of the forehead. This dilution is the very same as is used for aesthetic indications. As with other areas, it is important to perform a Minor starch test before the injection points are marked on the surface of the forehead to define clearly the hyperhidrotic area. Interestingly, the duration of effect in the frontal area is much more prolonged compared to axillary hyperhidrosis, probably due to the irregular sweating of brow compared with the continuous sweating of the axilla.

Anogenital

In sharp contrast to injecting BTX in the forehead, the dilution of the toxin when treating inguinal hyperhidrosis should be as high as possible to achieve maximum diffusion, since the areas of hyperhidrosis in the anogential area can be quite extensive. However, the rule of injecting 2 U per injection site remains the same in this indication. The injection technique in principle is similar to the way other areas of focal hyperhidrosis are treated, but it is very important to perform the injections intradermally to prevent paralyzing the muscles of the pelvis. Therefore, this procedure should only be performed by experienced practitioners.

Submammary

This indication is not as seldom as probably expected. Many female patients suffer from this specific form of hyperhidrosis, and even in most cases, they would not tell the doctor, mainly because they learned to live with it. In extended forms of axillary hyperhidrosis, patients may suffer from a submammary hyperhidrosis, which can be as bothersome as the axillary hyperhidrosis itself (Figure 18.3). Besides, this form is most often affected with secondary problems, mainly infection fungal, bacterial, and mixed infections (intertrigo).

BTX treatment on inter- and submammary is relatively easy to perform and as effective as in other recommended areas. The injection scheme remains the same with 2 U (6 U abobotulinum) per injection point in a distance of 1.0–1.5 cm. The marks of injection should be performed in circles, which have contact to each other in order not to leave an untreated gap. Similar to the hyperhidrosis of the front, the effect after BTX treatment is fortunately prolonged due to the same reason of sporadic sweating.

Rare Forms of Hyperhidrosis

Several rare syndromes associated with hyperhidrosis are described in the literature: POEMS syndrome, pachyonychia congenita, Apert syndrome, pachydermoperiostosis, Papillon–Lefèvre syndrome, nail–patella syndrome, etc. Only syndromes and diseases that can be treated with BTX will be discussed here.

Frey Syndrome

Gustatory sweating is a common complication following parotid gland surgery, infection, or trauma. It was first described by Lucie Frey in 1923 [36] (Figure 18.16). The most likely explanation for the condition is a misdirected resprouting of postsynaptic salivomotor parasympathetic fibers that have lost their glandular target organ. Following gustatory stimulation, the clinical picture includes pathological sweating of the preauricular area and sometimes a flushing reaction involving the superficial cutaneous vasculature. About 50% of patients experience gustatory sweating after parotidectomy and 15% consider their symptoms severe [37]. BTX is an effective therapeutic option for the treatment of gustatory sweating, and it can be considered as a first-line treatment. The duration of treatment effect in patients with Frey syndrome is much longer than in patients treated for other indications, such as hemifacial spasm or blepharospasm or even hyperhidrosis in other areas. We observe these findings also in other indications of hyperhidrosis such as sweating of the brow, the submammary, or the groin. This has probably to do with the sporadic onset of the sweating.

Figure 18.16 Minor starch test of a patient suffering from Frey syndrome. Also, dyeing of the hyperhidrotic area is most important here as the localization of the hyperhidrosis can vary a lot in patients with Frey syndrome.

Ross Syndrome

Ross syndrome was first described by the neurologist Alexander T. Ross in 1958 [38]. It is characterized by the triad of unilateral tonic pupil, generalized areflexia (Holmes–Adie syndrome), and progressive segmental anhidrosis with a compensatory band of excessive perspiration. Patients suffering from Ross syndrome usually do not perceive the hypohidrosis; instead, it is the compensatory segmental hyperhidrosis that is bothersome (Figure 18.17). In addition, many patients suffer from several symptoms of vegetative dysfunction, such as palpitation, angina pectoris, orthostatic hypotonia, and irritable colon [39]. The pathogenesis of Ross syndrome is unknown. Multiple neuropathies of the autonomic nervous system or a failure in the synthesis or release of neurotransmitters have been suggested as possible causes [38]. There is no histologic evidence of nerve fiber destruction. Therefore, Ross postulated a defect in ACh cholinesterase activity, rather than degeneration of sweat glands. The progression of Ross syndrome is very slow. There is no therapy for the segmental progressive anhidrosis. The bothersome compensatory hyperhidrosis can be improved, however, with systemic antimuscarinic drugs or with injections of BTX into the affected areas, usually the face. In 1992, Itin et al. [40] presented a case study of a patient suffering from Ross syndrome with a defined area of anhidrosis in the right hand, the right axilla, and the right side of the face. In the follow-up, after 11 years, the patient presented with additional anhidrotic areas in the right hemithorax and the underside of the left arm (Figure 18.18). Unfortunately, the

Figure 18.17 Clinical picture of a patient suffering from the very rare Ross syndrome. Note the sharply demarcated segmental hyperhidrotic area. (Reproduced from Kreyden OP, Botulinum toxin in treatment of axillary, palmar and plantar hyperhidrosis, in: Redaelli, A., ed., *Botulinum Toxin A in Aesthetic Medicine with Treatment for Hyperhidrosis and Odontostomatology*, Officina Editoriale Oltroarno, Firenze, Italy, 2010, pp. 199–219. With permission.)

Figure 18.18 Localized unilateral hyperhidrosis. A patient with an isolated area of hyperhidrosis restricted to the left wrist. The patient was treated successfully with botulinum. (Reproduced from Kreyden OP et al., *Hyperhidrosis and Botulinum Toxin in Dermatology*. *Current Problems in Dermatology*, Vol. 30, Karger Verlag, Basel, Switzerland, 2002. With permission.)

patient refused treatment with BTX, even though the hyperhidrosis was so severe that electrolyte replacement was necessary (unpublished data).

Localized Unilateral Hyperhidrosis

Localized unilateral hyperhidrosis (LUH) is a rare form of idiopathic localized hyperhidrosis and is defined as a confined area of hyperhidrosis of less than 10 × 10 cm, mainly found on the forehead or the forearm, whose pathogenesis is unknown. Besides the unusual localization, the major difference from essential hyperhidrosis is that LUH has no typical triggering factor and occurs even while patients are asleep. The etiology of LUH is unknown but may be due to a misdirected reconnection of the sympathetic nerve fiber network after injury, similar to Frey syndrome. Before BTX, no treatment was available for this distinctive but enigmatic skin disorder. However, excellent results have been experienced following the injection of 30 units of BTX in a patient suffering from LUH [3] (Figure 18.18).

Treatment of Compensatory Hyperhidrosis after Endoscopic Thoracic Sympathectomy

Compensatory hyperhidrosis can be a very embarrassing, disabling disease. The incidence after ETS is relatively high. Over 90% of operated patients suffer from compensatory hyperhidrosis, mostly in lumbar region or the inner part of the thighs but sometimes on the brow and in rare cases disseminated over the whole body. Those severe problematic cases with generalized severe sweating are fortunately rare. The treatment options for patients with copious sweating of almost the entire body are very limited. One possibility is the use of anticholinergic drugs with their list of attendant adverse side effects (see earlier). BTX treatment is limited by the potential toxic side effects associated with the high doses required (estimated LD50 of a human being is 3500–5000 U) and the expense of treating such large involved areas. BTX therapy in such cases does not seem to be as effective as it is when treating focal hyperhidrosis, i.e., axillary or palmoplantar hyperhidrosis. A further limiting problem is suppressing excessive sweating without the risk of hyperthermia. Under these circumstances, the aim of each individual therapy should be to combine several therapeutic modalities to achieve the best outcome. The patient should be aware of the difficulties in treating such conditions and should be counseled to be satisfied with the reality of achieving moderate success. An algorithm that can be used in treating such cases is first applying aluminum salt solutions, combined with the ingestion of anticholinergic drugs in an ever-increasing dosage, which is the mandatory first-line treatment. A few patients need additional therapy for well-defined areas of intensely active sweating. Such cases will benefit from injections of BTX. Again, it is most important to define the affected areas of hyperhidrosis by the use of the Minor starch test. Then, BTX can be injected as described earlier.

VIDEOS

Video 18.1. Iodine coloration: http://goo.gl/uGmN5X
Video 18.2. Starch powder: http://goo.gl/hXjZqn
Video 18.3. Marking the area: http://goo.gl/W2STgL
Video 18.4. Injections: http://goo.gl/NG8a2t
Video 18.5. Cryoanaesthesia: http://goo.gl/Rliu2g

REFERENCES

1. Schestatsky P, Callejas MA, Valls-Solé J. Abnormal modulation of electrodermal activity by thermoalgesic stimuli in patients with primary palmar hyperhidrosis. *Neurol Neurosurg Psychiatry* 2011 January; 82(1):92–96.
2. Iwase S, Ikeda T, Kitazawa H, Hakusui S, Sugenoya J, Mano T. Alters response in cutaneous sympathetic outflow to mental and thermal stimuli in primary palmoplantar hyperhidrosis. *J Auton Nerv Syst* 1997; 64:65–73.
3. Kreyden OP, Schmid-Grendelmeier P, Burg G. Idiopathic localized unilateral hyperhidrosis. Case report of successful treatment with botulinum toxin A and review of the literature. *Arch Dermatol* 2001; 137:1622–1625.
4. Hölzle E. Pathophysiology of sweating. In: Kreyden, O.P. et al., eds. *Hyperhidrosis and Botulinum Toxin in Dermatology. Current Problems in Dermatology*, Vol. 30. Basel, Switzerland: Karger, 2002, pp. 10–22.
5. Junker J, Kreyden OP. Essential focal hyperhidrosis severe illness or lifestyle disease? Cross sectional longitudinal study on impairment of life quality before and after treatment of focal hyperhidrosis. *Kosmetische Medizin* 2008; 2:32–36.
6. Ro KM, Cantor RM, Lange KL et al. Palmar hyperhidrosis: Evidence of genetic transmission. *J Vasc Surg* 2002; 35:382–386.
7. Kreyden OP. Botulinum toxin in the management of focal hyperhidrosis. Anatomy of sweat glands. In: Benedetto, A.V., ed. *Botulinum Toxin in Clinical Dermatology*. London, U.K.: Taylor & Francis Group, 2006, pp. 261–293.
8. Groscurth P. Anatomy of sweatglands. In: Kreyden, O.P. et al., eds. *Hyperhidrosis and Botulinum Toxin in Dermatology. Current Problems in Dermatology*, Vol. 30. Basel, Switzerland: Karger, 2002, pp. 1–9.
9. Sato H. Biology of the eccrine sweat gland. In: Freedberg, I.M. et al., eds. *Dermatology in General Medicine*, Vol. 5. New York: McGraw-Hill, 1993, pp. 155–164.
10. Papa CM, Kligman AM. Mechanisms of eccrine anhidrosis. II. The antiperspirant effect of aluminum salts. *J Invest Dermatol* 1967; 49:139–145.
11. Quatrale RP, Coble DW, Stoner KL, Felger CB. The mechanism of antiperirant action by aluminium salts. II. Histological observations of human eccrine sweat glands inhibited by aluminium chlorohydrate. *J Soc Cosmet Chem* 1981; 32:107–136.
12. Hölzle E, Braun-Falco O. Structural changes in axillary eccrine glands following long-term treatment with aluminium chloride hexahydrate solution. *Br J Derm* 1984; 110:399–403.
13. Darbre PD. Aluminium, antiperspirants and breast cancer. *J Inorg Biochem* 2005; 1912–1919.
14. Rodrigues-Peres RM, Cadore S, Febraio S, Heinrich JK, Serra KP, Derchain SF, Vassallo J, Sarian LO. Aluminum concentrations in central and peripheral areas of malignant breast lesions do not differ from those in normal breast tissues. *BMC Cancer* 2013 March 8; 13:104.
15. Ichihashi T. Effect of drugs on the sweat glands by cataphoresis and an effective method for suppression of local sweating. Observation on the effect of diaphoretics and adiaphoretics. *J Oriental Med* 1936; 25:101–102.
16. Levit F. Simple device for treatment of hyperhidrosis by iontophoresis. *Arch Dermatol* 1968; 98(5):505–507.
17. Sato K, Timm DE, Sato F et al. Generation and transit pathway of H+ is critical for inhibition of palmar sweating by iontophoresis in water. *J Appl Physiol* 1993; 75(5):2258–2264.
18. Hafner J, Beer GM, Axillary sweat gland excision. In: Kreyden, O.P. et al., eds. *Hyperhidrosis and Botulinum Toxin in Dermatology. Current Problems in Dermatology*, Vol. 30. Basel, Switzerland: Karger, 2002, pp. 57–63.
19. Tsai RY, Lin JY. Experience of tumescent liposuction in the treatment of osmidrosis. *Dermatol Surg* 2001 May; 27(5):446–448.
20. Kestenholz PB, Weder W. Thoracic sympathectomy. In: Kreyden, O.P. et al., eds. *Hyperhidrosis and Botulinum Toxin in Dermatology. Current Problems in Dermatology*, Vol. 30. Basel, Switzerland: Karger, 2002, pp. 64–76.
21. Lin TS, Fang HY. Transthoracic endoscopic sympathectomy in the treatment of palmar hyperhidrosis—With emphasis on perioperative management (1'360 case analyses). *Surg Neurol* 1999; 52:453–457.
22. Kreyden OP, Böni R, Burg G et al. Botulinum toxin: From poison to pharmaceutical. The history of a poison that became useful to mankind. In: Kreyden, O.P. et al., eds. *Hyperhidrosis and Botulinum Toxin in Dermatology. Current Problems in Dermatology*, Vol. 30. Basel, Switzerland: Karger, 2002, pp. 94–100.
23. Schantz EJ, Johnson EA. Botulinum toxin: The story of its development for the treatment of human disease. *Perspect. Biol. Med.* 1997; 40(3):317–327.
24. Scott AB, Rosenbaum A, Collins CC. Pharmacologic weakening of extraocular muscles. *Invest Ophthamol* 1973; 12:924–927.
25. Kerner JC. Vergiftung durch verdorbene Würste. *Tübinger Blätter Naturwiss Arz* 1817; 1–45.
26. Scott AB. Botulinum toxin injection of eye muscles to correct strabism. *Trans Am Ophthalmol Soc* 1981; 79:734–770.
27. Bushara KO, Park DM, Jones JC, Schutta HS. Botulinum toxin—A possible new treatment for axillary hyperhidrosis. *Clin Exp Derm* 1996; 21:276–278.
28. Naumann MK, Hamm H, Lowe NJ, Botox Hyperhidrosis Clinical Study Group. Effect of botulinum toxin type A on quality of life measures in patients with excessive axillary sweating: A randomized controlled trial. *Br J Dermatol* 2002; 147:1218–1226.
29. Allen SB, Goldenberg NA. Pain difference associated with injection of abobotulinumtoxin A reconstituted with preserved saline and preservative-free saline: A prospective, randomized, side-by-side, double-blind study. *Dermatol Surg* 2012 June; 38(6):867–870.
30. Wollina U, Karamfilov T, Konrad H. High-dose botulinum toxin type A therapy for axillary hyperhidrosis markedly prolongs the relapse-free interval. *J Am Acad Dermatol* 2002 April; 46(4):536–540.
31. Bigalke H, Wohlfarth K, Irmer A, Dengler R. Botulinum A toxin: Dysport improvement of biological availability. *Exp Neurol* 2001; 168:162–170.
32. Kreyden OP. Higher dilution of botulinum toxin is not more efficient in patients treated with Dysport for axillary hyperhidrosis. Oral presentation ICAD Bangkok 01.2010.
33. Kreyden OP. Botulinum toxin in treatment of axillary, palmar and plantar hyperhidrosis. In: Redaelli, A., ed. *Botulinum Toxin A in Aesthetic Medicine with Treatment for Hyperhidrosis and Odontostomatology*. Firenze, Italy: Officina Editoriale Oltroarno, 2010, pp. 199–219.
34. Kim M, Kini N, Troshynski TJ, Hennes HM. A randomized clinical trial of dermal anaesthesia by iontophoresis for peripheral antravenous catheter placement in children. *Ann Emerg Med* 1999; 33:395–399.
35. Kreyden OP. Botulinum toxin A: New method for anaesthesia in the treatment for palmoplantar hyperhidrosis. *Oral Presentation on the European Academy of Dermatology and Venerology (ESCAD) on the occasion of 12th congress of EADV (European Academy of Dermatology and Venerology),* Barcelona, Spain, 2003.
36. Frey L. Le syndrome du nerf auriculo-temporal. *Rev Neurol* 1923; 2:97–104.
37. Laskawi R, Ellies M, Rödel R et al. Gustatory Sweating—Clinical implications and ethiological aspects. *J Oral Maxillofac Surg* 1999; 57:642–648.
38. Ross AT. Progressive selective sudomotor denervation. *Neurology* 1958; 8:808–817.
39. Kreyden OP. Rare forms of hyperhidrosis. In: Kreyden, O.P. et al., eds. *Hyperhidrosis and Botulinum Toxin in Dermatology. Current Problems in Dermatology*, Vol. 30. Basel, Switzerland: Karger, 2002, pp. 178–187.
40. Itin P, Hirsbrunner P, Rufli T et al. Das Ross-Syndrom. *Hautarzt* 1992; 43:359–360.

Cosmetic tattooing

Nicolas Kluger

INTRODUCTION

Decorative tattooing is a custom thousands of years old that has gained popularity and visibility for the past 20 years. However, tattooing has also earned its path with medical applications such as radiotherapy field marking, corneal tattooing, endoscopic tattooing, or simply forensic medicine. Cosmetic tattooing, also called permanent makeup (PMU) or micropigmentation, has become popular since the end of the 1970s [1]. Nowadays, not only physicians but also nurses, cosmetologists, beauticians, makeup artists, and of course tattooists perform cosmetic tattooing. Cosmetic tattooing is a broad term that mainly includes tattooing of the eyebrows, the eyelids, and the lips. However, cosmetic tattooing is also used in the setting of plastic surgery for the reconstruction of nipple and areola after breast surgery or camouflage of vitiligo, especially mucosal, or alopecia. Unfortunately, cosmetic tattooing has its possible drawbacks and complications that have to be known.

TECHNIQUES

The tattooing procedure during PMU is no different to those of traditional decorative tattooing [2]. It involves the introduction of pigments and colorant in the dermis to obtain a permanent coloration of the area. Droplets are introduced by a tattooing pen with an oscillating needle [3]. Because of the nature of the procedure itself and the introduction in the dermis, the process has to be considered as giving a "permanent" result, even though the color may fade away with time. Progressive fading is explained by the quantity of introduced inks, which is less than in traditional tattooing, the physicochemical properties of the inks that are used in PMU as they are supposed to undergo a quicker elimination rate [4], and the facial chronic sun-exposed area where most of the PMUs are applied. Sun and ultraviolets (UV) exposure are known factors that increase the speed of tattoo aging [5]. The only main difference between traditional and cosmetic tattooing is the more limited range of color used for PMU (black, dark blue, brown, pink, red, brown).

The concept of "semipermanent" (or even "temporary" [1]) tattooing is often given by beauticians and cosmetologists as a selling argument; i.e., the makeup will disappear after several years. Interestingly, they usually provide quite a wide time span for the tattoo to disappear (usually a scale ranging from 2 to 8 years is given according to beauticians!). Besides, it is clear that PMU fading and "disappearance" (if it really disappears one day!) process is low and progressive. But customers may expect, consciously or naively, that PMU will have disappeared within one night. The progressive fading of the color often prompts the patient to seek advice for a tattoo removal before its complete disappearance because at some point the color of the remaining ink is not really acceptable from an aesthetic point of view. In other words, "temporary" cosmetic tattooing does not exist, and female customers should be aware of that.

Tattooing procedures are variable according to the tattooist and local legislation as regards the use of anesthetics for instance, and of course artistic competence of the individuals [1]. The inks and pigments are considered as cosmetic and color additives. Until recently, none of these products have been either tested or approved for tattooing. It is only recently that European countries and the European council started to take action to try to regulate the obscure market of tattooing and PMU [6]. In the United States, the color additives are under the supervision of the Food and Drug Administration (FDA). Any color additives should undergo a premarket approval to ensure their safety and appropriate use. However, none of them has been approved for the injection in the dermis. Besides, tattoo ink has never been considered as a priority because of other concerns. Nowadays, the increasing popularity of tattooing and PMU has been associated with an increased number of side effects reported, prompting to get new interest on such issue [1]. Moreover, not only tattoo inks have ever been tested for their safety for tattooing purpose, but there is also currently no valid test for the evaluation of tattooing safety! Indeed, usually toxicological tests include exposure by inhalation, absorption, application on the skin or on the mucosa but not as introduction in the skin through the dermis. Tattoo pigments are composed of inorganic and organic synthetic pigments [4]. Tattoo colorants include "pigments" that can be either inorganic metallic salts or organic molecules of different kinds and "dyes," which are organic molecules [4]. Some auxiliary ingredients/additives are usually found for various purposes to modify the properties of the ink and make it especially suitable for tattooing. However, in the specific cases of PMU pigments, inks are made of organic molecules and usually a stabilizing agent (barium sulfate) [4]. However, all the list of ingredients in one pigment can be important as illustrated in one case of granulomatous reaction [1,4,7].

COMPLICATIONS RELATED TO COSMETIC TATTOOING

Between 1988 and 2003, only five cases of adverse events have been reported to the FDA [1], while within a year (between 2003 and 2004), more than 150 adverse events were reported. Of these, 101 events were local reactions characterized by itching, tenderness, and infiltration. Most of these reactions were related to the use of an ink manufactured by a single American company in Texas. The latter recalled the associated pigment in September 2004 [1,8]. Because PMU and decorative tattooing do share a similar procedure, they share similar complications as well [2]. Complications include cutaneous infections;

hypersensitivity reactions to a component of the tattoo inks; development of benign or malignant tumors; localization of preexisting chronic skin disorders, especially if the disease is known to be associated with a Koebner phenomenon (psoriasis, eczema, vitiligo, etc.); or the revelation of an underlying disease by a local tattoo reaction, typically systemic sarcoidosis. Other issues related to cosmetic tattooing include mainly RMN imaging. However, the main complication are regret and dissatisfaction due to a disappointing or unaesthetic aspect ("unnatural", color, shape, fading) [3] or the "permanent" pigmentation while the customer expects a complete disappearance (Figures 19.1 through 19.3).

Figure 19.1 Unaesthetic result.

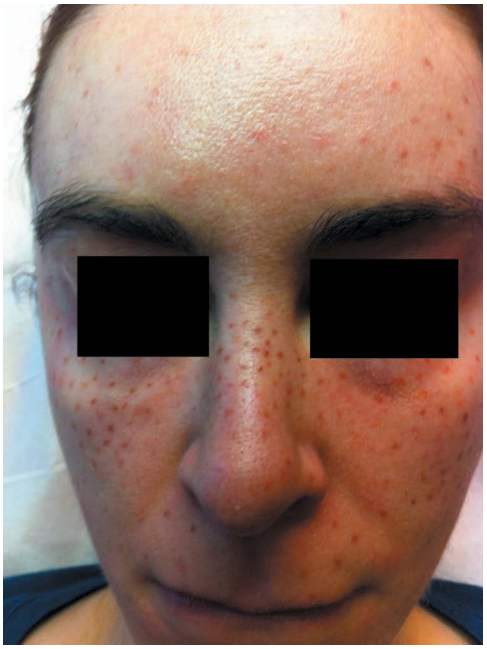


Figure 19.2 Fake "freckles" with disfiguring results. (Courtesy of Dr. Reberga, Toulouse, France.)

Figure 19.3 Progressive fading of eyebrow tattoos.

Acute Complications

Acute complications during the session include vasovagal syncope and pain during the procedure that can be alleviated by the use of local anesthetics. However, it should be stressed that according to local regulation, the use of anesthetics could be considered as illegal practice of medicine. Bleeding due to the puncture of the papillary dermis is usually transient [3]. The question whether patients with inherited blood disorders such as hemophilia or von Willebrand disease should get a PMU remains open. We recommended that those patients seek advice from their physicians before undergoing the procedure [9]. Local transient inflammation does develop at the site of tattooing as a result of the procedure. Swelling and crusting will last for 2–5 days before complete healing. Excess ink that has been deposited in the epidermis is progressively eliminated through shedding of the epidermis. Local antiseptics or antibiotics are commonly used during healing [3]. Yet again such attitude is variable according to laws and regulations of the prescription of local antibiotics. In the case of permanent tattooing, the application of a healing ointment (such as dexpanthenol) and washing with soap and lukewarm water three times a day allow an uneventful healing [5].

Cutaneous Infections

If the PMU is performed by a professional who applies strict rules of hygiene and asepsia and uses either sterilized or single-use material, the risk of inoculation of bacteria, namely, *Staphylococcus aureus* or other pyogenic bacteria, is highly improbable. Besides, infection can also occur during the healing phase at home if a correct aftercare is not performed by the customers. Since the beginning of the 2000s, outbreaks of environmental mycobacterial infections, due to rapidly growing *Mycobacterium chelonae*, have been reported worldwide in tattoo parlors [10–12]. Inoculation is mainly caused by the use of tap or distilled water to mix and dilute the inks. If most of the cases have been reported in decorative tattooing, cases of mycobacterial infections have been reported after PMU tattooing as well [7,13]. Giulieri et al. [13] reported in 2010 that an outbreak of infection by *M. haemophilum* affected 12 patients in Switzerland. All of them had undergone eyebrow tattooing by the same freelance tattoo artist who worked in different

cosmetic shops. Patients were all otherwise priorly healthy and developed limited skin lesions such as erythematous papules, pustules, or patches restricted to the tattooed eyebrows. Besides, they all developed ipsilateral palpable inflammatory lymph nodes in the parotid. Eight patients developed as well an abscess that evolved into a fistula in seven of them. Skin biopsies and lymph node aspiration confirmed the presence of acid-fast bacilli. Both culture and polymerase chain reaction (PCR) analysis confirmed the presence of *M. haemophilum*. Triple antibiotic therapy (clarithromycin, ciprofloxacin, and rifabutin) was initiated, but several patients had to undergo surgery, including parotidectomies. Fortunately, surgery was followed by an acceptable cosmetic result and no notable side effect such as facial paralysis [13]. No major infractions of standard hygienic rules were identified. The tattoo artist had performed PMU on approximately 400 women during the outbreak period, but it was not possible to identify and contact all the customers. The authors found the presence of *M. haemophilum* in some ink sample, however the origin of the inoculation of the microorganism could not be determined. Wollina reported a similar case in a 46-year-old patient who had been tattooed in Southeast Asia 8 weeks prior to the symptoms. Clinical lesions displayed a typical sporotrichoid disposition that is evocative of mycobacterial infection. Infection by *M. haemophilum* was confirmed. In this later case, triple oral antibiotherapy was efficient [7].

Hypersensitivity Reaction to Tattoo Pigments

Introduction of exogenous pigments and dyes during decorative tattooing may trigger a wide range of cutaneous reactions with histological patterns ranging from eczematous and lymphohistiocytic reactions to a more "organized" pattern such as lichenoid, granulomatous, sarcoidosis-like, and pseudolymphomatous reactions. However, if cosmetic tattooing can also induce such reactions in the setting of PMU, they mainly occur under the form of delayed foreign body and sarcoidal granulomatous reaction [14,15]. Reactions have been reported on the eyelids [14,16–19], the eyebrows [7,20,21], and the lips (Figure 19.4) [15,22,23]. Reaction develops within a few weeks [22] to even several years after tattooing [14,19,23] under the form of papules, nodules, swelling, or infiltration of the tattooed area associated with possible symptoms such as itch or numbness. Lesions can be asymptomatic. Besides, it can, in a few cases, raise concern for a potential malignant lesion in case of ulceration or madarosis [19]. Initial treatment includes local treatment such as local corticosteroids [7] or tacrolimus ointments 0.1% for 3–4 months [24] or intralesional injection of corticosteroid [19]. Systemic treatment may be given in some circumstances [14,15]. Surgical resection possibly followed by reconstruction can be performed in case of an isolated localized reaction [19]. Of note, a case of spontaneous resolution 4 months after biopsy has been reported in a female patient with granulomatous reaction to the vermillion of the lips [23]. Allergologic explorations are usually disappointing as patch testing is often negative [7,15]. Prick testing may be positive, not as an immediate reaction but as a delayed reaction. We consider prick testing and intradermal testing with tattoo inks as an authentic rechallenge test that does not bring any new data because the diagnosis of hypersensitivity reaction is already made. Indeed, the prick test and intradermal test will simply trigger a similar reaction on the tested area within a variable delay (days, months [18]), which will necessitate to treat this area as well! Tests do take value only if the precise composition of the ink is known [15] and if positive testing has consequences for the patient life. Despite the hypothesis is a delayed reaction, the reason why it occurs in some patients remains unclear. It is possible that personal background may predispose only a few patients to such reaction, and it is also possible that the "allergic" reaction is not direct against a component of the ink but rather a decomposition by-product that occurred during the aging process of the tattoo. Besides, we strongly recommend that the discovery of a granulomatous reaction, either a sarcoidal one or a foreign body type one, leads to an initial checkup for systemic sarcoidosis [2].

Sarcoidal Granuloma and Systematic Sarcoidosis

Sarcoidosis is an autoimmune disease of unknown etiology characterized by the presence of noncaseating epithelioid cell granulomas in multiple organs. Cutaneous manifestations occur in approximately 25% of the cases. Sarcoid reactions on old scars, traumatized skin sites, and around embedded foreign material have long been observed. For the past 70 years,

(a) (b)

Figure 19.4 (a and b) Granulomatous reaction on a PMU of the lip. (Courtesy of Dr. Colonna, Porto Vecchio, France.)

sarcoidal granulomas on tattoos and PMU have also been documented. Granulomatous and sarcoidal tattoo reactions may be the first and sometimes only cutaneous manifestation of systemic sarcoidosis [25].

Eight female patients (mean age: 48.9 years) tattooed 2–25 years prior to referral have developed sarcoidal granulomas on PMU (lips, eyebrows, eyelids) [26–33]. Lesions may occur on all sites of PMU or be restricted to some of them. Two patients had a history of lung sarcoidosis. Clinical presentation is unspecific, with asymptomatic, sometimes scaly or itchy, infiltration, papules, or nodules. Sarcoidal lesions may occur elsewhere [27,30,33] but remain still quite limited in numbers and close to the tattooed area [30,31]. Two patients had other scar involved as a result of a Koebner phenomenon [26,27]. Biopsies show features of sarcoidal granuloma or noncaseating granuloma. Systemic involvement is frequent with either mediastinal lymph nodes or lung involvement and can occur later in life or simultaneously to skin involvement. Management includes local or oral corticosteroids, tacrolimus ointment 0.1% twice daily, cyclines, mepacrine, allopurinol, or abstention. Reported responses ranged from slight improvement to efficacy. In one case, sarcoidosis occurred under interferon therapy for malignant melanoma. The therapy was conducted until its end and the sarcoidosis then resolved spontaneously [26].

Skin Cancers on PMU

As for decorative tattoos, the association between the occurrence of skin cancers and PMU remains fortuitous. Overall, only two cases of skin cancers on PMU have been reported. The first is a case of basal cell carcinoma (BCC) on the eyebrow of a 60-year-old Korean woman [34]. The lesion developed 3 years after tattooing. However, because of the chronically sun-exposed area of occurrence of the BCC, it remains difficult to make a true link between this case and the PMU. The dark color of the PMU may however delay the clinical diagnosis of the lesion. We had the experience of a woman who presented a BCC in its sclerodermal version on a prior PMU that was re-tattooed before the diagnosis was made. Second, a case of a rapidly growing keratoacanthoma-like squamous cell carcinoma (SCC) was reported within a week after lip tattooing [35]. To the best of our knowledge, these are the only two reported cases of skin tumors on tattoos. The association between tattoos, including PMU and skin cancers, remains so far fortuitous [36].

Pseudoepitheliomatous Hyperplasia on PMU

A few cases of pseudoepitheliomatous hyperplasia (PEH) have been reported after PMU, on the lips so far [35,37]. PEH is a benign reaction usually induced by chronic wound or inflammation. However, it has been more and more reported within red tattoos [38]. The main issue with PEH is related to the fact that it can clinically and histologically mimic keratoacanthoma or SCC prompting a complete excision for diagnosis confirmation [38]. The rapidity of development of the lesion after tattooing is strongly in favor for PEH or keratoacanthoma, while SCC are expected to developed several years after. However, in some cases, a precise diagnosis cannot always be assessed with complete certainty [39,40].

Magnetic Resonance Imaging (MRI)

Tingling or burning sensation has been sometimes associated with decorative tattoos containing iron oxide, mainly dark tattoos. However, the risk and intensity of this phenomenon has been excessively exaggerated, raising issues among radiologists who started to contraindicate such procedure on a simple basis of having a PMU [41]. Tope and Shellock [42] reported that only 1.5% of patients with a cosmetic tattoo (2 of 135) experienced dysesthesia (tingling for one and burning sensation for the other). In both cases, the MRI procedure was anyhow completed [42]. In most of the cases, MRI is uneventful and can be performed until the end [42]. An exceptional case of first-degree burn with transient edema of the eyelid and burning sensation has been reported [43]. Besides, PMU may be responsible for local artifacts in the case of the area of interest. PMU associated imaging artifacts can be attenuated by using correct parameters and choosing the optimal sequences. However, in the case of eyelid tattooing, the orbit may be difficult to visualize due to possible artifacts [44] in the area considered for the exploration. There is no reason to give contraindication for the patient to undergo an MRI if necessary. Nevertheless, the patient should be aware of the possibility of symptoms during the procedure and warn immediately the radiologist in case of such symptoms.

OTHER COMPLICATIONS

After blepharopigmentation, eyelash loss due to mechanical trauma to eyelash bulbs or eyelid necrosis is a rare phenomenon [3,14].

Micropigmentation has been used for the past two decades to cover stable cutaneous or mucosal patches of vitiligo and has apparently demonstrated excellent tolerability and no koebnerization [45–48]. Besides, patients may even use tattoos to camouflage their vitiligo. However, recent cases of vitiligo have been reported on permanent tattoo [49] and on PMU [50]. It is unlikely that tattoo does trigger the vitiligo, but it is possible that it may certainly reveal it [51]. From the experience of some colleagues, vitiligo may recur at the border of the tattooed area (data unpublished, Dr. C. Grognard). Because of the theoretical risk for the occurrence of the Koebner phenomenon on the sites of PMU or tattoos, patients with vitiligo should be advised to wait until their vitiligo has stabilized before undergoing a tattooing procedure. In other subjects, such as those who have no personal or past history of vitiligo but are likely to be predisposed toward it, as in both cases cited, here it is impossible to prevent in any way the occurrence of coincidental vitiligo [51].

LASER TREATMENT OF PMU

The gold standard treatment for PMU removal nowadays is laser therapy. Ablation can be performed using either a carbon dioxide laser or a Q-switched laser [52]. Because of the high concentration of titanium dioxide and ferric oxide in flesh tone/pink and red PMU, a so-called paradoxical reaction, i.e., the darkening after Q-switched laser ablation due to iron oxide or titanium dioxide shifting from their oxidized to reduced states, may occur. The darkening is then treated by another session with another wavelength [52].

REFERENCES

1. Ortiz AE, Alster TS. Rising concern over cosmetic tattoos. *Dermatol Surg* 2012; 38:424–429.
2. Kluger N. Cutaneous complications related to permanent decorative tattooing. *Expert Rev Clin Immunol* 2010; 6:363–371.

3. De Cuyper C. Cosmetic and medical applications of tattooing. In: De Cuyper C, Pérez-Cotapos ML, eds. Berlin, Germany: Springer-Verlag, 2010, pp. 53–60.
4. Bäumler W, Vasold R, Lundsgaard J, Talberg HJ. Chemical used in tattooing and permanent make up products. In: Papameletiou D, Schwela D, Zenie A, eds. *Workshop on Technical/Scientific and Regulatory Issues on the Safety of Tattoos, Body Piercing and of Related Practices*. Ispra, VA: European Commission, 2003, pp. 21–36.
5. Kluger N, Plantier F, Moguelet P, Fraitag S. Tattoos: Natural history and histopathology of cutaneous reactions. *Ann Dermatol Venereol* 2011; 138:146–154; quiz 144–155, 155.
6. Resolution ResAP(2008)1 on requirements and criteria for the safety of tattoos and permanent make-up (superseding. Resolution ResAP(2003)2 on tattoos and permanent make-up). https://wcd.coe.int/ViewDoc.jsp?id=1254065. Accessed May 30, 2013.
7. Wollina U. Nodular skin reactions in eyebrow permanent makeup: Two case reports and an infection by *Mycobacterium haemophilum*. *J Cosmet Dermatol* 2011; 10:235–239.
8. Straetemans M, Katz LM, Belson M. Adverse reactions after permanent-makeup procedures. *N Engl J Med* 2007; 356:2753.
9. Kluger N. Tattooing, piercing and inherited coagulation disorders Haemophilia; 19:e358–e359.
10. Kluger N, Muller C, Gral N. Atypical mycobacteria infection following tattooing: Review of an outbreak in 8 patients in a French tattoo parlor. *Arch Dermatol* 2008; 144:941–942.
11. Kennedy BS, Bedard B, Younge M et al. Outbreak of Mycobacterium chelonae infection associated with tattoo ink. *N Engl J Med* 2012; 367:1020–1024.
12. Falsey RR, Kinzer MH, Hurst S et al. Cutaneous inoculation of nontuberculous mycobacteria during professional tattooing: A case series and epidemiologic study. *Clin Infect Dis* 2013; 57:e143–e147.
13. Giulieri S, Morisod B, Edney T et al. Outbreak of *Mycobacterium haemophilum* infections after permanent makeup of the eyebrows. *Clin Infect Dis* 2011; 52:488–491.
14. Calzado L, Gamo R, Pinedo F et al. Granulomatous dermatitis due to blepharopigmentation. *J Eur Acad Dermatol Venereol* 2008; 22:235–236.
15. Wenzel SM, Welzel J, Hafner C et al. Permanent make-up colorants may cause severe skin reactions. *Contact Dermatitis* 2010; 63:223–227.
16. Klontz KC, Lambert LA, Jewell RE, Katz LM. Adverse effects of cosmetic tattooing: An illustrative case of granulomatous dermatitis following the application of permanent makeup. *Arch Dermatol* 2005; 141:918–919.
17. Vagefi MR, Dragon L, Hughes SM et al. Adverse reactions to permanent eyeliner tattoo. *Ophthal Plast Reconstr Surg* 2006; 22:48–51.
18. Schwarze HP, Giordano-Labadie F, Loche F et al. Delayed-hypersensitivity granulomatous reaction induced by blepharopigmentation with aluminum-silicate. *J Am Acad Dermatol* 2000; 42:888–891.
19. Bee CR, Steele EA, White KP, Wilson DJ. Tattoo granuloma of the eyelid mimicking carcinoma. *Ophthal Plast Reconstr Surg* 2013 March 18.
20. Yang DS, Kim SC, Lee S, Chung Y. Foreign body epithelioid granuloma after cosmetic eyebrow tattooing. *Cutis* 1989; 43:244–247.
21. Ro YS, Lee CW. Granulomatous tissue reaction following cosmetic eyebrow tattooing. *J Dermatol* 1991; 18:352–325.
22. Duke D, Urioste SS, Dover JS et al. A reaction to a red lip cosmetic tattoo. *J Am Acad Dermatol* 1998; 39:488–490.
23. Jones B, Oh C, Egan CA. Spontaneous resolution of a delayed granulomatous reaction to cosmetic tattoo. *Int J Dermatol* 2008; 47:59–60.
24. Wylie G, Gupta G. Lip-enhancing tattoo reaction resolving with topical tacrolimus. *Clin Exp Dermatol* 2008; 33:505–506.
25. Kluger N. Sarcoidosis on tattoos: A review of the literature from 1939 to 2011. *Sarcoidosis Vasc Diffuse Lung Dis*. 2013; 30:86–102.
26. Toulemonde A, Quereux G, Dréno B. Sarcoidosis granuloma on a tattoo induced by interferon alpha. *Ann Dermatol Venereol* 2004; 131:49–51.
27. Yesudian PD, Azurdia RM. Scar sarcoidosis following tattooing of the lips treated with mepacrine. *Clin Exp Dermatol* 2004; 29:552–554.
28. Landers MC, Skokan M, Law S, Storrs FJ. Cutaneous and pulmonary sarcoidosis in association with tattoos. *Cutis* 2005; 75:44–48.
29. Cervigón González I, Pérez Hortet C, Sandín Sánchez S et al. Tattoo granulomas: Initial manifestation of sarcoidosis? *Med Cutan Ibero Lat Am* 2004; 32:131–134.
30. Antonovich DD, Callen JP. Development of sarcoidosis in cosmetic tattoos. *Arch Dermatol* 2005; 141:869–872.
31. Martín JM, Revert A, Monteagudo C et al. Granulomatous reactions to permanent cosmetic tattoos successfully treated with topical steroids and allopurinol. *J Cosmet Dermatol* 2007; 6:229–231.
32. Tourlaki A, Boneschi V, Tosi D et al. Granulomatous tattoo reaction induced by intense pulse light treatment. *Photodermatol Photoimmunol Photomed* 2010; 26:275–276.
33. Lapresta A, Pérez C, García-Almagro D. Facial lesions after tattooing. *Actas Dermosifiliogr* 2010; 101:889–890.
34. Lee JS, Park J, Kim SM et al. Basal cell carcinoma arising in a tattooed eyebrow. *Ann Dermatol* 2009; 21:281–284.
35. Ortiz A, Yamauchi PS. Rapidly growing squamous cell carcinoma from permanent makeup tattoo. *J Am Acad Dermatol* 2009; 60:1073–1074.
36. Kluger N, Koljonen V. Tattoos, inks, and cancer. *Lancet Oncol* 2012; 13:e161–e168.
37. Coors EA, Wessbecher R, von den Driesch P. Beastly nodules instead of beauty: Pseudoepitheliomatous hyperplasia developing after application of permanent make-up. *Br J Dermatol* 2004; 150:1027.
38. Kluger N, Durand L, Minier-Thoumin C et al. Pseudoepitheliomatous epidermal hyperplasia in tattoos: Report of three cases. *Am J Clin Dermatol* 2008; 9:337–340.
39. Kluger N, Plantier F. Pseudo-epitheliomatous hyperplasia, keratoacanthoma, and squamous cell carcinoma occurring within tattoos: Diagnostic issues. *J Am Acad Dermatol* 2007; 57:901–902.
40. Kluger N. Issues with keratoacanthoma, pseudoepitheliomatous hyperplasia and squamous cell carcinoma within tattoos: A clinical point of view. *J Cutan Pathol* 2010 July; 37(7):812–813.
41. Kluger N. Tattoos and medical imaging: Issues and myths. *Presse Med* 2014; 43:529–533.
42. Tope WD, Shellock FG. Magnetic resonance imaging and permanent cosmetics (tattoos): Survey of complications and adverse events. *J Magn Reson Imaging* 2002; 15:180–184.
43. Franiel T, Schmidt S, Klingebiel R. First-degree burns on MRI due to nonferrous tattoos. *Am J Roentgenol* 2006; 187:W556.
44. Weiss RA, Saint-Louis LA, Haik BG, McCord CD, Taveras JL. Mascara and eyelining tattoos: MRI artifacts. *Ann Ophthalmol* 1989; 21:129–131.
45. Halder RM, Pham HN, Breadon JY, Johnson BA. Micropigmentation for treatment of vitiligo. *J Dermatol Surg Oncol* 1989; 15:1092–1098.
46. Mahajan BB, Garg G, Gupta RR. Evaluation of cosmetic tattooing in localized stable vitiligo. *J Dermatol* 2002; 29:726–730.
47. Center JM, Mancini S, Baker GI et al. Management of gingival vitiligo with the use of a tattoo technique. *J Periodontol* 1998; 69:724–728.
48. Singh AK, Karki D. Micropigmentation: Tattooing for the treatment of lip vitiligo. *J Plast Reconstr Aesthet Surg* 2010; 63:988–991.
49. Kluger N, Trouche F. Vitiligo on a tattoo. *Ann Dermatol Venereol* 2011; 138:549–550.
50. Pan H, Song W, Xu A. A case of vitiligo induced by tattooing eyebrow. *Int J Dermatol* 2011; 50:607–608.
51. Kluger N. Vitiligo on a tattoo: Association rather than cause. *Int J Dermatol* 2013; 52:1617–1618.
52. Mafong EA, Kauvar AN, Geronemus RG. Surgical pearl: Removal of cosmetic lip-liner tattoo with the pulsed carbon dioxide laser. *J Am Acad Dermatol* 2003; 48:271–272.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Body piercings

Nicolas Kluger

Body modification or body alteration is defined as the deliberate altering of the body for nonmedical reasons. Along with temporary and permanent tattooing, soft earlobe, and body piercing (BP) are the most common aspects of body modifications nowadays [1–4]. BP is defined as the penetration of jewelry through the skin. If earlobe piercing became a common practice in the 1950s, the trend of BP has really started only recently to gain popularity by the end of the 1980s [2].

EPIDEMIOLOGY OF BODY PIERCING

Traditionally, earlobe piercings are not considered as belonging to the group of BP and usually excluded from studies on BP. There are numerous studies that have been performed mainly in Western countries since the end of the 1990s regarding the prevalence of BP [5]. The results are highly variable according to the studied population: American versus European, teenagers versus general population, studies performed in various settings such as specific academic background (high schools, universities, etc.) and ethnic communities with additional cultural and religious factors that can come into account, and finally according to the type of BP studied—"all" piercings versus only a certain type of piercing (oral piercings, genital piercing, etc.) or inclusion or exclusion of the earlobe piercing. Therefore, prevalence should always be interpreted with caution according to the study and may not be easily extrapolated. BP prevalence has been estimated around 14% in the general population according to a national survey in the United States in 2006 [6], with a female predominance for both soft earlobe piercing and any other BPs. The prevalence appears clearly highest among the young aged 14–24 years, approximately around 20%–30% [5]. Mayers and Chiffriller reported in 2008 the highest prevalence of 51% [7] among undergraduate university students. Regarding specifically oral and perioral piercings, Hennequin-Hoenderdos et al. performed a retrospective study of 13 publications that had evaluated the prevalence of oral piercings [8]. It appeared that the prevalence of oral and perioral piercings was 5.2% among 11, 249 participants with a mean age of 20.6 years. The most common site of oral/perioral piercing was the tongue (5.6%), followed by the lips (1.5%). Females had oral piercing four times more frequently than males [8]. On the other hand, genital piercing remains the rarest variety of piercing, ranging from 0.6% to 2% according to studies [6,9–11]. The prevalence of genital piercing is higher among male for "anatomic" reasons as there is more "space" to pierce [12] and also because according to the World Health Organization (WHO), genital piercing in women is still considered as a form of genital mutilation (type IV), which could limit this practice in some countries and the field of possibilities for some piercers [13,14].

OVERVIEW OF THE MOTIVATIONS AND PSYCHOLOGICAL ASPECTS OF BODY PIERCING

Underlying motivations for obtaining BP are highly variable according to individuals but share similarities with those reported for tattooing [15]: aesthetic purposes; self-consciousness, identity, wish to demonstrate autonomy, and control of one's own body [16]; individuality; expression of a personal catharsis; physical endurance; group affiliations and commitment; resistance (against the society, family, administration, etc.); spirituality and cultural tradition; addiction; sexuality; and sometimes without any specific reason. Laumann et al. noted that 96% of the pierced individuals had someone pierced in their environment (a family member or a friend) [6]. Several studies suggested an association between BP and a large spectrum of high-risk behaviors: alcohol use, smoking, recreative or illicit drug abuse, and high-risk sexual behaviors [17]. Sensation and thrill seeking as well as impulsivity and verbal expression of anger also appeared to be associated with BP. Results seemed less consistent with depression, eating disorder, and suicidal ideation [17]. However, those results should be taken altogether carefully as studies are often restricted to one selected group, especially adolescent or college students, and therefore those results should not be or be extrapolated to a single individual with BP. Besides, data such as the number of BP [16], the presence of other body modifications (tattoos, implants, etc.), or the location of the BP are rarely, if not, taken into account. Finally, studies rely often on self-reported questionnaires. Altogether, BP is becoming increasingly frequent and a normal practice that it becomes difficult per se to consider it alone as a marker of deviance [17]. Further robust studies are necessary in that field to identify whether a subgroup of individuals with BP may be at high-risk behaviors and/or psychiatric symptoms [17].

PIERCING PROCEDURE

BP can be divided into orofacial piercings (nose, ears, eyebrows, lips, tongue), "body" piercings (navel, nipple), and "intimate" piercings (nipple, male and female genitalia). Besides, virtually any part of the skin surface can be pierced [18,19]. Therefore, some individuals may have the so-called surface piercings (pocketing or corset piercings) through the skin [18]. Ear and genitalia piercings are the ones that offer the most diversity with approximately 12 and 16 different types, respectively [1,9]. In a recent British study [20], the most common piercings in women were, in order, navel, nose, ear, tongue, eyebrow, nipple, and lip, while in men, they were nipple, eyebrow, ear, tongue, nose, lip, and genitals. The order varies according to studies [6]. Besides, microdermal piercings (also called surface anchor piercings) are a new uprising form of body modification very close to surface BP. They can be placed almost everywhere on

the skin, giving to the jewelry the appearance of being simply stuck on the skin's surface. They are implanted using a dermal punch [19].

Piercing is usually performed in a "professional" parlor. The piercer has undoubtedly acquired an experience and a technique that make him or her a real professional. However, until recently, their knowledge in anatomy, chemistry, and basic rules of hygiene was often limited and acquired by self-education. Nowadays, several European countries have adopted legislation for body art establishment to regulate this practice. Moreover, jewelers, hair dressers, or beauticians can perform a soft earlobe piercing with an automatic piercing "gun." Self-piercing should naturally be avoided because of the risks related to the lack of asepsis.

The jewelry is usually made of surgical steel, niobium, or titanium. Other metals such as gold are possible. Nickel, which is highly allergenic and sometimes found in alloy, has been limited up to a maximum concentration of 0.05% in Europe. Nonmetallic materials are also available (Teflon, Tygon, polymethyl methacrylate, etc.). Various shapes (ring, bar, barbell, stud, etc.), sizes, and ornaments are available. They vary according to the taste of the individual and also of the location of the desired piercing [21].

The piercing procedure includes the preparation of the sterile material (single-use needle, autoclave sterilization), localization of the piercing trajectory with gentian violet, and local disinfection with antiseptics. Gloves are nonsterile medical gloves, and the use of a surgical mask is variable according to the habits of the piercer. The piercing is performed without any local anesthesia by inserting quickly the sterile cannula needle followed by the jewelry. Forceps/clamps are used for tongue and septum piercings [19]. Aftercare advices are always given and include frequent daily soap wash and the use of a local disinfectant. The jewelry must be regularly "moved" to allow the elimination of local secretions and crusts. For tongue piercing, mouthwashes are recommended [3,19].

Delay of healing is variable according to the location of the ring. It usually takes from several weeks to months before complete healing is acquired according to localization (Table 20.1). The longest delay of healing concerns nipple and navel piercings due to the recurrent trauma and friction due to clothing [2–4].

Table 20.1 Approximate Healing Times of the Main Piercings

Ears
Earlobe 4–8 weeks
Ear cartilage 3–9 months
Eyebrows
6–8 weeks
Nose
Nostril 3–4 months (male), 6–9 months (female)
Tongue 4–8 weeks
*Lip*s 6–8 weeks
Nipple
3–4 months (in men), 6–9 months (in women, because of the clothing friction)
Navel
4 weeks–12 months (repeated trauma, clothing friction)
Female genitalia
Labia majora 4 weeks–4 months
Labia minora 2–8 weeks
Clitoris 2–10 weeks
Male genitalia
Urethral meatus (Prince Albert) 2–8 weeks
Coronal ridge 4 weeks–4 months

Sources: Holbrook J et al., *Am J Clin Dermatol*, 13, 1, 2012; Kluger N and Guillot B, *Ann Dermatol Venereol*, 137, 153, 2010; Meltzer DI, *Am Fam Physician*, 72, 2029, 2005; DeBoer S, *Body Piercing Removal Photo Guide for Healthcare Professionals*, Peds-R-Us Medical Education, Dyer, IN www.peds--r-us.com, 2013.

COMPLICATIONS

Complications related to piercing may be classified into several ways: (1) acute and chronic complications, (2) infectious and noninfectious complications, and (3) complications that are common to any piercing and those specific according to the pierced area [3]. The overall rate of complications due to piercing is variable according to studies as they are often assessed on self-reported questionnaires, subjected to bias of recollections, and also self-interpretation of signs that are not always complications. The estimated prevalence of complications may range from 17% [6] to 30% [20]. Besides, when pierced people have health concerns, most of them return to their body piercers or the Internet for applicable information [18,19]. This is explained by the fact that pierced individuals consider their piercer as being more experienced and fear judgmental approach of the physician.

Infections

Acute infections, and less often chronic infections, are from far the most important complication of BP [22]. They occur independently of the piercing site and range from 10% to 25% [2,23]. Inoculation may occur during the procedure (*primary inoculation*) or *secondarily*, during manipulation of the pierced tract or after changing jewelry. There is often a delay in the diagnosis as the symptoms may be underestimated by the patient, considered as taking part in the healing process, or by fear of consultation with potential approach judgment by the physicians [23]. Two or more of the following signs should alert for local infection: erythema, edema, pain, and local heat [23]. Pus discharge is naturally evocative of infection. The most commonly isolated bacteria are *Staphylococcus aureus*, group A *streptococci*, and *Pseudomonas aeruginosa* [2,22]. Severe infections with unusual bacteria (*Lactobacillus*) and fungi (*Aspergillus*) may occur in immunocompromised patients, especially in case of amateur piercings or medical conditions (uncontrolled diabetes, leukemia) [24–26]. Coinfection with several germs is also possible. Infection is often localized, while dissemination is rare but possible (glomerulonephritis, septic arthritis, bronchopneumonia, brain abscess, endocarditis) [2,22]. Nontuberculous mycobacteria have been recently reported as responsible for chronic abscess and mastitis after nipple piercing [27]. Pyogenic infection of breast/pectoral implants has prompted some plastic surgeons to suggest contraindication of nipple piercing in case of such implants [28,29]. Management of acute infection of a piercing includes irrigation, compresses, topical, or oral antibiotic therapy. The choice of the antibiotics is guided also by the location of the piercing. Removal of the jewelry is discussed. Some authors advocate that removal may be paradoxically associated with abscess formation as the piercing tract allows "natural" drainage of the pus [2]. However, in case of persistent infection,

removal is mandatory [2]. Overall, because of the high risk of infections of piercing site after the procedure, we strongly discourage patients with immunosuppressive conditions or immunosuppressive therapies to undergo any piercing, especially on the oral facial areas [30].

In the specific case of upper or high ear piercing infection, it is recommended to start treating empirically by fluoroquinolone against *P. aeruginosa* while waiting for results from bacteriological results [31,32] and perform disinfection with isopropyl alcohol or iodine solution. Benzalkonium chloride is ineffective antiseptic against strains of pseudomonas [33].

Regarding blood-transmitted infections, transmission of hepatitis B, C, D, and G is possible [2]. It is recommended that piercers as well as customers must be vaccinated against hepatitis B [2]. However, it should be stressed that recently inoculation of blood-transmitted diseases remained low in parlor that respected rules of hygiene, asepsis, and sterilization [34]. HIV transmission remains theoretical, but to date, only one case of HIV infection by piercing is considered "possible" [35].

Infective endocarditis is most likely the most severe complication to fear after piercing. It may occur in patients with congenital cardiopathies but not necessarily [36] and require valve replacement. Patients with congenital heart diseases may underestimate or be unaware of the risk related to piercing. Any patient with such condition should seek advice first with his cardiologist and discuss the possibility of undergoing a piercing according to the cardiopathy. Besides, prophylactic antibiotic therapy should be discussed and adapted according to the local flora of the pierced site [37]. Any unexplained general symptoms such as fever, chill, malaise, and arthromyalgia in the following months after piercing should evoke endocarditis, irrespective of any prior heart condition [2].

Finally, the potential role of the presence of oral or genital piercings in the acquisition or transmission of sexually transmitted diseases has been rarely assessed in the literature [38–40]. Unconventional HIV transmission has been suspected in five Australian male patients who had oral intercourse with an individual with genital piercing [41]. The potential risk related to oral and genital piercing in sexually transmitted diseases should be definitively investigated more in depth.

General Complications Common for Any Piercing

Besides local and systemic infections, piercing exposes to a wide range of complications that occur independently of most site (Table 20.2). Piercing procedure is usually painful and may remain sensitive a few days. Vasovagal syncope might occur during piercing. A small amount of bleeding is expected with any piercing and subsequent hematoma may occur (Figure 20.1). Antoszewski et al. found an overall prevalence of 12.3% of bleeding in their population [42]. Oral piercing appears highly at risk as bleeding has been reported with the 12 hours after piercing in 90% of individuals with oral piercing [43]. Only one case of bleeding that necessitated application of tranexamic acid in an emergency was reported in a male patient with hemophilia after nipple piercing [44]. However, several, but hopefully rare, cases of severe bleeding with hypovolemic shock after piercing in patients with no inherited blood disorders have been reported [45–47].

Table 20.2 Nonspecific Complication That May Occur at Any Site of Piercing

Pain
Vasovagal syncope
Swelling
Bleeding, excessive bleeding, and hypotensive shock
Trauma/tissue tearing (catching on clothing, contact sports, manipulation)
Stretching due to heavy jewelry
Embedding, migration, rejection
Asymptomatic pigmentation by traumatic tattooing
Pyogenic granuloma
Scar formation: hypertrophic, keloids
Allergies (contact dermatitis to metal or to disinfectant)
Infections • Pyogenic (*S. aureus*, *P. aeruginosa*, etc.) and nonpyogenic skin infections (atypical mycobacteria) • Systemic infections (tetanus, poststreptococcal glomerulonephritis, arthritis, brain abscess, hepatitis B, C, D, G, etc.) • Bacterial endocarditis, with possibly valve replacement, septic emboli, or death
Radiologic interferences

Sources: Holbrook J et al., *Am J Clin Dermatol*, 13, 1, 2012; Kluger N and Guillot B, *Ann Dermatol Venereol*, 137, 153, 2010; Meltzer DI, *Am Fam Physician*, 72, 2029, 2005.

Figure 20.1 Edema and transient hematoma after piercing of the lower lips (labret) in an individual with no history of inherited coagulation disorder.

Therefore, patients taking anticoagulants, antiplatelet medications, or those with an underlying risk for bleeding (hemophilia, Von Willebrand disease) are contraindicated for piercings. Aspirin should be avoided during the 7 days before the piercing and nonsteroidal anti-inflammatory drugs the day before [2]. Patients with inherited coagulations disorders should definitely seek advice among their physician to discuss the level of risk of bleeding related to their condition. A recent study showed that women with inherited blood disorders did not always perceive their condition as a risk before acquiring a piercing [48]. Swelling may occur, especially on

Figure 20.2 Irritation of a "surface" piercing between the breasts after changing the jewelry.

the mucosal area (lips, tongue). Tongue swelling impairs eating for approximately a week and implicates to eat only liquid and cold food to alleviate pain, eating difficulties, and accidental tongue bites. Irritation or secondary infection may occur in case of excessive manipulation or when changing the jewelry (Figure 20.2). Jewelry may be embedded (Figure 20.3), migrated, or expulsed (Figure 20.4) [49,50]. Allergic contact dermatitis, to either a component of metal jewelry (nickel, cobalt, palladium, gold, etc.) or disinfectant or ointment used during the healing phase, may occur as a localized eczematous rash. Granulomatous [51] and lymphomatoid [52] contact dermatitis have been reported as well especially for earlobe earrings. Piercing holes may be visible for years after the piercing has been withdrawn. Granuloma pyogenicum has been reported after nostril piercing in India [53], but it can occur in other locations. Hypertrophic scar and keloid may occur (Figures 20.5 and 20.6). Any patient with a history of keloid formation, on a prior piercing or elsewhere, should be discouraged to receive a piercing. Tissue tearing by accidental pulling out of the jewelry is a common injury ("split earlobe" due to trauma or repetitive wearing of heavy earrings, torn eyebrow [Figure 20.7]) [54]. Besides, earlobe distension with excessive laxity occurs after stretching, which is responsible for "air holes" or "flesh tunnels" [54]. Reconstructive plastic surgery is then necessary. Different techniques of reconstruction have been recently published for the reconstruction of expanded earlobe [55,56]. Accidental tattooing taking the form of an asymptomatic macular gray or bluish pigmentation can be noted after removal of the piercing. It is due to deposition of metallic impurities from the jewelry

(a) (b)

Figure 20.3 Embedded upper lip piercing (Monroe) with local inflammatory edema of the lip. (a) View from the skin side. (b) View from the inner side of the mucosae.

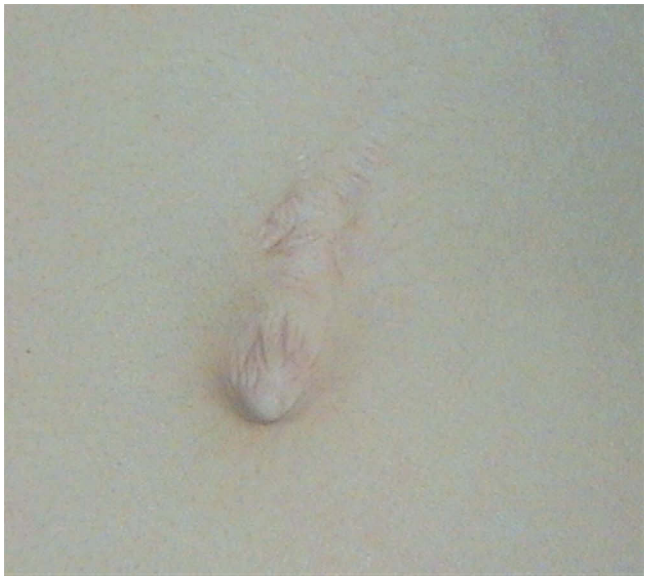


Figure 20.4 Navel scar in a young woman who kept her navel piercing until the end of her pregnancy resulting in expulsion of the piercing due to abdominal gravid distension. (Courtesy of Dr. Fabienne Trouche, Rodez, France.)

Figure 20.5 Hypertrophic reaction at the site of a cartilage piercing industrial type.

in the dermis. Q-switched laser has proved to be efficient in this indication [57]. Finally, the presence of piercing may interfere with medical procedure. Images may be distorted or more difficult to interpret as, for instance, for dental examination. In case of MRI, jewelry may move and therefore should be taken before imaging [2]. Oral piercings are problematic in case of anesthesia as they may result in difficulties for orotracheal intubation or nasogastric tube placement [58]. Cases of not only jewelry ingestions but also hypoxia, laryngospasm, and tongue bleeding have been reported. It is therefore mandatory that the anesthesiologist is aware of the presence of tongue piercing before any planned intubation [59]. Besides, in case of emergency, medical personnel should know how to remove any piercing safely. Several publications and books provide appropriate guidance [60–63]. Briefly, for barbell and labret jewelry, remove one end of the barbell by twisting counterclockwise and maintaining a grasp on the other end of the jewelry. For the ring jewelry, removal is best accomplished with the use of ring-opening pliers [62,63].

Patients may sometimes be reluctant to take their piercing out as they fear a quick close of the piercing tract. This aspect should not be neglected by the medical personnel. A discussion on the pros and cons for keeping a piercing during a procedure should be discussed with the patient. Besides, the physician should not lose from sight that the question of whether removal of the jewelry is indeed necessary, especially for elective or nonemergency healthcare, remains to be debated in the medical literature [61]. A plastic retainer may be inserted in place of jewelry in order to hold a piercing tract open [61,63].

Complications Specific to Body Site

According to the location, a wide number of complications have been reported [2–4]. They are summarized in Table 20.3. Special attention should be brought on oral piercings (lips and tongue) as they are frequent and responsible for numerous complications [64,65]. Briefly, lip piercings tend to be associated with gingival recession (Figure 20.8), while tongue piercing is associated with enamel fissures, enamel cracks, lingual recessions [66], tooth cracking, chipping, or fracture [64]. Besides, the presence of oral piercing seems to have an influence on the local bacterial flora with the progressive development of periodontopathogenic flora on the long term [67]. Piercing material (steel or methacrylate) may play a role in the modification of the flora [68]. A good oral hygiene is mandatory in case of oral and labial piercings (regular toothbrush, daily mouthwash, and annual dentist consultation). Several cases of cutaneous carcinomas at the piercing site have been reported [69–72]. However, a real physiopathological link between the piercing and the development of a basal cell or a squamous cell carcinoma on the very same site remains far from being clear. Belly button piercing may appear as the harmless one among all the piercings because of its location, and it is notoriously trendy among young women. However, a few complications have to be stressed. First, we have to insist on the long delay of healing as the navel is a frequently traumatized area. Besides, migration, rejection, and navel tearing or striae/stretch mark development during pregnancy are observed due to abdominal gravid distension [73,74]. Pregnant women should remove the navel piercing as early as possible but most of all as soon as the gravid abdominal distension starts to create a tension between the skin and the jewelry. We wish to stress that removing the piercing may not prevent the development of a pregnancy-related stretch mark at the pierced hole. Finally, intestinal adhesions to anterior abdominal wall [75,76] with potential risk of volvulus, intestinal infarction, and death [77] have been reported in a limited number of cases in the setting of navel piercings.

Besides, several recent reviews focused on various specific aspects of piercings such as pregnancies [78], lactation [78,79], and genital piercings [9,80].

(a) (b)

(c) (d)

Figure 20.6 (a) Large keloids on an industrial piercing. (b–d) Surgical procedure performed to cut the piercing stud and take it off under local anesthesia. (Courtesy of Dr. Véronique Blatière, Montpellier, France.)

Figure 20.7 Earlobe split on a soft earlobe piercing.

Figure 20.8 Gingival recession due to a lip piercing (labret).

Table 20.3 Site-Specific Complications

Ears
Embedded earrings
Hematoma
Chondritis and perichondritis
Ear deformation ("cauliflower ear")
Pseudolymphoma
Sarcoidal reaction
Relapsing polychondritis

Eyebrows
Tract splitting (weight, manipulation of the area)

Nose
Jewelry embedding in the nasal mucosa due to inflammation
Granulomatous destruction of the cartilage due to inflammation
Septum hematoma
Perichondritis
Necrosis of the nasal wall
Alar collapse
Nerve damage (nasal bridge piercing)
Bone necrosis (nasal bridge piercing)
Telangiectatic erythema of the nose (nostril piercing)
Jewelry swallowing or aspiration
Basal cell carcinoma

Tongue and perioral areas
Transient swelling, eating difficulty, bleeding, excessive salivation (immediately after piercing)
Increased salivation
Halitosis
Problems in chewing, swallowing, and speech alterations
Dysgeusia (metallic taste)
Inflammation and gingival recession: esthetic impairment, increased susceptibility to caries, dentin hypersensitivity
Accumulation of calculus around the piercing
Dental alterations (chips, cracks, fractures)
Nerve damage (loss of taste, numbness, atypical trigeminal neuralgia)
Uncontrolled drooling
Piercing rupture
Jewelry embedding, swallowing, or aspiration
Squamous cell carcinoma
Interference with radiographs
Interference with airways management (obstacle during general anesthesia or intubation)
Infection: modification of the local oral flora, Ludwig's angina (group A streptococci)

Nipple
Nipple enlargement
Galactorrhea due to hyperprolactinemia
Infectious mastitis
Potential difficulties during breastfeeding
Benign tumor (fusiform cell proliferation)

Navel
Delayed healing (up to a year, due to repeated trauma)
Migration, rejection, and navel tearing or striae/stretch mark development during pregnancy due to abdominal gravid distension
Intestinal adhesions to anterior abdominal wall with potential risk of volvulus, intestinal infarction, and death

Female genitalia
Local hypersensitivity, frictional irritation, compromise of barrier contraceptives, potential complications during vaginal childbirth, and urinary infection

(Continued)

Table 20.3 (*Continued*) Site-Specific Complications

Male genitalia
Frictional irritation, hypersensitivity, urinary flow interruption, compromise of barrier contraceptives (preservative), paraphimosis, penile engorgement, priapism, recurrent condyloma, urethral rupture, urethral stricture, loss of the jewelry during sexual intercourse, postcoital bleeding of partner (vaginal trauma), infection (skin infection, Fournier's gangrene, prostatitis, orchitis), squamous cell carcinoma of the penis

Sources: Holbrook J et al., *Am J Clin Dermatol*, 13, 1, 2012; Kluger N and Guillot B, *Ann Dermatol Venereol*, 137, 153, 2010; Meltzer DI, *Am Fam Physician*, 72, 2029, 2005.

CONCLUSION

There are many complications related to BP. As this trend is still popular, understanding the risks of the procedures as well as the medical and psychosocial implications of wearing is important for the physician [2–4]. Piercers and customers should also be involved.

1. *The physician*: A nonjudgmental approach by the medical personnel is mandatory, whether a pierced patient comes for a piercing complication or any other health issue.
2. *The piercer*: Regulations of piercing and formation of the piercers (rules of hygiene and asepsis, knowledge of the potential risks and complications) are mandatory. Piercing should be performed only by qualified trained piercers [19]. Clear oral and written aftercare instructions are crucial as care may last up to 1 year for some piercings (navel) [2–4].
3. *The patient*: Patients with chronic diseases (cardiac diseases, blood coagulation disorders, chronic immunosuppressive diseases ranging from uncontrolled diabetes to more severe diseases) or undergoing treatments (anticoagulation, immunosuppressive therapies) should seek medical advice before undergoing any piercing to evaluate the risk of complications or if any precaution should be taken. They should warn as well the piercer of their condition and the latter in doubt should refer the patient to his or her healthcare provider before performing the piercing.

REFERENCES

1. Stirn A. Body piercing: Medical consequences and psychological motivations. *Lancet* 2003; 361:1205–1215.
2. Holbrook J, Minocha J, Laumann A. Body piercing: Complications and prevention of health risks. *Am J Clin Dermatol* 2012; 13:1–17.
3. Kluger N, Guillot B. Body-piercing complications. *Ann Dermatol Venereol* 2010; 137:153–158.
4. Meltzer DI. Complications of body piercing. *Am Fam Physician* 2005; 72:2029–2034.
5. Lauman AE. History and epidemiology of tattoos and piercings. Legislation in the United States. In: De Cuyper C, Pérez-Cotapos ML, eds. *Dermatologic Complications with Body Art*. Berlin, Germany: Springer-Verlag, 2010, pp. 1–11.
6. Laumann AE, Derick AJ. Tattoos and body piercings in the United States: A national data set. *J Am Acad Dermatol* 2006; 55:413–421.
7. Mayers LB, Chiffriller SH. Body art (body piercing and tattooing) among undergraduate university students: "then and now". *J Adolesc Health* 2008; 42:201–203.
8. Hennequin-Hoenderdos NL, Slot DE, Van der Weijden GA. The prevalence of oral and peri-oral piercings in young adults: A systematic review. *Int J Dent Hyg* 2012; 10:223–228.
9. Kluger N. Genital piercings: Epidemiology, sociocultural aspects, sexuality and complications. *Presse Med* 2012; 41:21–31.
10. Skegg K, Nada-Raja S, Paul C, Skegg DC. Body piercing, personality, and sexual behavior. *Arch Sex Behav* 2007; 36:47–54.
11. Willmott FE. Body piercing: Lifestyle indicator or fashion accessory? *Int J STD AIDS* 2001; 12:358–360.
12. Armstrong ML, Caliendo C, Roberts AE. Genital piercings: What is known and what people with genital piercings tell us. *Urol Nurs* 2006; 26:173–179.
13. Anderson WR, Summerton DJ, Sharma DM, Holmes SA. The urologist's guide to genital piercing. *BJU Int* 2003; 91:245–251.
14. World Health Organization Classification of female genital mutilation, http://www.who.int/reproductivehealth/topics/fgm/overview/en/index.html. Accessed May 16, 2013.
15. Wohlrab S, Stahl J, Kappeler PM. Modifying the body: Motivations for getting tattooed and pierced. *Body Image* 2007; 4:87–95.
16. Stirn A, Oddo S, Peregrinova L et al. Motivations for body piercings and tattoos—The role of sexual abuse and the frequency of body modifications. *Psychiatry Res* 2011; 190:359–363.
17. Bui E, Rodgers R, Cailhol L et al. Body piercing and psychopathology: A review of the literature. *Psychother Psychosom* 2010; 79:125–129.
18. Armstrong ML, Koch JR, Saunders JC et al. The hole picture: Risks, decision making, purpose, regulations, and the future of body piercing. *Clin Dermatol* 2007; 25:398–406.
19. Thorne R. *Body Piercing. The Body Art Manual—The Essential Reference For Body Art.* London, U.K.: Apple Press, 2010.
20. Bone A, Ncube F, Nichols T, Noah ND. Body piercing in England: A survey of piercing at sites other than earlobe. *Br Med J* 2008; 336:1426–1428.
21. De Cuyper C, D'hollander D. Materials used in body art. In: De Cuyper C, Pérez-Cotapos ML, eds. *Dermatologic Complications with Body Art.* Berlin, Germany: Springer-Verlag, 2010, pp. 13–28.
22. Tweeten SS, Rickman LS. Infectious complications of body piercing. *Clin Infect Dis* 1998; 26:735–740.
23. Guiard-Schmid JB, Picard H, Slama L et al. Piercing and its infectious complications. A public health issue in France. *Presse Med* 2000; 29:1948–1956.
24. Razavi B, Schilling M. Chondritis attributable to Lactobacillus after ear piercing. *Diagn Microbiol Infect Dis* 2000; 37:75–76.
25. Assimakopoulos D, Tziouris D, Assimakopoulos AD. Bilateral auricular perichondritis and diabetes mellitus. *Otolaryngol Head Neck Surg* 2009; 140:431–432.
26. Kontoyiannis DP, Chagua MR, Ramirez I, Prieto V. Locally invasive auricular aspergillosis after ear piercing in a neutropenic patient with leukemia. *Am J Hematol* 2003; 73:296–297.
27. Kapsimalakou S, Grande-Nagel I, Simon M et al. Breast abscess following nipple piercing. *Arch Gynecol Obstet* 2010; 282:623–626.
28. Javaid M, Shibu M. Breast implant infection following nipple piercing. *Br J Plast Surg* 1999; 52:676–677.
29. de Kleer N, Cohen M, Semple J et al. Nipple piercing may be contraindicated in male patients with chest implants. *Ann Plast Surg* 2001; 47:188–190.
30. Kluger N. Tattooing and piercing: An underestimated issue for immunocompromised patients? *Presse Med*. 2013; 42:791–794.
31. Keene WE, Markum AC, Samadpour M. Outbreak of *Pseudomonas aeruginosa* infections caused by commercial piercing of upper ear cartilage. *J Am Med Assoc* 2004; 291:981–985.
32. Manca DP, Levy M, Tariq K. Case Report: Infected ear cartilage piercing. *Can Fam Physician* 2006; 52:974–975.
33. Rowshan HH, Keith K, Baur D, Skidmore P. *Pseudomonas aeruginosa* infection of the auricular cartilage caused by "high ear piercing": A case report and review of the literature. *J Oral Maxillofac Surg* 2008; 66:543–546.
34. Urbanus AT, van den Hoek A, Boonstra A et al. People with multiple tattoos and/or piercings are not at increased risk for HBV or HCV in The Netherlands. *PLOS ONE* 2011; 6:e24736.
35. Pugatch D, Mileno M, Rich JD. Possible transmission of human immunodeficiency virus type 1 from body piercing. *Clin Infect Dis* 1998; 26:767–768.

36. Armstrong ML, DeBoer S, Cetta F. Infective endocarditis after body art: A review of the literature and concerns. *J Adolesc Health* 2008; 43:217–225.
37. Kluger N. Bacterial endocarditis and body art: Suggestions for an active prevention. *Int J Cardiol* 2009; 136:112–113.
38. Altman JS, Manglani KS. Recurrent condyloma acuminatum due to piercing of the penis. *Cutis* 1997; 60:237–238.
39. Gokhale R, Hernon M, Ghosh A. Genital piercing and sexually transmitted infections. *Sex Transm Infect* 2001; 77:393–394.
40. Hounsfield V, Davies SC. Genital piercing in association with gonorrhoea, chlamydia and warts. *Int J STD AIDS* 2008; 19:499–500.
41. Richters J, Grulich A, Ellard J, Hendry O, Kippax S. HIV transmission among gay men through oral sex and other uncommon routes: Case series of HIV seroconverters, Sydney. *AIDS* 2003; 17:2269–2271.
42. Antoszewski B, Sitek A, Jedrzejczak M et al. Are body piercing and tattooing safe fashions? *Eur J Dermatol* 2006; 16:572–575.
43. Inchingolo F, Tatullo M, Abenavoli FM, Marrelli M, Inchingolo AD, Palladino A, Inchingolo AM, Dipalma G. Oral piercing and oral diseases: A short time retrospective study. *Int J Med Sci* 2011; 8:649–652.
44. Noble S, Chitnis J. Case report: Use of topical tranexamic acid to stop localised bleeding. *Emerg Med J* 2013; 30:509–510.
45. Hardee PS, Mallya LR, Hutchison IL. Tongue piercing resulting in hypotensive collapse. *Br Dent J* 2000; 188:657–658.
46. Rosivack RG, Kao JY. Prolonged bleeding following tongue piercing: A case report and review of complications. *Pediatr Dent* 2003; 25:154–156.
47. Sauer MW, Siano CJ, Simon HK. Presentation of an adolescent with delayed-onset massive hemorrhage and shock from a tongue piercing. *Am J Emerg Med* 2011; 29:e5–e7.
48. Khair K, Holland M, Pollard D. The experience of girls and young women with inherited bleeding disorders. *Haemophilia* 2013 April 22.
49. Timm N, Iyer S. Embedded earrings in children. *Pediatr Emerg Care* 2008; 24:31–33.
50. Antoszewski B, Szychta P, Fijałkowska M. Are we aware of all complications following body piercing procedures? *Int J Dermatol* 2009; 48:422–425.
51. Goossens A, De Swerdt A, De Coninck K, Snauwaert JE, Dedeurwaerder M, De Bonte M. Allergic contact granuloma due to palladium following ear piercing. *Contact Dermatitis* 2006; 55:338–341.
52. Conde-Taboada A, Rosón E, Fernández-Redondo V et al. Lymphomatoid contact dermatitis induced by gold earrings. *Contact Dermatitis* 2007; 56:179–181.
53. Kumar Ghosh S, Bandyopadhyay D. Granuloma pyogenicum as a complication of decorative nose piercing: Report of eight cases from eastern India. *J Cutan Med Surg* 2012; 16:197–200.
54. Lane JC, O'Toole G. Complications of ear rings. *J Plast Reconstr Aesthet Surg* 2012; 65:747–751.
55. de la Sotta P, Paredes N, Lasalle MA. Repair of dilated earlobe due to plug piercing. *Dermatol Surg* 2010; 36:1621–1623.
56. Bastazini I Jr, Pianaro C. New approach to repair of expanded earlobe. *Dermatol Surg* 2013; 39:1127–1129.
57. Kirby W, Alston DB. Successful treatment of an unintentional tattoo on the ala after the removal of nose piercings. *Dermatol Surg* 2013; 39:1120–1121.
58. Dhir S, Dhir AK. Intraoperative loss of nasal jewelry: Anesthetic concerns and airway management. *J Clin Anesth* 2007; 19:378–380.
59. Mercier FJ, Bonnet MP. Tattooing and various piercing: Anaesthetic considerations. *Curr Opin Anaesthesiol* 2009; 22:436–441.
60. Khanna R, Kumar SS, Raju BS, Kumar AV. Body piercing in the accident and emergency department. *J Accid Emerg Med* 1999; 16:418–421.
61. DeBoer S, McNeil M, Amundson T. Body piercing and airway management: Photo guide to tongue jewelry removal techniques. *AANAJ* 2008; 76:19–23.
62. DeBoer S, Seaver M, Vidra D, Robinson B, Klepacki J. Breasts, bellies, below, and beyond: Body piercing jewelry and the transfer technique—When in doubt, don't necessarily take it out! *J Emerg Nurs* 2011; 37:541–553.
63. DeBoer S. *Body Piercing Removal Photo Guide for Healthcare Professionals*. Dyer, IN: Peds-R-Us Medical Education. www.peds--r-us.com, 2013.
64. De Moor RJ, De Witte AM, Delmé KI et al. Dental and oral complications of lip and tongue piercings. *Br Dent J* 2005; 199:506–509.
65. López-Jornet P, Navarro-Guardiola C, Camacho-Alonso FV et al. Oral and facial piercings: A case series and review of the literature. *Int J Dermatol* 2006; 45:805–809.
66. Ziebolz D, Hildebrand A, Proff PR et al. Long-term effects of tongue piercing—A case control study. *Clin Oral Invest* 2012; 16:213–217.
67. Ziebolz D, Hornecker E, Mausberg RF. Microbiological findings at tongue piercing sites: Implications to oral health. *Int J Dent Hyg* 2009; 7:256–262.
68. Kapferer I, Beier US, Persson RG. Tongue piercing: The effect of material on microbiological findings. *J Adolesc Health* 2011; 49:76–83.
69. Ng MF, Clarkson JH, Hogg FJ. Basal cell carcinoma arising from nasal piercing: Cause or coincidence. *J Plast Reconstr Aesthet Surg* 2010; 63:e153–e154.
70. Khundkar R, Wilson PA. Basal cell carcinoma at the site of a nasal piercing. *J Plast Reconstr Aesthet Surg* 2009; 62:557–558.
71. Stanko P, Poruban D, Mracna J et al. Squamous cell carcinoma and piercing of the tongue—A case report. *J Craniomaxillofac Surg* 2012; 40:329–331.
72. Edlin RS, Aaronson DS, Wu AK et al. Squamous cell carcinoma at the site of a Prince Albert's piercing. *J Sex Med* 2010; 7:2280–2283.
73. Doumat-Batch F, Cuny JF, Brocard FG et al. Stria of pregnancy only in the site of a navel piercing (first reported case). *J Eur Acad Dermatol Venereol* 2007; 21:840–841.
74. Kluger N, Trouche F. Navel piercing during pregnancy: A cautionary tale for the family physician, the obstetrician and the midwife. *Presse Med* 2013; 42:367–368.
75. Ventolini G, Kleeman S. Adhesions caused by umbilical piercing. *J Am Assoc Gynecol Laparosc* 2003; 10:281.
76. Park MH, Mehran A. Intestinal injury secondary to an umbilical piercing. *J Soc Laparoendosc Surg* 2012; 16:485–487.
77. Ranga N, Jeffery AJ. Body piercing with fatal consequences. *BMJ Case Rep* 2011; 25:2011.
78. Kluger N. Body art and pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2010; 153:3–7.
79. Armstrong ML, Caliendo C, Roberts AE. Pregnancy, lactation and nipple piercings. *AWHONN Lifelines* 2006; 10:212–217.
80. Nelius T, Armstrong ML, Rinard K et al. Genital piercings: Diagnostic and therapeutic implications for urologists. *Urology* 2011; 78:998–1007.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

PART III

Minimally Invasive Surgery

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Office surgery for dermatologists

Leonardo Marini

INTRODUCTION

Dermatology has a long surgical tradition dating back to years when it was not even recognized as a formal specialty. Skin surgery was performed as long ago as 50,000 BC when prehistoric men used to pass a variety of suture material through the skin, and in Greek and Roman times, there were even physicians specialized exclusively in surgical procedures limited to the skin organ. After the second half of the nineteenth century, dermatologists progressively contribute to the development of the "surgical arm" of what can be clearly defined as a true, all-around organ-specific medical–surgical specialty. From the development of simple but extremely efficient instrumentation like the dermal curette by Henry G. Piffard, a founder and president of the American Dermatologic Association in 1870, to the pioneering use of laser sources by Leon Goldman, chairman of dermatology at the University of Cincinnati; from the first hair bearing graft transplantation described by Okuda, a Japanese dermatologists, in 1939, to chemical peels, liposuction, and fat transplantation; from skin cancer surgery with microscopically controlled frozen sections proposed by Theodore Tromovitch and Samuel Stegman as an innovative evolution of F. Mohs' original chemosurgery to nail surgery mastered by Robert Baran and Eckart Haneke, the list of operative procedures is quite large and is progressively increasing [1,2].

But just knowing how to perform dermatologic surgical procedures is not enough. Dermatologists need to work in a properly organized, well-designed, medical environment in order to achieve their best results and make their patients comfortable before, during, and after their surgical procedures [3]. Designing a well-organized surgical office space is not an easy task, but the final outcome is critical for all the three major figures on the operative stage: the surgeon, staff, and patient. Surgical experience and meticulous analysis of details help to achieve a high level of working efficiency that will be appreciated for years to come. Organization helps to reduce surgical accidents and optimize time efficiency besides acting as an extremely important ally in staff training and patient management. Many fundamental messages are delivered to the observer through the so-called unspoken language that a properly organized medical environment can express. Dermatologists should not be alone in this extremely challenging endeavor. Medical architects, interior designers, functional engineers, and IT consultants should be all part of the team, with dermatologists always at the wheel to "steer" toward the right direction, never loosing the course to reach the expected final destination in the shorter possible time. Traveling around the world to visit other colleagues who designed and built their own offices, observing them performing surgical procedures, and critically analyzing all operational steps with them constitute a tremendous resource to reach the goal of realizing an efficient dermatologic office without making too many mistakes. Scientific societies may strongly contribute to standardization of operative flowcharts, informed consent documents, staff training protocols, and behavioral guidelines. They should be periodically consulted. Dispensing active cosmeceuticals is becoming quite common in modern dermatological practices, particularly when cosmetic and aesthetic surgical procedures are concerned. They are prescribed as integral parts of pre- and posttreatment protocols. Regulations about this particular aspect of medical profession should be properly followed [4].

SURGICAL ENVIRONMENT DEFINITION, CERTIFICATION, AND ACCREDITATION

Performing invasive surgical procedures requires properly designed, well-organized surgical environments. A surgical environment can be defined as a space, within a medical–surgical facility, where all sequential steps and operative details, necessary to perform properly selected surgical procedures, can find an ergonomically organized place. Not all dermatologists perform the full range of invasive procedures offered by modern dermatologic surgery [5]. Surgical environment should therefore be planned according to different professional scenarios, respecting specific aims and requirements. Particular consideration should be given to the level of anesthesia usually required to perform invasive surgical procedures. Most dermatologic surgical procedures are performed under topical or local/regional/tumescent anesthesia, which should be considered as integral components of surgery. They do not usually require special authorization. More advanced invasive procedures might require IV sedation associated with local anesthesia or even general IV anesthesia. They should be included within the list of procedures performed by dermatologists in their office facilities, and specific authorizations should be obtained. Special professional assistance from board-certified anesthesiologists should be absolutely available [6,7].

Besides considering the level of structural and functional complexity surgical environments necessarily involve, there are specific requirements, rules, and regulations that should be necessarily taken into consideration before planning to realize a surgical dermatologic office. Regulations vary widely from country to country, state to state, region to region adding to the complexity of the whole project. All medical and surgical facilities, either small or large, need to be approved and certified by local health authorities in order to be authorized to provide surgical treatments. Considering the time, personal energy expenditure, and economic investment involved in designing and realizing a properly organized surgical environment, a very good strategy should certainly consider preliminary consults with local health authorities [8]. Consults should aim at

obtaining qualified, professional advice from the very health authorities that will be ultimately responsible for the final certification process of the new surgical facility. This very useful relationship should better be established at the early stages of the project. All possible efforts should be made to maintain this special relationship as active as possible until the new surgical facility is finished.

Safety, risk management, patient privacy protection (PPP), and quality of care are the four major concerns local health authorities usually consider when evaluating a medical–surgical facility for approval and certification.

Safety is number one on the list [9–12]. There are various important aspects concerning specific safety issues. They should all be properly considered during the development plans of a new surgical facility, even if different levels of importance are attributed by local health authorities around the world. Two main categories of safety issues may be taken into account: general intrinsic safety (GIS) and specific extrinsic safety (SES).

GIS relates to the quality of materials and technical solutions selected and adopted to realize a surgical environment. SES relates to the preventive analysis of possible adverse events that can potentially happen before, during, and after any surgical procedure performed in simple or complex surgical environments.

Risk management requires a thorough analysis of all potential hazards, either occupational or health related that might be involved before, during, and after surgical procedures. It implies proper elaboration of internal behavioral protocols and organizational guidelines aiming to protect staff and patients alike.

PPP is a complex issue involving many different structural and functional aspects pertaining to surgical environments: from staff education and training to room soundproofing and curtaining of patients' changing areas, from patient flow within hallways and functional units (FUs) to deidentification of their sensible data, from storing and retrieving patients' images and information when transferring them to other doctors and/or medical facilities, etc. Quite unfortunately even PPP rules are different from country to country, but their logical interpretation and properly structured implementation of PPP guidelines can definitely help to safely keep patients and surgical facilities under a reliably strong protective shield.

Quality of care shares the same importance with PPP, and its constant improvement, followed by proper implementation of innovative protocols, is essential to achieve the best end results in terms of surgical success, practice protection against medico-legal actions, and practice promotion through one of the simplest, yet quite effective, advertising strategies: the well-known *word of mouth* spontaneously spread by satisfied patients [13,14].

Continuous medical education of physicians and staff, along with periodically scheduled internal meetings, is extremely important in maintaining and improving quality of care within modern medical–surgical facilities.

Obtaining an accreditation for a medical–surgical facility is a different process from its official certification issued by local health authorities. Accreditations are given by independent accrediting agencies. Accrediting processes mostly concentrate in evaluating operative protocols concerning internal governance, charting, record keeping, and quality assurance [15].

While certification is an absolute requirement to allow a medical–surgical facility to properly operate, accreditation is not compulsory in many countries. It might help to negotiate lower insurance premiums and open the way to possible cooperations with larger public or private health systems.

SURGICAL ENVIRONMENT WITHIN DERMATOLOGICAL OFFICES

There are many different aspects to be considered when planning and designing the organization of a surgical environment within a dermatologic facility [16]. One of the most important is the analysis of the size and number of these Functional Units (FUs). A FU can be defined as an independent, organized space, specifically designed to contain all necessary technical and structural items allowing the performance of any of the fundamental tasks planned to take place within its physical limits, providing enough space be allocated to effectively and efficiently accommodate all persons selected to efficiently perform specifically allocated tasks. FUs should be designed according to the different kinds of surgical procedures preliminarily selected by dermatologists to be performed in their specific medical–surgical facilities. The size of a FU is closely related to the size and number of technical items structurally linked with it (primary technical equipment [PTE]) and size and number of facultative technical equipment (FTE) that might be temporarily positioned within its space to allow the performance of particular surgical and non-surgical procedures not included in the original list of preordered operational assignments. All FUs should obviously meet all necessary requirements set by local health authorities.

Surgical units are highly specialized FUs and can be divided into main functional units (MFUs) and service functional units (SFUs). MFUs are designed to accommodate all technical equipment necessary to perform surgical procedures of different levels of complexity. Three different levels of complexity can be described: level 1: MFUs allow the performance of minor surgical procedures, level 2: MFUs can accommodate more complex surgical procedures, and level 3: MFUs are suitable for advanced surgical procedures that might require IV sedation or IV general anesthesia (Figure 21.1).

Small dermatologic offices might consider more versatile, hybrid versions of main surgical units. These MFUs can efficiently accommodate both clinical and surgical activities, allowing to shift between them according to specific operational needs. Simple hybrid clinical–surgical units (SHCSUs) allow the performance of minor surgical procedures but are not suitable for more advanced, technically complex invasive surgeries (Figure 21.2). Advanced hybrid clinical–surgical units (AHCSUs) can accommodate more complex clinical and surgical procedures but not IV sedation and/or IV general anesthesia (Figure 21.3). When hybrid FUs are considered, surgical environment finds its "virtual place" within the space of the MFUs. Surgical functions are therefore "activated" when necessary in hybrid medical–surgical FUs. Efficiency in switching from clinical to surgical activities and vice versa strongly depends on intrinsic organization of working environment. Hybrid FUs are quite complex to organize and require a perfect design aiming at taking maximum advantage of every bit of available space, combined with a perfect, ergonomic positioning of each PTE.

Larger offices allow better and more efficient separation between clinical and surgical environments.

SFUs are designed to efficiently support surgical activities but are not suited to allow their performance. The same

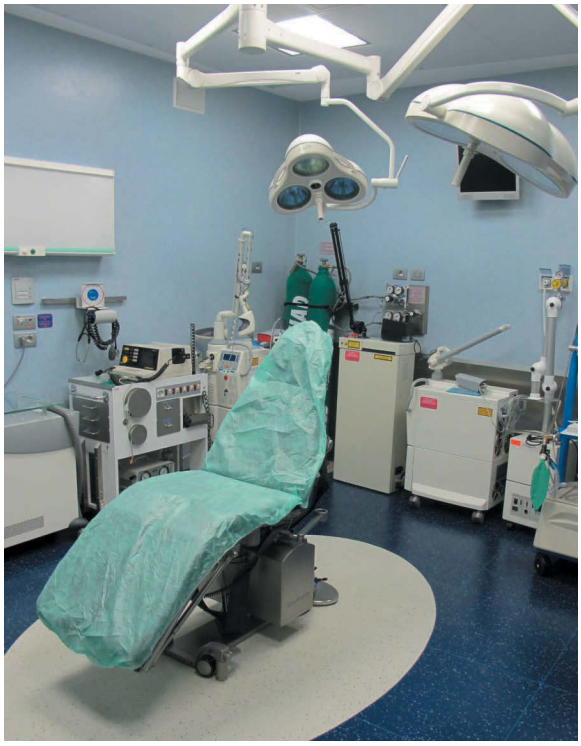


Figure 21.1 Main functional unit (level 3): dermatologic surgery operating theater.

organizational rules described for MFUs should be properly applied to all SFUs. They should provide efficiently organized spaces for an ergonomic positioning of all accessory, non-surgical services that cannot find their place within MFUs.

A simple dermatological surgery office (SDSO), with level 1 MFUs, can be quite easily organized since working space and PTE are relatively simple and their mutual ergonomic interaction is moderately complex. Efficiency of MFUs is necessarily subordinated to proper positioning of SFUs along the communication system responsible for connecting them together.

An advanced dermatological surgery office (ADSO) can accommodate both level 1 and level 2 MFUs and requires more complex ergonomic organization of workflow as well as much more efficient positioning and distribution of relatively larger number of PTE and FTE.

A dermatological day surgery office (DDSO) represents the highest level of organizational complexity within free-standing or hospital-based dermatologic facilities. It can accommodate an extremely efficient, modern surgical environment equipped with level 3 MFUs (operating rooms) along with all necessary SFUs intimately connected with them. In this special configuration, surgical environment is conveniently located in a well-identified, dedicated space within a dermatologic facility, allowing an efficient, logical separation between clean areas and dirty zones (Table 21.1). ADSO and DDSO should be always provided with a properly certified backup power source to support essential technical equipment in case of power failure. Irrespective of the complexity of dermatologic–surgical offices, a dirty-to-clean workflow should be always preliminary planned, constantly

Advanced hybrid medical-surgical unit

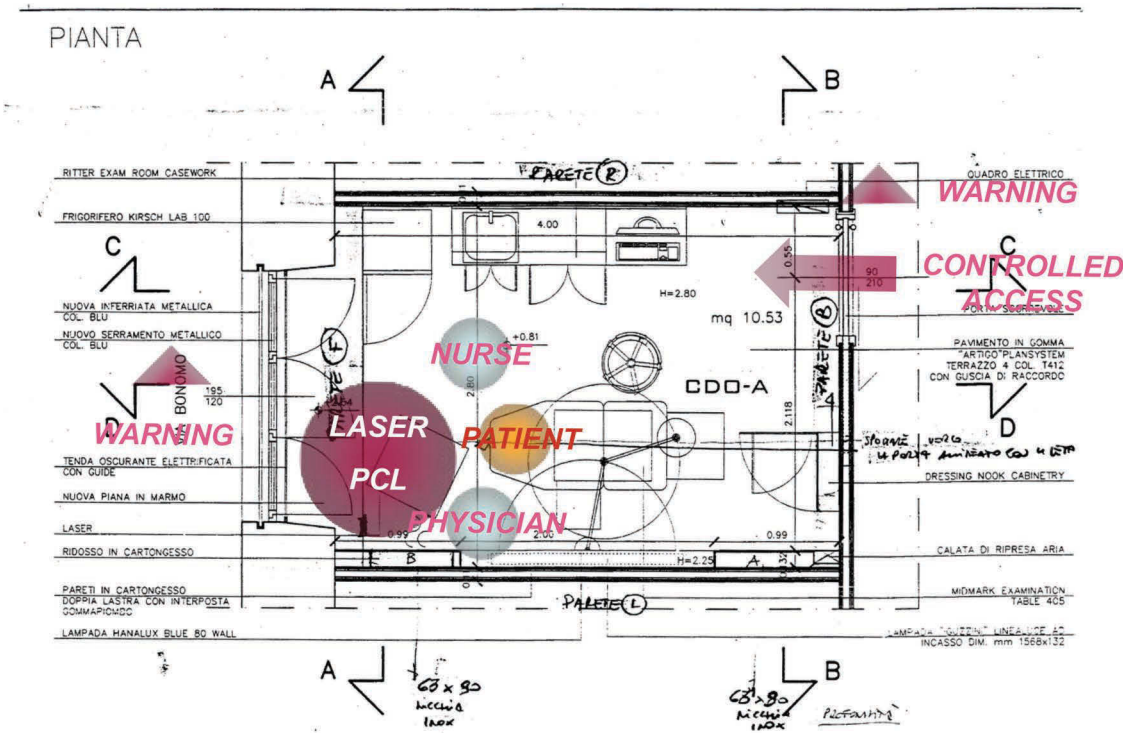


Figure 21.2 Simple hybrid clinical–surgical unit: schematic plan—see PPN description.

Figure 21.3 Advanced hybrid clinical–surgical unit.

implemented, and properly maintained, particularly when surgical instruments and contaminated surgical waste are considered.

Separate SFUs should be planned for dirty activities (decontamination, cleansing, inspection, and wrapping of surgical instruments) (Figure 21.4) and clean activities (sterilization, storage, distribution) (Figure 21.5). In a DDSO, different routes should be followed by patients and surgeons to get access to operating rooms to avoid possible cross contaminations. Surgeons previously involved in clinical activities should change their uniforms and wear surgical scrubs and change their clinical clogs and wear their surgical ones before entering surgical environments. These actions should take place in a properly located SFU identified as surgical changing room. This unit should be placed in the immediate vicinity of the surgical hand-washing unit (Figure 21.6), which in turn should be located close to level 3 MFUs (operating theaters).

Immediately before surgery, patients should be accommodated in the pre- and post-operative recovery room (Figure 21.7). They should be provided with lockers where to safely store clothes and personal belongings during surgical procedures. They should be properly dressed in surgical attire before being accompanied to operating theaters. Recovery rooms should be equipped with their own, dedicated toilet. Storage room for sterilized instruments should be conveniently located as close as possible to operating theaters. Contaminated surgical waste should be properly handled and stored within a dedicated locker to be subsequently discarded by authorized companies. This locker should be located in a position as far as possible from the clean zone of surgical environment. Centralized suction and medical oxygen supply should be available both in the recovery room and in operating theaters. Efficient air filtering systems should be constantly in action within operating rooms. Highly efficient operating tables, shadowless surgical lights, automatic access doors, emergency carts with resuscitative equipment, surgical stools, and anesthesia equipment should be available in each operating theater. An independent surgical nurse desk should be strategically located at the center of the surgical environment in order to efficiently control the full complexity of the surgical workflow (Figure 21.8). All MFUs and SFUs, within an independent surgical environment, should be connected by dedicated transit corridors, interrupted by security access doors, and provided with clearly readable signs indicating the access privileges required to cross them.

Special considerations should be made for class IV laser systems and intense polychromatic pulsed light (IPPL) sources in case they are used within main surgical units. Laser-proof eye protections for doctors and nurses should be easily accessible and readily available within and outside any surgical unit where a laser or IPPL is operated (Figures 21.9 and 21.10). Restricted and protected access to functional rooms should follow strict protocols and color-coded protecting eyewear should always match wavelength emissions specific for each laser or IPPL system (Figure 21.11). Filtered air evacuation systems should be always used when ablative laser procedures are performed in order to effectively aspirate biologically contaminated laser plume [17–19]. The same rule should apply to ablative electrosurgical procedures.

Table 21.1 Classification of Surgical Offices according to Their Level of Complexity

	Main functional surgical units				
Surgical offices classification	Level 1	SHCSU	Level 2	AHCSU	Level 3
Simple Dermatologic Surgery Office (SDSO)	X	X			
Advanced Dermatologic Surgery Office (ADSO)			X	X	
Dermatological Day Surgery Office (DDSO)			X	X	X

Notes: Level 1, minor surgical procedures (local anesthesia); SHCSU, simple hybrid clinical–surgical unit: clinical consultation + minor surgical procedures (local anesthesia). Level 2, intermediate complexity surgical procedures (local anesthesia); AHCSU—advanced hybrid clinical–surgical unit: clinical consultation and advanced clinical examination + intermediate complexity surgical procedures (local anesthesia + IV sedation). Level 3, advanced surgical procedures (local anesthesia + IV sedation/IV general anesthesia).

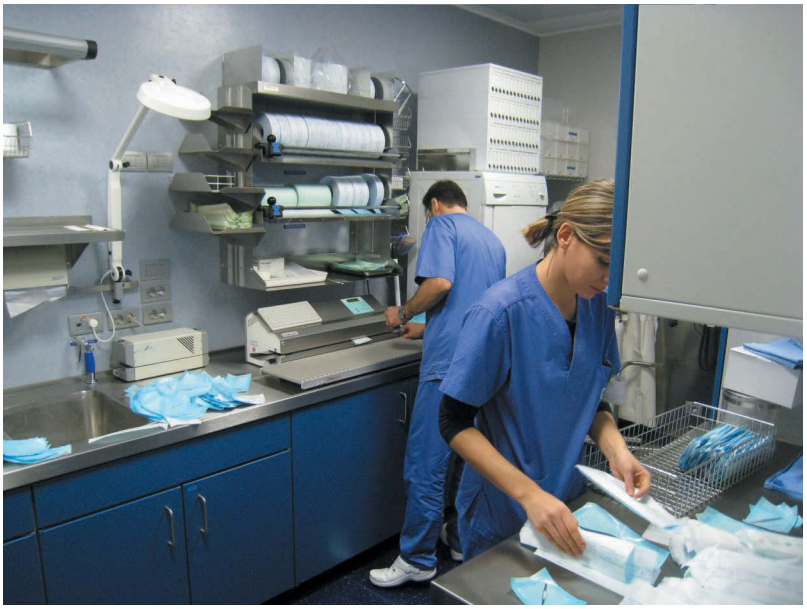


Figure 21.4 Dirty activity service functional unit (decontamination, cleansing, inspection, and instrument wrapping).

Figure 21.5 Clean activity service functional unit (sterilization).

Figure 21.6 Surgical hand-washing unit.

Figure 21.7 Pre- and postoperative recovery unit (Dermatological Day Surgery Office).

Figure 21.8 Surgical nurse station (Dermatological Day Surgery Office).

SURGICAL ENVIRONMENT: ERGONOMIC FUNCTIONAL CONSIDERATIONS

Ergonomics is the study of designing equipment and devices fitting human body and its cognitive abilities. The International Ergonomics Association defines ergonomics as the scientific discipline concerned with the understanding of interactions among humans and other elements of a system, and the profession that applies theory, principles, data, and methods to design with the aim of optimizing human well-being and overall system performance.

To assess the compatibility between a person and a specific technology, ergonomists consider the activity being performed and the demands on the user; the equipment used—its size, shape, and how appropriate it is for the specific task it was planned to perform—and the information provided to properly operate it. Ergonomics is a complex discipline that involves many different competences in different fields of science. Surgical environments, like all advanced professional working environments, need to be planned according to ergonomic rules in order to properly adapt to the multiple, complex tasks required by dermatologists willing to perform surgical procedures. Two major categories of ergonomic scenarios are to be taken into consideration: microergonomic scenarios and macroergonomic scenarios. Microergonomic scenarios pertain to dermatologic use of specific medical devices and equipment located within a MFU either as a PTE or as an FTE.

Macroergonomic scenarios pertain to the organization of surgical workflow among different MFUs and SFUs within dermatologic facilities.

Microergonomic Scenarios

Different medical–surgical devices and technical equipment should have been originally designed by their manufacturers

Figure 21.9 Laser/intense polychromatic pulsed light protective eyewear surgical environment storing rack.

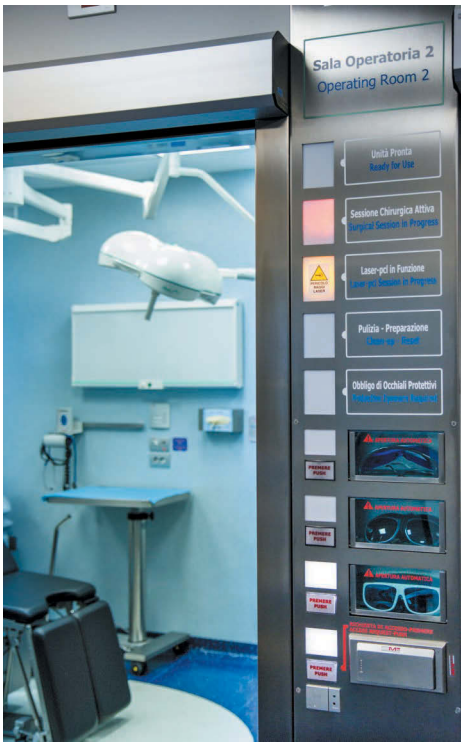


Figure 21.10 Level 3 (operating theater) main functional unit with external informative panel. Light signals provide information about actions taking place inside. Automated built-in laser/intense polychromatic pulsed light protecting eyewear boxes are located at hand reach.

in order to be operated at their best during specific dermatologic procedures provided proper ergonomic rules are implemented by operators within surgical environments. Each medical device and equipment need to be surrounded by a properly designed primary working space. A primary working space can be described as the optimal virtual space calculated to allow smooth and controlled operation of equipment-specific effector terminals by surgeon's and/or assistant's hands (Figure 21.12).

A secondary working space needs also to be considered. Each medical device and technical equipment is usually provided with specific accessories that need to find a proper place within a busy surgical environment (Figure 21.13). Their use should not negatively interfere with equipment-specific primary working spaces allowing operators to perform their tasks at their best. Secondary working space takes care of the spatial organization of specific equipment accessories within surgical environment. Since modern dermatologic surgical environments require multiple primary and facultative technical devices to be fully operational, planning proper positioning of each of them needs a careful preliminary consideration. Primary and secondary working spaces are complementary and should be properly calculated considering technical equipment at rest and during their activities (Figure 21.14). A successfully designed surgical environment can be easily and effectively prepared for surgery, allowing smooth and controlled surgical procedures and rapid cleaning when surgery is over. These sequential actions are usually repeated many times during a typical working day in a busy dermatologic office where surgical procedures are relatively short lasting and mostly local/regional anesthesia is performed (Table 21.2).

Main functional environments can accommodate different medical figures beyond patients. Their number varies according to their level of complexity. A maximum and minimum number of medical staff should be allowed to enter a MFU. These numbers should be properly calculated in order to allocate properly designed primary working spaces necessary for a smooth operation of each technical equipment staff is authorized and entitled to operate [20].

Working spaces should be designed and calculated considering the dynamic nature of surgical procedures, which are always divided into three main time intervals: time before, time during, and time after surgery.

Ergonomic organization of surgical environments is a challenging puzzle of dynamically interlocking primary and secondary working spaces, each specific for every PTE and FTE operated by the variable number of medical staff allowed to use them.

The statement "more space is better" is always applicable when a well-thought ergonomic surgical space has been properly planned, designed, and realized. When MFUs or SFUs are too big for their specific tasks, the risk of losing control of overall working processes is not negligible. Well-organized ergonomic surgical environments have many advantages to offer: time efficiency, reduced number of sporadic and repetitive

Figure 21.11 Advanced laser/intense polychromatic pulsed light (IPPL) automated protection system applied to main functional units. Step 1: activation of laser/IPPL working scenario featuring automatic external protection by laser-proof curtains (b,c,d,) and magnetic closure access doors (e,f). Step 2: selection of specific laser/IPPL wavelength-matching protective eyewear located outside main functional unit according to laser/IPPL unit chosen for a specific procedure (g,i,j,k). Step 3: automatic opening of operator-selected protective eyewear (h) when staff need to enter active functional unit.

errors by surgeons and staff, relaxed and comfortable operation, easy equipment control and maintenance, patient perception of safety, and efficiency.

The shorter distance between two points is a straight line; therefore, a well-organized surgical environment should be designed in a way that allows surgeons and staff to move and use their limbs following a series of straight lines connecting properly positioned medical devices and technical equipment to anatomical areas of patients during surgery. Practical implementation of this simple rule will save a consistent amount of time, optimizing surgical efficiency, adding to the comfort of surgeons and staff, inducing automatic behaviour, and providing more time for controlling instrument efficiency.

Multiple, well-positioned outlets should be planned and positioned according to PTE and FTE selected to be a part of specific MFUs. Level 1 and level 2 surgical units should accommodate an automatically operated surgical sink. It usually finds its place within the main surgical environment. Level 3 surgical units cannot accommodate a surgical sink within their surgical environment. All surgical environments should have perfectly sealed washable floors and walls. Once a perfect ergonomic organizational design has been obtained, MFUs and SFUs can be used as excellent templates to be "cloned" within the space allowed by the architectural plan of a new medical–surgical facility. "Cloning" of MFUs and SFUs within a medical–surgical facility introduces the advanced concept of standardization within medical–surgical environments (Figures 21.15 and 21.16). Standardization of working spaces within multiple, similar FUs helps to reduce staff training time, speed up automatic behaviour, and limit repetitive and sporadic surgical and procedural errors potentially performed by surgeons and staff (Table 21.3).

Medical and surgical staff is an extremely valuable and expensive working force of any aesthetic and cosmetic-oriented dermatological facility. Staff training is not an easy task and requires a considerable amount of time that inevitably needs

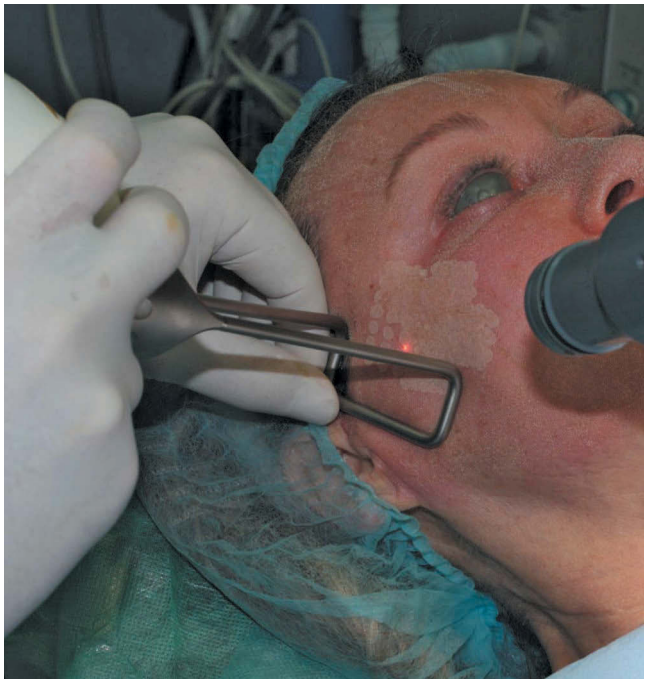


Figure 21.12 Surgical laser primary working space.

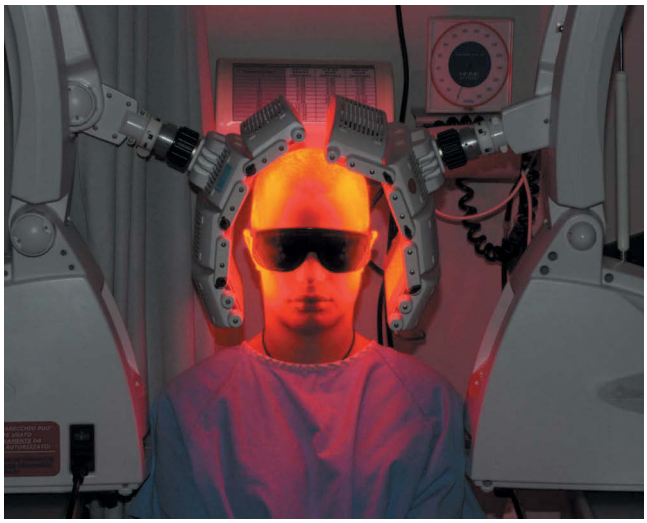


Figure 21.13 Photodynamic therapy LED irradiation systems an example of a secondary working space necessary to effectively operate two LED light sources around a patient's head.

to be subtracted from the already busy schedule of a doctor. Ergonomic organizational standardization of FUs makes the staff aware of the virtual presence of an "organized mind" behind it. Should that mind be identified with the dermatologist who plans his or her own office, the message delivered through a standardized organization should not be repeated. Automatic behavioral processes can be described as strongly interlinked sequential actions performed by doctors and staff

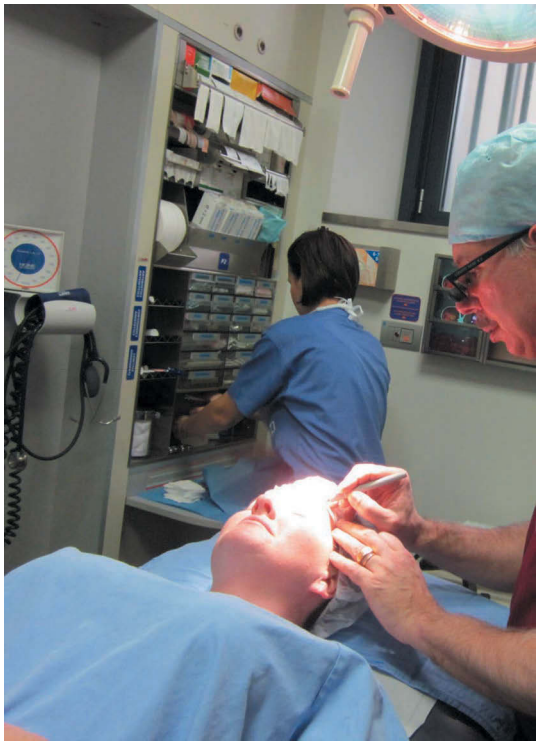


Figure 21.14 Advanced hybrid clinical–surgical unit: primary and secondary working space.

during the course of specific surgical and nonsurgical procedures. Automatic medical–surgical behaviors are not intended to be regarded as "automatic pilot" situations where everything is performed under the virtual control of a computer. They simply add to precision and time efficiency of specific procedures due to mental comfort of operators. Their minds should not be engaged in repetitively recalling of complex series of sequential procedural steps associated with potential fear of missing one of them, but should simply concentrate on the proper medical–surgical act taking place. Surgical and procedural errors cannot be obviously entirely avoided. They can be nevertheless reduced to a minimum thanks to the beneficial effects provided by constant reassuring messages originating from standardized, ergonomically organized functional environments [21,22]. These "unspoken language messages" are extremely valuable not only to doctors and staff but also to patients who feel quite comfortably reassured just observing precision and efficiency of a perfectly organized medical–surgical environment.

There is always some level of anxiety perceived by patients before entering a medical–surgical facility. The concept of pain related to invasiveness of surgical procedures is difficult to be properly dominated and controlled, particularly by psychologically vulnerable patients [23]. Well-organized, nicely illuminated, soothing colored FUs should help to reduce patients' anxiety before and during any kind of medical-surgical procedure. Professional efficiency produced by automatic functional behaviors by doctors and staff can generate more time to dedicate to a positive supporting emphatic behavior, further improving their level of confidence and comfort.

Table 21.2 List of Invasive Dermatologic Procedures Usually Performed in Office-Based Surgical Facilities along with Advisable Main Functional Units Levels Where They Should Take Place

	Main surgical units		
Invasive diagnostic procedures	Level 1	Level 2	Level 3
Electrosurgery	X	X	X
Cryosurgery	X	X	
Chemical peel—superficial	X	X	
Chemical peel—intermediate depth		X	X
Chemical peel—deep			X
Ablative laser procedures—simple	X	X	
Ablative laser procedures—intermediate		X	X
Ablative laser procedures—advanced			X
Nonablative laser procedures—simple	X	X	
Nonablative laser procedures—intermediate	X	X	
Nonablative laser procedures—advanced		X	X
Q–S laser procedures—simple	X	X	
Q–S laser procedures—intermediate		X	
Q–S laser procedures—advanced		X	X
RF ablative procedures—simple	X	X	
RF ablative procedures—intermediate	X	X	
RF ablative procedures—advanced		X	X
RF nonablative procedures	X	X	
Ultrasound cavitation procedures	X	X	
High-intensity focused ultrasound		X	
Polychromatic pulsed light	X	X	
LED photobiomodulation	X	X	
Needling—simple	X	X	
Needling—intermediate		X	X
Needling—advanced			X
Subcision—simple	X	X	
Subcision—intermediate		X	X
Subcision—advanced			X
Soft tissue augmentation—autologous			X
Soft tissue augmentation—fillers	X	X	
Botulinum toxin treatment	X	X	
Phlebologic procedures			X
Sclerotherapy	X	X	
Liposuction			X
Nail surgery		X	X
Circumcision			X
Oncologic surgery—simple	X	X	
Oncologic surgery—intermediate		X	X
Oncologic surgery—advanced			X
Blepharoplasty			X
Browlift			X
Face-lift			X
Excisional surgery—simple	X	X	
Excisional surgery—intermediate		X	X
Excisional surgery—advanced			X
Mohs micrographic surgery		X	
Surgical reconstruction—simple	X	X	
Surgical reconstruction—intermediate		X	X
Surgical reconstruction—advanced			X
PDT—conventional	X	X	
PDT—advanced		X	X
Intralesional infiltration procedures	X	X	
PRP	X	X	
Hair transplantation		X	X

Macroergonomic scenarios involve the strategic positioning of MFUs and SFUs within the space provided by a medical–surgical facility. FUs should be positioned following a thorough analysis of operational workflows of patients, medical, and secretarial staff. All FUs need to be connected to each other by well-planned routes. Properly organized surgical facilities allow fast recognition of specific routes dedicated to patient and staff. Hallways should be planned to avoid "congestions and traffic jams" (Figures 21.17 and 21.18). They should provide clearly intuitive access information to common service functional areas and regulated access to protected, restricted areas without or with minimal help from

Figure 21.15 Advanced hybrid clinical–surgical unit: standardized custom-made wall-mounted storing cabinet 1.

Figure 21.16 Advanced hybrid clinical–surgical unit: standardized custom-made wall-mounted storing cabinet 2.

facility staff. Hallways should be large enough to adequately accommodate the flow of patients, staff, and doctors as well as mobile technical equipment during their repositioning in different FUs without interfering with the operational efficiency of the whole medical–surgical facility. FUs should be separated by doors with different locking systems. All doors should be wide enough to allow wheelchairs and stretchers to pass through. Level 1 and level 2 surgical units may have manually operated doors with proper locking systems. Magnetic closure doors, even if more expensive, allow a properly monitored access control and are ideal choices when laser and IPPL operations are planned. Level 3 surgical units must have automatically operated sliding doors. Outside each MFU, there should be an information panel to provide visual information on what is actually happening inside. This will enormously facilitate the workflow of patients and staff within a busy dermatologic facility. In case potentially dangerous class IV lasers and IPPL equipment are used, properly allocated spaces for protective eyewear should be available outside MFUs. In more advanced dermatologic surgery facilities, automated systems allow operators to properly select specific protective eyewear outside each MFU.

PRIMARY TECHNICAL EQUIPMENT

Main surgical units need to ergonomically accommodate PTE within their working spaces. PTE defines a series of medical and nonmedical devices absolutely necessary to perform surgical procedures planned and approved for their specific level of complexity.

Ceiling Lights and Surgical Lights

Ceiling lights should provide a uniform bright, yet comfortable, illumination to allow proper clinical and diagnostic procedures. Washable screened fluorescent lights perform quite well for this task. Surgical lights belong to the key PTE category. Good surgical lights are quite expensive but their value is long lasting. Ceiling-mounted or wall-mounted surgical lights are preferred over wheeled ones since stands take up valuable working space and might interfere with the complex ergonomic organization of surgical environment.

Operating Room Tables and Advanced Clinical–Surgical Hybrid Tables

Another key PTE category is identified by operating tables. True operating tables are expensive but allow to modify their structure to conform with all kind of surgical positions. They usually come with a large series of accessories that need to be properly stored in dedicated cabinets. Surgical tables are usually hydraulic powered to allow smooth and precise micro- and macromovements (Figures 21.19 and 21.20).

Clinical–surgical hybrid tables allow both clinical and surgical performances. They are much simpler than true surgical tables but can feature up to four structural joints (head, back, seat, and legs) to comfortably adjust to main surgical and clinical positions. Hybrid tables are usually larger and more comfortable than true surgical tables. They are mostly electric powered and can lower their seats to a short distance from the floor in order to allow an easy access especially for handicapped and elderly patients. Most of the hybrid tables come equipped with built-in functional accessories that can transform them

Table 21.3 List of Main and Service Functional Units Usually Considered When Planning an Office-Based Dermatologic Surgery Facility

Functional units		Assigned tasks, functions, and equipment
Surgical units	Level 1	Minor surgical procedures, local anesthesia
	Level 2	Intermediate complexity surgical procedures, local anesthesia
	Level 3	Complex surgical procedures, IV sedation/IV general anesthesia
	SHCSU	Clinical consultation, simple clinical examination + minor surgical procedures, local anesthesia
	AHCSU	Clinical consultation, advanced clinical examination + intermediate complexity surgical procedures, local anesthesia
CU	Level 1	Clinical consultation, simple clinical examination
	Level 2	Clinical consultation, advanced clinical examination
Service units	Main entrance	Patient access without architectural barriers
	Secondary entrance	Staff access
	Reception	Front office (check-in/checkout), back office (administration)
	Waiting room	Patient waiting
	Doctor office room	Medical library, meeting
	Staff changing rooms	Personal clothes cabinets, medical uniforms
	Staff toilets	Specific for staff
	Patients' toilet	Specific for patients
	Kitchen	Staff refreshment room
	Cleaners' room	Cleaners' equipment storage
	Pharmacy	Restricted access medications storage
	IT server room	Restricted access air-conditioned IT station
	Technical room	Restricted heavy equipment (surgical suction, emergency power supply, air-processing units)
	Medical oxygen tank storage room	Restricted access centralized medical oxygen station
	Clinical nurse station	Medical documents printing and protected storage
	Clinical section toilet	Specific for patients
	Temporary surgical waste cabinet	Restricted access surgical waste storage
	Storage cabinets—safe items	Medical–surgical supplies and equipment accessories protective storage
	Storage cabinet—hazardous chemicals	Restricted access special air filtering + aspiration to safely store hazardous chemicals
	Preparation and recovery room	Preoperative patient preparation and postoperative recovery
	Surgical section toilet	Specific for surgical patients
	Surgical changing room	Surgical scrubs and protective items for surgeons and staff
	Cleaning and decontamination room	Surgical instruments decontamination, cleaning, and wrapping
	Surgical nurse station	Surgical documents protected storage
	Narcotics' safe	Restricted access highly protected narcotics storage
	Sterilization room	Autoclave room
	Surgical liquid waste cabinet	Surgical liquid waste cleaning
	Sterile instrument storage room	Restricted access sterile instrument storage
	Mohs' histologic laboratory	Frozen sections histology equipment

Note: Selection of functional units should match the level of complexity chosen for specific surgical treatment plans.

into a gynecological table, and leg rests can also work extremely well for leg ulcer management (Figure 21.21).

Surgical Stools

Surgical stools are extremely important for the comfort of the surgeon and his or her assistant during longer operations. They can be adjusted with a foot control mechanism and are small enough to allow the surgeon and assistant to get as close as possible to the anatomical sites of patients positioned on operating tables.

Mayo Stand and Surgical Carts

Mayo stands are the main working surface of surgical units. They can be easily moveable around surgical tables and adjustable to any position needed for all kind of procedures. Sterile surgical instruments and small surgical equipment can be laid down in a good array on their working surface. Different platform sizes can be accommodated on different movable stands. The choice depends on the surgical procedures mostly performed in a dermatologic facility and on specific surgeons' preference.

Surgical Suction and Surgical Gases

Surgical suction can be useful when operating in deep cavities or in patients with coagulative disorders. Portable suction units are quite handy to move to and from surgical units and are ideal in level 1 and level 2 MFUs. Level 3 surgical unit requires a centralized, wall suction system.

Simple and advanced dermatological surgical offices do not require any centralized medical oxygen distribution system. In case of need, portable oxygen tanks can be chosen. Level 3 MFUs and day surgery dermatological offices require centralized medical oxygen distribution.

Vital Functions Monitoring Equipment

Pulse oximeters are inexpensive, portable, and extremely useful monitoring instruments used to constantly check patients' blood oxygen saturation and pulse rate during any kind of

Figure 21.17 Clinical–surgical hallway serving level 1–2 main functional unit.

Figure 21.18 Surgical hallway serving level 3 main functional unit.

Figure 21.19 Operating room table: compact design.

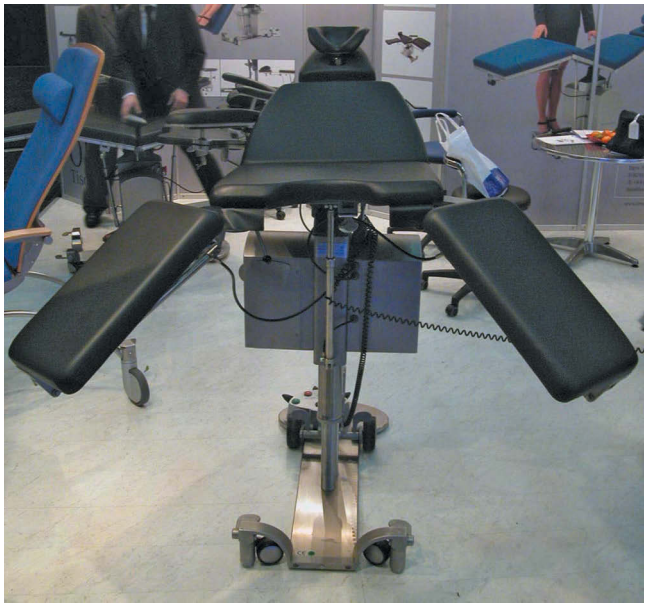


Figure 21.20 Operating room table: extremely versatile patient positioning capabilities.

operations. Conventional wall-mounted blood pressure cuffs, stethoscope, and electronic thermometers should be standard diagnostic equipment in any surgical rooms. Advanced monitoring systems feature EKG, blood pressure, oxygen saturation, CO_2, heart rate, and temperature. They are necessary when performing advanced IV sedation in level 3 main surgical units.

Resuscitative Equipment

All surgeons involved in more advanced cosmetic and aesthetic surgery should be certified in basic and advanced cardiopulmonary resuscitation (CPR) along with his or her scrub nurses. Automatic external defibrillators are needed in a day

Figure 21.21 Hybrid clinical–surgical treatment table.

surgery dermatological office. An emergency resuscitation cart with written pharmacological resuscitative protocols should be available in level 3 main surgical units. Its preparation is usually assisted by a professional advice provided by a certified anesthesiologist. Its periodic control should be performed by level 3 MFUs' scrub nurses. Adult and pediatric laryngoscopes, AMBU bag, disposable suction tubes, and mouth openers should be part of the emergency resuscitative set (Figure 21.22).

Figure 21.22 Emergency—anesthesiology cart.

Figure 21.23 Level 1–2 main surgical units—standardized storage cabinets.

Electrosurgical Units

Electrosurgical coagulation is essential during any kind of surgical procedure. Level 1 and level 2 MFUs can be equipped with simple wall-mounted hyfricators (Hyfricator 2000, Conmed, USA), but more powerful monopolar RF units are necessary when more invasive surgical procedures are performed. Level 3 main surgical units need a proper RF electrosurgical cutting and coagulation unit as part of its main technical equipment.

Cabinets

Level 1 and level 2 surgical units require proper storage space to accommodate all necessary disposables to be orderly distributed in hospital-grade medical cabinets (Figure 21.23).

Custom-made wall-mounted functional cabinets can be designed to host all main disposable medical devices to be easily seen and taken out during routine clinical–surgical operations. They can be quite expensive to make, but they pay off in time due to the high level of ergonomic efficiency and storage organization. Main storage cabinets are usually located outside MFUs in order not to take off precious working space. Level 3 surgical unit is usually served by a service unit located close by. Sterile disposables and sterile surgical instruments should be passed from the service unit to the main surgical unit through a protected sliding window.

Refrigerator

Many cosmetic and aesthetic procedures require cold skin contact with different medical devices during and after their performance. Cold (+4°C) can be easily generated by a regular refrigerator, where IPPL transparent light-coupling gel, canisters of spring thermal water, N/S bags, ice packs, BTX vials, and topical anesthetic creams can be easily and efficiently stored. Small-size refrigerators could find their place within each level 1 and level 2 MFUs, either as independent appliances or built-in cabinet appliances. Level 3 surgical units are served by refrigerators located in the adjacent SFU.

Figure 21.24 Digital camera wall-mounted protected stand.

Waste Disposal

Movable kick stainless steel waste buckets should be available in all surgical units. They should be positioned as close as possible to the surgical action site in order to minimize the distance between a potentially biologically contaminated site and its temporary storage. Wall-mounted sharp containers should be available in all surgical units as well. Surgical waste need to be properly handled according to approved written protocols while temporarily stored in dermatological offices. Certified surgical waste elimination companies should be responsible for its final destruction outside medical facilities.

X-Ray Film Viewer

A wall-mounted x-ray film viewer should be available in all main surgical units.

Surgical Clock

A wall-mounted surgical clock allows monitoring of the time of a surgical procedure. It should be considered in any level 3 main surgical units.

Photographic Equipment

A digital camera, preferably linked with a dedicated patients' electronic medical record system, should be available in every MFU since medical photography is absolutely essential to monitor clinical progression after cosmetic and aesthetic procedures [24]. Following the fundamental rule, "a place for everything and everything in its place," even digital cameras should have their protected place, better located away from busy and potentially *dangerous* working areas (Figure 21.24). More complex imaging systems like *Visia* (Canfield, United States) and Antera (Miravex, Ireland) should be considered as FTE to be used in case of need.

Audio System

Music is able to reduce anxiety in surgical patients, before, during, and after surgical procedures. Properly protected loudspeakers should be strategically positioned in each FU to "camouflage" potentially disturbing surgical sounds (unwrapping surgical instruments, preparing for local anesthesia, electrosurgical noise, etc.). Doctors and staff usually benefit from this simple environmental quality improvement. Advance audio systems can be used for internal staff communication.

FACULTATIVE TECHNICAL EQUIPMENT

Modern aesthetic and cosmetic dermatology uses a large number of medical devices and sophisticated technical equipment, either alone or in combination, in order to produce high-level clinical results. Even the most advanced, ergonomically designed FUs cannot accommodate all these technologies within their working spaces. FTE can be temporarily placed within FUs according to specific requirements associated with specific procedures. A typical case is the positioning of a class IV laser source, an IPPL system, a RF system, or a LED source (Figure 21.25). Enough space surrounding the operating room table is necessary to move these, sometimes bulky

Figure 21.25 Example of facultative laser + aspiration equipment temporarily positioned within an advanced hybrid clinical–surgical unit.

equipment around the patient, allowing comfortable primary and secondary working spaces for doctors and staff. Moving this kind of equipment in and out of a MFU should be an easy task since a busy practice can offer more treatments than its number of MFUs itself. The concomitant presence of many doctors within advanced dermatologic facilities inevitably calls for an extreme versatility in facultative equipment use within MFUs.

Delicate and potentially fragile high-tech equipment inevitably modify complex equilibriums of previously planned standard working environments within MFUs. Working environments and medical staff need to temporary adapt to potentially new functional situations. Each specific FTE is characterized by specific functional needs in terms of safety, operational requirements, and accessories. All these needs pertain exclusively to each of them and should be properly "transported" no matter where they are positioned. Doctors and staff should be properly trained in dealing with all specific operational functions of each FTE used within an advanced dermatologic facility.

SUMMARY

Office surgery is an integral part of modern dermatology. Dermatologists are performing most of the common cosmetic and aesthetic procedures available today, immediately followed by plastic surgeons [25]. A properly organized, well-planned working environment is necessary to effectively and safely perform office-based invasive surgical procedures. Application of advanced ergonomic concepts to surgical environments enormously optimizes overall efficiency of advanced medical–surgical facilities. Standardization of ergonomic solutions within a busy dermatological practice helps to reduce staff training time and contributes to efficiently implement habits among doctors and staff. Organizational efficiency of surgical environment positively influences patients' perception of safety before, during, and after surgical procedures. Due to the proliferation of aesthetic and cosmetic surgical procedures, it is imperative to continuously educate the public on the importance of surgical training and the performance of these procedures in well-organized, qualified surgical facilities.

REFERENCES

1. Geronemus R, Bisaccia E, Brody HJ et al. Current issues in dermatologic office-based surgery. *J Am Acad Dermatol* 1999; 41(4):624–634.
2. Stegman SJ, Tromovitch TA. Cosmetic dermatologic surgery. *Arch Dermatol* 1982; 118:1013–1016.
3. Maloney M. The surgical suite. In: Grekin RC, ed. *The Dermatological Surgical Suite, Design and Materials*, 1st ed. New York: Churchill Livingstone, 1991.
4. Whitaker-Worth D, Shahriari M, Slade K, Grant-Kels JM. The ethical controversies of office-based dispensing in academic health centers. *Clin Dermatol* 2012; 30:528–532.
5. Tierney EP, Hanke CW. Recent trends in cosmetic and surgical procedure volumes in dermatologic surgery. *Dermatol Surg* 2009; 35:1324–1333.
6. Mustoe TA, Buck DW II, Lalonde DH. The safe management of anesthesia, sedation, and pain in plastic surgery. *Plast Reconstr Surg* 2010; 126:165e–176e.
7. Bitar G, Mullis W, Jacobs W et al. Safety and efficacy of office-based surgery with monitored anesthesia care/sedation in 4778 consecutive plastic surgery procedures. *Plast Reconstr Surg* 2003; 111:150–156.
8. Balkrishnan R, Hill A, Feldman SR, Graham GF. Efficacy, safety, and cost of office-based surgery. A multidisciplinary perspective. *Dermatol Surg* 2003; 29:1–6.
9. Horton JB, Reece EM, Broughton G II, Janis JE, Thornthon JF, Rohrich RJ. Patient safety in the office-based setting. *Plast Reconstr Surg* 2006; 117:61e–80e.
10. Horton JB, Janis JE, Rohrich RJ. Patient safety in the office-based setting. *Plast Reconstr Surg* 2008; 122:1–21.
11. Morello DC, Colon GA, Fredericks S et al. Patient safety in accredited office surgical facilities. *Plast Reconstr Surg* 1997; 99:1496–1500.
12. Meneghetti SC, Morgan MM, Fritz J, Borkowski RG, Djohan R, Zins JE. Operating room fires: Optimizing safety. *Plast Reconstr Surg* 2007; 120:1701–1708.
13. Davey WP. Quality improvement and management in dermatology office. *Arch Dermatol* 1997; 133:1385–1387.
14. Kesheimer K, Davey WP. Continuous quality improvement in a dermatologic surgery office. *Arch Dermatol* 2000; 136:1400–1403.
15. Accreditation Association for Ambulatory Health Care. AAAHC Guidebook for Office Based Surgery Accreditation, 2003.
16. Tobin HA. Office surgery: The surgical suite. *J Dermatol Surg Oncol* 1998; 14:247–255.
17. Goldman MP. One laser for cosmetic/dermatologic practice. *J Clin Aesth Dermatol* 2011; 4(5):18–21.
18. Tzung TY, Tzung CP, Yang CY, Yang DJ, Kao MR. Decision factors and the recognition of medical specialty in patients receiving cosmetic laser and intense pulsed light treatment. *Dermatol Surg* 2007; 33:1499–1493.
19. Sliney DH. Laser safety. *Lasers Surg Med* 1995; 16:215–225.
20. Resneck JS, Kimball AB. Who else is providing care in dermatology practices? Trends in the use of nonphysician clinicians. *J Am Acad Dermatol* 2008; 58:211–216.
21. Haeck PC, Swanson JA, Iverson RE et al. Evidence-based patient safety advisory: Patient selection and procedures in ambulatory surgery. *Plast Reconstr Surg* 2009; 124 (suppl.):6S.
22. Fader DJ, Johnson TM. Medical issues and emergencies in the dermatologic office. *J Am Acad Dermatol* 1997; 36:1–16.
23. Vachiramon V, Sobanko JF, Rattanaumpawan P, Miller CJ. Music reduces patient anxiety during Mohs surgery: An open-label randomized controlled trial. *Dermatol Surg* 2013; 39:298–305.
24. Niamtu J III. Image is everything; Pearls and pitfalls of digital photography and power-point presentations for the cosmetic surgeon. *Dermatol Surg* 2004; 30:81–91.
25. Camp MC, Wong WW, Wong RY, Camp JS, Son AK, Gupta SC. Who is providing aesthetic surgery? A detailed examination of the geographic distribution and training backgrounds of cosmetic practitioners in southern California. *Plast Reconstr Surg* 2010; 125:1257–1262.

Aesthetic suture techniques

Eckart Haneke

Sutures are intended to approximate and coapt wound margins. In aesthetic surgery, they are mainly used to close wounds after cosmetic as well as oncologic and other operations. Their aim is the least obvious scar.

The principle of wound closure is probably as old as the treatment of wounds itself. From directly pulling wound margins together to using ants as staples and to sutures and a variety of suture substitutes, the history of wound closure mirrors both the human ingenuity and the technical progress.

Many factors have to be considered for an aesthetic suture:

- Wound condition
- Wound direction
- Localization
- Defect size and wound tension
- Particular wound healing characteristics
- Suture material and other wound closure materials
- Type and size of needles
- Suture techniques
- Dressing
- Suture removal

WOUND CONDITION, SIZE, AND TENSION

It is self-evident that only optimal wounds can be sutured with a near-perfect aesthetic result. Infected or chronic wounds, ulcers, wounds the margins of which have been squeezed or otherwise maltreated, or those in chronic radiodermatitis or with severe solar damage will not give a pleasing scar even with the best suture techniques. Large wounds in areas without skin availability will require a flap or graft to avoid undue tension, which in turn will cause an unsightly scar. In such a case, it is better to leave a tiny defect for second intention healing instead of risking wound margin necrosis [1].

WOUND DIRECTION

A prerequisite for optimal healing is that the wounds' long axis run as parallel to the relaxed skin tension lines as possible. This is usually the case for simple fusiform excisions and for the removal of subcutaneous lesions such as lipomas and cysts but may be difficult to follow when a large lesion had to be removed and a flap is necessary to close the defect.

LOCALIZATION

The localization of a wound plays an important role for the suture technique to be used. Suture lines can be hidden in body folds, natural creases, and wrinkles in the elderly. Exposed smooth and convex structures such as the cheeks, nose, or décolleté require finest sutures and respecting all the principles mentioned above and below.

PARTICULAR WOUND HEALING CHARACTERISTICS

It is well known that some persons tend to heal fast and with excellent inconspicuous scars, whereas in others, the wound healing process may always take longer, and the scars remain red for a long time and often become dehiscent. This can unfortunately not be influenced although optimal suture techniques help to prevent the worst.

The general condition of the individual to be operated is also important for the final result.

Particular attention has also been paid to regions that are prone to develop hypertrophic scars or even keloids. A personal and family history is important. It is noteworthy that individuals with a dark complexion tend to develop keloids more often and also of bigger size, whereas keloids have—to our knowledge—not been seen in albinos. In keloid-prone persons, all wound sutures have to avoid tension and surgery must be absolutely atraumatic.

SUTURE MATERIAL AND OTHER WOUND CLOSURE MATERIALS

Suture materials are classified according to the physicochemical structure of the material and configuration, their tensile strength that is usually associated with its thickness, the absorbability, their immunogenicity and tolerability, as well as other mechanical properties such as knot strength, memory, elasticity, and plasticity. Multifilament sutures have a wick effect and induce a stronger tissue reaction.

Biologic and synthetic materials are available. The former comprise catgut, cotton, and silk, and they are more immunogenic and usually provoke a more intense tissue reaction.

Absorbable Sutures

Absorbable sutures lose their tensile strength within a period of a few days to 2 months. However, it takes longer for complete absorption of all the material. In cosmetic skin surgery, they are mainly used for buried sutures, although monofilament sutures can well be used for percutaneous stitches but have to be removed like nonabsorbable sutures.

Catgut is multifilament twisted, fast absorbable, and of low tensile strength and knot stability. It is mainly used for vessel ligation and for sutures in the mouth and genitalia, lost in 7–10 days, but the absorption rates are unpredictable. Treated surgical gut such as chromic gut is more resistant.

Polyglycolic acid (Dexon®) is a braided multifilament thread with good handling properties and knot stability. It may be coated to improve its surface smoothness, allowing to pull it through the tissue with more ease and minimize the tissue reaction. Its tensile strength is decreasing more slowly than that of surgical gut, and its absorption rate is 60–90 days.

Polyglactin (Vicryl®) is another material with good handling and knot strength. Its tensile strength is higher than that of polyglycolic acid, which is still 50% after 3 weeks. It is completely absorbed within 8–10 weeks. Vicryl Rapide® loses its tensile strength and is completely absorbed much faster.

Lactomer (Polysorb®) is another braided multifilament absorbable suture with good handling, knot stability, and tensile strength.

Polydioxanone (PDS II®) is a monofilament absorbable material with very good tissue tolerability and high tensile strength, but handling and knot strength are poor. It remains stable for a long time. Absorption takes 3–6 months.

Polytrimethylene carbonate (Maxon®) is a monofilament with very good handling, knot stability, tensile strength, and tissue tolerance but is slightly more rapidly absorbed than polydioxanone.

Poliglecaprone 25 (Monocryl®) is comparable to polytrimethylene carbonate in handling, knot stability, and tissue tolerance but has the highest initial tensile strength.

Nonabsorbable Sutures

These sutures retain their tensile strength for a minimum of 2 months. Some sutures are then slowly degraded except for stainless steel, which is however rarely used in dermatologic aesthetic surgery.

Silk (Sofsilk®, Perma-Hand®) is a natural material spun from the cocoon of silk worms. It represents a foreign protein and thus elicits a strong tissue reaction. It is a braided multifilament with excellent handling and knot strength, low memory, and poor tensile strength.

Uncoated polyester (Dacron®, Mersilene®) and other multifilament sutures such as coated polyester (Ticron®, Ethibond®) show very good handling and tensile strength, good knot stability, and moderate tissue reactivity.

All monofilament sutures such as polypropylene (Prolene®) and nylon (Dermalon®, Etholon®) are very well tolerated but show poor handling with moderate to high memory resulting in poor knot stability.

Suture diameters define their tensile strengths, which also depend on the material. In cosmetic surgery, fine sutures are commonly used, between 4-0 and 6-0, and at the eyelids even 7-0. Scalp wounds may sometimes require 3-0. The diameter is less with a higher number before the zero. The appearance of stitch marks does not depend on the suture thickness but rather on the tension on the wound margins and the duration of stitches in the skin.

NEEDLES

Needles come in various shapes and designs, but few different types are used in aesthetic surgery of the skin. Nowadays, atraumatic needles are almost invariably used. The tip has to be sharp to allow it to slide easily through the dermis as virtually all other tissue component exerts much less resilience. The needle must be malleable in order not to break and strong enough to resist bending. Sharp tips cause less trauma and give better aesthetic results. The body may be coated with silicone to improve needle penetration. Three parts make up the needle: The shank where the thread is swaged to the needle; this is the weakest part. The body is about 75% of the needle curvature and extends between the shank and the tip. It is the strongest part. This part is grasped by the needle holder. Although it is generally shown to hold the needle one-half to two-thirds from the tip, we rather recommend to hold it one-third to one-half from the tip as this prevents the needle from being bent or even broken (Figure 22.1). The tip has to be sharp. Three types of tips are available: conventional with the cutting edge on the inside of the curvature (PC Ethicon®), reverse cutting (P, PS) with the cutting edge on the outside, and round without a cutting edge. FS means "for skin" and has lower quality honing and steel than the other needles. A very important point is the curvature of the needle. The most commonly used is 3/8 circle, but we prefer 1/2 circle as it allows to suture where there is even little space to evert the tissue or in very small spaces. Cutting needles are easier to run through the tissue, whereas those with a round tip are less traumatizing and do not tend to tear through tissue.

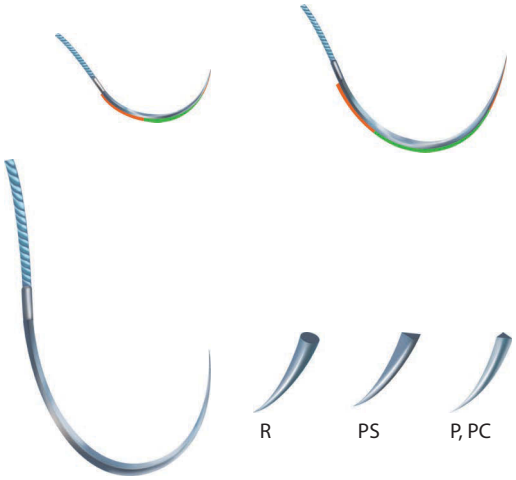


Figure 22.1 Needles commonly used in dermatologic surgery. Although the 3/8 curvature is used by most surgeons, the 1/2 curvature often allows easier handling. The needle should be held in the green area, which moves toward the tip in the semicircular as compared to the three eighths needle. P, PC cutting, PS reverse cutting, R round.

TISSUE ADHESIVES

Fibrin is a natural gluing substance. It is very useful to seal off diffuse capillary bleeding, but it is rarely used to close wounds as its mechanical strength is too low. It may be used in conjunction with skin closure tapes for wounds without tension and movement.

Cyanoacrylates are rapidly polymerizing glues used for the repair of skin lacerations, grafts, and wounds. Two compounds are available: *n*-butyl-2-cyanoacrylate (Histoacryl®, Indermil®) and octyl cyanoacrylate (Dermabond®). The latter, due to its longer alkyl side chain is said to have three times the bonding strength, is more flexible and less toxic. Its strength was found to be equivalent to a 5-0 nylon suture or intradermal running suture [2,3]. During polymerization, heat may develop. Allergy is a contraindication.

SKIN CLOSURE TAPES

Closure tapes are commonly also called suture strips. They are made of microporous tissue covered with an acrylate adhesive. They are used to support sutures. Their exclusive use is not advocated as this usually leads to inversion of the wound margins. The skin must be dry and defatted before using it. A tactifier (tincture of benzoin, Mastix®, Mastisol) enhances the strength of adhesion, particularly in summer when the patient may sweat.

Wide adhesive tapes with a zipper in the center have been proposed, particularly for wounds that may be closed over a period of some days, but their use is limited by the fact that the more tension they are expected to take the higher the risk of wound inversion.

STAPLES

Stainless steel staples are not often used in cosmetic surgery except for facelift wounds that reach into the hairy scalp. They are very strong, evert the wound margins, have an excellent tissue tolerability, and the risk of infection is reduced.

SUTURE TECHNIQUES

There is an amazing number and variability of sutures available to close skin wounds and defects. They are classified according to the structures they unite and the way of suture placing. The final scar greatly depends on the suture, and it has rightly been stated that the scar resulting from it be the "business card of the surgeon." Only in the last two decades has the attitude of many general surgeons changed who often left their patients with an unsightly scar—fulfilling their motto: a big surgeon leaves big scars. To the contrary, dermatologic surgeons were always aware of the importance of the postoperative aesthetic result.

An important point of all sutures techniques is to avoid trauma to the wound margin by squeezing the skin with a forceps. Instead, fine skin hooks should be used that evert the skin during the first movement of the needle into the dermis. This allows more deep dermis to be taken, which in turn will evert the wound. For the second stitch from inside out, the hook is first used to elevate the wound edge and then to exert counterpressure. The wound should be perpendicular to the skin surface or even about 85°, which makes it easier to evert it (Figure 22.2). The suture should always run perpendicular to the wound margin so that it will form a straight line when it is tied and the wound edges do not leave a gap anymore. Further, the cutaneous fat is a very sensitive tissue that will give in to pressure from a tied suture, thus allowing wound dehiscence. True subcutaneous stitches through the fat have virtually no mechanical strength but may be indicated to reduce the dead space after extirpation of a cyst or lipoma.

PERCUTANEOUS SUTURES

An *epidermal suture* as claimed in some surgery textbooks does not exist. The epidermis is far too thin—usually barely the diameter of a 5-0 needle—and cannot hold any tension.

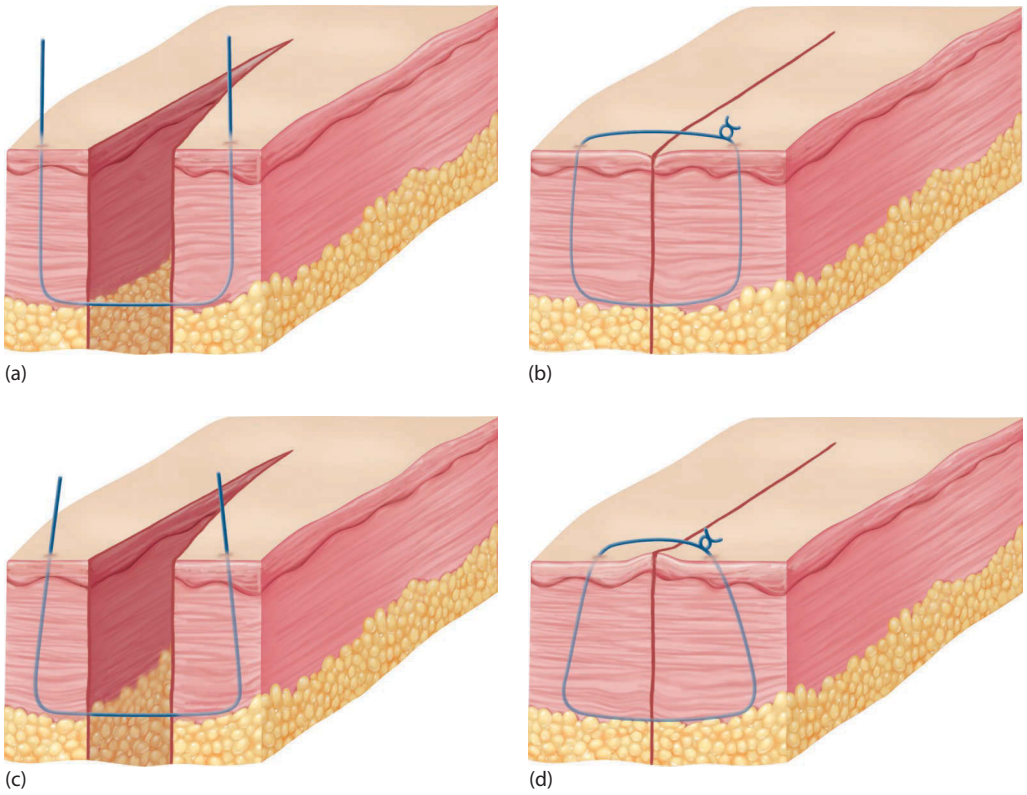


Figure 22.2 Simple interrupted stitch. A vertical wound margin tends to invert (a and b), whereas a wound margin slightly angled at around 85° results in wound eversion (c and d).

Simple interrupted stitches are the easiest and fastest to apply, but their cosmesis is hampered by the suture tracks they leave. The needle is inserted approximately 3–5 mm from the wound, directed slightly outward to grasp more dermis in the depth. It exits at the dermis–fat border and is reintroduced between the fat and the dermis so that again more dermis is taken. This creates a pear-shaped loop, which on tying the knot will evert the wound margins (Figure 22.2). The knot has to be tied tight enough not to allow a split between them but must not strangulate the wound. However, there is a conflict between the duration of this suture and the risk of suture tracks. After about 10 days, a wound has less than 10% stability of the surrounding skin. Certain regions, particularly the back, are prone to show wound dehiscence despite obvious suture tracks.

Vertical mattress sutures are used to more accurately bring the wound margins together and to evert them (Figure 22.3). Whether or not they decrease wound tension is disputed. The first half of the suture is identical to the simple percutaneous stitch, but the needle is inserted and exits about 6–10 mm from the margin. It is then reversed and again introduced into the dermis leaving about 3 mm between the exit and reintroduction points. This second stitch is more superficial as its main purpose is the exact coaptation of the margins. In order to withstand more tension, bolsters may be placed between the exposed parts of the loops. This suture is relatively time-consuming, and it is often difficult to remove the stitches after 8–10 days as the first loop tends to disappear in the skin.

A modification is the *half-buried vertical suture* (Figure 22.4). The needle is introduced as usual and exits under the dermis. The opposite wound margin is elevated as to allow the needle to be introduced into the undersurface and to exit in the wound margin below the epidermis. It is reintroduced on the opposite side at exactly the same level to avoid any step formation. Its cosmesis is superior, but again it tends to cut into the skin and stitch removal is often difficult.

Horizontal mattress sutures are good to decrease wound tension. They are right–right–left–left sutures compared to the vertical mattress sutures that run far–far–near–near (Figure 22.5). They evert the margins and may reduce dead space. Again, the exposed parts between the loops may be bolstered with rubber, gauze, or cardboard. The cosmetic results are usually not optimal. They may be improved by partially burying the suture [4].

Running sutures may be simple or locked. The *simple running suture* starts with a simple stitch that is knotted, but not cut. A second stitch is performed some 4–6 mm away, a third again at a distance of 4–6 mm, and so on (Figure 22.6). The last stitch is tied with a loop formed by the second last one. It is a fast—and provided the surgeon is experienced—and a very accurate suture. It allows wound margins of different lengths to be adjusted and gives excellent closure. Whether or not some buried stitches should be placed first depends on the wound tension.

Running locked sutures (Figure 22.7) exert pressure on the wound margin reducing bleeding. It is performed like the simple running suture, but the needle is passed through the remaining loop with each stitch. With all running sutures care has to be taken not to pull it too tight as this may strangulate the dermal vessels.

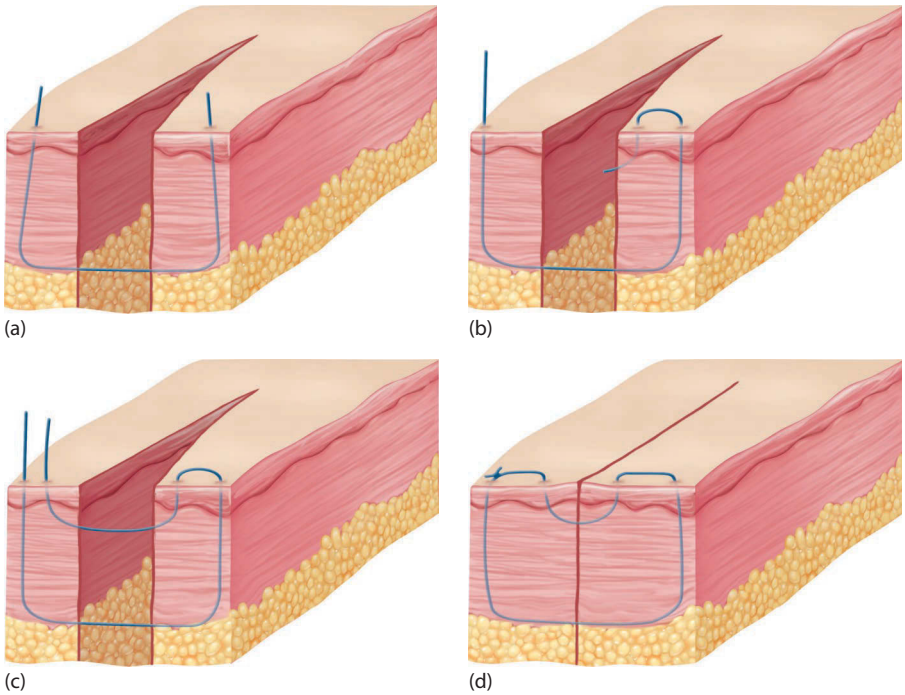


Figure 22.3 The vertical mattress suture starts like a simple stitch (a), but the needle is then reversed and reintroduced into the superficial dermis (b), exits at the border between the papillary and reticular dermis, and is reinserted in the same level at the opposite wound margin (c). Tying the knot elevates the tissue in between the superficial loop (d).

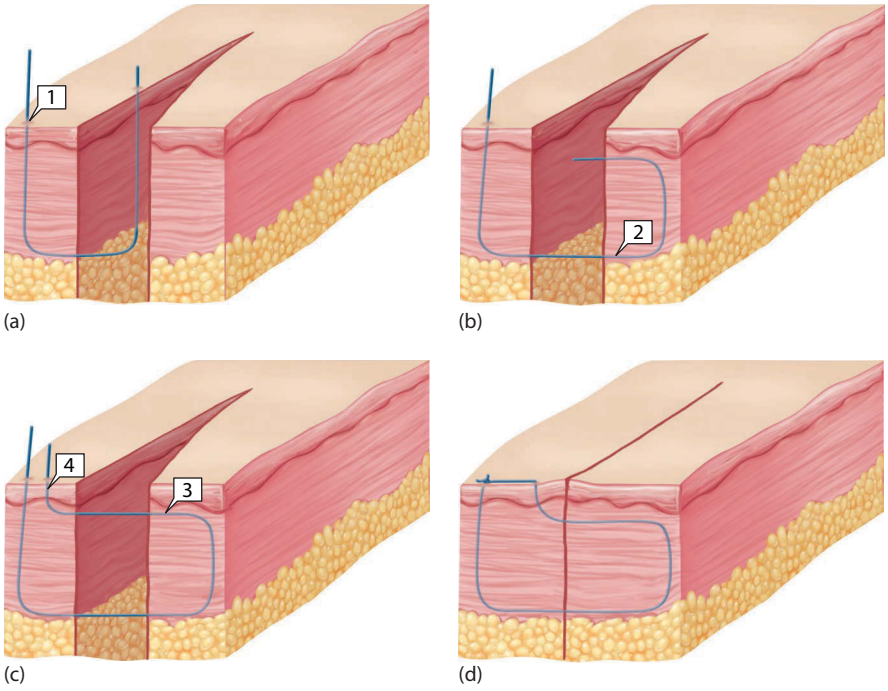


Figure 22.4 The partially buried vertical mattress suture starts like a common stitch (a) and exits at the opposite wound margin at the level of the papillary–reticular dermis (b) and reenters the opposite wound margin at the same level (c). Tying the knot has the same effect as the common mattress suture but half of the stitch material remains in the skin and is not exposed to the environment (d).

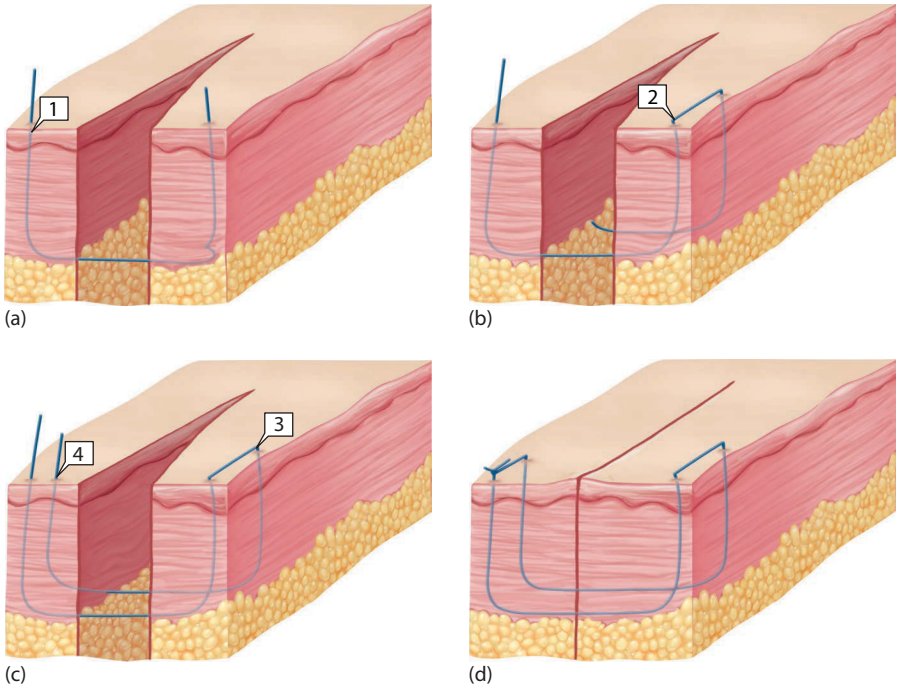


Figure 22.5 The horizontal mattress suture is a left–left–right–right suture similar to the vertical one, which is a far–far–near–near suture; it is like two simple stitches with the second loop in reverse direction: (a) first stitch, (b) beginning of second stitch in reverse direction and parallel to first stitch, (c) second stitch completed, (d) suture complete after tying the knot.

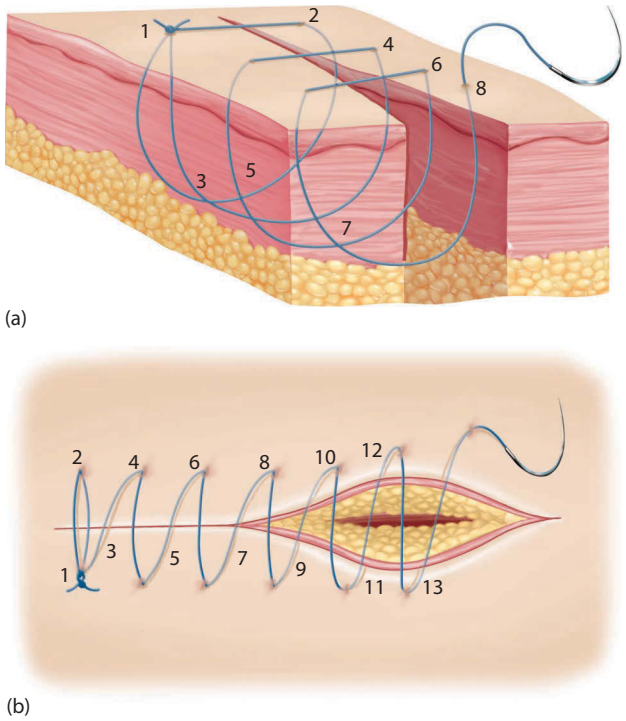


Figure 22.6 Simple running suture. After the first stitch is tied, a series of stitches one next to the other is performed. (a) Oblique and (b) dorsal view. The last stitch is secured with the loop of the last but one stitch.

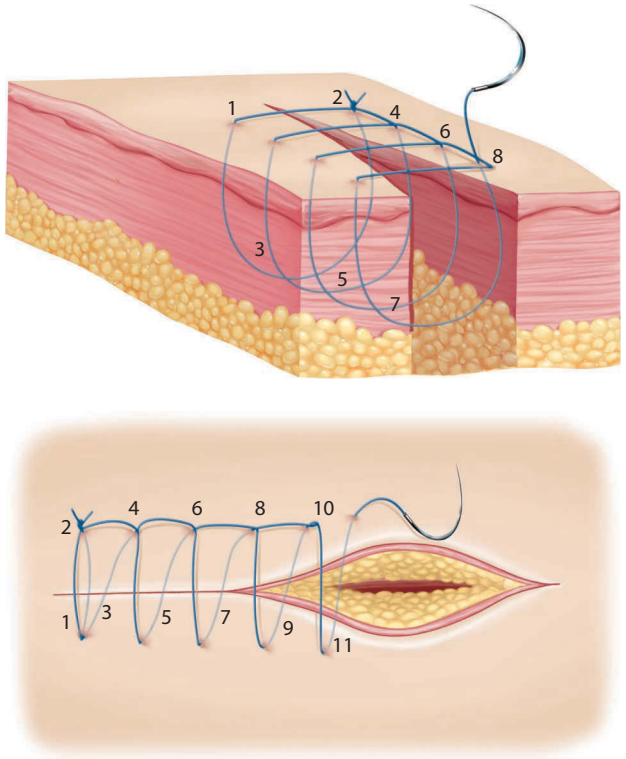


Figure 22.7 Running locked suture. The first loop is a simple stitch, and further parallel loops are added with the suture being slipped under the previous loop.

BURIED SUTURES

Buried stitches are preferred for good cosmetic results. They redistribute tension, appose wound edges, may close dead space, and decrease the risk of wound dehiscence as they do not have to be removed early. There are many different ways to place buried stitches that can be varied and adapted to the particular needs of the wound in question. All buried sutures take more time and require more surgical training and skills.

Simple buried stitches (Figure 22.8a and b) start from the undersurface of the dermis, which has to be everted for this purpose. The needle is inserted and exits at the level between the papillary and reticular dermis. It is reinserted at the opposite wound edge and exits at the undersurface of the dermis. Care has to be taken not to include fat in the bites as this will die and the wound will yawn within 2–5 days.

A *buried backstitch suture* (Figure 22.8c through f) may be used when the wound is small or the margins are tight so that no sufficient margin eversion is possible. The needle is inserted at the undersurface of the dermis and exits at the epidermis some 3–5 mm from the margin, and it is reversed and reintroduced at exactly the same point to exit in the superficial wound margin. It is again inserted into the superficial dermis, exits 3–5 mm away, is reversed, and reintroduced into the dermis to finally exit at the undersurface of the dermis. Upon tying the knot, the wound margin is slightly raised [5]. This suture appears more complicated and is more time-consuming but gives excellent postoperative results [6,7].

The *butterfly suture* [8] results in very good wound eversion. It is in fact a horizontal buried mattress suture. The needle is inserted into the undersurface of the everted dermis, directed obliquely up following the needle arc, and exited some 5 mm besides to reenter the dermis undersurface on the opposite side in a mirrorlike fashion. This suture may be repeated in a figure-of-eight fashion to give even more strength to the wound [9]. Strong tension can also be exerted by the so-called bootlace suture [10].

Running intradermal sutures are the prototypes of cosmetic sutures. There are two main types: the running horizontal and the running spiral intradermal sutures.

The *running horizontal intradermal suture*, often erroneously called subcuticular suture, is usually performed with nonabsorbable stitch material. The needle is inserted about 10 mm from the distal end of the wound in slightly oblique direction following the arc of the needle to exit in the wound margin approximately in the mid-dermis. It is reinserted at the opposite side to finally give a sinuous line until the last stitch exits again 10 mm from the other wound pole. The suture is

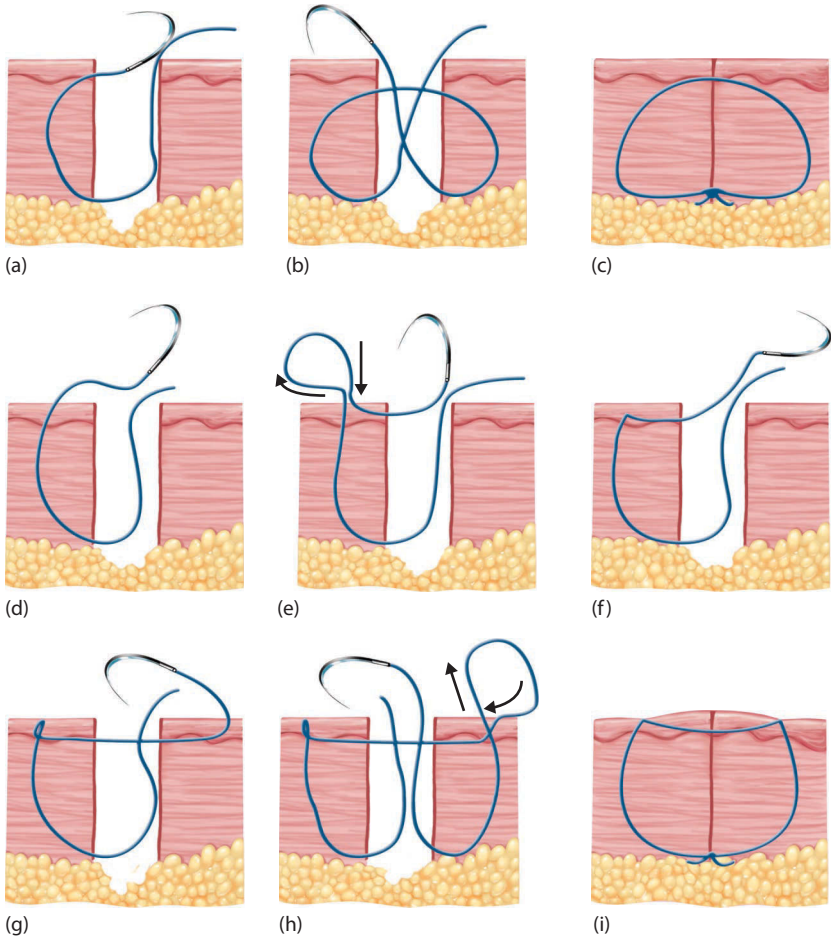


Figure 22.8 Buried sutures. Simple buried stitch (a–c) and buried backstitch suture (d–i). The suture takes deep dermis and goes up to the papillary dermis (a–c). As this technique requires eversion of the wound margins, which is often not possible, a buried backstitch technique was developed that circumvents the wound eversion during the procedure (d–i).

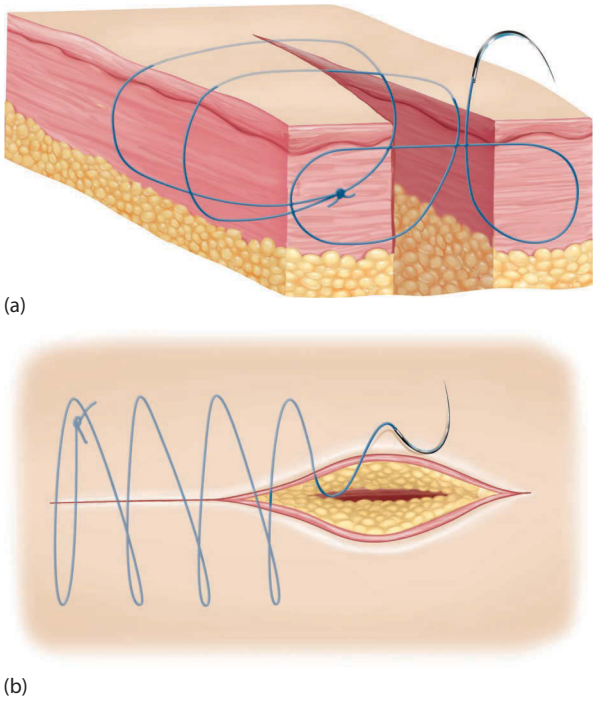


Figure 22.9 Buried spiral running intradermal suture. The first loop is identical to a simple buried stitch, and the following loops are placed in parallel always entering the undersurface of the dermis and going up to the border between the papillary and reticular dermis: (a) oblique view, (b) view from top.

tightened and secured with a tape or sometimes by knotting. The tail ends may also be tied together. This suture is good for wounds without tension in skin with a sufficiently thick dermis.

The *running spiral intradermal suture* (Figure 22.9) can be used almost everywhere and is also good to close wounds under tension. It is virtually identical to the running simple suture but starts with a simple buried stitch and is then continued as a buried suture. At the last stitch, it is tied with a loop of the last but one stitch. This suture is performed with absorbable material that holds strong for several weeks, such as polydioxanone, polytrimethylene carbonate, or poliglecaprone. It avoids all stitch marks and has remarkable mechanical strength. Of all sutures, it has the least tendency to develop scar dehiscence.

Tacking or *anchoring (pexing) sutures* are often used in flap surgery. They suspend the flap to a certain structure, like periosteum, that will not give in and thus prevent the flap from pulling a structure down, e.g., to avoid an ectropium. Depending on the importance of the structure to be kept in place, sometimes even nonabsorbable stitches are used. Facelifts, canthopexy, and many other plastic surgeries often use tacking sutures. They are also useful to avoid tenting over a concavity [11].

PULLEY SUTURES

Pulley stitches are used to close wounds under tension. The *classical pulley suture* is a far–near–near–far suture with the thread being in one line vertical to the wound margin: the needle is inserted about 10 mm from the margin to exit at the undersurface of the dermis, inserted into the dermis at the opposite side only about 5 mm from the wound edge, exits at the epidermis 5 mm from the edge, reenters the skin on the other side approximately 5 mm from the edge, and finally exits on the other side at 10 mm from the edge. It can take up considerable tension, and usually, the knot does not slip. However, this frequently causes very obvious stitch marks.

The *parallel pulley suture* (Figure 22.10) is a variation of a cross stitch [12,13]. In contrast to the classical one, it is a right–left–left–right suture. The first bite runs obliquely to the other side and the second one runs mirrorlike obliquely so that the exposed parts of the suture run parallel. This is as strong as the vertical pulley suture but can close double the length of the wound and disperses the tension much better instead of concentrating it into one line.

The *buried parallel pulley* suture gives optimal results. It is exactly like simple buried stitches but with two parallel bites that are finally tied. It is important to note that the superficial part of the loops run parallel. A buried triple suture (Figure 22.11) can be used for even greater tension or to close a wound that would otherwise require three buried sutures. It is recommended to start with the central loop, then going to one side, and finally to the other side. By gently pulling on the two tails of the suture, the wound is firmly closed. The advantages of the buried pulley sutures, whether double or triple, are that one can easily tie them even under tension without the knot slipping, the excellent wound edge coaptation, their superior strength, the equal distribution of tension with one single knot tying, and the decreased amount of foreign material brought into the wound. With slight modification, the pulley suture can also be used for tip suturing.

TISSUE-SPARING TECHNIQUES

Presuturing is a technique to reduce dermal tension (Figure 22.12). It is performed as a running horizontal mattress suture that invaginates the lesion to be excised later [14].

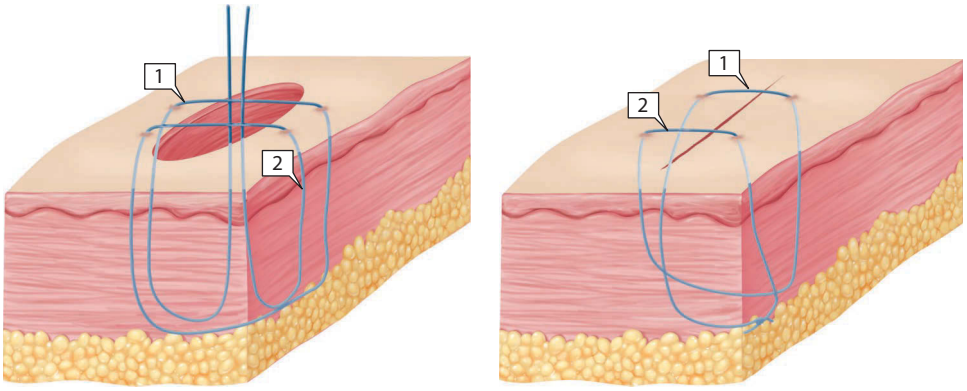


Figure 22.10 Parallel buried pulley suture. Two loops of buried stitches are placed next to each other at a distance between 5 and 8 mm and tied at the undersurface of the dermis.

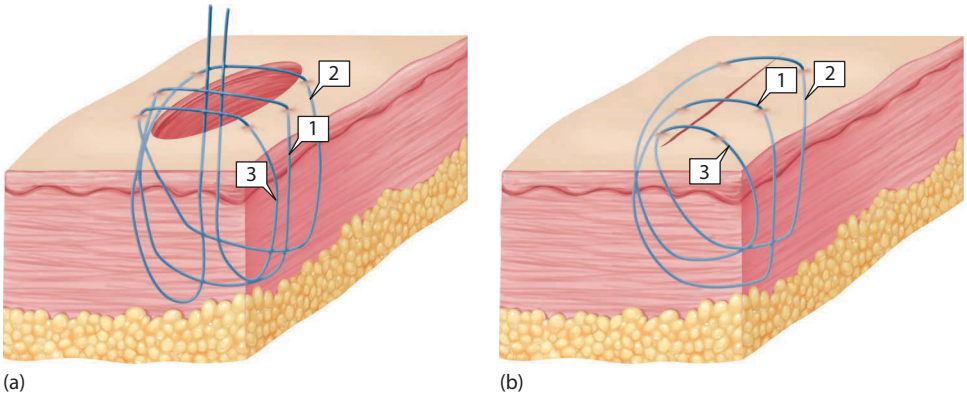


Figure 22.11 The triple buried suture starts with the central loop, the second is placed on one side, and the third loop is on the other side of the central loop (a). On tying the knot (b), this suture takes up a considerable amount of tension and distributes it evenly. Knot slipping does not usually occur.

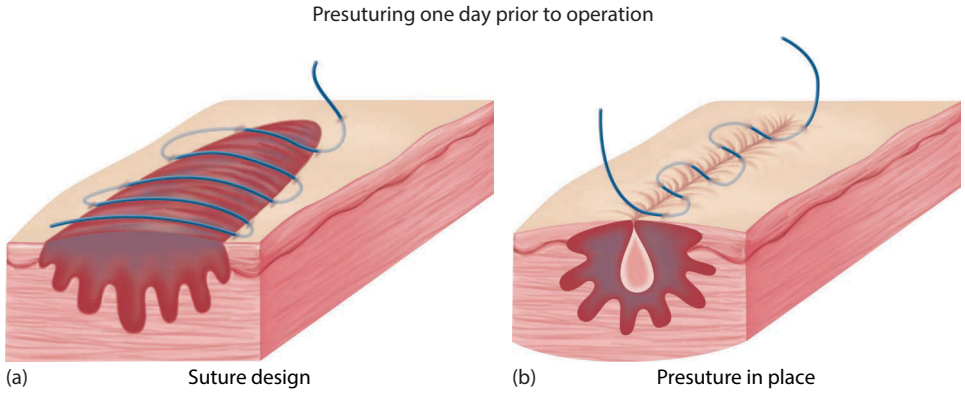


Figure 22.12 Presuturing. A series of sutures similar to horizontal mattress sutures are performed over the lesion to be excised. A day later, there is considerable tissue creep allowing easier suture after excision. (a) Suture design. (b) Presuture in place.

This brings the lesion margins together by tissue creep. During excision, supporting sutures maintain the achieved expansion [5].

It is generally held that a fusiform wound should have an angle not greater than 30° at the vertex and that this would require a 3:1 length-to-width ratio. However, a careful study found out that a length-to-width ratio of 7:1 is required for a wound angle of 30°, which would mean a tremendous tissue waste [15]. The vertex angle can be reduced by using a mosque-shaped or rhomboid excision. To avoid tissue waste completely, a round excision would be needed. Round or oval defects may be diminished by the *purse string suture*; decreasing the diameter by one-half means to reduce the size of the surface to one-quarter (Figure 22.13). Often, the small secondary defect heals rapidly by second intention with an optimal scar. The intradermal purse string is a series of horizontal bites along the circumference of the defect usually spaced at 5–8 mm apart. The suture is tightened by pulling its ends like reins until the wound size is decreased. This suture may also take transcutaneous bites, but stitch marks may later be seen. For oval and fusiform excisions of short length, two particular *tissue-sparing sutures* were devised in order to avoid the formation of standing cones [16]. The lesion is divided into two halves and along the relaxed skin tension lines. Beginning at the center of the defect, an oblique–horizontal suture is placed first to one apex and second to the other one. The needle is inserted at the dermal undersurface and is obliquely driven toward the apex exiting high in the papillary–reticular dermis, reinserted on the other side at exactly the same level, and exited at the undersurface opposite the first needle insertion. This suture is repeated to the other side. Due to their oblique direction, these stitches pull the apices of the wound down, preventing a standing cone. The center of the wound may be coapted with fine transcutaneous simple stitches. If a dog-ear is still visible, the *apex cutaneous suture* is added: The needle is vertically inserted on one side of the apex line directed 45° to the wound apex to exit at one side of the edge of the apex immediately below the epidermis, reintroduced, and redirected in a mirror image–like fashion to exit opposite the first needle insertion. Upon tying the suture, it will pull down the standing cones.

We have devised a modification of this suture as a *triple pulley suture with tissue-sparing effect* for small- to medium-sized defects (Figure 22.14). The central loop is made like a simple buried stitch, then a second loop is made that runs obliquely from about 3 to 5 mm lateral to the vertex of the wound, and the third is made in a mirror image fashion on the other side of the central loop. On tying the suture, the wound apices are pulled down, preventing dog-ear formation. This suture joins the advantages of the pulley suture with those of the tissue-sparing repair.

Dressing

At the end of the suture, the wound is cleansed and disinfected. Any blood should be removed, which is easily done using gauze soaked with 3% hydrogen peroxide. The wound is then dried. All wound sutures will benefit from the application of adhesive strips. They may be special strips (Steristrip®) or porous tape (Micropore®), the latter being considerably less expensive though usually not sterile. For sterile wounds, a dry dressing is then applied that should minimize movement as this will interfere with wound healing. Splinting is rarely necessary, but a thick bolster dressing may be advantageous.

Suture Removal

Patients are surprisingly afraid of suture removal. Therefore, it should be as comfortable as possible. It is self-evident that buried sutures do not require stitch removal. All percutaneous stitches, however, must be removed, possibly before 8–12 days as this is the time for suture tracks to develop. The stitch is grasped on one side, gently lifted, and cut. The cut end should be as short as possible in order not to pull potentially contaminated exposed stitch material through the skin. There are special stitch removal scissors that allow one hooklike branch to be easily slit under the suture and to cut it or special blades for stitch removal. Running simple

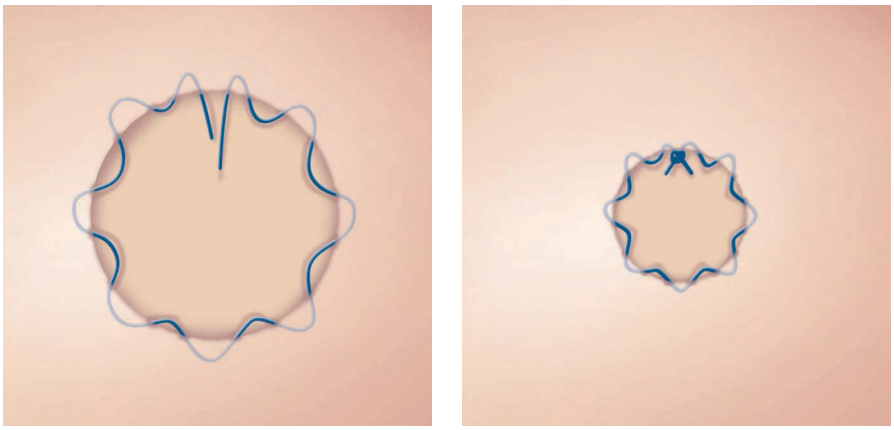


Figure 22.13 Purse-string suture. Sinuous sutures are performed around the circular defect, which can be decreased in size by simply pulling the tails of the suture. A reduction of 50% of the wound diameter results in a wound surface reduction of 75%.

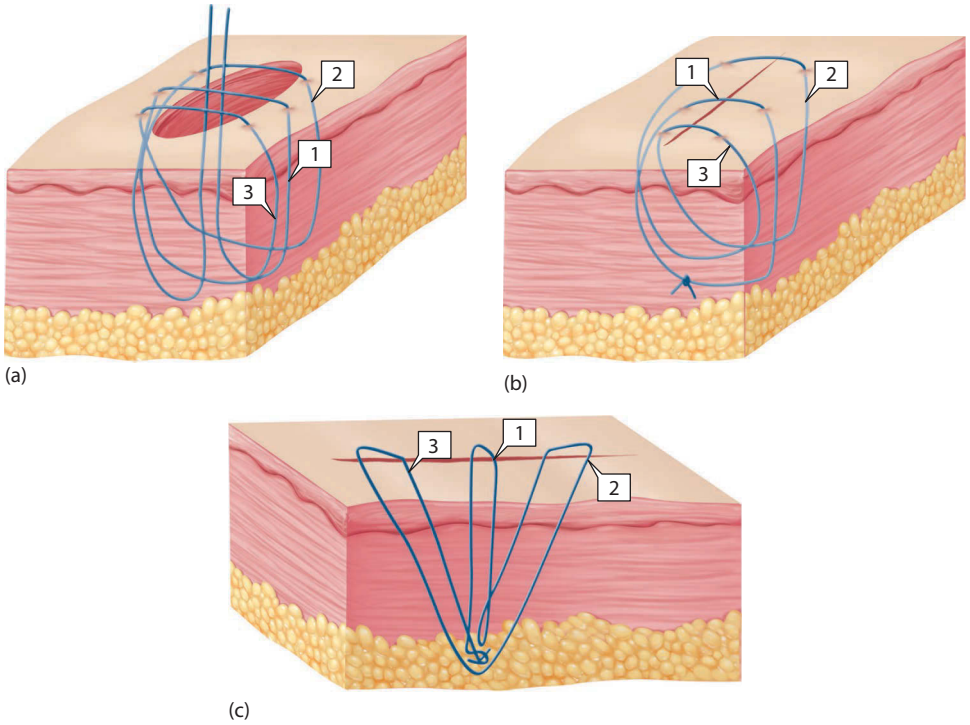


Figure 22.14 Triple pulley suture with tissue-sparing effect. This suture combines the buried triple pulley suture with the tissue-sparing tissue by placing the lateral loops in an oblique manner. (a) The first central loop of the suture runs vertically to the skin surface (1) and is placed in the middle of the wound, the second loop runs obliquely to one pole of the wound (2) to return to the center of the wound from where the third loop runs obliquely to the other pole of the wound (3) to return to the center of the wound. (b) Upon knotting the stitch, the central loop (1) pulls the wound margins together whereas the lateral loops (2 and 3) pull the standing cones at the ends of the wound down into the level of the surrounding skin. (c) View from the side.

stitches are removed loop by loop. Horizontal intradermal sutures are gently pulled to one side, often in several steps as they may exert considerable resistance to slipping through the skin.

Pitfalls

Needle bending is probably the most common problem for beginners. It depends on needle strength, sharpness and size, the tissue the needle has to penetrate, and, above all, the skills of the surgeon. We prefer semicircular needles that have to be grasped between the first third and half and to be moved straight forward until it is through the dermis before using an arc motion. Suture breaking is either due to low tensile strength, but old suture material may also break despite a large caliber. Knot slippage is typical for wound tension and for a low friction coefficient of the suture. Three or even four throws of the knot often help; if not a pulley suture is advised. Wound edge inversion is typical for bites that take more superficial than deep dermis.

SUMMARY

The best "deep tissue" surgery will not be estimated by the patient when an unsightly scar remains. Thus, utmost care has to be taken to perform a perfect suture with no stitch tracks, scar dehiscence, or hypertrophy.

REFERENCES

1. Zoltán J. *Atlas der chirurgischen Schnitt- und Nahttechnik zur Erzielung optimaler Wundheilung*. Budapest, Hungary: Akadémiai Kiadó, 1977.
2. Penoff J. Skin closures using cyanoacrylate tissue adhesives. Plastic Surgery Educational Foundation Data Committee. Device and Technique Assessment. *Plast Reconstr* 1999; 103:730–731.
3. Shapiro AJ, Dinsmore RC, North JH. Tensile strength of wound closure with cyanoacrylate glue. *Am Surg* 2001; 67:1113–1115.
4. See A, Smith HR. Partially buried horizontal mattress suture: Modification of the Haneke-Marini suture. *Dermatol Surg* 2004; 30:1491–1492.
5. Haneke E, Storbeck K. Developments and techniques in general dermatologic surgery. In: Dahl MV, ed. *Current Opinion in Dermatology*, Vol. 3. Washington, DC: Whitaker, 1996, pp. 151–157.
6. Vinciullo C, Bekhor P, Sinclair P, Richards S, Rosner L. Credit where credit is due. The Haneke-Marini suture: Not a "new" technique. *Dermatol Surg* 1995; 21:819.
7. Marini L. The Haneke-Marini suture: Not a "new" technique. *Dermatol Surg* 1995; 21:819–820.
8. Breuninger H, Keilbach J, Haaf U. Intracutaneous butterfly suture with absorbable synthetic suture material. Technique, tissue reactions, and results. *J Dermatol Surg Oncol* 1993; 19:607–610.
9. Breuninger H. Double butterfly suture for high tension: A broadly anchored, horizontal, buried interrupted suture. *Dermatol Surg* 2000; 26:215–218.
10. Motley RJ, Holt PA. Subcutaneous pulley and bootlace sutures. *XIV International Congress of Dermatologic Surgery*, Munich, Germany, Book of Abstracts 1993, p. 117.

11. Mortimer N, Tan E, Hussain W, Salmon P. 'Pin-point precision' for pexing sutures. *Br J Dermatol* 2013; 169:485–486.
12. Haneke E. Developments and techniques in general dermatologic surgery. In Dahl MV, ed. *Current Opinion in Dermatology*. Washington, DC: Whitaker, 1993, pp. 145–151.
13. Haneke E. Variations of the pulley sutures (in German). In: Mahrle G, Schulze H-J, Krieg T. *Wundheilung – Wundverschluß. Fortschritte der operativen und onkologischen Dermatologie*, Vol. 8. Berlin, Germany: Springer, 1994, pp. 158–164.
14. Seidel C, Frickert G, Hornsein OP. Vaskuläre Malformation mit tuberonodösem Hämangiom und epifaszialer Veneninsuffizienz. *Z Hautkr* 1994; 69:525–529.
15. Raveh Tilleman T, Tilleman MM, Krekels GA, Neumann MH. Skin waste, vertex angle, and scar length in excisional biopsies: Comparing five excision patterns—fusiform ellipse, fusiform circle, rhomboid, mosque, and S-shaped. *Plast Reconstr Surg* 2004; 113:857–861.
16. Stewart JB. Tissue sparing repair: A new approach to shorten excisional lines. *J Dermatol Surg Oncol* 1992; 18:822–826.

Dressing systems in cosmetic dermatology

Maurice J. Dahdah and Bertrand Richert

INTRODUCTION

- Wounds encountered in cosmetic dermatology are of the acute type.
- Dressings used following such procedures may be open or closed.
- Choice of dressing is of prime importance in cosmetic procedures.
- Optimal wound dressings should promote fast healing, reduce pain, and be practical.

Cutaneous wounds can be categorized into acute and chronic. An acute wound is one that results from an acute injury sustained by the skin due to a physical or chemical insult and that heals in a timely fashion with proper wound care. Normal wound healing starts with an inflammatory reaction that is followed by a proliferative phase and a remodeling phase (see Chapter 5, Skin Healing). Persistent wound inflammation, as seen in wounds with considerable necrotic tissue, pathogens, or foreign materials, delays healing and may lead to chronic wounds. The wounds that are encountered in the realm of cosmetic dermatology are of the acute type. Hence, this chapter will focus on the various dressings that are used in acute wounds that follow procedures such as chemical peels, electrocautery, curettage, dermabrasion and microdermabrasion, and ablative and nonablative laser resurfacing. The dressings that are used following such procedures may be open or closed. The choice of a particular type of dressing is a function of the degree of pain, the amount of wound exudates, the need for wound protection against trauma, and the ease of use and practicality of the dressing. Treatment of scars and scar revision are discussed in another chapter.

In an era when "lunchtime" cosmetic procedures with minimal downtime prevail, fast healing is a must. Therefore, the healing properties of the dressing material have to be taken into consideration as well. The optimal wound dressing should promote fast healing, reduce pain, and be practical. Dressings that combine these characteristics can greatly enhance the cosmetic experience of the patient.

OPEN DRESSINGS

- Consist of topical formulations that are applied to superficial wounds
- May be inert or may have added antibacterial and healing properties
- Are used following chemical peels, microdermabrasion, curettage, and electrocautery
- Are associated with slower wound reepithelialization compared to closed dressings
- Need to be applied at regular intervals and may be inconvenient for the patient

An open dressing consists of regularly applying a topical cream, gel, paste, or ointment to the wound site in order to prevent wound desiccation.

Uses

Open dressings are commonly used following superficial removal of lesions by curettage, electrodesication, or shaving that leave erosions or flat ulcerations to heal secondarily. They are also useful to treat superficial epidermal wounds, such as the ones induced by microdermabrasion, and to deeper dermal wounds that follow procedures such as laser skin resurfacing or dermabrasion. In the latter example, open dressings are often used on the third postoperative day when the wound is no longer exudative and no more under a closed dressing [1].

Examples

Petrolatum jelly, Fucidin®, Aquaphor Healing Ointment®, Catrix-10®, Elta crème®, CU-3 ointment®, Cicalfate®, Cicaplast®, and Cicabio®.

Advantages

- Useful in anatomic areas where the use of closed dressings is cumbersome.
- Allow regular ongoing surveillance of the wound. Most of them contain antiseptics preventing infection.
- Minimize the feeling of claustrophobia by the patient (for example, postablative laser resurfacing of the face) [2].
- Applying the cream in rotary motions may help removing the crusts resulting from heavy exsudation (dermabrasion).
- Affordable prices in most cases.

Disadvantages

- Slower reepithelialization [3]
- Not applicable in exudative wounds
- Inconvenience of repeated applications (especially at night, may ruin bedsheets)
- Greasy and not cosmetically nice
- Increased pain and erythema during recovery phase [3]
- Risky for developing bacterial infections if no antiseptic is included
- Risky for sensitization to topical antibiotics (notably bacitracin)

CLOSED DRESSINGS

These moisture-retentive dressings attempt to create the optimal wound environment (temperature, humidity, pH, growth factors, proteinases) that is necessary for wound healing [1].

Simple Dressings

- Self-adherent ready-to-use dressings
- Fast, practical, easy to use, and inexpensive
- Used for small, minimally exudative, superficial wounds
- Allergy to the adhesive may preclude their use

Consist of the application of an antiseptic solution or an antibiotic ointment followed by a dry, ready-to-wear dressing on top. The ready-to-wear dressings consist of a thin, absorbent, low-adherent wound pad located centrally on a piece self-adhesive fabric or film that is permeable to moisture. They are flexible, conform easily to body contours, and are available in a wide range of sizes [4] (Figure 23.1).

Uses

Lightly exuding superficial wounds that follow curettage, electrodesication, shaves, laser treatments, or suturing

Examples

Hansaplast®, Mepore®, and Opsite Post-Op®.

Advantages

- Convenient.
- Inexpensive.
- Thin sheet of waterproof polyurethane on some of the simple dressings (Opsite Post-Op®, Tegaderm Pad®) allows showering with the dressing on.

Disadvantages

- Cannot be used in exudative wounds unless the dressing is changed several times a day
- Allergy to the acrylic adhesive [4]
- Risk of wound desiccation and disruption of granulation tissue

Figure 23.1 Simple dressings come in a wide range of sizes.

Antiadhesive Dressings

- Usually part of a complex (multilayer) dressing.
- Do not disrupt the reepithelialization process.
- Some have useful antimicrobial properties.
- Risk of antibiotic resistance with prolonged use.

These are used as primary wound contact layers in order to reduce the adherence of a dressing to the surface of a granulating wound. They are also used for the prevention or treatment of bacterial infections in minor skin injuries and ulcerative wounds. They consist of cotton leno weave fabric, impregnated with white soft paraffin with or without an added antimicrobial agent. Some, like Fucidin Intertulle®, contain a potent antibacterial agent (fusidic acid) and can be used in the management of infected wounds. Fusidic acid is active against nearly all strains of *Staphylococcus aureus* and also effective against Streptococci, Corynebacteria, Neisseria, and some species of Clostridia. Others, like Betadine Tulle®, Bactigras®, and Atrauman Ag®, are used to prevent rather than treat wound infections. They contain broad-spectrum antiseptics that are less likely to induce bacterial resistance than antibiotics. Betadine Tulle releases iodine into the wound at a concentration that is high enough to provide antibacterial activity without being toxic to cells. Bactigras contains chlorhexidine, an antimicrobial agent that covers both gram-negative and gram-positive bacteria but is more effective against the latter. Atrauman Ag releases silver ions that have a broad-spectrum antimicrobial effect. These dressings are usually applied directly over the wound. Their low adherence means that they do not strip away the delicate epithelium upon change of dressing. They are usually covered with an absorbent gauze or pad held in place with a tape or a bandage as part of a complex dressing [4,5] (Figure 23.2).

Uses

Ulcerated wounds, infected wounds, grafts, flaps, and nail surgery.

Figure 23.2 Antiadhesive dressing after nail surgery is a must as removal should not hurt the fragile nail bed.

Examples
Adaptic®, Bactigras, Betadine Tulle, Fucidin Tulle®, Mepitel®, Unitulle®, and Atrauman Ag.

Advantages
- Low cost
- Low adherence
- Antibacterial activity
- May be left in position for a long time

Disadvantages
- Nonabsorbent
- Risk of hypersensitivity to the antibacterial agent
- Development of antibiotic resistance

Occlusive Dressings

Occlusive dressings have many advantages, the most notable being an increase in reepithelialization rates by up to 50%. The relatively anaerobic, moist, and cytokine-rich microenvironment they create provides the main stimuli (low oxygen tension, soluble growth factors) that transform keratinocytes from the proliferative into the migratory type. Keratinocyte migration from the wound edges is a necessary step for reepithelialization of the wound [5].

Occlusive dressings also prevent crust formation and contamination with pathogens, which can lead to persistent wound inflammation and delay healing.

Although they are more commonly used in chronic wounds, some of the occlusive dressings such as the hydrocolloid dressings have been successfully used to hasten the healing of acute wounds [6]. The high level of bacterial colonization under occlusive dressings, especially following full-face laser resurfacing procedures, does not seem to translate into a higher rate of wound infections [7]. However, the reports in the literature of infections occurring in this setting highlight the importance of concomitant use of oral antibiotic prophylaxis to avoid such complications [1,3].

Polymer Films

- Allow easy wound monitoring.
- Protect against microorganisms.
- Slippage of dressing may be a problem.

These are self-adhesive sheets of thin (0.2 mm) synthetic polymers, which are transparent and highly elastic. They are nonabsorbent and impermeable to microorganisms and fluids but permeable to gases (oxygen, carbon dioxide, water vapor). The film should be allowed a minimum overlap of 3–4 cm from the margin of the wound onto the surrounding skin in order to adhere properly [4]. Silon-TSR is a polymer film that is designed as a face mask and is popular after laser resurfacing procedures [2]. Silon-TSR films have slits in them that allow the escape of excess exudates to overlying gauze pads. Omiderm is a copolymer film that is permeable to antimicrobial agents. This offers the convenience of keeping the dressing in place and applying an antibiotic ointment over it when needed [7] (Figure 23.3).

Uses Polymer films may be used on minor burns, donor sites, and superficial surgical wounds and following laser resurfacing. They are also commonly used to occlude topical anesthetic creams such as EMLA® before cosmetic procedures for better percutaneous delivery.

Figure 23.3 Small polymer dressings after minor surgery keep the antiseptic ointment in place for several days and allow showering.

Examples Silon-TSR® (sold as a mask), Tegaderm®, Opsite Flexigrid®, and Omiderm.

Advantages
- Malleability
- Constitute an effective barrier to external contamination
- Prevent scab formation
- Allow faster reepithelialization
- Facilitate frequent inspection as they are translucent
- Do not need frequent changing

Disadvantages
- Only adhere to intact skin
- Accumulation of fluid beneath the dressing
- Not for exsudating wounds
- Risk of infection if left too long in place

Hydrocolloids

- They may be used on moderately to heavily exuding wounds.
- Impermeability to oxygen leads to a foul smell upon removal.

Hydrocolloids are a group of products that in their intact state are impermeable to water vapor and therefore provide an effective occlusive barrier. They consist of semipermeable polyurethane films coated with mix formulations containing carboxymethylcellulose as the principal absorbent and gel-forming agent. Upon contact with wound exudates, the carboxymethylcellulose swells to form a cohesive gel that does not tend to disintegrate or leave residues in the wound. The gel is permeable to water vapor, increasing the ability of these dressings to cope with wound exudates.

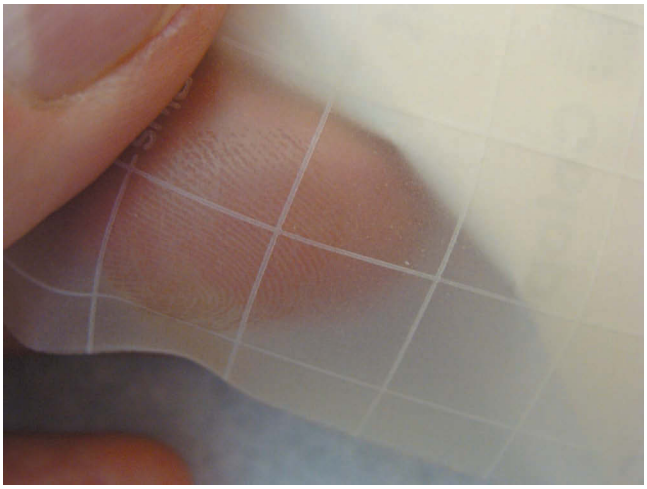


Figure 23.4 Thin translucent hydrocolloid film that may be used for wounds with very low exudate such as surface abrasion, sutured wounds, and superficial thermal burns.

Examples Duoderm®, Granuflex®, Comfeel®, Tegasorb®, Sureskin®, and Restore®.

Uses Although more commonly used in the treatment of chronic wounds, hydrocolloids can be used on a variety of acute wounds. These include thermal burns, sutured wounds, superficial wounds healing by secondary intention, split-thickness skin graft donor areas, and nail avulsion [6,8] (Figure 23.4).

Advantages

- Improved healing rates
- Reduction in wound pain
- Ability to bath or shower with the dressing in position [6]

Disadvantages

- Expensive
- Need to be changed frequently on heavily exuding wounds
- Impermeable to oxygen (use cautiously on wounds with possible anaerobic infections) [8]
- Foul smell upon dressing removal

Hydrogels

- Cooling effect provides a degree of pain reduction.
- Used with an overlying absorbent layer on heavily exuding wounds.
- May stick to relatively dry wounds.

Hydrogels are sheets (Vigilon®) or amorphous gels (Intrasite®, Sterigel®) that consist of a network of cross-linked hydrophilic polymers (polyethylene oxide, polyacrylamides, polyvinylpyrrolidone) and are made up of 96% of water [4,7].

Hydrogels have a unique ability to cool the skin on application, reducing pain and inflammation, and may be stored in the refrigerator for added comfort to the patient [9]. These dressings provide a moist wound environment and are permeable to water vapor. Although hydrogels are capable of absorbing close to their own weight in wound exudates, an overlying absorbent layer is needed when they are used on heavily exuding wounds. Hydrogel sheets may stick to relatively dry wounds and in that case can be readily rehydrated with sterile water or normal saline prior to removal.

Examples Vigilon, Intrasite, Sterigel, 2nd Skin®, Nugel®, and Hydrogel 3M®.

Uses Hydrogels are useful after dermabrasion, chemical peels, minor burns, and laser resurfacing procedures.

Advantages

- Semitransparent, permitting a degree of wound monitoring.
- Cooling effect decreases postoperative pain and inflammation.

Disadvantages

- Nonadherent (require a secondary dressing to fix them in place) (Figure 23.5)
- May be permeable to microorganisms and permit overgrowth of gram-negative bacteria [7]

Foam Dressings

- Opaque dressings
- Able to absorb heavy exudates
- Useful in awkward anatomic areas

Foam dressings are a category of closed dressing with absorptive properties, some of them come with an adhesive border, and others do not and have to be kept in place by a secondary dressing (Figure 23.6). They come in thin sheets composed of an inner mesh of absorbent polyurethane foam and an outer semipermeable membrane and are permeable to water vapor and gases but impermeable to microorganisms. Upon exudates absorption, foams expand and take up the shape of the

Figure 23.5 Hydrocolloid gel in a wound. As this is an exuding wound, closure with an overlying absorbent layer is needed.

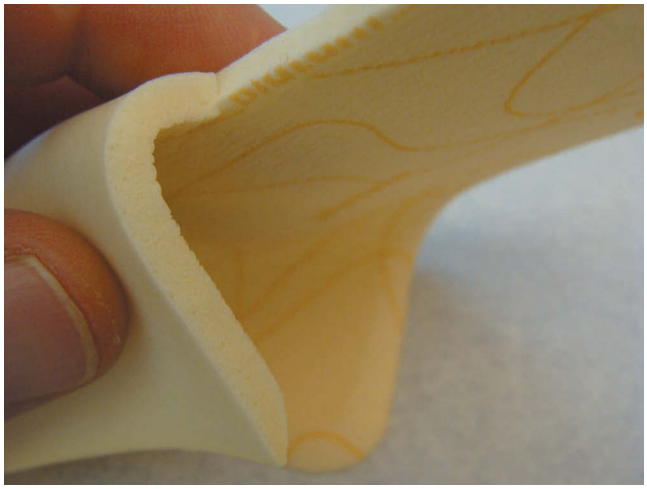


Figure 23.6 Foam dressings: inner mesh of absorbent polyurethane foam and an outer semipermeable membrane.

wound bed. They are supplied in opaque, white-colored sheets that are layered in an overlapping manner over the wounded area to avoid slippage [4,7,9].

Some products have silver ions incorporated in the foam material (Allevyn Ag®, Mepilex Ag®) that would help in the control of the bacterial load of the wounds.

The Mepilex® foam brand adheres to the skin via a silicone-based border that avoids the trauma to the fragile skin induced by more traditional adhesive materials.

Examples Flexzan®, Flexzan Extra®, Revitaderm®, Silastic foam®, Tielle®, Allevyn®, Allevyn Ag, Mepilex, and Mepilex Ag.

Uses Moderate to heavily exuding wounds, laser skin resurfacing, and dermabrasion.

Advantages

- Provide thermal insulation to a wound
- Easily shaped to fit awkward areas

Disadvantages

- Expensive
- Must be removed to inspect the skin
- Cannot be used on dry wounds

Tapes

- Easily conformable to various anatomic sites
- Used to secure complex and pressure dressings in place
- May damage fragile skin when applied under tension

Tapes consist of fabrics that are coated with a layer of an acrylic adhesive. They are usually conformable products with a high tensile strength and limited extensibility. Some tapes use a silicone-based technology to create skin adherence and less risk of sensitive skin damage.

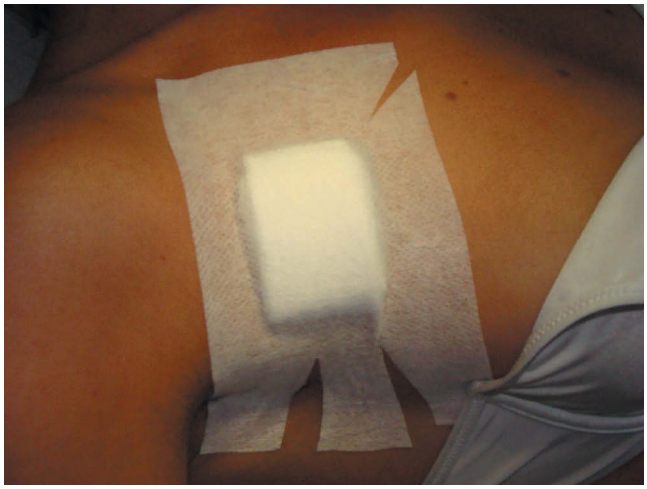


Figure 23.7 After removal of a cyst in a curved area (armpit), pressure is provided by a bulky dressing, anchored by a large fabric tape, and notched at several corners to allow perfect fitting to the area.

Examples

Mefix®, Micropore®, Hypafix®, and Mepitac®.

Uses

- Tapes are mostly used for retention of nonadherent dressings in place.
- Tapes can also provide hemostasis by applying proper pressure through the use of a bulky dressing.

Advantages

- Very useful on joints or body sites with awkward contours (ears, fingers, toes) (Figure 23.7)
- Come as rolls of varying width that are easily cut to desired length
- Permeable to water and water vapor and will not cause maceration

Disadvantages

- Nonsterile.
- Shearing forces may cause damage to fragile skin if applied under tension [4].
- With time may induce irritation from repeated peel off.

CONCLUSION

Due to the lack of specific guidelines, the choice of wound dressings is based largely on physician preferences. There is little evidence supporting the superior healing outcomes with the use of one particular dressing compared to another. Hence, physicians tend to select dressings based on other properties such as relief of pain, ability to absorb and contain exudates, avoidance of wound trauma on dressing removal, and comfort of use [10,11]. Being familiar with the basic characteristics of the dressings discussed earlier will help in deciding which dressing is most appropriate for the cosmetic procedure being performed. These procedures often injure the skin in a controlled manner in order to achieve the desired cosmetic outcome. For patients going for cosmetic procedures, a short and uneventful

"downtime" period is as important as the outcome for overall satisfaction. Therefore, choosing a practical and comfortable dressing that optimizes skin healing is an essential aspect of cosmetic dermatology.

REFERENCES

1. Goldman MP, Roberts TL 3rd, Skover G, Lettieri JT, Fitzpatrick RE. Optimizing wound healing in the face after laser abrasion. *J Am Acad Dermatol* 2002 March; 46(3):399–407.
2. Batra RS. Ablative laser resurfacing—Postoperative care. *Skin Therapy Lett* 2004 August–September; 9(7):6–9.
3. Christian MM, Behroozan DS, Moy RL. Delayed infections following full-face CO_2 laser resurfacing and occlusive dressing use. *Dermatol Surg* 2000 January; 26(1):32–36.
4. www.dressings.org.
5. Li W, Dasgeb B, Phillips T, Li Y, Chen M, Garner W, Woodley DT. Wound-healing perspectives. *Dermatol Clin* 2005 April; 23(2):181–192.
6. Thomas S. Hydrocolloid dressings in the management of acute wounds: A review of the literature. *Int Wound J* 2008 December; 5(5):602–613.
7. Ramos-e-Silva M, Ribeiro de Castro MC. New dressings, including tissue-engineered living skin. *Clin Dermatol* 2002 November–December; 20(6):715–723.
8. Goetze S, Ziemer M, Kaatz M, Lipman RD, Elsner P. Treatment of superficial surgical wounds after removal of seborrheic keratoses: A single-blinded randomized-controlled clinical study. *Dermatol Surg* 2006 May; 32(5):661–668.
9. Newman JP, Fitzgerald P, Koch RJ. Review of closed dressings after laser resurfacing. *Dermatol Surg* 2000 June; 26(6):562–571.
10. Ubbink DT, Vermeulen H, Goossens A, Kelner RB, Schreuder SM, Lubbers MJ. Occlusive vs gauze dressings for local wound care in surgical patients: A randomized clinical trial. *Arch Surg* 2008 October; 143(10):950–955.
11. Chaby G, Senet P, Vaneau M, Martel P, Guillaume JC et al. Dressings for acute and chronic wounds: A systematic review. *Arch Dermatol* 2007 October; 143(10):1297–1304.

Local anesthesia for dermatological surgery

José J. Pereyra-Rodriguez, Javier Domínguez Cruz, and Julian Conejo-Mir

INTRODUCTION

Pain and suffering have been inherent in humanity since its earliest existence. Their alleviation and control have been one of the important advances of modern medicine. Local anesthesia has been used not only to reduce pain but also to make possible surgical treatments hitherto unimaginable.

Local anesthesia can be defined as the loss of touch and pain sensation due to inhibition of nerve impulses in nerve terminals, peripherals, or spinal roots. Local anesthetics (LAs) are pharmacological agents that disrupt nerve conduction in a focal area temporarily with subsequent complete recovery of sensation in that area.

Although LAs have been used since the nineteenth century and were used as a scientific basis for clinical observation, most were developed in the last four decades.

HISTORY OF LOCAL ANESTHETICS

General anesthesia has the potential for significant side effects. Currently, mortality rate for general anesthesia is estimated at 1 per 10,000 operations due to biochemical, pharmacological, and iatrogenic factors [1]. Modern LAs were developed to attempt to avoid the side effects of general anesthetics. It is estimated that their use has reduced mortality to less than 1 in 2,000,000 patients anesthetized locally [2].

The first LA agents used were cold and heat. However, from a pharmacological point of view, the use of LA dates back to the ancient Inca civilization in Peru, employing coca leaves (*Erythroxylum coca*). When a coca leaf is chewed, it produces a desensitization effect in the oral cavity and pharynx, as well as a stimulating effect. The active alkaloid of coca, *erythroxylon*, was identified and extracted from coca plants in 1855, and in 1860 Albert Niemann isolated cocaine from coca leaves [3].

Although cocaine was used in the late nineteenth century by Peruvian surgeons, the current application of cocaine was the result of the investigation of two Viennese physicians, Karl Koller and Sigmund Freud [4]; who used it as a topical solution, only 2% of which can numb the surface of the eye (e.g., the outermost layer of the cornea). Von Anrep was the first to publish its use for subcutaneous infiltration [3]. The versatility of cocaine was appreciated by William Stewart Halsted at Johns Hopkins Hospital, who used it in more than 1000 cases of nerve-blocking conduction. Unfortunately, Halsted ended up becoming addicted to the drug [5].

An important aid for the local implementation of LA was the introduction of the metal syringe by Rynd in Ireland in 1845, up Wood in England in 1853, and Pravaz in France in 1853 [6].

In the early twentieth century, in an effort to reduce the toxic side effects of cocaine, Einhorn isolated procaine, an ester of para-aminobenzoic acid. Other ester derivatives, such as chloroprocaine and tetracaine, were subsequently developed and widely used in the years 1950–1960. However, the most widely used LA was lidocaine, which was discovered by Lofgren in 1948 [7]. It has the prototype amide–amino group with the following advantages over the other LAs: high tissue penetration, low toxicity, and high anesthetic effect.

For the last three decades, new LAs such as prilocaine, etidocaine, mepivacaine, and bupivacaine have been used in daily practice, among which, probably, mepivacaine is the most widely used today [8].

NEURAL MECHANISM

Anatomy

Nerve fibers transmit impulses to other areas of the body by a complex electrochemical mechanism initiated by various chemical, mechanical, or electrical stimuli. These pulses are conducted along the nerve fibers or axons. The key anatomical structure for anerve impulse is the cell membrane that surrounds the axons, which is the axolemma, as the chemical properties of this membrane will affect nerve transmission. It is a lipoprotein structure with a bimolecular phospholipid area. Schwann cells are not related to nerve transmission, although they are very important for the synthesis of the myelin sheath.

Peripheral nerves are classified into three categories: fibers A, B, and C [9] (Table 24.1). In humans, pain is transmitted by myelinated A-delta and unmyelinated C fibers. Although the sizes of each of these fibers are different, at a practical level, both are equally blocked by LA. However, while low concentrations of LA completely block myelinated A-delta fibers, C fibers need higher concentrations [10]. A-delta fibers are responsible for severe acute pain and C fibers for mild pain.

Physiology

An external stimulus to the nerve causes a nerve impulse. This pulse is called an action potential. The phenomenon of electrical impulses in the nerve membrane is dependent on the concentration gradient of sodium and potassium ions in the axoplasm and extracellular fluid, as well as the permeability of these ions in the nerve membrane. At rest, the concentration of intracellular potassium is 110–170 mEq/L (extracellular 3–5 mEq/L), while that of intracellular sodium is 5–10 mEq/L (extracellular 140 mEq/L). These gradients will change with the membrane potential. Nerve stimulation alters

Table 24.1 Types of Nerve Fibers

Fiber type	Diameter (μm)	Conduction speed (m/s)	Function
Aβ	5–12	30–70	Touch and pressure
Aδ	2–5	12–30	Pain and temperature
C	0.3–1.2	0.5–2	Pain and temperature

the permeability of the nerve cell to sodium and potassium ions, leading to potassium efflux and sodium influx. When the membrane potential rises, the door of a sodium channel closes. At this moment, the membrane potential is +40 mV. Repolarization of the membrane starts with the help of an energy-dependent sodium pump, thus restoring membrane equilibrium. This active transport requires energy from oxidative phosphorylation.

Nerve impulse is generated and propagated along the nerve fibers. Conduction occurs from one node of Ranvier to the next in "frog jumps," so the transmission of pulse acquires great speed in myelinated nerves.

Biochemistry

The anesthetic action of LA depends on several factors:

a. Lipid solubility
b. Binding protein
c. pH
d. Diffusivity in nonneural tissues
e. Intrinsic vasodilator activity

The lipid solubility of LA is extremely important because of the lipid composition of the nerve membrane. Thus, lipophilic LA has a quick entrance and a lasting blocking effect. Likewise, binding protein is also important because protein composes 10% of the axolemma.

The duration of anesthetic effect is related to the binding proteins in the nerve membrane [11].

Most of the LAs are prepared as salts (RNH + Cl–), which are poorly soluble in water. Salts of these LAs are in aqueous solution having an unloaded tertiary amine base (RN) and a cationic, positively charged quaternary amine (RNH +). The total concentration (C) of LA may be expressed as follows:

$$\text{RNH RN} = \text{C} + (+)$$

Tissue pH significantly affects the efficacy of the LAs. Most of the LAs are acidic, especially those with epinephrine. Infected tissue has a high concentration of lactic acid and a lower pH, and LAs have less effect. For the oral mucosa, where pH is also lower than the skin, LA is less effective. For this reason, anesthetics used in the oral cavity are at higher concentrations than usual, for example, lidocaine has been used at up to 4% to achieve sufficient anesthesia. Benzocaine is an excellent topical anesthetic for the oral mucosa because it has a p*K*a of 3.5, and its low pH acts as a base when it is unionized [12].

Other chemical modifications influence the activity of LA. Potassium [13], dextran [14], and carbon dioxide [15] were added to LA for a greater anesthetic effect. Potassium mixed with 2% lidocaine prolonged nerve blockage because increased concentration of extraneural potassium delay repolarization. Dextran mixed with LA increases its effect by delaying absorption. Carbonated solutions increase the duration of anesthesia, as carbon dioxide diffuses through the nerve membrane, decreasing the pH.

Table 24.2 Chemical Classification of Local Anesthetics

Esters	Benzoic acid esters (cocaine and piperocaine)
	Aminobenzoic acid esters (with high solubility, procaine, chloroprocaine, and tetracaine, and with limited solubility, benzocaine)
	Para-ethoxybenzoic acid (intracaine)
	Carbamic acid esters (dithane)
	Complex synthetics
Amides	Straight-chain acid derivatives of xylidide: Acetic acid (xylocaine) Propionic acid (propitocaine)
	Pipecolic derivatives of xylidide (mepivacaine and bupivacaine)
	Oxy-cinchoninic acid (dibucaine)
Alcohols	Ethyl alcohol
	Aromatic alcohols (benzyl alcohol)
Miscellaneous	Quinoline derivatives (eucupine)
	Ammonium compounds (tetraethylammonium)

Almost all LAs have intrinsic vasodilatory capacity, except cocaine. For example, lidocaine *in vitro* has the same potency as that of mepivacaine; however, lidocaine *in vivo* has a shorter effect because of its intrinsic vasodilatory effect.

The location of the area to be anesthetized is also important because it will determine the absorption of LA. Highly irrigated areas, such as the face and scalp, quickly absorb LA [11].

The difference between amine and ester is their metabolization. Esters are hydrolyzed in plasma by the enzyme pseudocholinesterase while amines are degraded in the liver. Patients with pseudocholinesterase deficiency have minimal LA tolerance. This deficit should be suspected in those patients who do not get anesthetic infiltration following any method to numb an area. The same thing happens to those with hepatic impairment.

Understanding LA allergies is important. Their metabolite is para-aminobenzoic acid, which is commonly a sensitizing agent. Procaine can cause immediate allergic reactions. Amines do not induce sensitization and side effects are rare. There are no cross-reactions between amine and ester LAs. Clinical utility of LA agents are listed in Table 24.2.

Mechanisms of Action

Four different mechanisms of action of LA have been proposed [16–18]:

1. Interaction with receptors at the level of the sodium channel, which they block. It is known that some marine toxins, such as tetrodotoxin and saxitoxin, block the external opening of the sodium channel, thus prolonging duration of action.
2. Expansion of the nerve membrane by blocking the sodium channel. Some LAs produce axolemmal lipoprotein expansion due to spatial realignment of proteins.
3. Exchange of surface charges. Some LAs produce a positively charged surface of the nerve membrane. Thus, a positive cation membrane repels positive sodium and calcium ions.
4. Physical lock of the outer door of the sodium channel.

Most authors agree that the most important mechanism is the first of these four.

Anesthetic Agents

Chemical Agents

LAs have three portions, each well individualized in their chemical structure:

1. A midportion identical to all
2. Portion b, aromatic or ester, which is lipophilic
3. Portion c, amine or amino–amide, which is hydrophilic

The properties of each LA depend on different portions. It should be noted that the hydrophilic portion determines the intrinsic potency of the LA [19] (Table 24.2).

Esters Cocaine is an ester derivative of benzoic acid and para-aminobenzoic acid. A derivative, benzocaine (ethyl-4-aminobenzoate), is a widely used topical anesthetic agent. Its effect is very fast but only lasts for 4–6 minutes. Sometimes, it causes tachycardia, hypertension, and CNS excitation, so it should be used with caution in patients with cardiovascular problems. Use of these LAs in the eye is contraindicated because cocaine causes corneal epithelial damage.

Procaine, the first LA used routinely in daily clinical practice, was synthesized by Einhorn in 1905. He also coined its trade name, "Novocain." Its true indication was its use by injection. Administered topically, it has little effect. It has low toxicity and does not irritate the tissues [20]. Procaine, an ester-type LA, is metabolized in plasma by the enzyme pseudocholinesterase.

Tetracaine is a powerful ester-type LA, 16 times more powerful than procaine but four times more toxic due to its low hydrolysis in plasma, so its use is greatly restricted. Chloroprocaine is an injectable ester-type LA with low toxicity [21].

Amides The first of this LA group was synthesized in 1943 in Sweden. These LAs were advantageous over the ester-type LAs as the latter produced strong allergic reactions. The first amino–amide-type LA was lidocaine. It is a useful anesthetic for both infiltration and topical application, applicable at concentrations ranging from 0.5% (infiltration) to 5% (topically). To increase its effectiveness, it is associated with vasoconstrictors, particularly with adrenaline. It is metabolized in the liver by microsomal oxidases and amidases [23]. Its metabolites (monoethylglycinexylidide and glycine xylidide) are excreted by the kidneys. Because they possess antiarrhythmic properties, that at high concentrations they can be toxic. Its half-life is 90–120 minutes [24].

Mepivacaine is an amino–amide LA with similar effects to lidocaine except that it is not active topically. Some authors consider it less potent because it has less lipid solubility [25]. However, its toxicity is much lower. This is because the liver metabolizes mepivacaine differently from lidocaine as it produces carbon dioxide. A small amount of mepivacaine is metabolized in newborns and excreted mostly by the kidney.

Bupivacaine is an anesthetic more powerful but more toxic than earlier long-acting LAs [26]. Its safe maximum dose is 200 mg. Its half-life is 3.5 hours.

Etidocaine is the most recent LA introduced in 1973 by Lund et al. [27]. It is structurally similar to lidocaine; it is four times more potent and has at least two times more prolonged effect. Its toxicity is controversial, though less subcutaneously than bupivacaine. Its maximum safe dose is 300 mg and it has a half-life of 114 minutes.

Prilocaine is a mild anesthetic agent and has little absorption but a prolonged effect [28]. It is contraindicated in patients with cardiovascular problems.

Some authors include two more groups of LAs: guanidine-type LAs (tetrodotoxin and saxitoxin) and derivatives of tetraethylammonium. These are of little use in practice.

Other Local Anesthetics For patients with a history of allergy, they are referred to alternative LAs. Thus, one can achieve good LA with sedative antihistamines. The most used drugs are promethazine, tripelennamine, pyrilamine maleate, diphenhydramine, and pyribenzamine, among which pyribenzamine gives excellent results. They may be used alone or in combination with vasoconstrictors [18,22].

Also, the infiltration of water produces useful anesthesia in dermatological surgery. Modern derivatives of quinolones, including centbucridine, seem to have a good anesthetic effect, but we still do not have enough experience with them [8,23].

Vasoconstrictor Agents

Vasoconstrictor agents combined with LA have the property to increase efficacy, prolong the anesthetic effect, and reduce LA absorption into plasma, and minimize immediate bleeding (Table 24.3). Most agents are adrenergic or sympathomimetic amines, such as adrenaline, which is a potent stimulator of both alpha and beta receptors [24].

1. Effect on anesthesia. Vasoconstrictors cause a longer reduction in local flow, slowing tissue metabolism, and transient anoxia.
2. Effect on bleeding. They reduce bleeding during surgery. Ten minutes or less should be expected between infiltration and early intervention for the ischemic effect to be optimal. It should be recalled that in the immediate postoperative vascular reflex, paralysis might occur, which may be responsible for extensive bruising, if intraoperative hemostasis is not adequate.
3. General effects. Absorption of adrenaline can cause symptoms of beta-adrenergic stimulation, such as palpitations, tachycardia, increased blood pressure, and chest pain, especially in hyperthyroid patients. Also, the use of vasoconstrictors in acral areas doe not need to be avoided

Table 24.3 Maximum Doses of Ester and Amide Local Anesthetic Agents

	Maximum dose (mg/kg)	
Anesthetic	Without epinephrine	With epinephrine
Esters		
Procaine	7.1	8.5
Tetracaine	1.4	—
Amides		
Lidocaine	3	7
Mepivacaine	4.5	7
Bupivacaine	2.5	3.2
Prilocaine	5.7	8.5

(e.g., the fingertips) [25]. Vasoconstrictors can never be used in patients undergoing antihypertensive treatment because they can enhance the sympathomimetic effect of medication and produce necrosis [26,27].

Cryoanesthesia

Cold has been used since ancient times as an anesthetic. There is evidence of extensive interventions made centuries ago, in which ice and salt were used as anesthetics. However, the first real cryoanesthetic agent, ethyl chloride, was introduced in surgery in the late nineteenth century. It is a flammable and explosive liquid, with rapid volatilization, and has a very low boiling point (12.2°C). Its fast and fleeting effect is its indication, which is useful only for minor surgeries. It should be handled with caution when large areas are to be anesthetized since the surgeon may suffer from the damaging effects of the drug when inhaled as compared to other general anesthetic agents. Fluoroethyl, also used as a cryoanesthetic agent, is composed of 25% chloride and 75% ethyl dichlorotetrafluoroethane [28,29].

In 1955, Freon was introduced into dermatologic surgery, particularly Freon-114, which is very suitable for dermabrasion [30]. This cryoanesthetic agent has a lower boiling point than ethyl chloride (3.6°C) and skin is numb from 0°C to –32°C; therefore, the freezing and numbing effect lasts longer. It has the advantage of not being explosive or flammable. Subsequently, Freon-11 (trichlorofluoromethane) and Freon-12 (dichlorodifluoromethane) were used, the latter has a freezing point of –60°C.

Liquid nitrogen has also been used to excise small tumors, but its low freezing point (–196°C) makes its use severely restricted as it causes pain and extensive burns.

Cold's mechanism of action entails blocking the specific fiber conduction of pain, temperature, and tactile sensation, progressively and chronologically. This action is similar to that produced by infiltration with modern LAs [29,31].

Cryoanesthesia has a very limited application because of its many side effects. The most important of these is neural damage, with loss of sensitivity, and surprisingly extensive tissue necrosis, which can occur when used in combination with adrenaline, although this fact has been exploited for the treatment of certain malignancies. It must not be forgotten that all cryoanesthesia is very persistent and it causes unsightly pigmentation, which must be taken into account when it is used in exposed areas [32,33].

Iontophoresis

Iontophoresis is the therapeutic use of an electric field on the skin, in order to facilitate the action of various topically applied drugs. This procedure was first used nearly two centuries ago, with multiple drugs being administered in this manner [34].

This method is based on the laws of ion transport described by Hittorf [35]. An effective, but transient, anesthesia of several minutes, is achieved if 1% lidocaine is used. If this is associated with adrenaline, the effect is greater, almost 30 minutes.

The advantages of this method are that it is painless, it requires minimal concentration of the drug, and it involves non-morphologically altered tissue [36]. The drawback of this method is that it requires equipment at the skin-medicine interface, chemical reactions at the electrode, and a minimum sufficient quantity of the drug administered [37,38].

CLINICAL USE OF LA

Here are the clinical uses of LA agents (Table 24.4).

Topical Application

The stratum corneum acts as barrier for efficient penetration when LA is topically applied. When this barrier is removed, much higher absorption is required. To avoid this negative effect, LA use has been attempted with a penetrating agent, dimethyl sulfoxide. However, it produces greatly limited hyperesthesia. Other important factors for an effective optimal use of LA are its basic compounds and suitable pH [39].

In order of potency, tetracaine, cocaine, lidocaine, benzocaine, pramoxine, and tripelennamine are among the commonly used topical LAs. Cooling agents are utilized in minor surgery and dermabrasion [40].

An interesting section is that of the formulation of new topical LA creams. Lidocaine was used in children at a concentration of 30% for minor surgery, requiring 45 minutes for anesthesia. A solution of 2.5% lidocaine combined with 2.5% prilocaine is called a eutectic mixture of LAs [41]. Its low power only allows anesthetic use in minor surgery. Another combination (tetracaine 0.5%, epinephrine 0.05%, and 11.8% cocaine) has also been used, but it favors secondary infection and tissue laceration. Topical ketocaine is a new ester-type LA agent, using this causes loss of touch sensitivity, so it can be used to anesthetize 10% graft donor sites [37] (Table 24.5).

Table 24.4 Clinical Utility of Local Anesthetic Agents

Anesthetic agents	Uses	Remarks
Procaine	Infiltration and spinal	Limited use because of slow onset, short duration, and allergic potential
Lidocaine	Infiltration, intravenous regional anesthesia, peripheral nerve blocks, epidural and spinal blocks, and topical anesthesia	Versatile agent (see Table 24.5)
Mepivacaine	Infiltration, peripheral nerve blocks, and epidural blocks	Versatile agent
Bupivacaine	Infiltration, peripheral nerve blocks, epidural, and spinal blocks	Sensory or motor separation

Table 24.5 Systemic Toxicity and Lidocaine Levels

Serum levels (μg/mL)	Symptoms and signs
3–6	Light-headedness, euphoria, digital and circumoral paresthesia, restlessness, and drowsiness
5–9	Nausea, vomiting, blurred vision, tinnitus, confusion, excitement, psychosis, tremors, and muscular fasciculations
8–12	Seizures and cardiopulmonary depression
12–20	Coma and respiratory arrest

Perilesional Infiltration

A key to expand the use of LA was the discovery of the syringe. This made LA feasible in intradermal, hypodermic, or intramuscular administration.

The choice of thickness and volume loading of the syringe are extremely important. An injection of LA is much less painful if the syringe diameter is smaller. This is defined in the following formula:

$$P = \frac{F}{A}$$

where

P is the output pressure of the syringe
F is the force of the plunger
A is the area of the piston

Thus, syringes of larger diameters, for example 10 mm, require a strong force output pressure at the point of injection resulting in pain during infiltration. Similarly, the diameter of the needle also contributes to a painful infiltration with 30 gauge needles; however, 25 gauge needles are the best for this purpose. Finally, efforts should be made in choosing the shortest needle possible, for example, those used for injecting insulin.

Therefore, at the moment of infiltration, the size of the syringe and needle does not affect the intensity of pain caused. It must be added to the effect of the dermohypodermic and fiber tracts produced by the penetration of anesthetic peel. A good move to reduce pain is to infiltrate a small volume of LA.

The technique of infiltration of anesthesia is easy: push the needle into the skin into one of the corners of an imaginary diamond and, without removing the needle, infiltrate along each side of the rhombus until it reaches the middle area. Then the same procedure might be done for the opposing angle. Therefore, two punctures are enough to anesthetize a relatively large area. It is convenient to introduce the needle in close proximity to tumor areas, as the LA can be injected directly into the cavity. Simple habit of sucking before injecting the LA avoids introducing LA directly into the bloodstream, which substantially avoids anesthetic accidents.

Tumescent anesthesia is an LA technique that consists of the infiltration of a large volume of solution with a low concentration of the LA agent and epinephrine (Table 24.6). Its main advantages are that it achieves adequate anesthesia and it reduces intraoperative and postoperative bleeding, leading to greater ease of surgery with the added benefit of facilitating tissue dissection. The simplicity and numerous applications and benefits of this technique make it very useful in current dermatologic surgical practices.

Table 24.6 Recipe for a Tumescent Anesthetic Solution

0.05 mL of epinephrine (1 mg/mL)
1 mL of sodium bicarbonate (1 mol/L)[a]
10 mL vial of 1% mepivacaine
10 mL vial of 2% mepivacaine
50 mL of 0.9% physiological saline solution

[a] Optional.

Table 24.7 Local Anesthetics Used in Dermatology

Type of local anesthetic	Relative potency	Onset of action	Duration of action (minutes)
Low potency and short duration			
Procaine	1	Slow	60–90
Chloroprocaine	1	Fast	30–60
Intermediate potency and duration			
Mepivacaine	2	Fast	120–240
Prilocaine	2	Fast	120–240
High potency and long duration			
Tetracaine	8	Slow	180–600
Bupivacaine	8	Intermediate	180–600
Etidocaine	6	Fast	180–600
Dibucaine	12	Slow	220–600

To summarize, we can divide the LAs used for infiltration into three categories, depending on potency and duration of effect (Table 24.7):

1. Low: procaine and chloroprocaine
2. Intermediate: lidocaine, mepivacaine, and prilocaine
3. High: tetracaine, bupivacaine, and etidocaine

Nerve Blocks

Nerve blocks are designed to inhibit the transmission of nerve impulses from the same nerve trunk, to a large body area with a minimal amount of anesthetic. Hence, this technique is also called as truncal or regional anesthesia.

These blocks can be done in two ways:

1. Injecting LA in the same compartment of the nerve trunk fascia
2. Infiltrating the anesthetic into the perineurium or immediately adjacent to the nerve trunk

The first method is infiltration, which is an approximate procedure. The tip of the needle is set on the nerve trunk without infiltration, based on minimum anatomical knowledge; when the patient reports a small "cramp," the needle should be immediately withdrawn a few millimeters to infiltrate. Intraneural infiltration of LA should be avoided since temporary or permanent nerve damage with paresthesia may occur. To satisfactorily block a nerve fiber, at least three nodes of Ranvier need to be exposed to the anesthetic, which in practice results in an infiltration within 1.5–6 mm. Nerve trunks of medium or large size require more time and amount of anesthetic than those with small regional areas [42].

Interestingly, this type of anesthesia is used to test the chronology of blocking each of the different nerve fibers that comprise the nerve trunk. Thus, pain fibers are blocked before the temperature and pressure fibers, the latter being those that require more time to inhibit the nerve impulse. For this reason, some patients do not feel the handling and cutting of the operative site until a few minutes after the start of the intervention. Another curious fact is the "Wedensky effect": the nerve is blocked to an isolated stimulus rather than continuous stimulation. This means that during the immediate postinfiltration, the sensation of pain to needle sticks, but not the cutting scalpel,

is abolished. If this occurs, it is not necessary to inject more anesthetic, but to wait for a few minutes until nerve blocking is complete [43].

For the successful implementation of this type of LA, surgeons must acquire extensive knowledge of nerve anatomy.

The biggest advantage of nerve blocking is that a very small amount of anesthetic is required to numb an extensive operative field. Also, this allows the increase in the concentration of the LA, for example, lidocaine can be used at 2%–5%, instead of the 1% typically used [44,45].

Among its drawbacks is that it requires somewhat lesser perilesional infiltration anesthesia; it needs at least 8–10 minutes to complete nerve blocking for small/medium caliber, especially if the trunk is large. Laceration of the nerve with the needle tip can cause temporary nerve paralysis or paresis. Inadvertent intravascular injection can lead to an immediate damage to the nerve, artery, and vein. The pain of injection can be overridden with infiltration in the oral mucosa, particularly the infraorbital and inferior alveolar nerves [45,46].

SIDE EFFECTS

Although LAs can be considered as highly safe chemical agents, sometimes side effects may occur, usually by overdose or by passage into the bloodstream.

To avoid these side effects, the first and most important measure is to consult the patient's medical history, that is, the patient's intolerance to LA and his or her regular medication. Phenothiazines (chlorpromazine and thioridazine), tricyclic antidepressants, beta blockers, adrenergic blockers, and thyroid hormones can cause anesthetic accidents [1,19,47].

The most common complication is allergic reaction to the anesthetic. While anaphylactic reaction most often occurs in ester-type LAs and exceptionally in the amino–amide group, there are published reports of death involving each of the two groups. Identically, contact dermatitis is common in the ester group; procaine and tetracaine are notorious in causing dermatitis but it is very rare in the amino–amide group. There may be cross-reactions between the ester group LAs and sulfonamides.

Cardiovascular system toxicity is due to the relaxing effect on vascular smooth muscle of all LA, which cause sudden hypotension (only cocaine produces hypertension). When the dosage is massive, circulatory collapse can lead to death [27,48].

The most feared complication is in the central nervous system. In these cases, tinnitus, loss of consciousness, and nystagmus occur. If toxicity progresses, tonic–clonic seizures may develop, as well as seizures with decreased respiratory rate, drop in blood pressure, and circulatory collapse. These symptoms must be differentiated from a vagal reaction or LA allergy [17,26].

The basic rules to avoid the occurrence of any aforementioned side effects will be the following: [18]

1. Place the patient in a supine position.
2. Ensure respiration by providing oxygen masks.
3. Perfuse a vein immediately using levulose or physiological saline.
4. If CNS excitement occurs, infuse diazepam 10 mg IV slowly.
5. For a cardiocirculatory problem, infuse vasopressor agents.
6. For anaphylaxis, infuse adrenaline 5 mL 1/10,000 iv every 5–10 minutes. If we can administer the dosage sublingually or intratracheally, use 1/1,000.

In most instances, the problem is not toxic but psychogenic, leading to a significant vasovagal attack. It is characterized by sweating, pallor, nausea and vomiting, hyperventilation, and syncope. In these cases, the patient should be placed in the supine position, with his or her head lower than the legs. The patient has to take off his or her clothes in a lateralized head position, to prevent aspiration of vomit. It is advisable to ensure fluid therapy is applied accordingly.

Other adverse effects are observed with LA: impaired immune function of lymphocytes, myotoxic effect, reduced ability of wound healing, and infections [2,19,21,26,49].

REFERENCES

1. Dillane D, Finucane BT. Local anesthetic systemic toxicity. *Can J Anaesth* 2010 April; 57(4):368–380.
2. D'Eramo EM, Bontempi WJ, Howard JB. Anesthesia morbidity and mortality experience among Massachusetts oral and maxillofacial surgeons. *J Oral Maxillofac Surg* 2008 December; 66(12):2421–2433.
3. McAuley JE. The early development of local anesthesia. *Br J Dent* 1966; (121):139–142.
4. Liljestrand G. Carl Koller and the development of local anesthesia. *Acta Physiol Scand Suppl* 1967; 299:1–30.
5. Olch PD. William S. Halsted and local anesthesia: Contributions and complications. *Anesthesiology* 1975 April; 42(4):479–486.
6. Greene NM. A consideration of factors in the discovery of anesthesia and their effects on its development. *Anesthesiology* 1971 November; 35(5):515–522.
7. Lofgren N. *Studies on Local Anesthesics: Xylocaine. A New Synthetic Drug*. Stockholm, Sweden: Haeggstroms, 1948.
8. De NP, Ivani G, Tirri T, Favullo L, Nardelli A. New drugs, new techniques, new indications in pediatric regional anesthesia. *Minerva Anestesiol* 2002 May; 68(5):420–427.
9. Gasser H, Erlanger J. The role of the fiber size in the establishment of a nerve block by pressure or cocaine. *Am J Physiol* 1929; (88):581–586.
10. White JL, Durieux ME. Clinical pharmacology of local anesthetics. *Anesthesiol Clin North Am* 2005 March; 23(1):73–84.
11. Jackson T, McLure HA. Pharmacology of local anesthetics. *Ophthalmol Clin North Am* 2006 June; 19(2):155–161.
12. Ganzberg S, Kramer KJ. The use of local anesthetic agents in medicine. *Dent Clin North Am* 2010 October; 54(4):601–610.
13. Aldrete JA, Barnes DR, Sidon MA, McMullen RB. Studies on effects of addition of potassium chloride to lidocaine. *Anesth Analg* 1969 March; 48(2):269–276.
14. Aberg G, Friberger P, Sydnes G. Studies on the duration of local anaesthesia: A possible mechanism for the prolonging effect of dextran on the duration of infiltration anaesthesia. *Acta Pharmacol Toxicol* 1978 February; 42(2):88–92.
15. Barsa J, Batra M, Fink BR, Sumi SM. A comparative in vivo study of local neurotoxicity of lidocaine, bupivacaine, 2-chloroprocaine, and a mixture of 2-chloroprocaine and bupivacaine. *Anesth Analg* 1982 December; 61(12):961–967.
16. Koay J, Orengo I. Application of local anesthetics in dermatologic surgery. *Dermatol Surg* 2002 February; 28(2):143–148.
17. Culp WC, Jr., Culp WC. Practical application of local anesthetics. *J Vasc Interv Radiol* 2011 February; 22(2):111–118.
18. Walsh A, Walsh S. Local anaesthesia and the dermatologist. *Clin Exp Dermatol* 2011 June; 36(4):337–343.
19. Harmatz A. Local anesthetics: uses and toxicities. *Surg Clin North Am* 2009 June; 89(3):587–598.
20. Tait CA, Reese NO, Davis DA. A comparative study of hexylcaine, procaine, and lidocaine with specific attention to tissue irritation. *South Med J* 1958 March; 51(3):358–366.
21. Morau D, Ahern S. Management of local anesthetic toxicity. *Int Anesthesiol Clin* 2010; 48(4):117–140.

22. Upadya M, Upadya GM. Anesthesia for dermatological surgery. *Indian J Dermatol Venereol Leprol* 2005 May; 71(3):145–154.
23. Barnett P. Alternatives to sedation for painful procedures. *Pediatr Emerg Care* 2009 June; 25(6):415–419.
24. Shoroghi M, Sadrolsadat SH, Razzaghi M et al. Effect of different epinephrine concentrations on local bleeding and hemodynamics during dermatologic surgery. *Acta Dermatovenerol Croat* 2008; 16(4):209–214.
25. Lalonde D, Martin A. Epinephrine in local anesthesia in finger and hand surgery: The case for wide-awake anesthesia. *J Am Acad Orthop Surg* 2013 August; 21(8):443–447.
26. Shalom A, Westreich M, Hadad E, Friedman T. Complications of minor skin surgery performed under local anesthesia. *Dermatol Surg* 2008 August; 34(8):1077–1079.
27. Conrado VC, de AJ, de Angelis GA et al. Cardiovascular effects of local anesthesia with vasoconstrictor during dental extraction in coronary patients. *Arq Bras Cardiol* 2007 May; 88(5):507–513.
28. Kontochristopoulos G, Gregoriou S, Zakopoulou N, Rigopoulos D. Cryoanalgesia with dichlorotetrafluoroethane spray versus ice packs in patients treated with botulinum toxin-a for palmar hyperhidrosis: Self-controlled study. *Dermatol Surg* 2006 June; 32(6):873–874.
29. Hughes PS. Cold air anesthesia in dermasurgery: Comparative study. *Dermatol Surg* 2006 January; 32(1):165–166.
30. Redbord KP, Hanke CW. A new combination technique of local anesthesia for full-face dermabrasion. *J Drugs Dermatol* 2007 August; 6(8):801–803.
31. Matthias N, Robinson MA, Crook R, Lockworth CR, Goodwin BS, Jr. Local cryoanalgesia is effective for tail-tip biopsy in mice. *J Am Assoc Lab Anim Sci* 2013 March; 52(2):171–175.
32. Berman B, Amini S. Pharmacotherapy of actinic keratosis: An update. *Expert Opin Pharmacother* 2012 September; 13(13):1847–1871.
33. Goldberg LH, Kaplan B, Vergilis-Kalner I, Landau J. Liquid nitrogen: temperature control in the treatment of actinic keratosis. *Dermatol Surg* 2010 December; 36(12):1956–1961.
34. Rai R, Srinivas CR. Iontophoresis in dermatology. *Indian J Dermatol Venereol Leprol* 2005 July; 71(4):236–241.
35. Purves RD. The physics of iontophoretic pipettes. *J Neurosci Methods* 1979 August; 1(2):165–178.
36. Saliba SA, Teeter-Heyl CL, McKeon P, Ingeroll CD, Saliba EN. Effect of duration and amplitude of direct current when lidocaine is delivered by iontophoresis. *Pharmaceutics* 2011 December 6; 3(4):923–931.
37. Shipton EA. New delivery systems for local anaesthetics-part 2. *Anesthesiol Res Pract* 2012; 2012:289373.
38. Wilson JR, Kehl LJ, Beiraghi S. Enhanced topical anesthesia of 4% lidocaine with microneedle pretreatment and iontophoresis. *Northwest Dent* 2008 May; 87(3):40–41.
39. Huang W, Vidimos A. Topical anesthetics in dermatology. *J Am Acad Dermatol* 2000 August; 43(2 Pt 1):286–298.
40. Anitescu M, Benzon HT, Argoff CE. Advances in topical analgesics. *Curr Opin Anaesthesiol* 2013 August; 26(5):555–561.
41. Houck CS, Sethna NF. Transdermal analgesia with local anesthetics in children: Review, update and future directions. *Expert Rev Neurother* 2005 September; 5(5):625–634.
42. Capdevila X, Ponrouch M, Choquet O. Continuous peripheral nerve blocks in clinical practice. *Curr Opin Anaesthesiol* 2008 October; 21(5):619–623.
43. Jacob AK, Walsh MT, Dilger JA. Role of regional anesthesia in the ambulatory environment. *Anesthesiol Clin* 2010 June; 28(2):251–266.
44. Gramkow C, Sorensen J. Regional nerve block in facial surgery. *Ugeskr Laeger* 2008 February 11; 170(7):513–517.
45. Rochette J. Regional anesthesia and analgesia for oral and dental procedures. *Vet Clin North Am Small Anim Pract* 2005 July; 35(4):1041-ix.
46. Quaba O, Huntley JS, Bahia H, McKeown DW. A users guide for reducing the pain of local anaesthetic administration. *Emerg Med J* 2005 March; 22(3):188–189.
47. Horlocker TT. Complications of regional anesthesia and acute pain management. *Anesthesiol Clin* 2011 June; 29(2):257–278.
48. Holm SW, Cunningham LL, Jr., Bensadoun E, Madsen MJ. Hypertension: Classification, pathophysiology, and management during outpatient sedation and local anesthesia. *J Oral Maxillofac Surg* 2006 January; 64(1):111–121.
49. Hebl JR, Niesen AD. Infectious complications of regional anesthesia. *Curr Opin Anaesthesiol* 2011 October; 24(5):573–580.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Management of abnormal scars

Roland Kaufmann, Eva Maria Valesky, and Markus Meissner

INTRODUCTION

Despite a growing number of possible treatment techniques, the basic principles and limits in scar revision and keloid control remain an ongoing challenge. Management of scar formation in dermatosurgery encompasses several aspects including pre- and postoperative prevention, such as resurfacing procedures or compression following surgery in critical sites. Therapeutic options include a combination of sequentially applied procedures. Among those, attempts to correct functional impairments (e.g., fibrotic contractures) have to be differentiated from methods addressing the configuration of the cicatricial tissue area (e.g., elevated, depressed) or its overall appearance (e.g., degree of pigmentation, vascularization), the latter preferentially including different nonsurgical techniques (e.g., cryotherapy, laser- or light-mediated procedures, intralesional application of steroids or cytostatic agents). However, the decision when and how to intervene is the most critical one. In most instances, conservative timing is advised. Above all, when considering approaches in the treatment of scars, one has to understand the dynamics and biology.

DEFINITION OF NORMAL AND ABNORMAL SCARRING

A cutaneous scar is the end stage of an unimpaired spontaneous healing process after wounding of the skin. Normally, a wounded skin surface will be repaired spontaneously by a well-defined biologic process of secondary healing with an overlapping sequence of early-, intermediate-, and late-stage molecular and cellular events (hemostasis and inflammation during first week, proliferation up to the third week, maturation and remodeling within the first year) [1].

In skin wounds following an accidental trauma or a surgical procedure, a stable and controlled tissue repair (primary healing) is usually facilitated and accelerated by appropriate closure techniques of the defect and subsequent adaptation of the edges with sutures in order to achieve an optimized healing with minimized scar. Scarless healing meaning wound repair resulting in a nearly invisible scar can only be expected in moisturized environments adjacent to or within visible mucous membrane surfaces, such as the lips, mouth, or anogenital regions, while a scar-free tissue regeneration (without any scar formation at all) only occurs during mammalian fetal development or in lower vertebrates [2,3].

The overall appearance of any cutaneous scar formation will in the early stages primarily depend on the time course of its development during the multistage process of tissue repair, while the final outcome will largely be governed by the size and site of the defect, the type and depth of tissue injury, and the overall healing conditions potentially influencing the complex molecular and cellular interplay during the different phases of skin regeneration [4].

Hence, abnormal scarring can be the result of a variety of factors harming normal spontaneous wound healing or complicating surgical wound repair and depends on other risk factors (Table 25.1). Usually, this will lead to a functional and/or aesthetic impairment within the area of the regenerated skin potentially resulting in different clinical aspects (Figure 25.1) and treatment options (Table 25.2). Sometimes scarring is transiently hypertrophic, which typically is contained to the original wound and may regress over time. In contrast, keloids instead exhibit a proliferative growth beyond the margins of the scar and remain persistent or even progressive and may also become symptomatic (Table 25.3). Though both examples of fibrotic proliferations are regarded as different sides of the same coin [5], they yet follow a different clinical course resulting in diversities of management and treatment response [6].

PREVENTION OF ABNORMAL SCARS

Following a surgical procedure, every effort to avoid disturbances during the healing process of the resulting skin wound helps to prevent the development of abnormal scars. In this regard, major goals are to control bleeding, infection, tension, and any other mechanical forces, as well as to apply an appropriate technique to achieve optimal closure of the wound [7].

To identify patients or regions at high risk of abnormal scar development, some basic considerations (also shown in Table 25.1) should be taken into account. Generally, the greater the number of risk factors that apply, the more prevention strategies should be considered.

Basic Prevention Strategies

One important method to circumvent abnormal scars from developing involves reducing mechanical tension and, in turn, dehiscence after surgery. This method can be achieved by paying close attention to the relaxed skin's tension lines, using appropriate sutures, and reducing motion after surgery. The additional fortification of the sutures by taping (e.g., by Steri-Strip™) might be of additional benefit [8]. Along with reducing mechanical stress, preventing inflammation is fundamental, since inflamed tissue is a significant pathogenetic correlate of keloid or hypertrophic scar development. To this end, excellent

Table 25.1 Risk Factors for Scar Development

Risk factors
Body sites (e.g., earlobe, shoulder, anterior chest, juxta-articular)
Age (<30 years)
Family or personal history of abnormal scars
Afro-Caribbean descent
High wound tension
Wound infection

wound care should be provided, and if possible, not braided but monofilament sutures should be used [9]. In addition to reduced tension and inflammation, the suture technique might impact scar development; horizontal and vertical mattress sutures in particular seem to facilitate good wound healing by effective eversion of the skin's edges [10]. Deep dermal sutures with buried knots can remove tension from superficial interrupted sutures, which then can be removed at an earlier date to prevent crosshatching.

Figure 25.1 Examples of scar variants. (a) Normal thin depigmented older scar, (b) dehiscent scar, (c) hypertrophic scar, and (d) keloid.

Table 25.2 Clinical Features of Abnormal Scar Formations as Targets for Interventions

Type	Potential for intervention	Preferred ways of management
Dehiscent (stretched)	Limited	Surgical revision
Hypertrophic	Yes	"Wait and see" compression, laser
Keloidal	Limited	Usually combination therapy
Depressed	Yes	Tissue augmentation
Hyperpigmented	Yes	Q-switched lasers, IPL
Depigmented	Limited	Phototherapy (e.g., excimer laser)
Erythematous	Yes	Laser, IPL
Acne scar variants	Yes	Monotherapy or combination (e.g., fractional lasers, subcision, excision, elevation) depending on types
Artifacts	Restricted to few exceptions	Depending on type of scars

Table 25.3 Comparison of Keloids and Hypertrophic Scars

Keloid	Hypertophic scar
Occurrence within years spontaneously or after surgery/injury	4–6 weeks after surgery/injury
No spontaneous regression	Spontaneous regression possible
Predilection sites: the shoulder, earlobe, upper arm, cheeks, etc.	Predilection sites: the shoulder, sternum, flexor sites of the joints, etc.
Scar outgrows the original injury	Restricted to the original injury
Equal in sex distribution	Equal in sex distribution
Highest incidence in patients below 30 years	Mainly age independent
Higher incidence in darker skin types, association with HLA-BW16,21,35	Lower association with skin pigmentation but higher association with puberty and pregnancy
May be symptomatic (pain, pruritus)	Usually asymptomatic

Specific Nonsurgical Prevention Strategies

Though the aforementioned basic prevention strategies should always be considered, more specific strategies can be applied when necessary. The array of antiscarring agents includes silicone layers, corticosteroids, pressure dressings, onion extracts, imiquimod, 5-fluorouracil (5-FU), and bleomycin, among others. All of these options are used not only for scar prevention but also for the treatment of existing or developing scars. Their use is therefore described in the treatment chapter.

Negative-Pressure Wound Therapy

More recently, another preventive strategy of abnormal scarring has emerged called negative-pressure wound therapy (NPWT) (Figure 25.2). In their retrospective study of 235 patients,

Figure 25.2 Negative-pressure wound therapy (NPWT) as a scar prevention strategy. (a) Excision defect after a malignant melanoma, (b) skin closure with a transposition flap, (c) installation of a single-use NPWT device (Pico™, Smith & Nephew), and (d) wound situation after 3 days of NPWT.

Reddix et al. [11] demonstrated that implementing NPWT on primary closed wounds reduced the frequency of wound infections from 6.2% to 1.3%. In another retrospective study of 263 patients, Stannard et al. [12] showed that the incidence of suture dehiscence of primary closed incisions could be reduced from 16.5% to 8.6% by implementing NPWT. The mechanism of action might be explained by the reduction of both the mechanical tension on the wound edges by approximately 50% and hematoma and seroma, as well as by an increase of microvascular blood flow, which induces better wound healing [13–16]. All of these mechanisms of action are important features for preventing abnormal scarring.

Serial Excision

The serial excision of benign skin tumors is a basic method in dermatological surgery often used in smaller and medium-sized congenital nevi (CN). It principally involves the serial excision of the skin lesion in different sessions at intervals of 12–16 weeks (Figure 25.3). The incision should follow the longitudinal axis and the shape of the skin lesion so that the lesion can be excised stepwise without causing exorbitant mechanical tension on the wound edges in order to prevent scar dehiscence, reduce the risk of infection, and therefore avoid the development of abnormal scars. In our experience, the additional use of subcutaneous nonabsorbable polypropylene sutures with stable tensile strength for the duration until the next excision reduces the incidence of scar dehiscence, decreases the number of excisions needed and improves the cosmetic outcome [17].

Laser Treatment

Lasers are not only limited to scar revision and treatment but also can be used for scar prevention. The best evidence for the effectiveness of preventive lasers can be demonstrated with pulsed dye lasers (PDLs) 585 and 595 nm [18]. Conologue and Norwood [19], for example, demonstrated that using a 595 nm PDL beginning on the day of suture removal improved the cosmetic appearance of surgical scars.

Capon et al. also showed that an 810 nm diode laser used immediately after surgery could prevent abnormal scar development, given its ability to elevate the temperature of the skin and thereby modify the wound healing process [20,21].

Fractional lasers have also been used to prevent the formation of hypertrophic scars. For instance, Choe et al. [22] demonstrated that a 1550 nm fractional Er-glass laser used 2–3 weeks after surgery repressed the formation of hypertrophic scars. Comparable results were shown by Jung et al. [23] who used a fractional CO_2 laser system. Nevertheless, further research is necessary in order to confirm the effectiveness of different laser systems for scar prevention.

MANAGEMENT OF DEHISCENT SCARS

Stretching or dehiscence of scars is a frequent complaint and might involve only parts of some scars and the entire whole length in others. Re-excision and narrowing of widespread scar areas is the treatment of choice. The approach can also be divided into serial excision in longer scars.

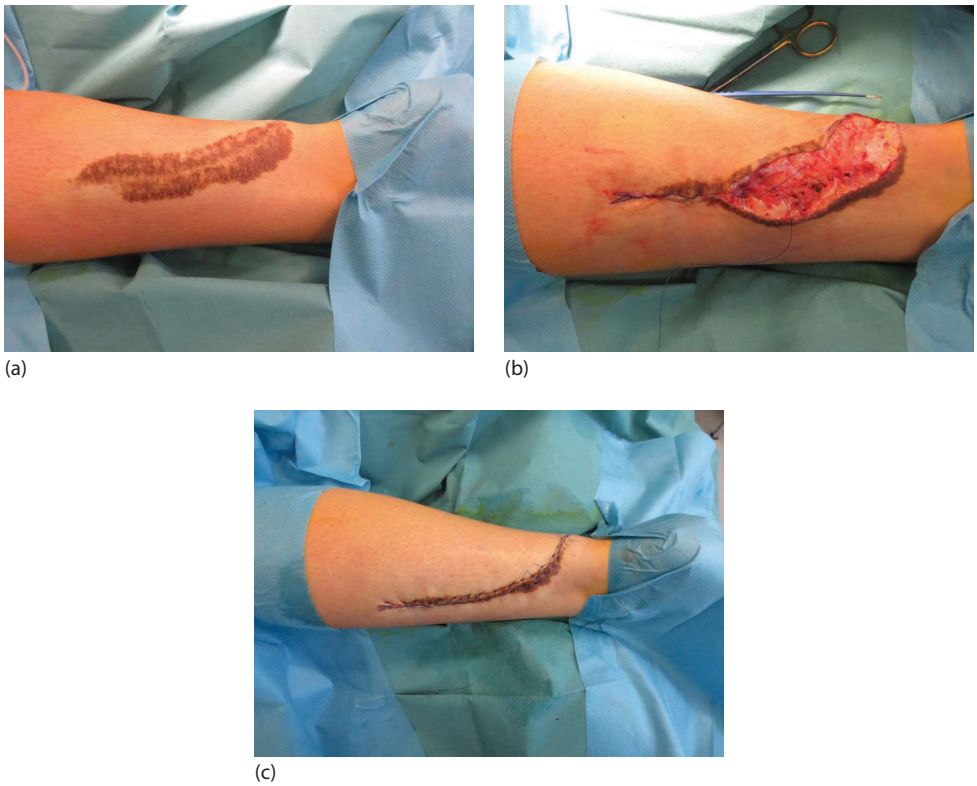


Figure 25.3 Serial excision as a scar prevention strategy. (a) Congenital nevus of a 12-year-old girl after two serial excisions, (b) intraoperative view following serial excision using subcutaneous nonabsorbable polypropylene sutures, and (c) after wound closure with a horizontal mattress suture.

MANAGEMENT OF HYPERTROPHIC AND KELOID SCARS

While asymptomatic hypertrophic scars can improve spontaneously over time, this is usually not the case with keloids. Moreover, keloids show a clear ethnic predisposition with highest prevalence in darker pigmented skin, in which they remain a particular therapeutic challenge [24]. They develop more frequently in certain areas of the body, such as the chest, shoulder, or ear. Due to considerable psychological impact and significant discomfort, including pruritus and even pain, keloids can considerably interfere with quality of life [25].

In contrast to hypertrophic scars, keloids tend to recur or even worsen after attempts at surgical removal. Despite a wide range of therapeutic modalities currently available to potentially target both types of lesion, their individual outcome is mostly unpredictable and there is still a need for evidence-based trials defining the precise role of each particularly in the case of keloid treatments. Moreover, treatment benefits are limited as a result of significant side effects, e.g., pigment changes or atrophy.

In most cases, a first-line monotherapy is not sufficient and combinations of several options will be required instead, be it in a simultaneous or a sequential mode. In cases of treatment failure, a second-line approach with surgical intramarginal revision in combination with intra- and postoperative adjuvant treatments can be chosen (Figure 25.4). Therefore, based on a careful evaluation of the personal circumstances and history, the choice of appropriate therapeutic options and a potential individual treatment scenario have to be sensibly considered with the patient in order to avoid unrealistic expectations.

In early stages, hypertrophic scars can be usually expected to improve spontaneously or otherwise tend to improve by topical treatment options. In late stages of development and in cases with functional impairment, surgical revision can be considered. Present therapeutic modalities for keloids include compression, topical agents, intralesional injections, cryotherapy, different lasers, photodynamic therapy (PDT) or electrostimulation, and combinations among them or, in refractory cases, other options, such as excision combined with adjuvant measures [6,24,26–29].

Topical Treatments

Compression garments, splints, silicone gel sheets, or other skin-taping procedures are widely used among the first-line noninvasive treatments of keloids and hypertrophic scars. They are in many situations practicable and without side effects and can also be applied in children. These products should best be worn over the scar for 12–24 hours per day for at least 2–3 months. Silicon elastomer sheeting is basically used to soften, flatten, and blanch hypertrophic and keloid scars and also to increase their range of motion by improving scar elasticity. In addition, silicone elastomer sheeting has been shown to reduce symptoms of pruritus and pain associated with hypertrophic and keloid scars [30]. Some of these silicone devices currently on the market are durable and adhere well to the skin. Although their precise mode of action is not yet fully understood, these methods are thought to increase pressure on the scar, to immobilize the involved skin area, and to form an occlusion on the surface with better hydration and reduction of scar tension. The mechanisms by which the external or superficial actions of these treatments cause remission of a protruding scar may also be related to mechanoreceptor responses [31]. Interestingly, even negative pressure seems to have a beneficial effect on keloids [32].

While silicone gel sheeting is frequently utilized to improve or avoid hypertrophic scars, its benefit in keloids as a single mode of therapy is rather insufficient and can best support other measures in combination [33,34]. In a short-term control after 6 months, silicone sheeting has proved to be beneficial

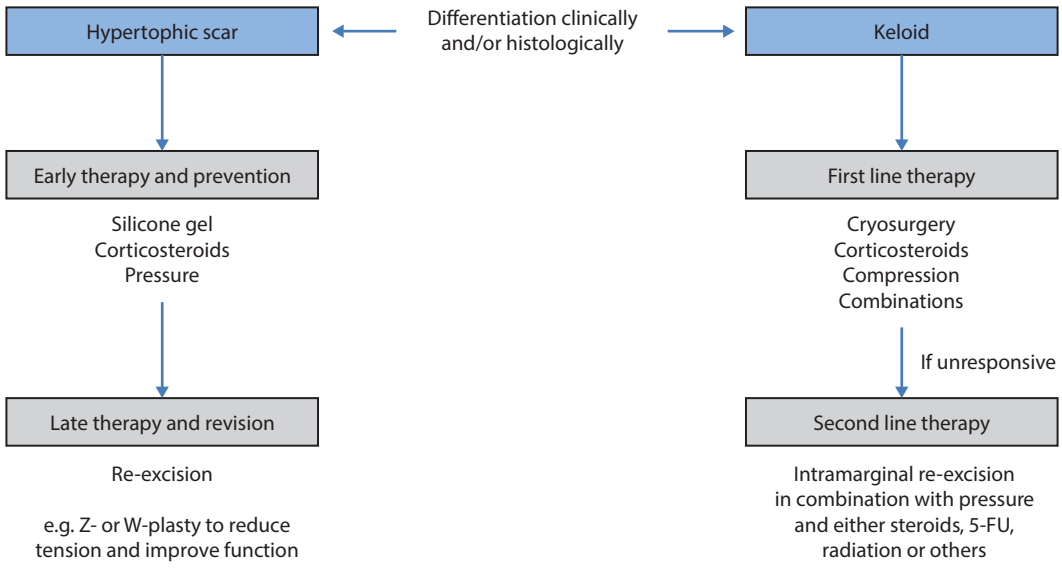


Figure 25.4 Algorithm in the management of hypertrophic scars and keloids.

as compared to controls [35]. However, in a meta-analysis of 13 trials examining the effect of silicone gel sheeting in the management of abnormal scarring in high-risk patients prone to hypertrophic and keloid scars, there was only a weak correlation, and other authors highlighted the absence of level-one evidence in the treatment of keloid [36,37].

Scars should be covered at least 12–24 hours per day, and the treatment is usually advised for a minimum of 4–6 months [38].

Intralesional Treatments

Intralesional corticosteroid injections are also commonly used among the first-line approaches and most frequently performed with triamcinolone acetonide [39]. They decrease collagen synthesis, inhibit fibroblast proliferation, and thus lead to scar regression, tissue atrophy, and flattening of the surface.

Best candidates in clinical use are active erythematous lesions with signs of inflammation. There is no consensus regarding the optimal dosage or concentration for injection, and also the efficacy of single or multiple injections is variable with good initial results but with recurrence rates of up to 50% after 5 years [40–42]. In a more recent study, Ud-Din and coworkers reported a 77% response rate of triamcinolone acetonide injections in 65 patients with keloid scars [43].

In clinical practice, triamcinolone acetonide (10–40 mg) will be diluted with lidocaine (up to 1:4) and is injected strictly into the firm lesional tissue using a syringe or a Dermojet device. Usually, it is applied repetitively at 4–6 weekly intervals.

Intralesional treatment of keloids has also been successfully performed using a multiple puncture injection of 1.5 IU/mL of bleomycin in a series of up to five treatment sessions. The authors demonstrated a flattening of lesions with only 2/13 patients showing recurrence after 12 months [44]. In another trial with 14 patients and up to 6 treatment sessions, a flattening of lesions could be induced without recurrence within a 19-month observation period [45].

Moreover, the antimetabolite and pyrimidine analogue 5-FU, the substrate of which interferes with DNA synthesis, can be used to inhibit keloid growth. However, noteworthy side effects including injection pain, hyperpigmentation, or even ulceration can cause a problem [46,47], and it is contraindicated in pregnant and breast-feeding women as well as in immunosuppressed individuals. A double-blind controlled trial examined the effects of 5-FU and topical silicone in 50 patients and found that the treated group had less recurrence and greater scar improvements in their keloid formations [34]. Supporting these results, an even more recent double-blind randomized trial demonstrated that 5-FU was significantly more effective than intralesional steroids in the treatment of keloids [48].

Cryotherapy

Cryofreezing with liquid nitrogen or cryo probes is also frequently used in hypertrophic scars and keloids, either alone in a repetitive mode at 4–6 weekly intervals or in combination such as with sequential steroid injection treatments. The mechanism of cryotherapy is thought to be mediated by ischemic damage leading to cellular anoxia and tissue necrosis and subsequent shrinkage of the size and via inducing differentiation of keloid fibroblast toward a more normal phenotype [49]. Irrespective of the technique employed (open cryospray or probe-contact mode) in each individual treatment session, the entire scar should be frozen twice for about 10–20 s. After the first cycle, it has to completely thaw prior to the second cycle. Usually up to 10 treatment sessions will be required. Typical adverse effects include acute pain and blistering (second-degree burn) on the following day with consecutive development of erosions and crusts prior to re-epithelization. In darker skin types, depigmentation can occur later.

An interventional trial in 30 keloid patients showed that cryosurgery was an effective treatment modality particularly in smaller lesions of recent onset, with duration and thickness of keloids being the most important predicting factors for treatment success [50].

Lasers

Ablative lasers (Er:YAG, CO_2) can be used as an alternative to electrosurgical or scalpel debulking of the exophytic keloid volume. As with all surgical procedures employed in the treatment of keloids, these laser types are typically combined with other therapeutic modalities in order to prevent recurrence. However, Nicoletti and colleagues have used high-energy pulsed CO_2 laser treatment as a monotherapy in 50 consecutive patients with moderate to severe keloids and recently demonstrated significant immediate and prolonged clinical improvement in skin tone, texture, and appearance in all cases. Dermal remodeling was observed also on histologic examination of biopsied tissue after treatment [51].

Also, nonablative lasers such as the 532 frequency-doubled Nd:YAG laser have been used. The most promising results have been reported with the flashlamp-pumped dye laser (585 nm wavelength) with a response rate of about 75% and only minimal discomfort [52]. However, like others [53], we were not able to confirm such good effects. Regarding the mode of action, suggested theories are based on selective photothermolysis in which the light energy emitted from the laser is absorbed by hemoglobin, generating heat and leading to coagulation necrosis, neocollagenesis, collagen fiber heating with dissociation of disulfide bonds, and subsequent collagen fiber realignment [54].

PDT

Apart from its main indication in the treatment of actinic keratosis and early epithelial skin cancer, PDT has been studied in a growing number of disorders including keloid scars. Mendoza and coworkers experimentally demonstrated a cytotoxic effect of PDT on fibroblasts from keloids [55].

After an initial positive case report of the successful use of PDT [56], a recent series in 20 keloid patients confirmed an inhibitory effect on blood flow and collagen with a reduction of lesional volume and no recurrence during a follow-up of 9 months [57].

Others

In more recent years, degenerate electrical waves have been shown to downregulate collagen I expression in keloid fibroblasts, and the technique of electrostimulation has been used successfully in abnormal scars [58–60].

Moreover, due to a better understanding of underlying molecular mechanisms in abnormal scar development and keloid formation, new targeted therapies are expected to be developed in the future [61].

Excision

For patients with refractory and disfiguring hypertrophic scars and in cases with additional functional impairment, surgical revision with simple excision or, if required, a Z- or W-plasty will usually be the treatment option of choice (Figure 25.5). In keloids, however, excision has to be performed in an intramarginal fashion and a combination with an adjuvant treatment is mandatory in order to prevent a relapse.

Combinations

There are several possible combination approaches in the management of hypertrophic and keloid scars, in particular as a sequential treatment after scalpel or CO_2-laser removal but also in combination with different types of single options. In many cases, even multiple approaches have to be combined [62].

Surgery plus Compression

One option is postsurgical compression therapy. However, constant pressure is not easy to realize in all locations, and sometimes sophisticated solutions such as specially manufactured splints are required, e.g., in earlobe keloids [63].

Surgery plus Imiquimod

Among the topical treatments, imiquimod, a widely used immune response modulator that inhibits fibroblast collagen production via cytokine induction at the site of application, has also been used in combination with surgical keloid excision in an attempt to prevent recurrence.

Its prophylactic use in 12 patients [64] immediately after surgery over a period of 8 weeks showed success during an observation of 24 weeks. While its use has shown promising results after keloid shaving from the earlobe, there were no such benefits on other body sites [65,66]. Also, in a case with presternal keloids, recurrence appeared as soon as imiquimod was discontinued [67].

Surgery plus 5-FU

In a recent study of patients treated for earlobe keloids, intralesional 5-FU was used successfully [68]. Twenty-eight patients were injected in doses of 50–150 mg divided between the excision margin and the wound bed, and the wound was closed primarily, while 24 patients with involvement of 32 earlobes were treated with intralesional triamcinolone at 2 weekly intervals as a control. Of the 28 patients treated with 5-FU, only one showed evidence of hypertrophy of scar but no worsening of the lesion over 22 months of follow-up, while in the control group, seven patients suffered from keloid reappearance.

Surgical Procedures plus Steroid Injection

Surgical excision of keloids is associated with a high rate of recurrence and the potential to develop an even bigger lesion in this event. Therefore, excisions should be accompanied by adjuvant therapies [7]. They are also advised after laser removal or in combination with cryosurgery. Moreover, patients with keloids operated in a high risk of recurrence, such as the earlobe or in areas of mechanical stress and under mobility, such

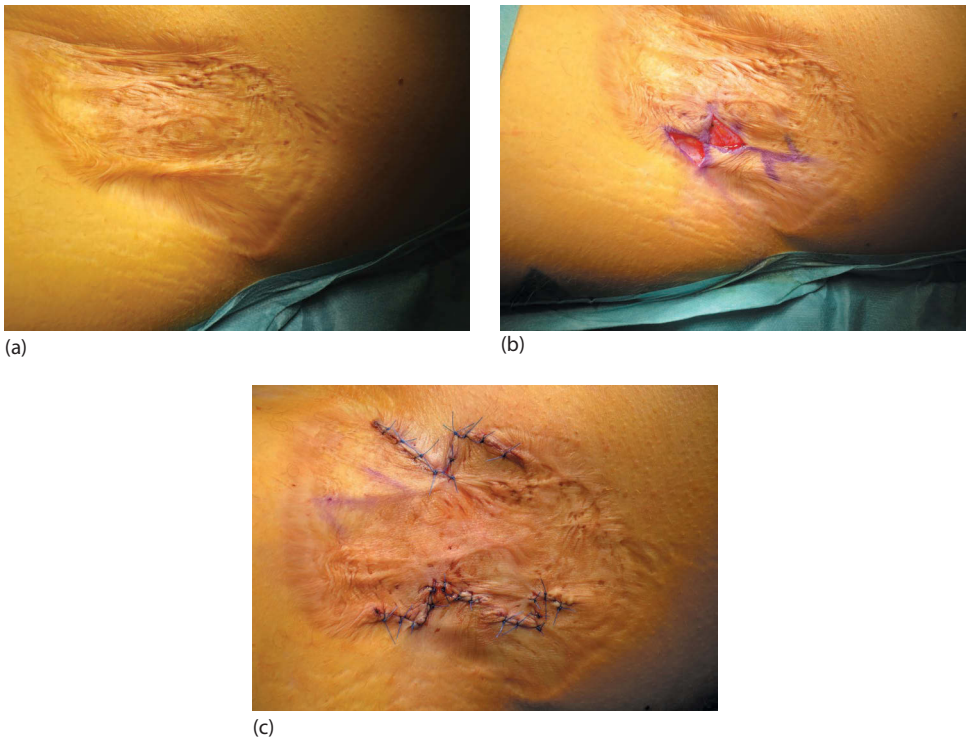


Figure 25.5 Z-plasty in the axillary region after hidradenitis suppurativa excision and split-thickness skin transplantation and the development of scar cords. (a) Preoperative situs, (b) Z-plasty releasing the tension, and (c) completed operation.

as the shoulder, should be supported by postsurgical pressure or splintage whenever feasible.

As an adjuvant treatment, surgical procedures including excisions, CO_2-vaporization, and also cryosurgery are most frequently combined with intraoperative and postoperative intralesional injections of steroids in a repetitive mode at 4–6 weekly intervals [69,70].

Surgery plus Radiation

Though radiotherapy is of limited value as a monotherapy, several studies have evaluated its role combined with surgery, where success rates up to 98% have been documented [71]. Reported doses range from only 3 up to 40 Gy with larger doses reducing the recurrence rate more effectively in some studies. In a case report of a giant keloid, adjuvant radiotherapy was successful in preventing recurrence within a 3-year period of observation [72]. Radiotherapy can be applied immediately after surgery [73]. It has also been used successfully following surgery in the challenging event of earlobe keloids [74]. However, in a randomized controlled trial, treating 50 earlobe keloids using intralesional steroid injections, and comparing these patients with a group managed by postoperative radiotherapy, did not show any significant differences in the recurrence rate [75].

MANAGEMENT OF ACNE SCARS

Acne scarring is a frequently met yet exceptionally puzzling problem to treat. Although early treatment of acne lesions and inflammation with isotretinoin is beneficial in preventing acne scarring, many patients still present with troubling noticeable scars. As it can cause low self-esteem and substantial psychological suffering, it is of utmost importance to have effective treatments in the dermatologist's armamentarium. However, many treatments still remain suboptimal and are tainted with several adverse effects, leading to patient frustration. Therefore, all potential options in an individual case have to be carefully evaluated to start a treatment plan.

Basically, all different types of abnormal scarring can be found in acne patients. They might range from macular erythematous to depigmented or hyperpigmented scars or from atrophic to hypertrophic or even keloid scars as predominantly seen on the chest or shoulders of young acne patients. Apart from these considerations, there are some specific aspects in facial acne scarring that have implications for the choice of treatment. Here, most frequently atrophic depressed lesions are seen that can appear with typical clinical features, configuration or shaping, usually described as ice-pick-, box-, or rolling-scar variants. Sometimes, the three different types of atrophic scars can be observed in the same patient, and it can be a challenge to differentiate between them (Figure 25.6). For this reason, several scales have been proposed, among which the simple qualitative one of Goodman and Baron is universally applicable [76]. According to this classification, four different grades can be distinguished as outlined in Table 25.4.

Apart from an adequate management of the different clinical stages of active acne disease in order to prevent new inflammatory lesions and subsequent scarring, the treatment of existing scars is therefore mainly guided by the specific type of scars seen and by the overall grade of severity in a given patient. Today, there are numerous treatment options including chemical peels, dermabrasion/microdermabrasion, laser treatment, punch techniques, dermal grafting, needling, silicone gels, intralesional steroid therapy, or cryotherapy [77–80]. Inflammatory erythematous or hyperpigmented variants can be targets for laser treatments as already described within this chapter.

Figure 25.6 A 46-year-old male patient with a grade 4 acne scarring and a mixture of different depigmented atrophic and hypertrophic scar types.

Table 25.4 Qualitative Grading of Acne Scars

Grade	Level of disease	Clinical features
1	Macular	Erythematous, hyper- or hypopigmented scars. Problem of color, not of contour
2	Mild	Minimal atrophic or hypertrophic scars, which usually may be covered by makeup
3	Moderate	Atrophic or hypertrophic scarring that is obvious at social distances of 50 cm and is not covered easily by makeup, but if atrophic is still able to be flattened by manual stretching of the skin
4	Severe	Severe atrophic or hypertrophic scarring that is evident at social distances >50 cm and is not covered easily and is not able to be flattened by manual stretching of the skin

Source: Modified from Goodman GJ and Baron JA, *Dermatol Surg*, 32, 1458, 2006.

Treatment of Atrophic Acne Scars

Chemical Peeling

In acne, chemical peels can be helpful for the treatment of active skin lesions as well as scars, with the best results achieved in macular types. Different hydroxy acids can be used. Among these, glycolic acid, an alpha-hydroxy acid, acts by thinning the stratum corneum, dispersing basal layer melanin and increasing dermal collagen and hyaluronic acid gene expression via IL-6 secretion. Apart from initial irritation, the procedure is well tolerated. The level of skin damage increases in a dose- and time-dependent manner, and the best results achieved for acne scars regard five sequential sessions of 70% glycolic acid every 2 weeks [78].

Other well-tolerated formulations used for this purpose include Jessner's solution combining salicylic acid, resorcinol, and lactic acid (another alpha hydroxy acid) in 95% ethanol as an excellent alternative to achieve corneocyte detachment and subsequent desquamation of the stratum corneum. Rarely observed allergic contact dermatitis and systemic allergic reactions to resorcinol have to be considered as contraindications.

Trichloroacetic acid (TCA) as a further peeling agent introduced by the German dermatologist P.G. Unna already in 1882 causes protein denaturation visible as a "white frost." While 10%–20% TCA peels only result in superficial effects not penetrating deeper than the stratum granulosum, higher concentrations of 25%–35% will lead to a full-thickness peel of the epidermis and those of 40%–50% can produce injury to the papillary dermis. TCA concentrations above 35% can produce unpredictable results including new scarring. Therefore, the use of TCA in concentrations greater than 35% should be avoided. It is also not indicated for dark skin because of the high risk of posttreatment hyperpigmentation.

Mechanical Dermabrasion

Among the abrasive resurfacing techniques with mechanical devices, microdermabrasion and dermabrasion both ablate the involved skin area to promote stimulation of tissue repair and re-epithelialization. Microdermabrasion as a more shallow variation only ablates the outer layer of the epidermis, thereby accelerating the natural process of exfoliation. All microdermabraders include a pump that generates a stream of aluminum oxide or salt crystals with a vacuum to remove the crystals and exfoliate the skin. The procedure can be repeated at short intervals and does not require anesthesia.

It is only rarely associated with any side effects but is also less effective than full-depth dermabrasion. Dermabrasion instead completely removes the epidermis and penetrates to the level of the papillary or even reticular dermis, leading to a bleeding wound area that induces a remodeling of the structural dermal proteins. Dermabrasion of larger aesthetic units is preferentially performed under general anesthesia using a modern high-speed diamond fraise [81]. Depending on the depth of skin ablation, patients will experience different degrees of early- (until re-epithelialization has been completely achieved) and late-occurring side effects or complications. Acute effects can be expected following the injury and include pain, edema, bleeding, and crusts, while early complications include superinfection. Among late side effects is erythema that as a complication can also persist over longer periods. Another frequent complication is postinflammatory hyperpigmentation, which might be transient and can usually be managed successfully with topical agents such as azelaic acid and hydroquinone. Especially deeper dermabrasion can be followed by a later onset (after 1 year) of permanent depigmentation.

Microneedling

Microneedling (skin needling, needle dermabrasion, dermaroller therapy) is a relatively new addition to the treatment armamentarium, which has also been used in atrophic acne scars, especially in the rolling type or in more superficial box scars [82]. It offers a simple, inexpensive, and reportedly effective office procedure with no downtime. Of 36 acne patients treated with multiple sittings of microneedling for atrophic facial scarring, 34 patients achieved a reduction in the severity of their scarring by one or two grades and more than 80% of patients assessed their treatment as "'excellent" on a 10-point scale. No significant adverse effects were noted in any patient [83]. A sequential combination of microneedling and glycolic acid peels was found to give excellent results in the treatment of scars coexisting with areas of postinflammatory hyperpigmentation in Indian skin (skin types III–IV) [84].

Laser Ablation

Pulsed CO_2 lasers and the even less tissue heating Er:YAG system are the most commonly used ablative light sources to resurface acne scars. They have also been successfully applied with different operational modes in pigmented Asian skin type [85,86]. In a pulsed mode, they ablate or vaporize the surface and induce dermal inflammation and collagen remodeling dependent on the depth of ablation. In contrast to mechanical dermabrasion, they are not dependent on the surgeons' manual skills but only on the laser parameters used. Therefore, there is a better and more reliable control of depth of tissue injury and a more homogenously distributed effect over the entire surface of a given aesthetic unit. Moreover, the laser can be more easily used in delicate skin areas such as around the lips or the eyes with less risk of unwarranted mechanical injury. As with dermabrasion, the "downtime" of patients after surgery and the amount and severity of side effects as well as of potential complications largely depend on the area and depth of tissue damage.

A special way of more delicate and tissue-sparing laser resurfacing inducing a microscopic pattern of ablative or thermal injury (microthermal treatment zones) with less postsurgical "downtime" is the fractional technique employing a second-generation Er-doped 1550-nm fractional photothermolysis laser [87] or modified CO_2- and Er:YAG-laser systems (Figure 25.7) in an either ablative or nonablative mode [88–90]. Analyzing subjective and objective assessment of scar appearance, pre- and postoperative treatment, side effects, and pain scores in 26 studies performed in acne patients with both ablative and nonablative fractional laser systems, ablative lasers had an improvement range of 26%–83%, whereas nonablative systems had an improvement range of 26%–50%. However, in patients who underwent treatment with an ablative fractional laser, there was more discomfort during the procedure and the observed side effects (erythema, postinflammatory hyperpigmentation) were more frequent, more severe, and of longer duration [91].

In active acne patients suffering from inflammatory scar lesions, fractional laser treatment has also been sequentially combined with intense pulsed light (IPL) treatments (successive sessions of 4–6 IPL treatments followed by 2 sessions of fractional CO_2 laser treatments) [92] and also used after PDT

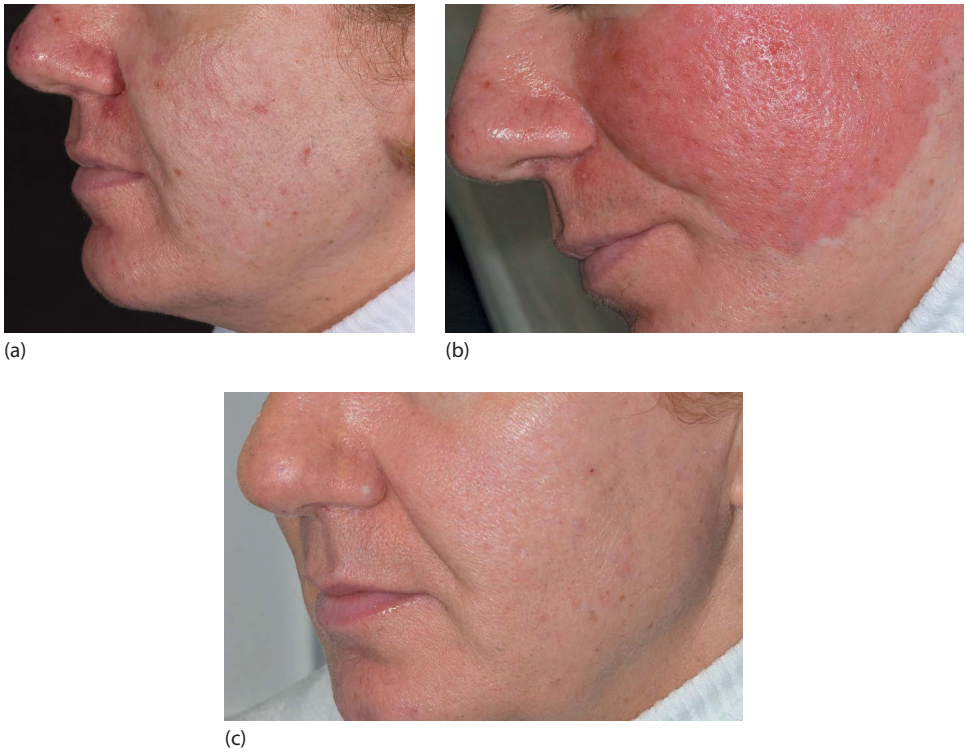


Figure 25.7 Fractional Er-doped 2940 nm laser in the treatment of acne scars. (a) Preoperative situation, (b) condition after fractional therapy (fluence 144 J/cm^2, 5 mm spot; Burane XL, WaveLight®), and (c) status after four treatment intervals.

(15% ALA-PDT for four times at 10-day intervals followed by ablative fractional Er:YAG laser treatment five times at 4-week intervals) [93].

Special Aspects in Box Scar, Ice-Pick Scar, and Rolling Scars

Figure 25.8 schematically displays the configuration of these typical scar variants in acne patients (also compare Figure 25.6). Apart from the fact that these types might benefit from repetitive peeling or resurfacing procedures (e.g., Fraxel laser ablation) also in a focal fashion [94], particularly in mild to moderate grade 2–3 patients, additional surgical procedures can be performed especially in box and ice-pick scars. As with scars resulting from varicella infection, also the round and sharply demarcated box scars can benefit from a simple punch elevation (Figure 25.8d) slightly above the level of the adjacent skin followed by later resurfacing or peeling. An alternative can be undermining and detachment of the fibrotic base by means of subsicion. Ice-pick scars, instead, are better removed by multiple small punch excisions (Figure 25.8e) of the entire lesion. In more shallow rolling scars, additional fillers, especially serial microdroplet silicone injections, can improve the aspect in some patients and also autologous fibroblasts might be considered as an alternative [95,96].

Treatment of Hypertrophic and Keloid Acne Scars

The current first- and second-line options mentioned earlier (also compare Table 25.4) also apply to scars developing in young acne patients.

MANAGEMENT OF ERYTHEMATOUS SCARS

Erythematous scars are mostly less than 1 year of duration, and the treatment goal is to achieve a paler and less visible skin surface by targeting the capillary vessels within the fibrotic tissue. For this purpose, either a deeper photocoagulation (e.g., diode laser, Nd:YAG laser) or a more superficial selective photothermolysis (flashlamp-pumped dye laser) with respective parameter settings can be tested.

MANAGEMENT OF HYPERPIGMENTED SCARS

In contrast to some other disorders characterized by circumscribed hyperpigmentation of the skin (e.g., actinic lentigo, Nevus of Ota), the outcome of therapeutic interventions is usually less favorable in hyperpigmented scars. However, they are a potential target for "pigment lasers" in a Q-switched mode, such as the frequency-doubled Nd:YAG laser (532 nm) and the alexandrite laser (755 nm).

LIMITS OF SCAR REVISION

Despite the diverse armamentarium of therapeutic tools and techniques used in the treatment of abnormal scars, there are always patients in whom therapeutic interventions do not make sense, are not far reaching enough, or become unexpectedly complicated.

Dermatitis artefacta (DA), in which self-inflicted skin lesions have resulted in scars, is a disease for which the therapy of the scar is secondary (Figure 25.9a and b).

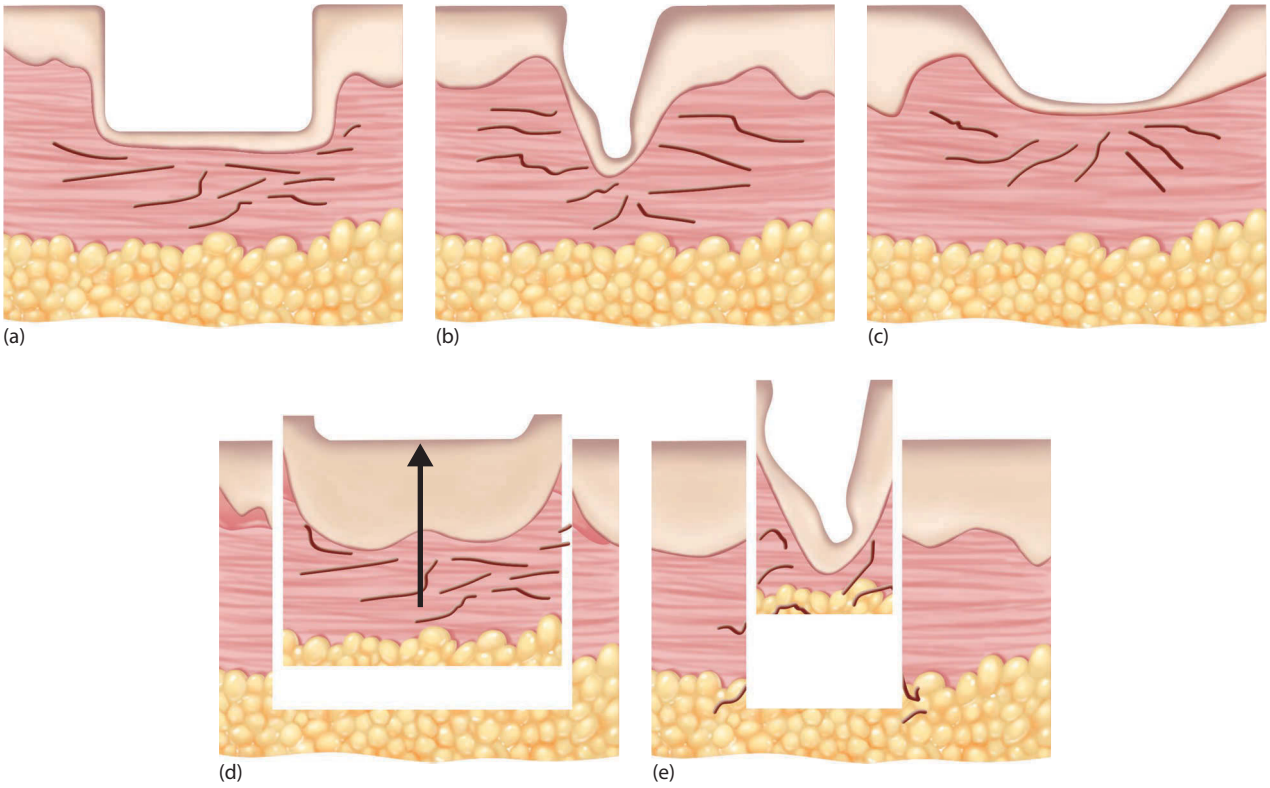


Figure 25.8 Schematic display of three major types of acne scars and corresponding treatment options. (a) Varioliform "box scar." (b) Ice-pick scar. (c) Depressed "rolling scar." (d) Punch elevation. (e) Punch excision.

Figure 25.9 Artefactual scars. (a) A patient with the history of dermatits artefacta over years with depressed depigmentated scars and (b) the forearm of a patient with borderline disorder and hypertrophic scars after self-harm with a knife.

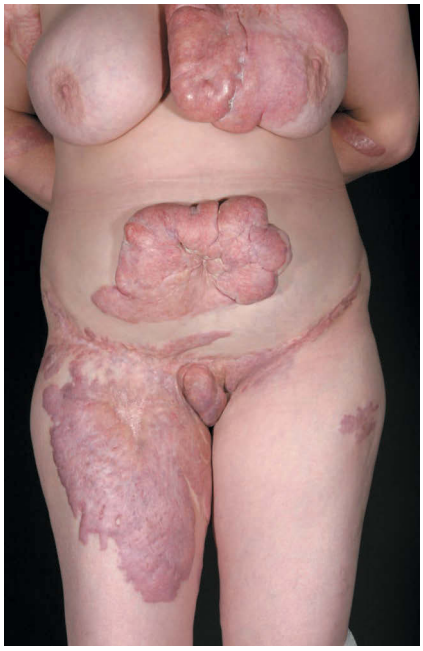


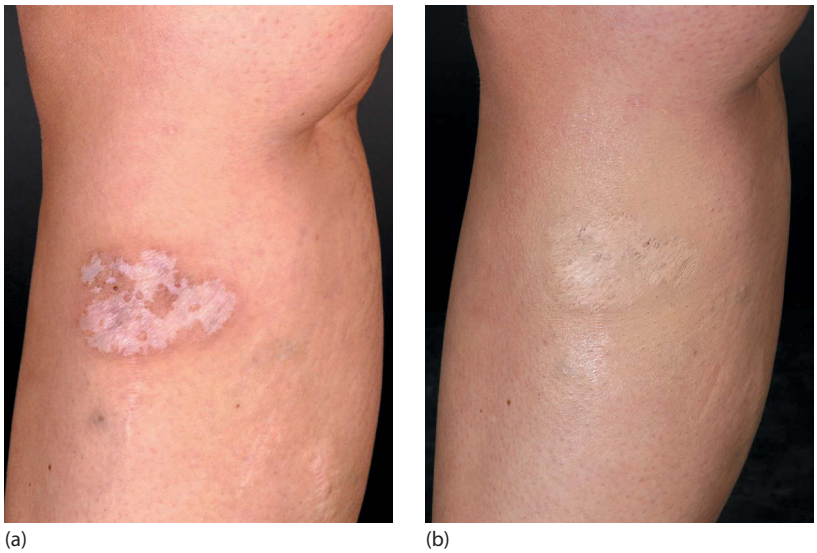
Figure 25.10 A patient developing extraordinary keloids spontaneously or after minor trauma.

DA is a manifestation of a primary psychiatric disorder in which the patient self-inflicts skin lesions in order to fulfill a psychological need. Various psychopathological diseases are prone to the development of DA, such as a borderline disorder and anorexia nervosa, as well as in the context of shared psychosis [97]. The therapeutic intervention must primarily be performed psychologically; only after successful psychological therapy can the treatment of scars become promising.

Aside from this psychiatric peculiarity, there are cases where the classic therapeutic tools and techniques are ineffective and therapy becomes frustrating (Figure 25.10). In these cases, extraordinary therapeutic options, such as electrochemotherapy, might be considered. Manca et al., treated 20 patients (either suffering from very large keloids or nonresponders to other treatments) with electrochemotherapy and bleomycin, which resulted in a median reduction of 87% in volume size [98]. Electrochemotherapy therefore might be a promising new treatment for very large scars or scars not responding to standard treatments.

Depigmented scars pose additional challenges, and treatment by epidermal grafting has been tested [99]. Unfortunately, there are no major studies to support such treatment, since the therapy is costly and often limited in success. Alternatives involve using a 308 nm excimer laser, an Er-doped 1550 nm fractionated laser, tattooing the depigmented area, or applying classical camouflage (Figure 25.11) [100,101]. For laser treatments especially, results are limited and thus larger studies are needed.

Increasing knowledge of the pathophysiology of scar formation regarding inflammation, fibrogenic response, and matrix regulation promises new innovative therapeutic options that will hopefully overcome current limitations in scar treatment and prevention.



(a) (b)

Figure 25.11 Camouflage of depigmented scars (a) before treatment and (b) after treatment.

REFERENCES

1. Velnar T, Bailey T, Smrkolj V. The wound healing process: An overview of the cellular and molecular mechanisms. *J Int Med Res* 2009; 37:1528–1542.
2. Glim JE, van Egmond M, Niessen FB, Everts V, Beelen RH. Detrimental dermal wound healing: What can we learn from the oral mucosa? *Wound Repair Regen* 2013; 21:648–660.
3. Ferguson MW, O'Kane S. Scar-free healing: From embryonic mechanisms to adult therapeutic intervention. *Philos Trans R Soc Lond B Biol Sci* 2004; 359:839–850.
4. Greaves NS, Ashcroft KJ, Baguneid M, Bayat A. Current understanding of molecular and cellular mechanisms in fibroplasia and angiogenesis during acute wound healing. *J Dermatol Sci* 2013; 72:206–217.
5. Köse O, Waseem A. Keloids and hypertrophic scars: Are they two different sides of the same coin? *Dermatol Surg* 2008; 34:336–346.
6. Wolfram D, Tzankov A, Pülzl P, Piza-Katzer H. Hypertrophic scars and keloids—A review of their pathophysiology, risk factors, and therapeutic management. *Dermatol Surg* 2009; 35:171–181.
7. Tziotzios C, Profyris C, Sterling J. Cutaneous scarring: Pathophysiology, molecular mechanisms, and scar reduction therapeutics. Part II. Strategies to reduce scar formation after dermatologic procedures. *J Am Acad Dermatol* 2012; 66:13–24.
8. Atkinson JA, McKenna KT, Barnett AG, McGrath DJ, Rudd M. A randomized, controlled trial to determine the efficacy of paper tape in preventing hypertrophic scar formation in surgical incisions that traverse Langer's skin tension lines. *Plast Reconstr Surg* 2005; 116:1648–1656.
9. Niessen FB, Spauwen PH, Kon M. The role of suture material in hypertrophic scar formation: Monocryl vs. Vicryl-rapide. *Ann Plast Surg* 1997; 39:254–260.
10. Zuber TJ. The mattress sutures: Vertical, horizontal, and corner stitch. *Am Fam Physician* 2002; 66:2231–2236.
11. Reddix RN, Jr, Tyler HK, Kulp B et al. Incisional vacuum-assisted wound closure in morbidly obese patients undergoing acetabular fracture surgery. *Am J Orthop* 2009; 38:446–449.
12. Stannard JP, Gabriel A, Lehner B. Use of negative pressure wound therapy over clean, closed surgical incisions. *Int Wound J* 2012; 9 (Suppl 1):32–39.
13. Timmers MS, Le Cessie S, Banwell P et al. The effects of varying degrees of pressure delivered by negative-pressure wound therapy on skin perfusion. *Ann Plast Surg* 2005; 55:665–671.
14. Kilpadi DV, Cunningham MR. Evaluation of closed incision management with negative pressure wound therapy (CIM): Hematoma/seroma and involvement of the lymphatic system. *Wound Repair Regen* 2011; 19:588–596.
15. Wilkes RP, Kilpad DV, Zhao Y et al. Closed incision management with negative pressure wound therapy (CIM): Biomechanics. *Surg Innov* 2012; 19:67–75.
16. Valesky EM, Kaufmann R, Meissner M. Special indications for negative pressure wound therapy in dermatologic surgery. *Hautarzt* 2013; 64:585–591.
17. Kaufmann R, Podda M, Landes E. *Dermatologische Operationen*, 4th ed. Stuttgart, Germany: Thieme, 2011, pp. 40–41.
18. Vrijman C, van Drooge AM, Limpens J, Bos JD, van der Veen JP, Spuls PI, Wolkerstorfer A. Laser and intense pulsed light therapy for the treatment of hypertrophic scars: A systematic review. *Br J Dermatol* 2011; 165:934–942.
19. Conologue TD, Norwood C. Treatment of surgical scars with the cryogen-cooled 595 nm pulsed dye laser starting on the day of suture removal. *Dermatol Surg* 2006; 32:13–20.
20. Capon A, Iarmarcovai G, Gonnelli D, Degardin N, Magalon G, Mordon S. Scar prevention using Laser-Assisted Skin Healing (LASH) in plastic surgery. *Aesthetic Plast Surg* 2010; 34:438–446.
21. Capon AC, Gossé AR, Iarmarcovai GN, Cornil AH, Mordon SR. Scar prevention by laser-assisted scar healing (LASH): A pilot study using an 810-nm diode-laser system. *Lasers Surg Med* 2008; 40:443–445.
22. Choe JH, Park YL, Kim BJ, Kim MN, Rho NK, Park BS, Choi YJ, Kim KJ, Kim WS. Prevention of thyroidectomy scar using a new 1,550-nm fractional erbium-glass laser. *Dermatol Surg* 2009; 35:1199–1205.
23. Jung JY, Jeong JJ, Roh HJ, Cho SH, Chung KY, Lee WJ, Nam KH, Chung WY, Lee JH. Early postoperative treatment of thyroidectomy scars using a fractional carbon dioxide laser. *Dermatol Surg* 2011; 37:217–223.
24. Ud-Din S, Bayat A. Strategic management of keloid disease in ethnic skin: A structured approach supported by the emerging literature. *Br J Dermatol* 2013; 169 (Suppl 3):71–81.
25. Bock O, Schmid-Ott G, Malewski P, Mrowietz U. Quality of life of patients with keloid and hypertrophic scarring. *Arch Dermatol Res* 2006; 297:433–438.
26. Chike-Obi CJ, Cole PD, Brissett AE. Keloids: Pathogenesis, clinical features, and management. *Semin Plast Surg* 2009; 23:178–184.
27. Marneros AG, Krieg T. Keloids—Clinical diagnosis, pathogenesis, and treatment options. *J Dtsch Dermatol Ges* 2004; 2:905–913.
28. Reish RG, Eriksson E. Scars: A review of emerging and currently available therapies. *Plast Reconstr Surg* 2008; 122:1068–1078.
29. Ogawa R. The most current algorithms for the treatment and prevention of hypertrophic scars and keloids. *Plast Reconstr Surg* 2010; 125:557–568.
30. Beman B, Perez OA, Konda S, Kohut B, Viera MH, Delgado S, Zell D, Li Q. Review of the biologic effects, clinical efficacy, and safety of silicone elastomer sheeting for hypertrophic and keloid scar treatment and management. *Dermatol Surg* 2007; 33:1291–1303.
31. Yagmur C, Akaishi S, Ogawa R, Guneren E. Mechanical receptor-related mechanisms in scar management: A review and hypothesis. *Plast Reconstr Surg* 2010; 126:426–434.
32. Fraccalvieri M, Sarno A, Gasperini S, Zingarelli E, Fava R, Salomone M, Bruschi S. Can single use negative pressure wound therapy be an alternative method to manage keloid scarring? A preliminary report of a clinical and ultrasound/colour-power-doppler study. *Int Wound J* 2013; 10:340–344.
33. Sidle DM, Kim H. Keloids: Prevention and management. *Facial Plast Surg Clin North Am* 2011; 19:505–515.
34. Hatamipour E, Mehrabi S, Hatamipour M, Ghafarian Shirazi HR. Effects of combined intralesional 5-fluorouracil and topical silicone in prevention of keloids: A double blind randomized clinical trial study. *Acta Med Iran* 2011; 49:127–130.
35. Gold MH. A controlled clinical trial of topical silicone gel sheeting in the treatment of hypertrophic scars and keloids. *J Am Acad Dermatol* 1994; 30:506–507.
36. de Oliveira GV, Nunes TA, Magna LA et al. Silicone versus non-silicone gel dressings: A controlled trial. *Dermatol Surg* 2001; 27:721–726.
37. Durani P, Bayat A. Levels of evidence for the treatment of keloid disease. *J Plast Reconstr Aesthet Surg* 2008; 61:4–17.
38. Karrer S. Therapy of keloids. *Hautarzt* 2007; 58:979–989.
39. Jalali M, Bayat A. Current use of steroids in management of abnormal raised skin scars. *Surgeon* 2007; 5:175–180.
40. Wu WS, Wang FS, Yang KD et al. Dexamethasone induction of keloid regression through effective suppression of VEGF expression and keloid fibroblast proliferation. *J Invest Dermatol* 2006; 126:1264–1271.
41. Gauglitz GG, Korting HC, Pavicic T et al. Hypertrophic scarring and keloids: Pathomechanisms and current and emerging treatment strategies. *Mol Med* 2011; 17:113–125.
42. Kill J. Keloids treated with topical injections of triamcinolone acetonide (kenalog): Immediate and long-term results. *Scand J Plast Reconstr Surg* 1977; 11:169–172.
43. Ud-Din S, Bowring A, Derbyshire B et al. Identification of steroid sensitive responders versus non-responders in the treatment of keloid disease. *Arch Dermatol Res* 2013; 305:423–432.
44. Espana A, Solano T, Quintanilla E. Bleomycin in the treatment of keloids and hypertrophic scars by multiple needle punctures. *Dermatol Surg* 2001; 27:23–27.

45. Saray Y, Gulec AT. Treatment of keloids and hypertrophic scars with dermojet injections of bleomycin: A preliminary study. *Int J Dermatol* 2005; 44:777–784.
46. Apikian M, Goodman G. Intralesional 5-fluorouracil in the treatment of keloid scars. *Australas J Dermatol* 2004; 45:140–143.
47. Gupta S, Kalra A. Efficacy and safety of intralesional 5-fluorouracil in the treatment of keloids. *Dermatology* 2002; 204:130–132, 2004; 30:54–56.
48. Sadeghinia A, Sadeghinia S. Comparison of the efficacy of intralesional triamcinolone acetonide and 5-fluorouracil tattooing for the treatment of keloids. *Dermatol Surg* 2012; 38:104–109.
49. Har-Shai Y, Amar M, Sabo E. Intralesional cryotherapy for enhancing the involution of hypertrophic scars and keloids. *Plast Reconstr Surg* 2003; 111:1841–1852.
50. Barara M, Mendiratta V, Chander R. Cryotherapy in treatment of keloids: Evaluation of factors affecting treatment outcome. *J Cutan Aesthet Surg* 2012; 5:185–189.
51. Nicoletti G, de Francesco F, Mele CM et al. Clinical and histologic effects from CO2 laser treatment of keloids. *Lasers Med Sci* 2013; 28:957–964.
52. Alster TS, Williams CM. Treatment of keloid sternotomy scars with 585 nm flashlamp-pumped pulsed-dye laser. *Lancet* 1995; 345:11998–11200.
53. Paquet P, Hermans JF, Pierard GE. Effect of the 585 nm flashalmp-pumped pulsed dye laser for the treatment of keloids. *Dermatol Surg* 2001; 27:171–174.
54. Bouzari N, Davis SC, Nouri K. Laser treatment of keloids and hypertrophic scars. *Int J Dermatol* 2007; 46:80–88.
55. Mendoza J, Sebastian A, Allan E et al. Differential cytotoxic response in keloid fibroblasts exposed to photodynamic therapy is dependent on photosensitiser precursor, fluence and location of fibroblasts within the lesion. *Arch Dermatol Res* 2012; 304:549–562.
56. Nie Z, Bayat A, Behzad F, Rhodes LE. Positive response of a recurrent keloid scar to topical methyl aminolevulinate-photodynamic therapy. *Photodermatol Photoimmunol Photomed* 2010; 26:330–332.
57. Ud-Din S, Thomas G, Morris J, Bayat A. Photodynamic therapy: An innovative approach to the treatment of keloid disease evaluated using subjective and objective non-invasive tools. *Arch Dermatol Res* 2013; 305:205–214.
58. Sebastian A, Syed F, McGrouther DA et al. A novel in vitro assay for electrophysiological research on human skin fibroblasts: Degenerate electrical waves downregulate collagen I expression in keloid fibroblasts. *Exp Dermatol* 2011; 20:64–68.
59. Perry D, Colthurst J, Giddings P et al. Treatment of symptomatic abnormal skin scars with electrical stimulation. *J Wound Care* 2010; 19:447–453.
60. Ud-Din S, Giddings P, Colthurst J et al. Significant reduction of symptoms of scarring with electrical stimulation: Evaluated with subjective and objective assessment tools. *Wounds* 2013; 25:212–224.
61. Mrowietz U, Seifert O. Keloid scarring: New treatments ahead. *Actas Dermosifiliogr* 2009 December; 100 (Suppl 2):75–83.
62. Asilian A, Darougheh A, Shariati F. New combination of triamcinolone, 5-fluorouracil, and pulsed-dye laser for treatment of keloid and hypertrophic scars. *Dermatol Surg* 2006; 32:907–915.
63. Hassel JC, Löser C, Koenen W, Kreuter A, Hassel AJ. Promising results from a pilot study on compression treatment of ear keloids. *J Cutan Med Surg* 2011; 15:130–136.
64. Berman B, Kaufman J. Pilot study of the effect of postoperative imiquimod 5% cream on the recurrence rate of excised keloids. *J Am Acad Dermatol* 2002; 47:S209–S211.
65. Stashower ME. Successful treatment of earlobe keloids with imiquimod after tangential shave excision. *Dermatol Surg* 2006; 32:380–386.
66. Cacao FM, Tanaka V, Messina MC. Failure of imiquimod 5% cream to prevent recurrence of surgically excised trunk keloids. *Dermatol Surg* 2009; 35:629–633.
67. Malhotra AK, Gupta S, Khaitan BK, Sharma VK. Imiquimod 5% cream for the prevention of recurrence after excision of presternal keloids. *Dermatology* 2007; 215:63–65.
68. Khare N, Patil SB. A novel approach for management of ear keloids: Results of excision combined with 5-fluorouracil injection. *J Plast Reconstr Aesthet Surg* 2012; 65:315–317.
69. Rosen DJ, Patel MK, Freeman KPH, Weiss PR. A primary protocol for the management of ear keloids: Results of excision combined with intraoperative and postoperative steroid injections. *Plast Reconstr Surg* 2007; 120:1395e400.
70. Careta MF, Fortes AC, Messina MC, Maruta CW. Combined treatment of earlobe keloids with shaving, cryosurgery, and intralesional steroid injection: A 1-year follow-up. *Dermatol Surg* 2013; 39:734–738.
71. Norris JE. Superficial x-ray therapy in keloid management: A retrospective study of 24 cases and literature review. *Plast Reconstr Surg* 1995; 95:1051–1055.
72. Troiano M, Simeone A, Scaramuzzi G et al. Giant keloid of left buttock treated with post-excisional radiotherapy. *J Radiol Case Rep* 2011; 5:8–15.
73. Ragoowansi R, Cornes PG, Moss AL, Glees JP. Treatment of keloids by surgical excision and immediate postoperative single-fraction radiotherapy. *Plast Reconstr Surg* 2003; 111:1853–1859.
74. Wagner W, Alfrink M, Micke O et al. Results of prophylactic irradiation in patients with resected keloids: A retrospective analysis. *Acta Oncol* 2000; 39:217–220.
75. Sclafani AP, Gordon L, Chadha M, Romo T III. Prevention of earlobe keloid recurrence with postoperative corticosteroid injections versus radiation therapy: A randomized, prospective study and review of the literature. *Dermatol Surg* 1996; 22:569–574.
76. Goodman GJ, Baron JA. Postacne scarring: A qualitative global scarring grading system. *Dermatol Surg* 2006; 32:1458–1466.
77. Rivera AE. Acne scarring: A review and current treatment modalities. *J Am Acad Dermatol* 2008; 59:659–676.
78. Fabbrocini G, Annunziata MC, D'Arco V, De Vita V, Lodi G, Mauriello MC, Pastore F, Monfrecola G. Acne scars: Pathogenesis, classification and treatment. *Dermatol Res Pract* 2010; 2010:893080.
79. Jansen T, Podda M. Therapie der Aknenarben. *J Dtsch Dermatol Ges* 2010; Suppl 1:S81–S88.
80. Levy LL, Zeichner JA. Management of acne scarring, part II: A comparative review of non-laser-based, minimally invasive approaches. *Am J Clin Dermatol* 2012; 13:331–340.
81. Kaufmann R, Podda M, Landes E. *Dermatologische Operationen*, 4th ed. Stuttgart, Germany: Thieme, 2011, pp. 53–56.
82. Fabbrocini G, Fardella N, Monfrecola A, Proietti I, Innocenzi D. Acne scarring treatment using skin needling. *Clin Exp Dermatol* 2009; 34:874–879.
83. Majid I. Microneedling therapy in atrophic facial scars: An objective assessment. *J Cutan Aesthet Surg* 2009; 2:26–30.
84. Sharad J. Combination of microneedling and glycolic acid peels for the treatment of acne scars in dark skin. *J Cosmet Dermatol* 2011 December; 10:317–323.
85. Lee SJ, Kang JM, Chung WS, Kim YK, Kim HS. Ablative nonfractional lasers for atrophic facial acne scars: A new modality of erbium:YAG laser resurfacing in Asians. *Lasers Med Sci* 2014; 29:615–619.
86. Nirmal B, Pai SB, Sripathi H, Rao R, Prabhu S, Kudur MH, Nayak SU. Efficacy and safety of erbium-doped yttrium aluminium garnet fractional resurfacing laser for treatment of facial acne scars. *Indian J Dermatol Venereol Leprol* 2013; 79:193–198.
87. Chrastil B, Glaich AS, Goldberg LH, Friedman PM. Second-generation 1,550-nm fractional photothermolysis for the treatment of acne scars. *Dermatol Surg* 2008; 34:1327–1332.
88. Chapas AM, Brightman L, Sukal S, Hale E, Daniel D, Bernstein LJ, Geronemus RG. Successful treatment of acneiform scarring with CO2 ablative fractional resurfacing. *Lasers Surg Med* 2008; 40:381–386.

89. Hu S, Chen MC, Lee MC, Yang LC, Keoprasom N. Fractional resurfacing for the treatment of atrophic facial acne scars in Asian skin. *Dermatol Surg* 2009; 35:826–832.
90. Sobanko JF, Alster TS. Management of acne scarring, part I: A comparative review of laser surgical approaches. *Am J Clin Dermatol* 2012; 13:319–330.
91. Ong MW, Bashir SJ. Fractional laser resurfacing for acne scars: A review. *Br J Dermatol* 2012 June; 166(6):1160–1169.
92. Wang B, Wu Y, Luo YJ, Xu XG, Xu TH, Chen JZ, Gao XH, Chen HD, Li YH. Combination of intense pulsed light and fractional CO(2) laser treatments for patients with acne with inflammatory and scarring lesions. *Clin Exp Dermatol* 2013; 38:344–351.
93. Yin R, Lin L, Xiao Y, Hao F, Hamblin MR. Combination ALA-PDT and ablative fractional Er:YAG laser (2,940 nm) on the treatment of severe acne. *Lasers Surg Med* 2014; 46:165–172.
94. Schweiger ES, Sundick L. Focal Acne Scar Treatment (FAST), a new approach to atrophic acne scars: A case series. *J Drugs Dermatol* 2013; 12:1163–1167.
95. Halachmi S, Ben Amitai D, Lapidoth M. Treatment of acne scars with hyaluronic acid: An improved approach. *J Drugs Dermatol* 2013; 12:e121–e123.
96. Munavalli GS, Smith S, Maslowski JM, Weiss RA. Successful treatment of depressed, distensible acne scars using autologous fibroblasts: A multi-site, prospective, double blind, placebo-controlled clinical trial. *Dermatol Surg* 2013; 39:1226–1236.
97. Rodríguez Pichardo A, García Bravo B. Dermatitis artefacta: A review. *Actas Dermosifiliogr* 2013; 104:854–866.
98. Manca G, Pandolfi P, Gregorelli C, Cadossi M, de Terlizzi F. Treatment of keloids and hypertrophic scars with bleomycin and electroporation. *Plast Reconstr Surg* 2013; 132:621e–630e.
99. Açikel C, Ulkür E, Güler MM. Treatment of burn scar depigmentation by carbon dioxide laser-assisted dermabrasion and thin skin grafting. *Plast Reconstr Surg* 2000 May; 105:1973–1978.
100. Massaki AB, Fabi SG, Fitzpatrick R. Repigmentation of hypopigmented scars using an erbium-doped 1,550-nm fractionated laser and topical bimatoprost. *Dermatol Surg* 2012; 38:995–1001.
101. Alexiades-Armenakas MR, Bernstein LJ, Friedman PM, Geronemus RG. The safety and efficacy of the 308-nm excimer laser for pigment correction of hypopigmented scars and striae alba. *Arch Dermatol* 2004; 140:955–960.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Cosmetic surgery of the scalp

Pierre Bouhanna

In recent years, aesthetic surgery for male and female androgenetic alopecia or scarring alopecia has benefited from considerable progress. A diversity of techniques, on the one hand, and a better assessment of their reliability, on the other hand, allow surgeons to better focus on their operations.

This surgery, which we limit here to hair transplant, obeys one overriding technical principle: the collection or preparation of autologous form of micrografts or follicular units. Three techniques—mainly related to their sampling method—will be discussed here. Their indications are essentially guided by many parameters such as the area (size) and the location of the alopecia; the sex, age, and ethnicity of the patient; characteristics of the scalp and hair; and the degree of alopecia evolution. A dynamic multifactorial classification combining all these elements facilitates the choice of a suitable treatment for each case. A macrophotographic analysis or digitalized phototrichogram will complement this preliminary assessment.

FOLLICULAR UNIT TRANSPLANTATION

History

- In 1930, Sasagawa [1] reported the original hair implantation method.
- In 1939, Okuda [2] described for the first time the principle of autografts for the surgical correction of alopecia of the scalp, eyebrows, and mustaches.
- In 1943, Tamura [3] described the pubic reconstruction in women with one hair transplantation.
- In 1953, Fujita [4] reported an eyebrow reconstruction puncture hair transplants among lepers.
- In 1959, Orentreich [5] published a method of harvesting cylindrical autografts with a cylindrical scalpel 4 mm in diameter (a "punch"). This process, which has prevailed for 25 years for the surgical treatment of male baldness, included some negative elements that led to its being neglected, such as an unsightly and unnatural appearance of tufts ("doll hair") and unsightly appearance of scars round "bees' nests" on the occipital donor area.
- In 1976, Bouhanna and Nataf [3,6,7] published a sampling technique for a graft strip.
- Marritt [8] in 1980 proposed the use of micrografts for finishing earlier front lines.
- Limmer [9] in 1988 developed the anatomical concept of follicular units by cutting strip in micrografts (follicular unit transplantation [FUT]).
- In 1989, Bouhanna [10] published the technique of follicular units with long hair (FUL), without prior shaving.
- In 2002, Rassman and Bernstein [11] published the process of follicular unit extraction (FUE) with sampling with a microcylinder after shaving.

Principles

The main principle is to prepare micrografts or follicular units of 1–4 hairs:

- By follicular extraction [12] with a micropunch (by hand or motorized) of less than a millimeter (FUE)
- By follicular segmentation using a stereomicroscope of a strip of scalp unshaved (FUL) [10] or shaved (FUT)

Essential point: Hairs taken from the crown region in men and the median occipital region in women keep their ability to grow further once implanted on the bald or sparse area.

Goal

The following are the goals of this process, which seeks to recreate the natural emergence of one to four hairs (the "follicular unit") through each pilosebaceous orifice (Figure 26.1):

- To perform the final hair transplant on bald areas of the scalp in a man, woman, or transsexual in order to give it an aesthetic and natural appearance
- To blur some apparent scars (post-face-lift, postradiotherapy, afterburns, pseudopelade, etc.)
- To make some hairy areas (eyebrows, eyelashes, beard, mustache, pubis) denser

Preoperative Stage

A minimum of 15 days between the consultation and intervention is required before any act of cosmetic surgery.

Medical photographs are always performed for the face—profile view, aerial view, and the surface to be implanted.

Preoperative blood tests and an electrocardiogram are routinely prescribed.

Drawing the Anterior Frontal Line (Figure 26.2)

A preliminary sketch with a dermographic marker delimits the area to be transplanted.

In women, androgenetic alopecia usually allows a more or less hairy frontal line to persist.

In men, androgenetic alopecia determines a more or less complete receding from the frontal line.

The first stage of the design is one of the important aspects of reconstruction for frontal male alopecia. It takes into account the several factors with a particularly harmonious equation between the aesthetic requirements, age, and ethnic peculiarities of the patient on the one hand and the capacity of the donor area, the characteristics of the hair, and aesthetic values on the other hand (*Il disegno e una cosa mentale* ["design is a process in the mind"]—Leonardo da Vinci). A photograph of the patient a few years ago may be helpful. The frontotemporal

Figure 26.1 One, two, or three hairs (a *follicular unit*) emerging through the same follicular orifice.

recession will need to be more or less deep, and the frontal line more or less rounded with some irregularities.

Local Anesthesia [13,14]

The preparation, disinfection, and anesthesia of the donor and recipient areas are similar to those usual for dermatologic surgery. Disinfectants based on flammable alcohol are avoided on the scalp.

Anesthesia of the scalp is obtained by the following:

- A local anesthetic all around the bald or hairy surface to be treated by intradermal infiltration of 1% lidocaine with epinephrine. The addition of bicarbonates makes these injections painless.
- A nerve block infiltration of the frontal and occipital nerves. The prior application of EMLA cream could make these injections virtually painless.
- The inhalation of a nitrous oxide gas (Kalinox—nitrous oxide) and a hypnosophrology session provide significant sedation in anxious patients.

Technique

FUL [10,13–15] (Figure 26.3)

The hairs are not shaved and are therefore harvested with their stem length.

The FUL technique we described and refined since 1989 allows the removal and transplantation of grafts of varied shapes and sizes with long hair.

Without shaving the donor area, the strip will be cut taken under a microscope in micrografts or FUL.

The FUL process allows the patient immediately after surgery to mask scabs of the grafted area, thereby alleviating a source of postoperative aesthetic embarrassment (Figure 26.4).

These long hairs will have two possible developments:

1. Hair shedding occurs in the third week, and regrowth occurs 3 months after surgery.
2. All or part of the hair continues to grow, possibly stimulated by medical prescription such as minoxidil lotion [16], finasteride tablets [17], or platelet-rich plasma (PRP) intradermal injection.

The advantages of a FUL technique are as follows:

- For the patient:
  - The donor area of micrografts is not shaved off.
  - The patient sees immediately the result, even though all or part of the hair can fall out in 2–3 weeks; the policy of "wait and see" has been replaced by one of the policies of "see and wait." Note the positive effect in the case of minoxidil and/or finasteride and/or PRP.
  - The scabs that persist from 10 to 12 days are hidden by long hair. Thus, the patient can quickly resume professional and social activities after 24–48 hours.
- For the physician:
  - A better assessment of the direction and angle of the hair (Figure 26.5)
  - A better choice, especially at the frontal hairline and whether hair is thick or thin, dark or light
  - A large amount of hair can be harvested at each session (4000 hairs per session)

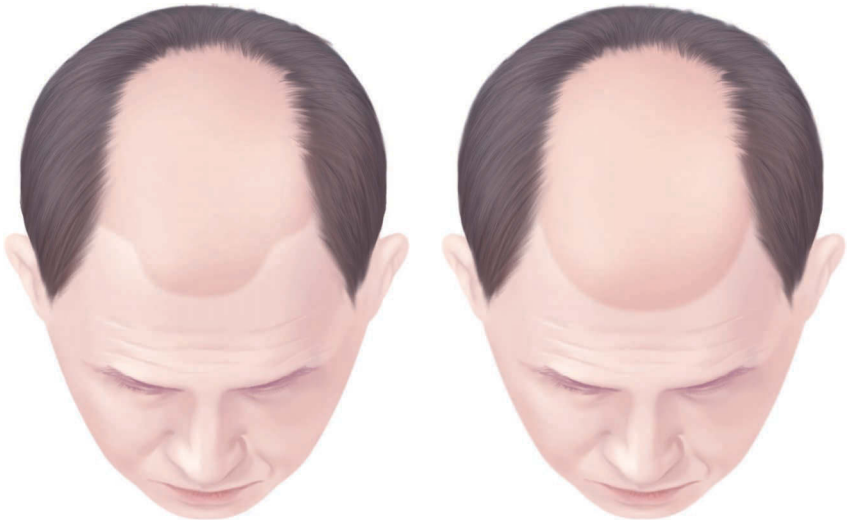


Figure 26.2 Schematic designs of the frontal hairline.

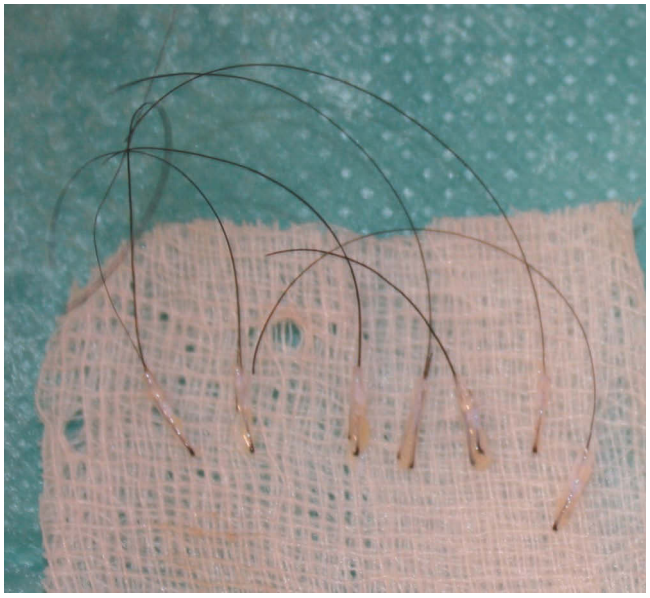


Figure 26.3 Follicular units for long hair after segmentation under a microscope.

Here are the disadvantages of a FUL technique:

The only drawback of the technique would be that FUL sometimes leaves a scar line. To avoid this, it is possible to implement a trichophytic technique. This consists of removing about 1 mm of epidermis at the bottom edge of the excision of the strip. The hair will be able to grow through the epidermic and upper end to reduce scar line edge. This method is derived from the subepidermal technique we described for the front edge of the flaps for frontal reconstruction [7].

Anyway, if the patient wants for personal reasons to shave his scalp and the fine scar line becomes visible, it is very easy to implant few FUE in a second time.

Donor Area: Preparation of Follicular Units Without shaving, removal of the occipital donor area previously infiltrated with saline is accomplished by excision with a scalpel blade No. 11 of a strip 10–30 cm long and 10–20 mm wide: the size depends on the desired number of follicular units [18,19] (Figure 26.6).

The closure of the edges of the donor area will be made with a resorbable suture with 3/0 thread or with skin staples (Figure 26.7).

The graft strip is placed on a gauze in a petri dish containing saline and placed on a frozen container. The segmentation is performed by cutting the pieces on a wooden tongue depressor with a No. 11 blade or blades with large microtomes. One to four assistants cut the strip of scalp follicular units,

(a) (b)

Figure 26.4 (a) Frontal hairline with multiple microincisions. (b) Immediately after insertion of FUL, the new implanted hair is combed.

Figure 26.5 A frontal region grafted with FUL allows a better choice of orientation, size, and color of hair.

Figure 26.6 Strip harvested with long hair.

Figure 26.7 Running absorbable suture for closure of the donor area.

Figure 26.8 Segmentation of FUL under a stereomicroscope.

under a good light, using magnifying glasses or stereomicroscopes (Figure 26.8). Cutting will be parallel to the bulb in the strip, held by fine forceps by the epidermis in variable portions according to the number, size, and shape of grafts required.

On average, 500–1500 grafts (1000–4500 hairs) will be cut, and each element will be cleared of all air shaft fragments or hypodermic debris before being placed in the receiving tray filled with chilled saline solution.

Preparation of the Recipient Area During the cutting, the operator prepares the anaesthetized recipient area with perforations and incisions [8,15,20].

Perforation This step varies according to different authorities.

Most of them pierce the skin with a Nokor or conventional needle of 16–18 gauge or ophthalmic microsurgical blades (Figure 26.9).

Others use a drill with small punches of 1 mm in diameter, operated by hand or by a motor.

Implantation Most authorities handle the skin fragments using forceps without teeth, very fine jeweler's forceps, or forceps with curved ends; others prefer straight tweezers (Figure 26.10).

Each follicular unit is delicately positioned to its full height in the clamp, threaded through the skin surface that has previously been perforated or incised.

Currently, it is possible during a session to transplant up to 1500 follicular units. When rebuilding a balding frontal region, the fragments selected to achieve the end of the line will be one hair (the puncture of a No. 18 gauge needle) on the first row and then two or three hairs on the other rows (No. 16 gauge needle).

With a magnifying glass helmet, transplants are checked to control the correct insertion and proper orientation or to swap some of them.

The patient should remain lying down for 1–2 hours.

FUT [8,18]

After preshaving the donor area, the technical progress of the removal of a strip and its segmentation into follicular units is then strictly similar to that of FUL.

FUE [11,21]

FUE consists of a preliminary shave, hence raising follicular units with the use of a punch (0.7–1 mm in diameter) at the occipital and temporal donor areas.

Although the quality of the sample is directly dependent on the experience of the operator, improvements on the instrumentation have increased the speed of withdrawal and significantly reduced the loss of follicular units per transection.

Technique The harvesting area region is shaved (Figure 26.11). On average, an area of 100 cm^2 (20 × 5 cm) can provide 500–1500 follicular units.

The procedure is performed under local anesthesia.

The patient is positioned lying face down. The head is placed on a suitable pillow at the level of the face to ensure adequate comfort.

The follicular unit is extracted one by one using micropunches of 0.7–1 mm in diameter (Figures 26.12a through c and 26.13a). The instrument is rotated either manually or by a motor (Figure 26.13b).

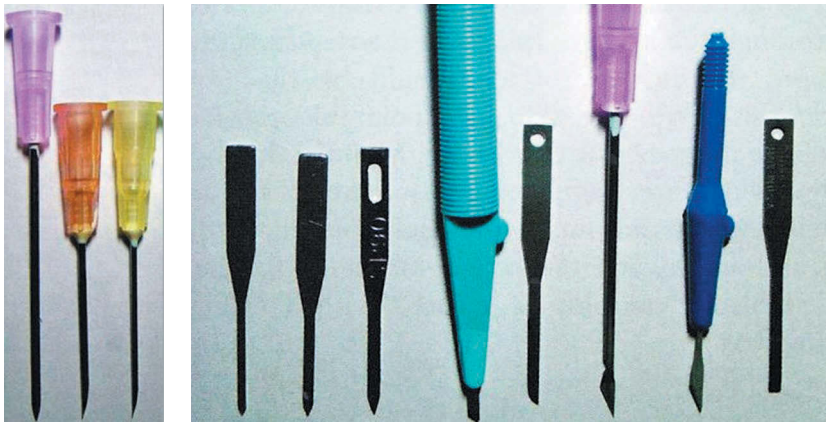


Figure 26.9 Hardware needed for surgery: needles and microsurgery blades.

Figure 26.10 Microsurgical forceps (straight or curved) for insertion of grafts.

The grafts are checked to verify their quality and maintained in ice-cold saline before being inserted (Figure 26.14).

On average, 500–1500 follicular units are removed in 2–3 hours.

Each follicular unit contains 1–3 hairs, so 1000 follicular units correspond approximately to 2000 hairs.

After taking all follicular units, the patient is in semisitting position.

The recipient area is perforated with ophthalmic microsurgical blades (spearpoint) or 18 gauge needle.

The establishment of follicular units is carried out with jeweler's pliers or using a Choi implanter [22]. This allows the operator to store the graft in the microslot while inserting (Figure 26.18).

The procedure takes between 4 and 6 hours, depending on the length of the session.

Figure 26.11 The donor area is shaved.

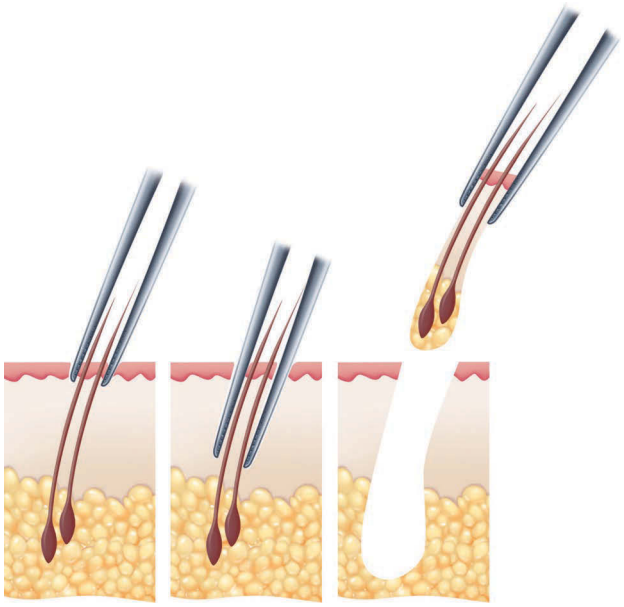
Sometimes the process is called "stick and place": one operator performs the perforation and the other operator inserts the FUE.

Indications of FUE

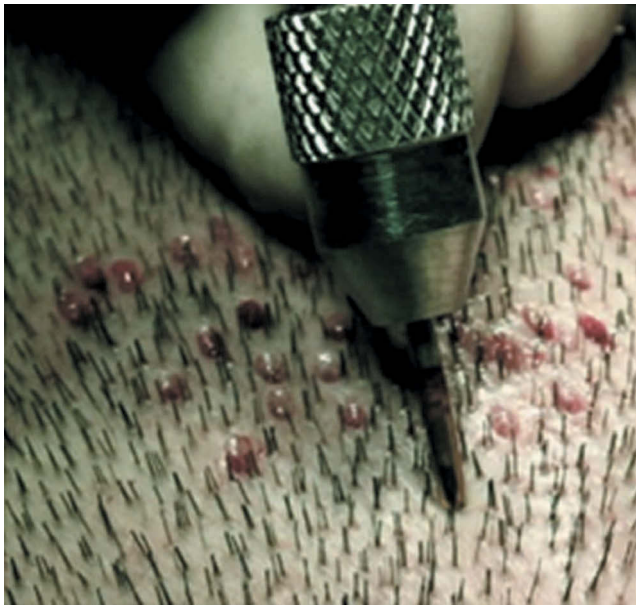
- Correction of male or female androgenetic alopecia in the patient of average size (Figure 26.15).
- Patients who have a habit of shaving the hair (Figure 26.16).
- Patients with limited laxity of the scalp (a limiting factor for sampling per strip).
- Patients with sufficient hair density in the donor area.
- A patient does not want a scar for the sampling line strip, since the latter, although very thin, can be blurred by some FUE in a second session.

Advantages of FUE

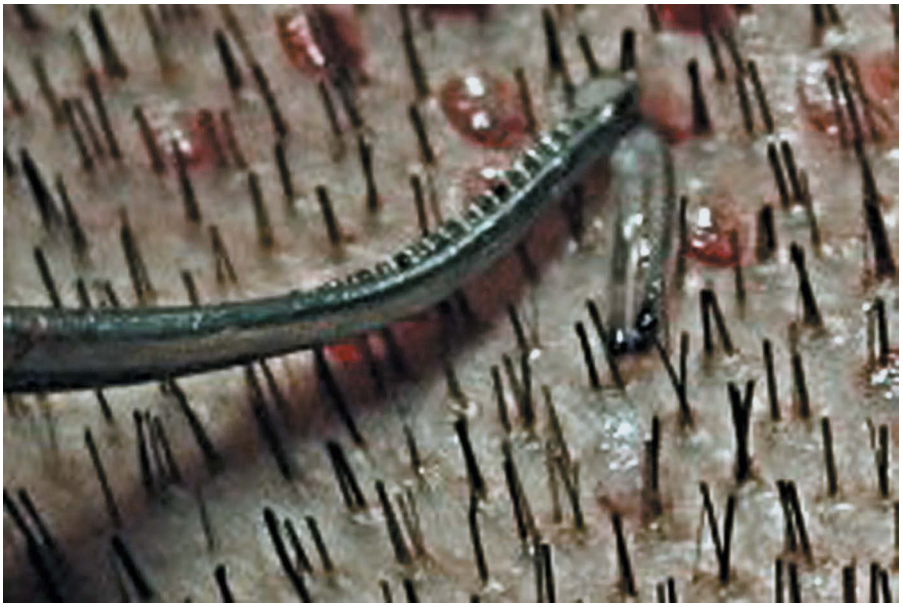
- The microscars in the donor area are, in principle, almost imperceptible to the naked eye.



(a)



(b)



(c)

Figure 26.12 (a) Incision and extraction of follicular unit extraction, (b) incision with the punch, and (c) follicular unit extraction.

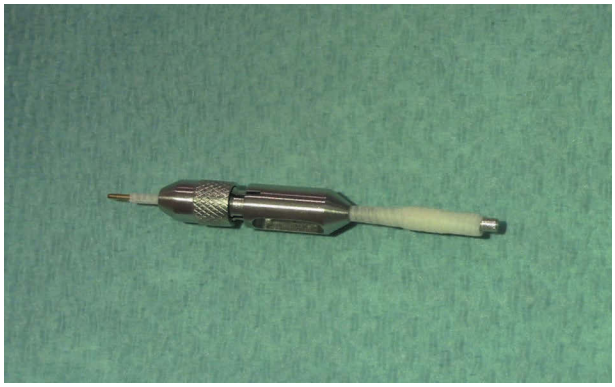
- The microperforations associated with harvesting follicular units in the occipital and temporal regions heal within a few days after surgery.
- There are no sutures and at most moderate postoperative pain.

Disadvantages of FUE

- FUE is usually reserved for small and medium baldness, especially in men.
- FUE is worst for choosing the best angle and orientation during implantation.
- FUE is more hazardous during any subsequent sessions.
- In women, a sparse donor area often counterindicates FUE, especially since women rarely agree to have a preshave.
- In post-op, scabs are not hidden by hair shaft.
- The capacity of the donor area will be reduced if there is inexorable evolution of the alopecia process to greater baldness.

Postoperative Course after Follicular Transplant

- A bandage is sometimes applied for one night.
- A first cleaning with shampoo can be made the next day and long implanted hairs can be dried with a hot-air dryer.



(a)

(b)

Figure 26.13 (a) Micropunch of 0.7–1 mm sufficient to allow extraction. (b) Micromotor for incision with a micropunch.

- Swelling in the forehead may appear within 24–48 hours after surgery and will take 2–4 days to disappear.
- Small crusts and implanted hair will take approximately 7–10 days to fall out. Long hair may remain implanted.
- The shafts of the implanted hair may fall out with the crusts. Implanted follicles can have interrupted hair growth during the first 3 postoperative months.
- The regrowth of new hair starts between the third and fourth months after surgery.
- We should emphasize the extreme reliability of follicular units but still report the occurrence of secondary cysts due to the unfortunate inclusion of skin debris or a second hair transplant into the hole. This exceptional small complication should be treated as an outbreak of acne vulgaris with antibiotic orally, sometimes with an incision of the cyst [20].
- Twelve months is necessary to determine the final outcome of the intervention.

Actions Simulating the Hair Growth on Transplants

Effect of Minoxidil [10,16,17]

Usually 2–4 weeks after a hair transplant, the scabs over the transplants fall out, involving the bulbs of transplanted hair. This fallout, albeit transient with an average regrowth 3 months later, is sometimes aesthetically annoying.

Figure 26.14 Aspect of follicular units immediately after extraction.

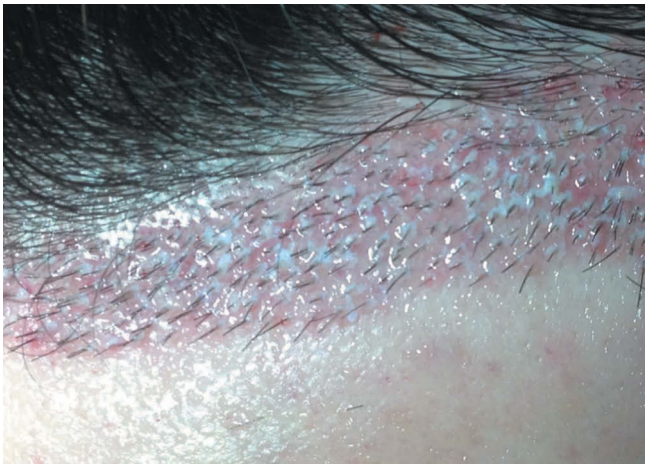


Figure 26.15 Aspect immediately after insertion of follicular unit extraction on a frontal hairline.

An independent personal study has shown that the application of a minoxidil 2% lotion before and after transplantation allows persistent growth of part or all of the hair on more than 2/3 of the grafts and causes fallout in less than half of the transplanted hair on less than 1/3 of the grafts.

So it seems that the pre- and postoperative implementation of minoxidil 2% or 5%, or the oral intake of finasteride 1 mg, allows the continuation of the anagen process in a large number of transplanted hairs.

Figure 26.16 Follicular unit extraction transplant in one session on the frontal hairline.

Effect of Platelet Growth Factors (PRP) [23,24] (Figure 26.17)

Platelets contain *growth factors*.

The PRP process is a technique that involves isolating platelets from a blood sample, concentrating them (by centrifugation), and injecting them back into the scalp.

Various evaluations show that it is possible to observe an increase in the number of hairs per square centimeter and an increase in hair diameter.

New Instruments for Hair Transplants

In recent years, various instruments or devices have been proposed and tested for their interest, reliability, and safety.

- The Choi implanter [22] allows the introduction of micrografts one by one (Figure 26.18). It may possibly be used for

Figure 26.18 A Choi implanter for skin puncture and insertion of the micrograft.

Figure 26.17 Platelet growth factors (platelet-rich plasma) after centrifugation of a blood sample and before transdermal injection.

Figure 26.19 Automatic system and transplantation of follicular unit extraction (Safer®-NeoGraft®).

Figure 26.20 Robotic system and transplantation of follicular unit extraction. (Courtesy of Artas.)

the reconstruction of the eyebrows and previous frontal lines with hair implanted "one by one" in a more close-set manner.

- A device for automatic FUE transplant (Figure 26.19) (Neograft–Safer) may be recommended in the absence of contraindication to FUE. Compared to the conventional manual FUE technique, it avoids the need for additional assistance; however, for good results in practice, a long apprenticeship is essential. A very important point is the failure of the machine during the transplant session and the difficulties to get the disposable devices from the company.
- Robotic FUE (Figure 26.20): This robot enables FUE. A double concentric punch on a mechanical arm is guided by a video image. Its purpose is to minimize human error and fatigue while taking a greater number of transplants than the conventional extraction techniques allow (≈2000 grafts in 2 days). The recipient area incisions and the graft insertion are done manually. Anyway, with this machine, also, it is not sure to minimize its failure.

INDICATIONS FOR MICROGRAFTS [25]

The goal is to obtain a harmonious adjustment between the aesthetic requirements—the desire, age, ethnic, gender, and psychology—the evaluation of parameters for different classifications, the degree to which the alopecia has evolved, the capacity of the donor area, and the technical possibilities of the surgery.

Androgenetic Alopecia

Various Parameters of the Multifactorial Classification [26,27] (Figure 26.21)

Measurements are made according to the Bouhanna multifactorial classification that takes into account multiple factors such as the extent of the bald and hairy surfaces relative to some fixed points of the face, the elasticity and thickness of the scalp, and the strength of the hair covering according to the density, size, shape, length, speed of growth, and color.

Digital Phototrichogram [28–30] (Figure 26.22)

The phototrichogram that is described by Bouhanna in 1983 provides an objective measure, using a camera, of the hairy surfaces, donor sites, and recipient sites for the transplant. The parameters of the hair growth will be measured and digitalized—their density, size, number of miniaturized hairs, number of terminal hairs, and growth rate.

Male Androgenetic Alopecia [27,31]

The degree of baldness is rated to one of the three schematic stages of the simplified classification [7] (Figure 26.23).

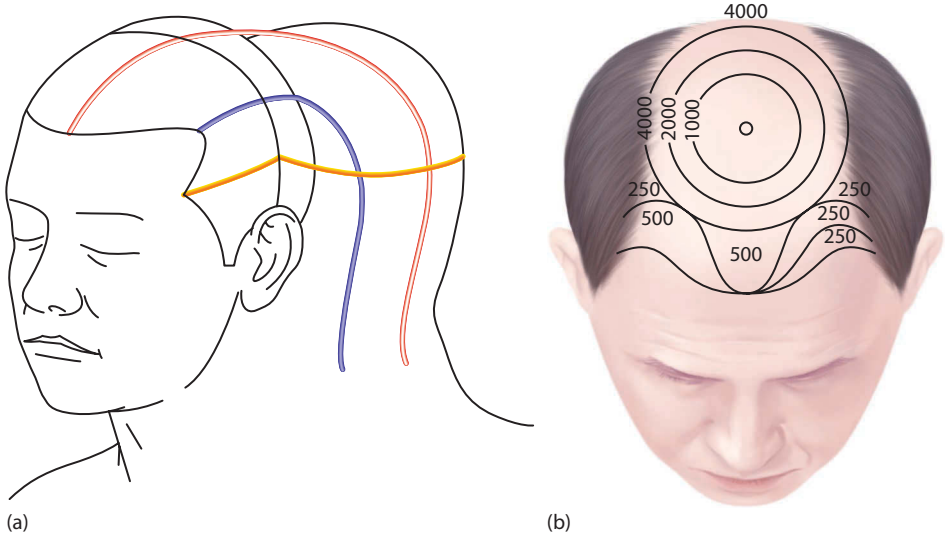
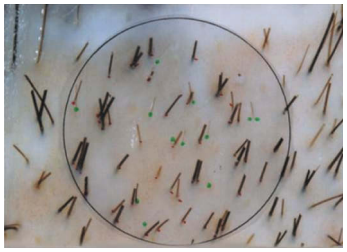


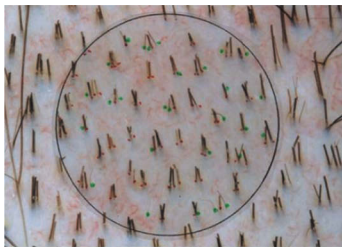
Figure 26.21 (a) Patterns of multifactorial classification with the evaluation of the four axes and (b) evaluation of the number of hairs required depending on the location and the implant surface (b). ([a] From Bouhanna P. Multifactorial classification of male and female androgenetic alopecia. *Dermatol Surg* 2000; 26:555–561.)



Frontal recipient area

	1 cm^2
Total hair count	94
Hair <40 µm	19
Hair >40 µm	75

(a)



Occipital donor area

	1 cm^2
Total hair count	171
Hair <40 µm	44
Hair >40 µm	127

(b)

Figure 26.22 Digital phototrichogram of (a) donor and (b) recipient area.

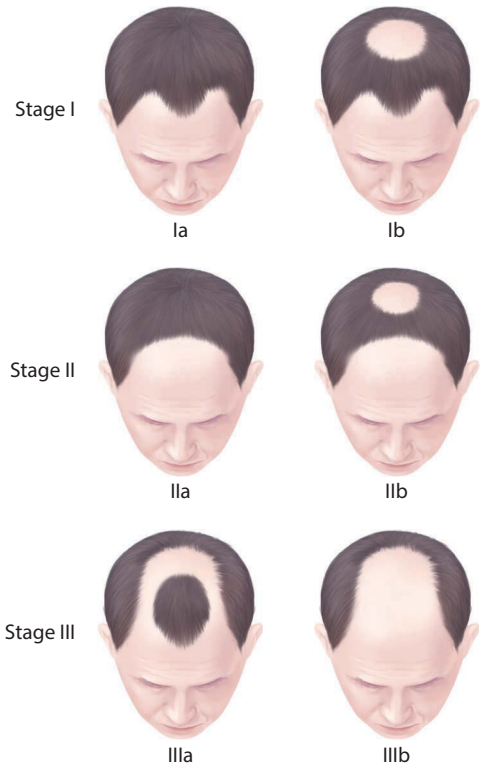


Figure 26.23 The three stages of evolution of the classification of male androgenetic alopecia. (From Bouhanna P, Nataf J, *Rev Chir Esth*, 7, 17, 1976.)

Surgical correction involves transplantation of micrografts, as adapted from one of the following steps:

- Stage I (accentuation of the frontotemporal recession, with possible crown alopecia at the vertex): implementation of 1000 hairs in 1–2 sessions (implantation of 2000–3000 hairs is sometimes required when there is associated crown alopecia) (Figures 26.24 and 26.25)
- Stage II (recession of the frontal line to the top of the head, associated with a crown alopecia): implantation of 2000–3000 hairs in 1–2 sessions (up to 4000 hairs when there is associated crown alopecia) (Figure 26.26)
- Stage III (baldness called "Hippocratic" where the hairs remain as a crown at the temples and neck): up to 7000 implanted hairs in 2–3 sessions (Figure 26.27)

The implantation of micrografts may be associated with a local anti–hair loss treatment (minoxidil 5%), intradermal injection of PRP, and/or general use (finasteride 1 mg, orally), which aims to decrease the loss of residual hair between the grafts, to reduce the transient loss of grafted and nongrafted hair, and to accelerate the regrowth of grafted and nongrafted hair.

Female Androgenetic Alopecia [13,14,20,27]

The degree of female baldness or androgenetic alopecia can be evaluated using the classification of Ludwig or more precisely assessed through the multifactorial classification of Bouhanna. Indications following the classification of Ludwig define three stages of evolution [32] (Figure 26.28):

- Stage I (moderate baldness on the top of the head baldness but respecting the frontal line): treated with implantation of 1000 hairs in one session (Figure 26.29)
- Stage II (frank alopecia with short hairs, located 1 cm behind the frontal line): treated with 1500–2000 implanted hairs in one or two sessions (Figure 26.30)
- Stage III (almost total alopecia, with preservation of a thin strip of hair on the forehead): treated with 3000–4000 implanted hairs in two to three sessions (Figure 26.31)

The introduction of micrografts may be associated with a local anti–hair loss treatment (minoxidil 2%), intradermal injection of PRP, and/or oral antiandrogens such as cyproterone acetate or spironolactone.

Figure 26.24 Male frontal alopecia (stage 1) with FUL transplantation (1500 hairs) in one session.

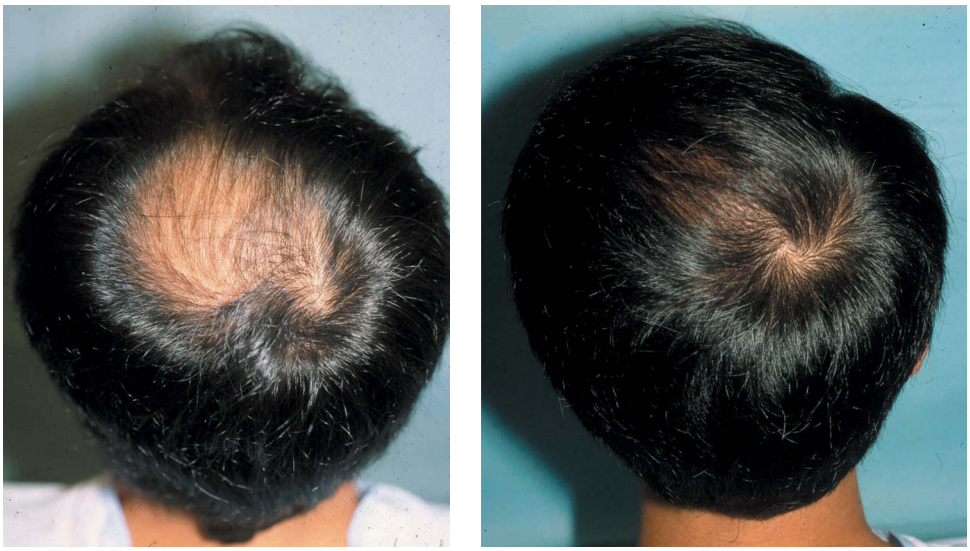


Figure 26.25 Male crown alopecia with FUL transplantation (1600 hairs) in one session.

Figure 26.26 Male androgenetic alopecia (stage 2) with FUL transplantation (5100 hairs) in two sessions.

Figure 26.27 Male androgenetic alopecia (stage 3) with FUL transplantation (7400 hairs) in three sessions.

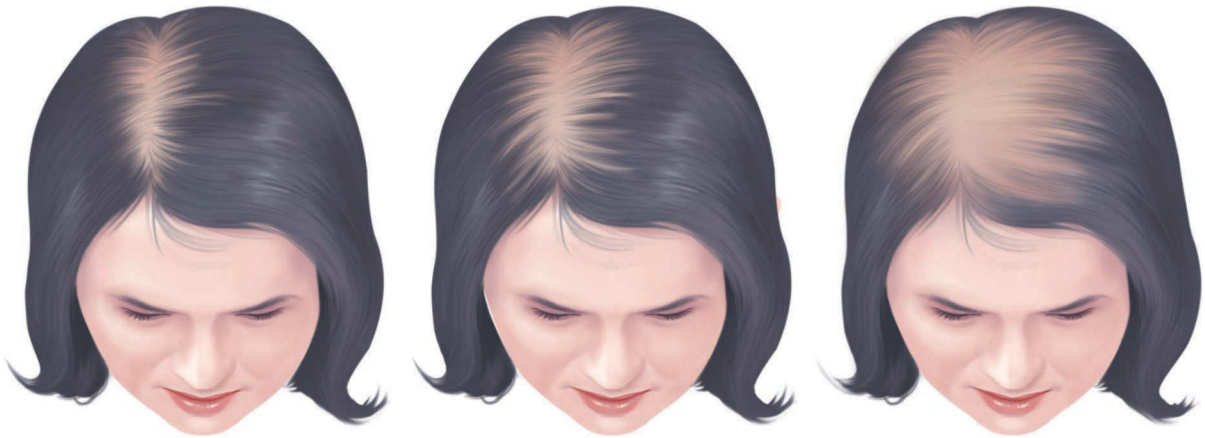


Figure 26.28 The three stages of evolution of the classification of female androgenetic alopecia. (Following the classification of Ludwig E, *Br J Dermatol*, 97, 247, 1977.)

Figure 26.29 Female androgenetic alopecia (stage 1) with FUL transplantation (1200 hairs) in one session.

Figure 26.30 Female androgenetic alopecia (stage 2) with FUL transplantation (1600 hairs) in one session.

Figure 26.31 Female androgenetic alopecia (stage 3) with FUL transplantation (1700 hairs) in one session.

In Transsexuals

We must close the frontal recessions and give a fine frontal line of a feminine pattern.

Other Forms of Alopecia

- Traction alopecia [33]: repeated pulls (blow drying, straightening, braids, etc.), especially in African-American patients (Figure 26.32), can induce alopecia of the fronto-temporal region. Before considering implementation, one must verify the absence of regrowth despite the application of minoxidil 2% and stopping traction for at least 6 months.
- Pseudopeladic alopecia, which is stabilized if the occipital donor area is definitely spared.
- Alopecia and scars after face-lift of the head and neck (Figure 26.33).
- Scarring alopecia after burns, radiotherapy, posttraumatic stress, etc. (Figure 26.34).

Body Hair Growth Alopecia [34–36]

Permanent Alopecia of the Eyebrows (Figure 26.35)

Implantation "hair by hair" allows one to completely rebuild the eyebrows. The oblique orientation of the hairs will be upward to the head of the eyebrow, downward to the tail of the eyebrow, and horizontal to the body of the eyebrow. These refinements are easier to do with the long hair (FUL).

Alopecia of the Eyelashes (Figure 26.36)

The introduction of micrografts allows a definitive aesthetic reconstruction by implanting chosen hairs "one by one." The lashes will be cut to the desired length every 15–20 days.

Figure 26.32 Traction alopecia in an African-American patient with FUL transplantation (1800 hairs) in two sessions.

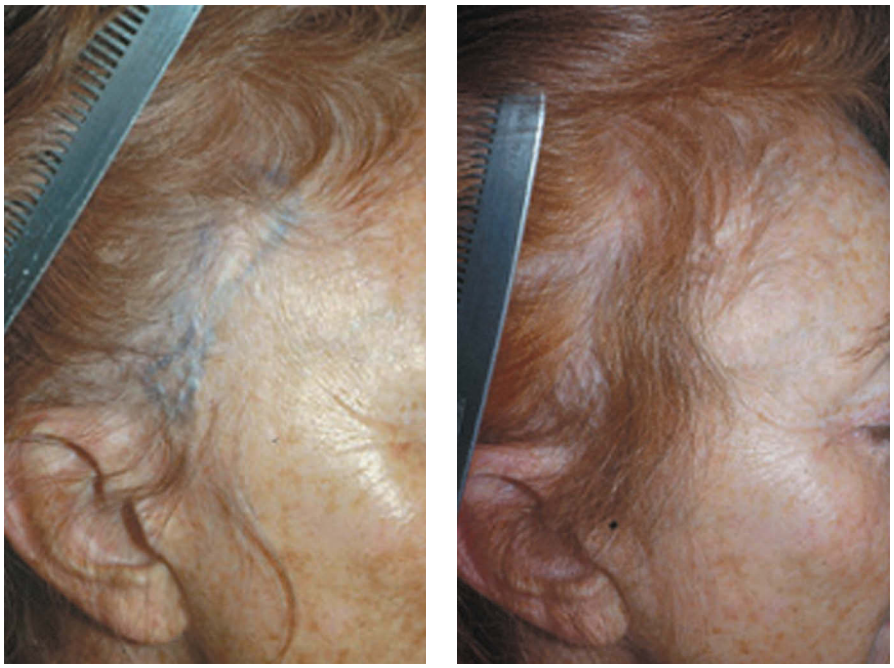


Figure 26.33 Preauricular alopecia after a face-lift with FUL transplantation (900 hairs) in one session.

Figure 26.34 Alopecia after radiotherapy for a malignant brain tumor with FUL transplantation (2200 hairs) in two sessions.

Figure 26.35 Eyebrow alopecia with FUL transplant in one session. (Courtesy of Eric Bouhanna.)

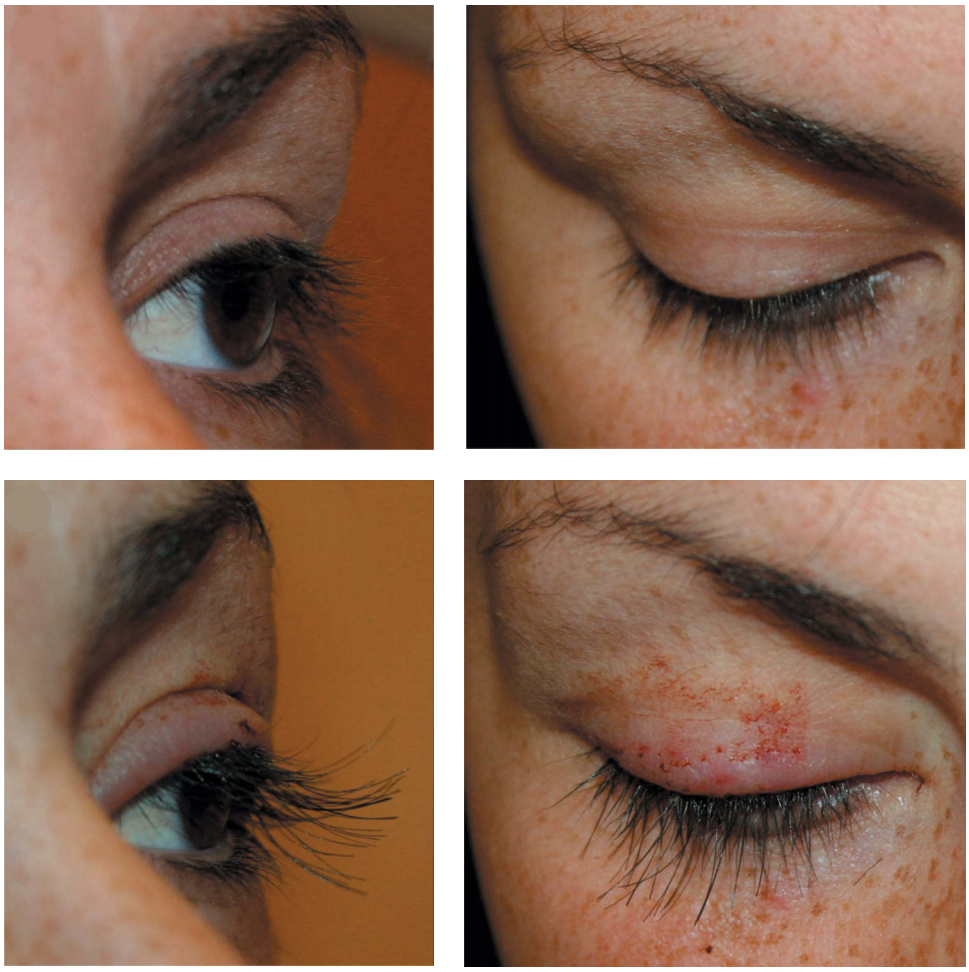
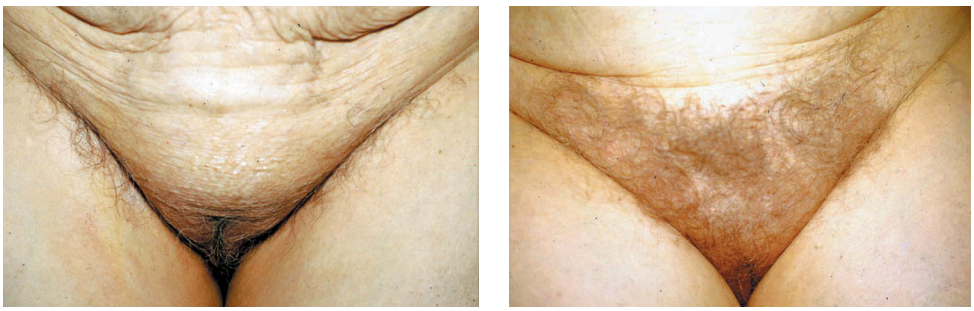


Figure 26.36 Eyelash FUL transplantation. (Courtesy of Eric Bouhanna.)

(a) (b)

Figure 26.37 (a) Beard alopecia; (b) 4 days after FUL transplantation.



(a) (b)

Figure 26.38 (a) Pubic alopecia; (b) 9 months after FUL transplantation.

Alopecia of the Beard and Mustache (Figure 26.37)

In humans, alopecia of the beard and mustache is most often of scar origin (harelip, acne scars). Increasingly for ethnic and religious wishes, a densification of the beard or mustache is requested. In these cases, it is very important to understand the psychological profile [37].

Alopecia of Pubic Hairs (Figure 26.38)

This hair loss can be due to certain gynecologic surgery procedures or hormonal effects of menopause.

Densification of pubic hair obeys many parameters, and an oblique centripetal orientation of the implants is of great importance to achieve a natural appearance (Figure 26.38).

CONCLUSION

Transplantation of hair micrografts in male and female androgenetic alopecia can usefully complement the favorable effect of various hair growth drugs (minoxidil, finasteride, intradermal injections of PRP, hormonal treatments, antiandrogens, etc.) on densifying permanently bald areas.

FUL, FUT, and FUE can solve most problems of hair thinning (scalp, beard, mustache, eyebrows, or eyelashes) in men and women. The methods also can treat most established alopecia of other origin, even if they are located at the pubis.

Dermatological cosmetic surgery of the scalp requires, because of its specificity, a good knowledge of anatomy, physiology, and pathology of the hair and perfect handling of all the techniques of skin surgery.

SIX IMPORTANT KEY POINTS

1. Establish an accurate analysis of the psychological profile of the patient (whether male or female).
2. Offer guidance to the treatment planning, explaining the advantages and disadvantages of each procedure.
3. Thanks to the phototrichogram and a multifactorial classification, make both an immediate and a prospective evaluation of the aesthetic result, taking into account the possible evolution of the alopecia process in the recipient area and in the donor area.

4. Do not implement any techniques that are unscientific, unreliable, or inadequately established.
5. Be well aware of complications and the better ways to avoid or correct them.
6. Examine the patient every year to verify the evolution of the alopecia process and to determine if any additional refinements are required.

REFERENCES

1. Sasagawa M. Hair transplantation. *Jpn J Dermatol* 1930; 30:493 (in Japanese).
2. Okuda S. Clinical and experimental studies of transplantation of living hairs. *Jpn J Dermatol Urol* 1939; 46:135–138 (in Japanese).
3. Tamura H. Pubic hair transplantation. *Jpn J Dermatol* 1943; 53:76 (in Japanese).
4. Fujita K. Reconstruction of eyebrow. *La Lepro* 1953; 22:364 (in Japanese).
5. Orentreich N. Autografts in alopecias and other selected dermatological conditions. *Ann N Y Acad Sci* 1959; 83:463–479.
6. Bouhanna P. Le cuir chevelu. Les alopécies définitives et leurs traitements. Thèse de doctorat en médecine, Université Paris XII, Paris, France, 1976.
7. Bouhanna P, Nataf J. A propos des transplantations de cuir chevelu. Critiques et propositions. *Rev Chir Esth* 1976; 7:17–23.
8. Marritt E. Single hair transplantation for hairline refinement: A practical solution. *J Dermatol Surg Oncol* 1984; 10:962–966.
9. Limmer BL. Elliptical donor stereoscopically assisted micrografting as an approach to further refinement in hair transplantation. *J Dermatol Surg Oncol* 1994 December 12; 20:789–793.
10. Bouhanna P. Greffes à cheveux longs immédiats. *Nouv Dermatol* 1989; 8(4):418–420.
11. Rassman WR, Bernstein RM, McClellan R et al. Follicular unit extraction: Minimally invasive surgery for hair transplantation. *Dermatol Surg* 2002; 28:720–728.
12. Bernstein RM et al. Standardizing the classification and description of follicular unit transplantation and mini-micrografting techniques. *Dermatol Surg* 1998; 24(9):957–963.
13. Bouhanna P, Dardour JC. Autogreffes. In *Chirurgie de la calvitie*. Paris, France: Springer Verlag, 1994, pp. 109–167.
14. Bouhanna P, Dardour JC. Autografts. In *Hair Replacement Surgery*. Paris, France: Springer Verlag, 1996, pp. 70–114.
15. Bouhanna P. Newer techniques in hair replacement. In: Roenigk RK, Roenigk H, eds. *Surgical Dermatology. Advances in Current Practice*. Londres, U.K.: Martin Dunitz Publishers, 1993, pp. 527–553.
16. Bouhanna P. Topical minoxidil used before and after hair transplantation surgery. *J Dermatol Surg Oncol* 1989; 15:50–53.
17. Bouhanna P. Androgenetic alopecia: Combining medical and surgical treatments. *Dermatol Surg* 2003; 29:1130–1134.
18. Limmer B. The density issue in hair transplantation. *Dermatol Surg*, 1997; 23:747–760.
19. Unger WP. Density issue in hair transplantation. *Dermatol Surg* 1998; 24:297.
20. Bouhanna P. Technique personnelle de minigreffes pour le traitement de l'alopécie de la femme ménopausée. In: Mole B, ed. *Actualités de Chirurgie Esthétique*, SOFCEP, Vol. 7. Paris, France: Masson, 1992, pp. 46–59.
21. Harris J. New methodology and instrumentation for follicular unit extractions lower follicle transaction rate and expanded patient candidacy. *Dermatol Surg* 2006; 32:56–62.
22. Choi YC, Kim JC. Single hair transplanting using the Choi hair transplanter. *J Dermatol Surg Oncol* 1992; 18:945–948.
23. Greco J, Brandt R. The effects of autologous platelet rich plasma and various growth factors on non-transplanted miniaturized hair. *Hair Transplant Forum Int* 2009; 19(2):49–50.
24. Bouhanna P, Amgar G. Platelet-rich plasma: A therapy for hair growth. *Prime* 2013; 3(4):20–31.
25. Bouhanna P. Hair research and the newest micrograft techniques. *Prime* 2011; 1(2);44–57.
26. Bouhanna P. Classification plurifactorielle des alopécies androgénétiques masculines et féminines. In *Pathologie du cheveu et du cuir chevelu*. Paris, France: Editions Masson, 1999, 350pp.
27. Bouhanna P. Multifactorial classification of male and female androgenetic alopecia. *Dermatol Surg* 2000; 26:555–561.
28. Bouhanna P. The phototrichogram and a macrophotographic study of the scalp. *Bioeng Skin* 1985; 1(3):265.
29. Bouhanna P. Le tractiophototrichogramme, méthode d'appréciation objective d'une chute de cheveux. *Ann Dermatol Vénéréol* 1988; 115:759–764.
30. Bouhanna P. The phototrichogram: An objective technique used in hair replacement surgery evaluation. In: Unger WP, Nordström REA, eds. *Hair Transplantation*, 3rd ed. revised and extended. New York: Marcel Dekker Inc., 1995, pp. 61–68.
31. Bouhanna P. Traitements actuels des alopécies androgénétiques masculines et féminines. *Praxis* 1997, 86: 996–999.
32. Ludwig E. Classification of the types of androgenetic alopecia (common baldness) arising in female sex. *Br J Dermatol* 1977; 97:247–254.
33. Bouhanna P. Les greffes de cheveux chez les patients afro-américains. *Dermatol Pratique* 2010; 344:12–13.
34. Bouhanna P. Alopécie frontale fibrosante post-ménopausique. *Revue Dermatologique du cheveu* 2005; 08:22–26.
35. BOUHANNA P. Microgreffes de cheveux et de poils: les nouveautés. *Nouv Dermatol* 2010; 29:441–446.
36. Bouhanna E. Traitement de l'alopécie du sourcil par greffes folliculaires. *Nouv Dermatol* 2011; 30(2):97–100.
37. Bouhanna P., Bouhanna E. The alopecias: Diagnosis and treatments. Boca Raton, FL: CRC Press, 2015; 245pp.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Endovascular procedures for treating chronic venous insufficiency

Claude Garde

The new approach to treating venous insufficiency is determined by four rules: increased efficacy of the therapeutic agent, decreased postoperative disability, improved aesthetic results, and, above all, reduced side effects and complications. For most of the previous century, the treatment approaches adopted classical stripping and sclerotherapy. New techniques such as cryosurgery in the 1980s and endovenous procedures in the 1990s appeared, as well as laser endovenous and radio-frequency ablation procedures, for example, the Closure® procedure. Also, several improvements to sclerotherapy were undertaken (for example, echo-guided sclerotherapy in 1985 and foam sclerotherapy [FS] in the 1990s).

All these techniques have in common the following prerequisite for an efficient, safe, and nonsurgical approach to treating venous insufficiency in that the vein is not stripped but destroyed in situ by a chemical or physical agent.

THERAPEUTIC STRATEGY AND PROCEDURE SELECTION

Venous insufficiency occurs due to two phenomena: a constitutional weakness of the venous wall that cannot tolerate venous blood pressure in a standing position, especially when worsening factors are present, and an increased flow coming from deep venous networks through perforators and saphenous networks that provokes a dilation of all superficial veins, tributary veins, and telangiectasias, or spider veins. For more than half a century ago, a consensus was administered to treat the primary refluxes, the main incompetent saphenous trunks, and the tributaries, from the biggest to the smallest, and to complete the result for the treatment of varicosities. The blue veins must be treated first, then the purple ones, and finally the red ones [1].

To achieve best results, all the territories have to be assessed by a duplex scan. This procedure is mandatory because the major fault in varicose vein treatment is that of worsening their appearance. In all cases, a complete screening of the affected vessels has to be done. Then a strategic choice of treatment has to be decided. Using endovenous, nonsurgical methods, it is possible to treat even the most severe varicose veins. In this chapter, we approach these techniques considering strategic aspects, especially indications, pitfalls, and follow-ups.

TECHNIQUES FOR TREATING SAPHENOUS VEIN INSUFFICIENCY

For all the techniques we deal with in this chapter, an important factor to consider is how to avoid the classical surgical procedure with its inherent risks and to propose lighter treatments for high-risk patients (elderly, obese patients, fragile patients). This allows improvement for all patients suffering from chronic venous insufficiency. The second important factor to consider is how to manage effectively the treatment of the disease from the largest vessels to the smallest ones, that is, the telangiectasias. The consequence is to modify the frontier between the functional disease and the aesthetic disease. This has major implications for the health-care industry and insurance companies.

It is possible to destroy a vein by three ways: physical (heat, cold), chemical (sclerotherapy and FS), and mechanical (surgery—not included in this chapter) means.

Endovenous Laser Treatment

Endovenous laser treatment (EVLT) was approved by the FDA in 2002 [2]. The Heat is brought in contact with the lumen of the vessel wall through a fiber delivering either 810, 940, 980, or 1470 nm amplified light. At these wavelengths (1470 nm and greater), water is the target to absorb the increase in heat [3].

Indication

In our experience, EVLT delivers best results for the great saphenous veins with a diameter not exceeding 8 mm when measured at 3 cm from the saphenofemoral junction. The amount of the reflux is also to be considered: when there is a huge reflux to the junction, a surgical procedure is a better option. When the reflux is confined to the trunk of the nerve, EVLT is indicated. EVLT is not an option when the insufficiency extends below the knee because of the risk of nerve damage (saphenous nerve near the femoral nerve and its tributary). If the lower part of the saphenous vein needs to be treated, we perform ambulatory phlebectomy with the use of a rigid small stripper.

From a literature review, it can be seen that the position of the saphenous vein varies for patients, the position being determined by the competence and characteristics [4,5]. Criteria to be considered for EVLT are the length of the vein ranging from 5 to 13 mm in the thigh in a standing position, a skin–vein separation of more than 5 mm, the presence of intervening fascia, and, above all, the degree of tortuosity of the vein. Some physicians perform EVLT on the lesser saphenous veins and on their tributaries when they are not too tortuous, albeit with a higher risk of nerve damage. We consider this a better procedure compared to surgical great saphenous vein removal because the surgeon need not perform a phlebectomy or sclerotherapy.

Materials and Methods

There are several useful diode lasers with different wavelengths. The most common of these devices is the 810 nm diode laser, which is the focus of this chapter. However, lasers with higher wavelengths (1470 nm and greater) seem to give

the same results with less pain during the procedure and less bruising as a side effect.

A complete mapping of the vein is mandatory before the procedure is performed to evaluate the depth of the vein and to determine the caliber of the vein and its tributaries, especially the large ones. The entire procedure can be performed in an office or in outpatient surgical facilities. We use the same protocol for installation and asepsis, rather than those used for classical venous surgery. A tumescent local anesthetic is injected along the vessel to increase the skin–vein separation, to mechanically compress the vessel using the tumescent fluid, and to contract the vein using adrenaline, an adjunct in the tumescent solution (Figure 27.1).

This type of anesthesia allows the patient to feel no pain posttreatment. In our practice, we use a 250 mL saline solution with 200 mg of lidocaine and 0.15 mg of adrenaline. The amount of adrenaline can vary from 0.10 to 0.20 mg depending on the vessel's caliber [6].

There are several differences as regards the components of a tumescent solution, but whether it contains adrenaline or not is of major importance. For the comfort of the patient and the ease of the physician, neuroleptanalgesia is performed by an anesthesiologist; however, this is not the rule.

There are different types of optical fibers, from 200 to 600 microns; they can be bare or coated in a guidewire. The fiber tip can execute an axial ray or a ring ray, with an open or closed angle, depending on the model. Currently most of the devices use radial tips because with direct fibers, it has been noted that a blood carbonization layer can damage the fiber tip and, most importantly, can affect the quality of the treatment. The fiber is introduced with a guide generally under echographic guidance or directly into the vein that has been isolated through a small incision with a Muller's hook. The fiber is introduced at 1.5–2 cm from the saphenofemoral junction for the large saphenous vein and 2 cm from the saphenopopliteal junction for the small saphenous vein. For small saphenous vein, we recommend not to cross the popliteal fold even if the saphenopopliteal junction is located high because of the closeness to the nerve. The fluence and the withdrawal speed depend on the device used, the size of the vessel, and the degree of insufficiency of the vein [7]. The radio-frequency value is the main difference between EVLT and

Figure 27.1 Vasoconstriction with tumescent local anesthesia.

Figure 27.2 Compressive garment before nonremovable elastic bandage application.

the Closure® technique for which another principle of heating is used. In fact, the laser can be operated using different parameters: power (10–14 W), fluence (50–350 J/cm^2), and withdrawal speed (0.5–1 cm/second). All these parameters must be adapted according to the caliber of the vessel, its depth in the fat pad, and skin risk in case of Fitzpatrick 3/4. Using too low a setting for the laser leads to recurrence of the presenting problem and a very strong likelihood of skin pitfalls or burning damage. The "end point" is the transformation of the collagen in the vein's media and endothelial damage.

Toward the end of the session, in our practice, a nonremovable high stiffness compression is applied on a tube of gauze that allows to place, along the marks of the treated vessel, ABD pads to improve local compression. This dressing is not replaced for a week (Figure 27.2).

A class 2 compression stocking is given for 2 weeks or more. In the literature, several solutions have been proposed: gauze pad and elastic wrap for 24 hours + class 3 compression stocking for 3–4 weeks.

Results, Side Effects, and Pitfalls

According to a large review of bibliographic references, the rate of complete venous occlusion is more than 95% with a remaining occlusion of 90% at 1 and 2 years post treatment. A study by Rasmussen comparing EVLT (980 nm) and classical stripping found the same efficacy for both techniques. The side effects are classical:

- *Paresthesias*: These are generally caused by not following safety rules or observing atypical nerve vicinity. For this risk, we consider that the treatment of LSV between the ankle and the knee dangerous and the treatment by EVLT of the lesser saphenous vein is not a good indication because of the permanent vicinity of the sural nerve. However, numerous physicians perform SSV treatment by EVLT.

  It is important to know that the saphenous nerve can be very close to the vein in the thigh for LSV treatment.
- *Induration and pigmentation*: These can occur when the vein is too close to the skin because the tumescent anesthesia modifies the distance during the sessions but this effect

decreases quickly and the vein becomes palpable. People with dark skin (Fitzpatrick 3/4/5) have more chances of inflammation. Selective compression along the vessel allows the decrease of these side effects because the more the severity of fibrosis, sclerosis, and inflammation, the more the volume of clot remaining in the vessel will be needed, leading to pigmentation.

- *Deep vein thrombosis (DVT) and pulmonary embolism*: It is difficult to foresee what the patient can be risking with these complications, but special attention is given for patients who present a history of DVT, thrombophilic disease, and thrombogenic disease. In our practice, low-molecular-weight heparin treatment is mandatory for 5–7 days. The decision to include heparin can vary depending on the physician. It is dangerous not to stop the fiber tip when the groin is reached (at 1.5–2 cm from the SF junction), as for the SSV, and it should never be used beyond the popliteal fold [8].
- *Bruising and pain*: These are caused due to perforation by bare fibers. These side effects decrease with radial fibers. Accurate compression can reduce these side effects.

Radio Frequency: The Closure® Procedure

This technique has been used for more than 16 years now; it is also an endovascular venous procedure like EVLT but the fiber is replaced by a radio-frequency probe. The Closure procedure was replaced in 2007 by the ClosureFast® procedure. The first device was inadequate and subject to failure by carbonization of the probe's edge. The terminal part of this device allows it to obtain a temperature of 120°C of 1–7 cm length. This heating provokes destruction of the intima and coagulation of the media's collagen. The main difference between the use of a laser and the Closure procedure is the amount of heat applied on the complete vessel using "domestic iron" instead of a spot or ring ray where the temperature varies hugely if the fiber is not directly in contact with an area (Fibrotome's phenomenon). Today, there are several companies that propose techniques that heat the vein directly by a fiber using different processes, but the goal remains the same.

Indications

This technique is almost the same as EVLT with minor differences. But in the literature the maximum caliber of the vein that can be treated by this technique can reach up to 13 mm or more [9]. Close follow up is required, to be ready to treat any possible recurrences by means of sclerotherapy. We have to know that a repeat surgery after EVLT or Closure is never simple, which might lead to poor results and to complications such as lymphatic damage due to incorrect modifications of connective tissue around the vein. So we recommend another technique for applications with a vessel caliber of more than 8 or 9 mm.

Materials and Methods

The procedure is similar as that of EVLT described in the previous section, that is, mapping, installation of requirements, injection of tumescent local anesthesia, limitations due to superficial and tortuous vessels, and positioning. Also, the probe is introduced at the same level with the same material (guidewire or bare probe). The level at which the treatment begins, which is near the SF junction and SP junction, is also the same as that of the ELVT, but the radio-frequency values differ. The protocol is standardized and does not take into account the size of the vein to be destroyed, and the laser is applied in two sequences lasting 20 seconds each. For points nearest to the SP and SF junction then, one sequence is required 6 cm. If the vessel is large, it is possible to apply more energy on two zones (two sequences). During the withdrawal procedure, gentle compression is applied on the probe's tip to improve contact with the vessel. The energy delivered per cm is 60 J/cm. This procedure is faster than that of EVLT. In addition, the post op is the same as that for EVLT, especially the dressing and low-molecular-weight heparin.

Results and Complications

Complete occlusion of the long saphenous vein is around 99% at 1-year control and 97% at 2-year control [10]. Several studies have shown the same level of efficacy as that of classical surgery. Some quality-of-life studies show that this technique has the best results in comparison with EVLT; In our experience, we find equally comparable results with surgical techniques, for example, cryosurgery under tumescent local anesthesia. However, in cryosurgery the vein is removed.

Side Effects and Complications

The Closure procedure, like all other physical techniques, has similar side effects and complications such that the Closure procedure is comparable to the EVLT. However, there are some differences as regards laser ablation.

Thromboembolism: In all the cases, the heated blood is transformed into a clot. The main problem of this clot is its location, its ability to grow, and its cohesion and fibrosis to avoid embolism. Generally, the clots generated due to heating are cohesive and fibrous; this procedure can be an alternative treatment for fixing weak clots. Spontaneous DVT is rare because the heating is very local, but for us a medial saphenous vein too close to the superficial femoral vein and artery is a contraindication for treatment by a physical method. So we recommend the same protocol as with EVLT: LMWH and eccentric compression are used to reduce the size of the vessel and of the clot. The contraindications remain the same.

Paresthesias and hypoesthesias: The causes as well as the solutions to avoid these pitfalls are the same as with the aforementioned technique. On the other hand, no under-the-knee procedure is performed; remember the short saphenous vein is a contraindication because of the presence of the sural nerve.

Hematomas: This technique is not frequently used because the probe does not induce a perforation. Bruising is only noted at the level of introduction and at the zone of complementary phlebectomy.

Pigmentation: The causes and management of pigmentation are the same as that of EVLT, but differ with that of radiofrequency techniques. Also, the temperature applied is higher (120°C) and the application lasts longer (20 seconds) per zone. So we recommend in all the cases elective nonremovable compression along the vein to decrease the volume of the remaining clots and a complete closure of tributaries and perforators that can reinject the vessel and provoke new high pressure blood flow.

Matting: As described in some articles, the appearance of matting is always due to a high blood pressure reflux through a perforator or through a feeding branch. This complication makes it necessary to recognize the reflux by a duplex scan and to treat it immediately by echo-guided sclerotherapy (in our practice, we use FS). A poor result from the procedure may lead to leakages in the superficial network. Before proposing a solution, it is better to perform a complete duplex scan with a 10–13 mHz probe to search for all the tributaries.

Good knowledge of the territories of each superficial vein is mandatory.

Foam Sclerotherapy

This technique is in use since WWII, used by Belgian and Swiss physicians. The air block technique uses a bolus of ethanolamine introduced along with air to push blood away, followed by injection of a sclerosing agent that can act strongly on the venous wall; however, in some cases air doesn't mix well with a liquid solution. FS has been in use for 20 years now, and it is approved by health authorities in Europe and America. The ratio of saline solution to air can vary between 1:3 and 1:5. In our experience (more than 15 years), the volume of air depends on the concentration of the sclerosing agent. Polidocanol and tetradecyl sulfate are closely related to soap formulations (tensioactive agents). The foam is obtained from two syringes linked by a bypass that allows the mixture of air and liquid by 10–30 passages from one syringe to the other one [12]. So three parameters have to be understood. The more the product is concentrated, the more the foam is stable and thick, and the more the product is agitated, the more the compactness of the foam remains. The lesser the product is concentrated, the less stable is the foam, and in all the cases the efficacy is decreased after 2 min. Some authors recommend the replacement of air with CO_2 or O_2, but with CO_2 the foam will not be of good quality (i.e., leading to shorter half life), and O_2 is not recommended by pharmacologists.

Materials and Methods

Several studies have proved a better efficacy of FS vs. liquid sclerotherapy (LS), and according to 84% of these physicians, the best indications for FS are the saphenous veins and the large tributaries. But FS can also be used in treating tributaries, reticular networks, and other venous diseases (e.g., congenital malformations, angiomas, etc.) [12].

FS is also performed complementary with EVLT, Closure, and other classical surgical approaches. It allows to improve the efficacy of both techniques and sometimes to avoid surgical procedures, providing good results.

A long saphenous vein and a vessel caliber no more than 7–8 mm are good indications for this technique. Some publications indicate a larger caliber, but we do not recommend it unless there are no other options to FS. The volume that can be injected cannot be more than 7–8 cc. In the literature, sometimes even a foam volume of 40–50 cc is recommended for application. This volume is advised for us to avoid the injection performed in ultrasound-guided sessions to avoid the need to inject under ultrasound guidance.

The injections are administered one each from 15 cm behind the knee and from 10 cm below the groin. Echography allows reaching the vessel even if it is deep, providing a good view of the vessel if the patient is obese, and to visualize the vicinity of the superficial femoral vein and artery especially in treating the medial long saphenous vein in thin patients, and in the popliteal fold to avoid the gastrocnemius artery and cutaneous artery.

The foam is echogenic and can be pushed with the echography probe if needed but we have to know that even if the foam is visible, the bubbles release the sclerosing agent very fast without efficacy. The injection must be administered slowly to avoid the entry of huge volumes of air into the blood. The injections are performed with the patient in a lying position to have better contact of the bubbles with the venous wall. An elevation of the limb pushes the bubble to flow to the heart (logically the bubbles lighter than blood will travel down to the foot). Local compression with the echography probe can stop the blood flow to increase the contact of the sclerosing agent and the vein.

At the end of the procedure, compression is necessary. According to different schools [13], it is possible to apply local compression to compress only the vessel (small pads) or to apply nonremovable compression for a few days or elastic stocking compression for 1 to 3 weeks. A randomized study showed benefits for class 3 compression and centered compression on the vein. This improved the efficacy and the quality of the sclerosis and decreased local pain and inflammation. In our practice, we consider that the compression must be adapted according to these criteria: the size of the vessel that needs to be injected, the risk of deep venous thrombosis, the location on the leg, the depth of the vessel in the fat layer, and the Fitzpatrick classification of the patient's skin.

Results

The efficacy of FS on saphenous network is excellent and close to that for endovenous ablative techniques at two years. The efficacy rate of FS on large vessels is from 76% to 85% according to different studies. But the main advantage of this technique is its simplicity, and, most importantly, not having mandatory contraindications such as acquiring patent foramen ovale and migraines (with aura) and other classical contraindications of sclerotherapy.

Follow-Up

Immediately after injection, the foam induces a spasm of the vessel if the concentration is at the correct threshold. This phenomenon can be visualized with a duplex probe and can be increased by compression of the vessel to increase foam contact with the vessel. Pain can occur but not necessarily at the injection point. In our practice we apply selective compression. The reaction to sclerosis can occur some weeks after the injections and the patient has to be informed of an unexpected painful reaction, which should be treated by local nonsteroidal anti-inflammatory agents. The compression allows the decrease of this normal side effect. If the vessel is superficial, a red, ray-like pigmentation can follow the vessel. During this period, the main risk is pigmentation on Fitzpatrick 3/4/5 skins. After this first step of the treatment is accomplished, the treatment for tributaries can begin with LS. Some physicians continue to use FS for all venous networks with a lower concentration of foam (1%–0.5% polidocanol or tetradecyl sulfate). We must remember that if the result with foam is faster than with saline, it can lead to local side effects like clots or pigmentation.

Side Effects and Complications [14]

Neurologic Events (Occurring in 1.2%) These include visual disturbances, simple dazzling to blindness for a few minutes, epileptic fits, paresthesia of a limb or of the face, cerebral vascular events, and migraine with or without visual trouble. All the authors consider that the main cause is a leakage of foam through the foramen ovale in the arterial network. For this reason as some authors agree, we recommend to exclude patients not only with known patent foramen ovale but also with septal defects, congenital heart defects, and coronary diseases.

Deep Venous Thromboembolism (Occurring in 1%) The path followed by the foam is visualized by echography, and especially on the lower part of the leg and the tributaries, the foam is aspirated into the deep network through competent perforators. Rapid dilution and increased flow prevent, in most cases, DVT. We do not recommend FS for patients with a history of DVT or pulmonary embolism, in patients with thrombophilic disease, and to exercise caution when treating sedentary or elderly patients. In all cases, we think that stocking compression is important to be applied. We do not hesitate to inject low-molecular-weight heparin for a few days for risky patients.

Thoracic pain and myocardial infarction and one death have been reported in the literature, and two cases of angina syndrome have been examined in our practice (over thousands of injections). We think that the main cause is arterial spasm or thrombotic complications.

Side Effects

Skin Pigmentations These are very common (occurring in 18%). The causes of pigmentation in the treatment of the saphenous vein with FS are uncompleted sclerosis of the vein with a reflux on the upper part of the vessel, a strong sclerosis reaction, a superficial vessel, and a Fitzpatrick 3/4/5 skin. We discuss all the causes of pigmentation with sclerotherapy in the next section. We recommend some rules to decrease this side effect: to begin the first injection in the first half of the upper part of the thigh, to increase the number of injection sites rather than administer a huge bolus too low on the leg, and to aplly elective local compression all along the vessel along with complete compression and, sometimes, fixed compression (on the calf). Inflammation is a known precursor of sclerosis but is also the cause of pigmentation. A good technique is to find the right concentration of foam to avoid these two phenomena.

Skin Necrosis (Occurring in 1%) This side effect is very rare during the treatment of LSV or SSV because of the depth of these vessels and the visualization of extravasation with a duplex scan. Skin necrosis occurs due to the leakage of the foam in the connective tissue. A standardized procedure allows avoidance of this complication: visualization of the target (the vein), introduction of the needle, control of the reflux (color of the blood), and injection/aspiration with one hand. Skillful application of the technique is the key to success. A third hand is appreciated for beginners or when the vessel is deep or tortuous to reach.

TREATMENT OF MIDDLE-SIZED VEINS AND SPIDER VEINS

Sclerotherapy

This technique, more than a century old, eventually became the gold standard in the treatment of all types of varicose veins. Improvement of the patient's assessment by Doppler, PPG, duplex scan, echo-guided sclerotherapy, and FS has increased its field of indications, safety, and efficacy. Nevertheless, we cannot consider it to be the solution in all cases although it can be used for most cases [1]. For us, sclerotherapy remains the last option when all other procedures fail or when they cannot be applied because their efficacy is not always able to stop venous insufficiency.

The principle consists of injecting a corroding agent into the vein to be destroyed, but this simple principle masks underlying complexity and requires good knowledge of the weapon (the sclerosing agent), of the target (the vein), and, above all, of the different field constraints: the size, the deepness, the level on the leg of the vein to be treated, its territory of drainage, the main reflux that provokes its dilation, the quality of the skin, the weight of the patient, and the quality and complexion of the skin. Initially, a lot of products were used: hypertonic glucose (66%), sodium salicylate (12–20%), iodine, and corroding agents such as chromated glycerin. Three agents remain in use: polidocanol, tetradecyl, and chromated glycerin.

We must recollect some physiopathologic aspects of chronic venous insufficiency before we propose a guideline for treatment [15]. According to the most recent approach for treatment, the quality of the result is correlated to the complete closure of leakage from the deep network to the superficial network, that is, the saphenous network and tributaries (systematized network) and also the reticular network (nonsystematized network) (Figure 27.3).

It is admitted that the most part of the saphenous network and tributaries present valves, which organize the venous flow. The presence of a valvular system in the reticular network seems impossible to correlate with the flow. There are several permanent links between these two superficial networks and also between the deep network and the superficial network.

We should understand all the strategic aspects for a good therapeutic result:

- Closure of all leakage at the incompetent junction between depth and surface.
- This closure has to take into account gravity because the reflux flow goes from the top to the bottom, so we have to begin to treat the higher reflux (saphenofemoral junction for the LSV territory and saphenopopliteal junction for the lesser saphenous vein territory) and the incompetent perforators even in this case, from the thigh to the foot.
- Closure of the long reflux because it acts as a column of pressure.
- Closure of the short reflux and the small tributaries, considering the role of the gravity.
- Closure of the reticular network that is frequently involved in the disease. To treat it, we recommend to begin from the top of the thigh and then go down to the foot.

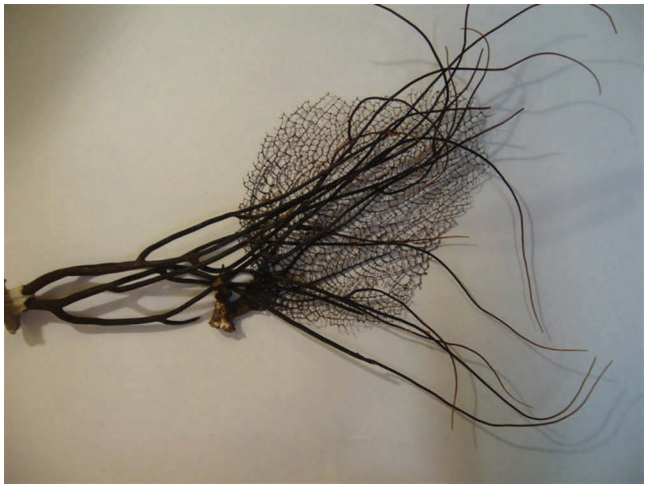


Figure 27.3 There are two types of network: one of a main network and branches and the other intricate and reticular.

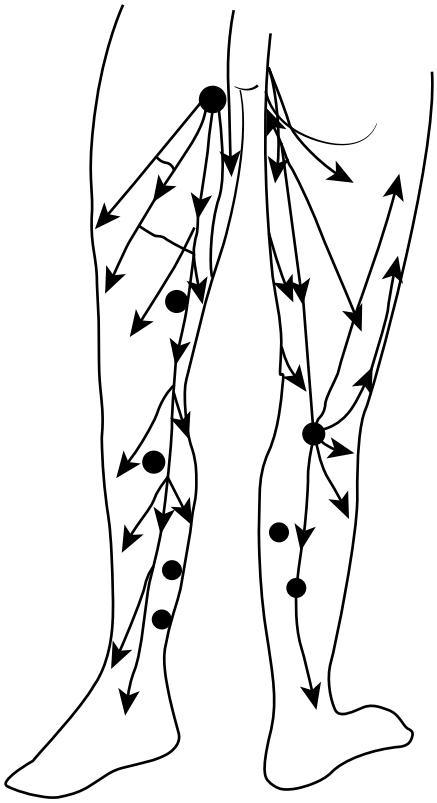


Figure 27.4 Territories of superficial reflux (anteroposterior view). The treatment must be performed from the point of leakage following the arrow, decreasing the concentration of the sclerosing agent.

For treating telangiectasias or spider veins taking into account the role of systematization and of the reticular network, it is mandatory to begin with the blue and larger telangiectasias, and then the purple ones, and finally the red ones.

To have the best results without pitfalls, we recommend the mapping as shown in Figure 27.4 to be followed.

In respect of volume of injection and concentration of the different sclerosing agents, we will discuss the frequently used sclerosing agents all over the world: tetradecyl sulfate (STS®, Fibrovein®, Trombovar®) and polidocanol (Aetoxisclerol®). These two products are tensioactive solutions that modify the intima and the layer of endothelial cells. Chromated glycerin (Scleremo®) or pure glycerin has poor corroding ability and is reserved for treating telangiectasias or spider veins. The result is an immediate inflammation of the vessel with a rich fibrin clot close to the vein. Within three months, the vessel is replaced by a fibrotic string or will disappear for small veins. There is no better product over the other; the best product is the one you commonly use, but it is important to use all of them because allergic reactions that can prevent the product from being used again.

The following are the characteristic of the products:

- Tetradecyl sulfate (0.2%–3%) is the strongest among the products when used in liquid solutions (equal to Aetoxisclerol in foam). There is no pain during injection, but severe pain if extravasation occurs; there is a high risk of necrosis if injected outside the vessel, and risk of allergy with possible shock. The volume of the product to be injected depends upon its concentration. Before the "foam revolution," 3% concentration was injected to treat the LSV and SSV, but rarely with more than 3 cc. At a lower concentration (1%–0.2%), it is common to inject 10 cc in both legs without complications.
- Polidocanol (0.25%–3%) has a lower sclerosing power when used in liquid but can be used with foam to treat veins with 0.8 caliber. There is no pain during injection if there is no extravasation. It provokes a rapid spasm of the vessel so operator skill is required to inject the complete vessel in a single session. The pain is frequent in small veins and telangiectasias or spider veins. There are two possible options: to inject less amount of product in several points so as to never reach the "pain point" and to add 0.1 mL of lidocaine that suppresses pain and stops the spasm. This, however, poses a risk of necrosis equal to tetradecyl at the same concentration. Occurrences of allergies can happen but are rare.
- *Chromated glycerin*: This product has a low sclerosing power and cannot be used to treat large varicose veins. When used at half its concentration (with isotonic saline or sterile water), it provokes cramps in the muscles if the injection is intravascular and burns if the injection leaks out of the vessel. To erase this discomfort, it is mandatory to add lidocaine 1% 1 cc for 9 cc of diluted solution. Some case reports of hematuria have been described. There is no risk of necrosis although some cases have been described. Allergic reactions can occur, particularly with any chrome worn by the patient.

Complications and Side Effects

There are two types of complications: major and minor.

The major complications are rare:

- *Thromboembolism*: Deep venous thrombosis and its main complication, embolism, can occur for patients with a history of deep venous thrombosis, superficial venous thrombosis, and thrombogenic conditions such as thrombophilic pathology (ATIII, ProtC, ProtS, RPCA, FV, and FII mutations, anticardiolipin antibody, lupus, homocysteinemia, and other coagulation disorders), cancer, sedentary lifestyle, and obesity. In these situations, sclerotherapy is permitted but with less concentration of the product, followed on occasion by LMWH, wearing a compression stocking for more than a week, or prolonged rest or immobility.
- *Intra-arterial injection*: This dramatic complication can lead to the loss of a limb, but more frequently to skin necrosis or muscle stroke. The main areas of concern are the saphenofemoral and saphenopopliteal junctions if the injection is performed near the junctions, and the perforators especially in the calf and ankle. Inclusion of foam is not necessary if injected at these levels. Echo-guided sclerotherapy must be the rule for the following cases: the injection to a double medial long saphenous vein can be very close to the superficial femoral vessels, especially in thin patients, and the saphenopopliteal junction because two arteries are very close to each other, the gastrocnemius artery (risk of muscle necrosis) and a small subcutaneous artery called subcutaneous artery or short saphenous artery (risk of skin necrosis). With echo guidance and injecting at a safe distance from the popliteal fold, this risk can be avoided (FS) for all the perforators and those above the calf because a small artery is attached

to the perforator, which can be visualized by a duplex scan and the injection administered at a safe distance.

- Allergy leading to heart failure has been described with tetradecyl sulfate. We have to remember that generally the sensibilization is not immediate—cutaneous rash or breathing difficulties are reported first. In this case, it is mandatory not to use the product for subsequent sessions.

There are numerous minor side effects that are generally operator dependent.

Pigmentation This side effect is the most frequent in our experience (3.5% on 1000 control cases). There are Brown spots appear on treated vessels but also occur after surgery (especially with phlebectomy with incomplete treatment of reflux). Sometimes, there is an underlying microthrombus if the varicosities are very superficial and blistered.

Risky situations in pigmentations can be foreseen and usually avoided. The important points are as follows.

The choice of the sclerosing agent depends upon the operator's preference. Too high a concentration of the product is always a cause of spot formation. The concentration must be reduced according to the level of injection on the limb, with decreasing concentration from the groin to the ankle. Even if there is no reflux in the large veins, the internal part of the knee and of the calf (long saphenous vein area) and the posterior part of the calf (lesser saphenous vein) are always risky areas. In this case we recommend the addition of local compression with dressing for 48 hours, which can exist at high pressure due to hypoactive perforators or microshunts. These can be transitory (due to hormonal or neurovegetative influences) or permanent. These can be located when fast recoloration after local compression with a finger is obtained. These points require higher concentration of the product, accompanied with the risk of microclots, matting, and pigmentation.

The concentration used must be adapted according to the Fitzpatrick classification. The first and second phototypes are not considered high risk but the third and, especially, the fourth must be injected with a lower concentration.

The microvascular network underneath has to be considered for patients presenting with "livedo reticularis" or acrocyanosis especially in the medial part of the thigh, the knee, and the calf. These patients have a special risk of pigmentation. In this case, we must reduce the concentration and volume of the injection.

The type of the varicosity is variable. Sometimes, there is varicosity with systematization, an increase of the blood flow with dilation of these veins. In this case, we have to choose a higher threshold of concentration for the larger veins and decreasing volume of injection for the smallest ones.

Sometimes, there are nonsystematized telangiectasias that are purple or red, looking like heather. In this case, the sclerosing injection cannot exceed 1 or 2 cm^2 in the same area. The use of compression is important.

Pigmentation Treatment Pigmentation is due to hemosiderin deposits associated with increased melanogenesis in the deeper part of the epidermis. It can disappear without treatment in some months, but sometimes remains. There are a lot of treatments available albeit with poor efficacies.

Microclots must be evacuated with a lancet or an 18 gauge needle by aspiration and then rinsed with a saline and lidocaine solution (aspiration of the clot, the vessel, and some adipocytes).

When there are no more clots but a spot, we can use the Kligman trio that gives some results. We prefer to use the following three techniques:

In the three cases mentioned earlier, the treatment is preceded or followed by the Kligman trio and retinoic acid.

Derma sanding: We use sterile wet sand paper 280/800 micromesh on roll, and the paper is maintained wet by a lidocaine solution (2%). The skin is removed to obtain a white red prickly area that is covered with vaseline tulle. The healing can be long and must be controlled for complete results. The same result can be obtained by surgical removal of the epidermis (L. Tretbar). The results are good but long to obtain, sometimes leaving scars (hypo- or hyperpigmentation).

TCA peel (E Bernier): TCA is considered as a medium peel. In our experience, we use it at 30% concentration after preparation of the skin with retinoic acid and corticoids three weeks before the procedure. When frosting is obtained on the area to be treated, the peeling is neutralized and the same treatment is continued for 3 weeks. This procedure gives inconsistent results with sometimes hypo- or hyperpigmentation.

With the Q-switched alexandrite laser and QS Nd:YAG laser before treatment, an EMLA patch is applied on each spot to be removed. If needed, coloration can be increased with Mno4K or lode. If the skin is incompletely removed, it is possible to complete the result with derma sanding. Generally, two or three sessions are necessary.

Intradermal injection of small amounts of desferoxamine (iron chelator) can give excellent results on small spots of brown pigmentation. The injections are painful and must be mixed with lidocaine. In our experience, two cases of allergies were noted (itching) on a small series of less than 30 patients.

It is most important to note that the skin of one's legs is not the same as that of the face because of blood stasis that provokes a leakage of hemosiderin and a stimulation of melanogenesis, on the one hand, and a lower local purification by the reticuloendothelial system on the other hand. In all these situations, even without varicose vein reflux, healing is longer to obtain on a foot than on a thigh. The lower the pigmentation on the leg, the most difficult it is to treat.

Spots due to Hematomas Large tanned areas remain when a hematoma disappears.

These patients experiencing capillary weakness with a spontaneous tendency for bruising are sometimes treated with corticoids and nonsteroidal anti-inflammatory agents such as Plavix®, aspirin, and Coumadine®. Four-handed operation is required, two to inject and two for immediate local compression (dental roller and Transpore®). When patients present a transparent skin, the reticular network treatment can lead to this type of hematomas. When they arise after sclerotherapy, we consider that this situation is provoked by an inappropriate treatment that increased the blood pressure (flow toward the deep venous network through continent microperforators or continent vessels), which very frequently occurs in treating the lateral part of the thigh with the use of the Albanese network. In this case, there is no other option but to close the reticular network. At the end, these hematomas can be induced by the remaining reflux (tributary, perforator). When a treatment gives an unexpected result, it is advisable to perform a control duplex scan. This leakage can be treated by sclerotherapy. The area of the tanned skin will disappear fast. During this period, sun exposure is harmful.

Figure 27.5 The injection site was 7 cm from the knee (lateral part).

Necrosis Necrosis is the death of tissues characterized by black spots (Figure 27.5) that can occur at the level of injection or higher (>10 cm from the site of injection).

During its early stage, this cell injury should be treated by a large inflammatory process that might be very painful. In most cases, these tissues can be treated by the use of an extravascular injection (technical fault), but unfortunately, this is not always the case (no injection fault).

When to Fear This Risk? Some spider veins can lead to necrosis even if the injection was completely intravascular (e.g., they are very superficial [with frequent hemorrhage] and very blistered [high weakness] and located in a high blood pressure zone [14] [lower part of the leg, foot ankles]) or if a huge unknown reflux remains visible (perforator). These spider veins can be treated with highly diluted sclerosing agents, with low pressure during injection. The treated area must be compressed by elastic sticky bandage.

Some microcirculation problems are sometimes involved: livedo reticularis and acrocyanosis are two favorable conditions for vascular spasm that can occur during or a few seconds after the injection. First, a white area can appear at the level of injection (usually >5–8 cm), followed by a purple retracted area. The black zone of necrosis is formed within 1 week. For patients experiencing such conditions, it is better not to use sclerosing agents that induce spasm (polidocanol +++ and tetradecyl sulfate ++) and, in all the cases, to inject small volumes even if the desire to use such a measure is considerable, because this may lead to a "spectacular" whitening of a large area (maximum of 3–4 cm^2). There is no proven pathophysiological explanation for this phenomenon but the pathophysiology of livedo reticularis and acrocyanosis is well described by capillaroscopy (spasm and opening of an arteriovenous shunt).

Some products can frequently cause more necrosis than others. However, all extravascular injections can lead to this complication, and the classical rule of 3–4 cm^2 is not for us absolute because the resistivity during injection a promotes more or less homogenous and visible areas. It is better to consider the homogenicity of the zone and the whitening of the injected zone around the spider vein (in this case, we have to stop the injection). At the end, the pain during the injection is not a good sign because polidocanol is always painful when injected in spider veins, at the contrary even with no pain when a large volume tetradecyl sulfate is injected.

Treatment of this Complication This complication is, in all the cases, hard to manage as well as difficult to heal as it is sometimes hard to explain to the patient. It is important to keep on monitoring the patient's continuous recovery until total healing and, most importantly, in cases when the scar is healed but remains visible or ugly. We must explain to the patient that there are two targets for this treatment: (1) to heal the ulceration and (2) to erase the scar that can last for a very long time.

The debridement of necrotic tissues is obtained by removing necrotic tissues with a blade under highly diluted local anesthesia. We can also use lidocaine without epinephrine. First, the dressing is performed by the physician and then the method is completed through compression (we prefer to use elastic sticky, nonremovable bandages). When healing is obtained, it appears as a white or pink zone of atrophy surrounded by a brown ring.

At first, we need to remove the zone of atrophy. In case of too much redness or depth, we perform a small lipofilling of pure fat (without hemocytes), but not for the white zone of atrophy, and sometimes in rare cases, a tattoo can complete the process. The surrounding brown pigmentation is treated after as a classical method of treatment (as discussed in the previous section). It is not safe to apply local corticoids on the atrophic zone (the red zone). In some cases and if badly needed, we propose a complete removal of the scar with a Z or a simple skin plast with lipofilling [17].

Matting The term "matting" was first proposed by American physicians to describe a flourishing zone of nonsystematized telangiectasias colored blue purple and red. It is the consequence of surgical or nonsurgical removal of trunks, tributaries, reticular networks, and sometimes telangiectasias (e.g., endovenous laser, VNUS, sclerotherapy). Knowledge about the pathophysiology of this phenomenon is useful to limit the risks involved. In this section, we will consider only matting that occurs during sclerotherapy, and even microsclerotherapy, for small vessels.

Risk Factors Stasis, hyperpressure of the venous network, weakness of the smallest vein that is unable to support new blood pressure constraints [17], and inflammation induced by a previous treatment are common risk factors. Some capillaries that were not visible at first appear eventually and neogenesis is increased by endothelial and erythrocyte growth factors.

The role of the hyperpressure is as follows: matting is a direct consequence of an unknown reflux, a nondetected feeding branch, an incontinent perforator, or a simple direct branch of the saphenous network where the blood pressure is high even if there is no reflux in this vein. In all the cases, it is mandatory to assess all areas with a good correlation with the theoretical zone of drainage (Figure 27.4) of the superficial venous network. It is also necessary to assess the complete saphenous network because segment incompetency can induce a local high blood pressure change on an involved tributary and finally matting in case of inappropriate sclerotherapy or ligation.

Two situations are especially risky: an important reticular network and a transitory reflux on an involved untreated vessel.

The reticular network is located in between the dermis and the hypodermic area. Its design looks like the stitches of a net. Its drainage is possible by three ways: direct perforators in the deep venous system, direct connection with saphenous veins, and connection with superficial tributaries. There are several articles that confirm the role of the reticular network in matting; however, we think it is quite impossible to foresee the blood flow pattern at this level. In fact, a reflux occurring in this network provokes a new flow distribution that is localized in a small surrounding zone that can be dilated. There are two factors that can lead to matting: several leaking points in the reticular network and inappropriate sclerosis of a competent drainage flow. This explains the controversies on the treatment of spider veins in a reticular network. In spite of this risk, it is the only technique for obtaining a good and long-lasting result for telangiectasias. In all the cases, in our experience, there is only one way to obtain a good result, that is, to carry out a complete treatment of the reticular network.

In matting, spider veins located on a saphenous territory (medial part of the knee and of the calf for great saphenous vein and lateral part of the calf and of the thigh for the lesser saphenous vein) appear after injection. It is logical to consider a trunk reflux of the saphenous vein even if the duplex scan is normal [18]. This is called a transitory reflux that can appear after a long standing position, after long sessions of sport, during pregnancy, and, in other cases, during venous dilation. We must assess again by duplex scan these patients to find these transitory refluxes. When we find a segmental reflux, can we destroy a saphenous vein because of a very small aesthetic defect? This is a debate for arterial surgeons whether this needs surgical vein bypass. The answer depends on the patient's wish.

Also, we have to remember that in some cases the removal of a normal vein can give poor results due to the increased pressure in the reticular network upon the introduction of several zones of spider veins. To be patient and to persevere with sclerotherapy are the only solutions.

The risk is linked to patients with hematomas. This causation was noted in the previous section. When hematomas after sclerosing injection occur and remain, there is high venous pressure and unknown reflux. This situation can lead to a flush of spider veins. This is helpful to patients with capillary weakness as the hematoma transforms to a posttraumatic hematoma in an area with spider veins. Apparently, this is provoked by angiogenesis linked to growth factors located on the erythrocyte endothelium. Finally, we can consider the vessel's healing by the creation of a small capillary to restore vascularization. If hematoma is evident after surgery, the local inflammation can induce matting that, in this case, must be treated as a local complication of the surgery (although this is not applicable for all patients).

Treatment of Matting A local assessment must be done with a duplex scan using a radio-frequency probe between 13 and 20 mHz in order to find all the feeding vessels. The territories of drainage are usually the same and have been described earlier. When feeding vessels are not found, these territories must be replaced with the treatment proposed earlier based on two schemas. Only when all the reticular vessels are treated then matting is also treated. The classical pattern proposed is to begin with the blue one and then the purple ones and finally with the red ones. Today, we widely use the Nd:YAG laser that allows us to target very small telangiectasias to treat matting. But we must know that the result can be very poor if it remains with feeding vessels or high venous pressure (new matting, redness, pigmentation).

There is a need for us to find out first all the causes of these possible complications and then determine the appropriate solutions. Hence, knowledge about dermatology, cosmetic medicine, and surgery is required.

When similar treatments give similar poor results, there must be something we have missed. A complete assessment by the physician is mandatory. We consider, for instance, the duplex scan as the "third hand" of the physician in this case.

BIBLIOGRAPHY

1. Garde C. Comment gérer la maladie veineuse? Montrouge, France: John Libbey Eurotext, 1996.
2. Min RJ, Khilnani NM. Endovenous laser ablation of varicose veins. *J Vasc Surg* 2005; 46:395–405.
3. Panier F, Rabe E, Maurins U. First results with a 1470 nm diode laser for endovenous ablation in incompetent saphenous vein. *Phlebology* 2009 February; 24(1):26–31.
4. Jung IM, Min SI, Heo SC et al. Combined endovenous laser treatment and ambulatory phlebectomy for the treatment of saphenous vein incompetence. *Phlebology* 2008; 23(4):172–178.
5. Elmore FA, Lackey D. Effectiveness of endovenous laser treatment in eliminating superficial venous reflux. *Phlebology* 2008; 23(1):21–32.
6. Garde C. l'anesthésie tumescente en chirurgie veineuse superficielle. *Phlébologie Mars* 2014; 1:64–71.
7. Elmore FA, Lackey D. Endovenous laser treatment of truncal reflux can be 100% successful when sufficient energy is utilized. *Phlebology* 2008; 23 Suppl 1:4.
8. Testroote MJG, Wittens CHA. Prevention of venous thromboembolism in patients undergoing surgical treatment of varicose veins. *Phlebology* 2013; 28 (Suppl 1):86–91.
9. Fassiadis N, Kianifard B, Holdstock JM et al. A novel endoluminal technique for varicose vein management: The VNUS closure. *Phlebology* 2002; 16:145–148.
10. Das SK, Sahoo N, Shanaz M. Experience with radiofrequency closure of varicose veins (VNUS). *Phlebology* 2005; 20(2):82–86.
11. Breu FX, Guggenbichler S, Wollman JC. *Second European Consensus Meeting on Foam Sclerotherapy 2006*, Vasa Tegensee, Germany, 2008, pp. S/713–S/729.
12. Rathbun S, Norris A, Morrison N et al. Performance of endovenous foam sclerotherapy in the USA. *Phlebology* 2012; 27:59–66.
13. Coleridge-Smith P. Sclerotherapy and foam sclerotherapy for varicose veins. *Phlebology* 2009 December; 24(6):260–270.
14. Guex JJ. Complications and side effects of foam sclerotherapy. *Phlebology* 2009; 24(6):270–275.
15. Garde C. Physiopathologie de la maladie veineuse. *Angiologie* 2008; 60(5):29–37.
16. Goldman MP. Complications and sequelae of sclerotherapy. In: Goldman MP, Weiss RA, Bergman JJ, eds. *Varicose Veins and Telangiectasias: Diagnosis and Treatment*. St. Louis, MO: Quality Medical Publications, 1999.
17. Albanese AR, Albanese AM, Albanese EF. Lateral subdermic varicose vein system of the legs: Its surgical treatment by the chiseling tube method. *Vasc Surg* 1969; 3:81–89.
18. Garde C. Signification d'une veine sentinelle dans le tiers supero interne de la face interne de la jambe étude sur 100 cas. *Phlébologie* 2002; 4:32–38.

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Phlebectomy

Albert-Adrien Ramelet

Ambulatory phlebectomy (AP) is a safe and effective surgical procedure that enables the removal of incompetent varicose veins, perforators, and reticular veins, including the feeding veins of telangiectasias or even blue telangiectasias. AP may also be used in varicophlebitis and superficial phlebitis or for dilated veins in other locations, for instance, periorbital, temporal, or frontal venous networks, as well as abdomen, arms, or dorsum of the hands.

HISTORY

Phlebectomy has been performed since antiquity. Aulus Cornelius Celsus (ca. 25 BC–ca. 50 AD) described such an operation and so did later by Plutarch (46–125 AD) [1–3].

Serefeddin Sabuncuoglu, a pioneer of surgery, defined again phlebectomy; a hook is illustrated in his surgery textbook, *Cerrahiyyetu'l Haniyye* (Imperial Surgery), which was written in Turkish in 1465 AD [4].

The technique was reinvented by Robert Muller (1919–2012), a Swiss dermatologist in Neuchâtel, and progressively adopted all over the world [1,5–8].

SCIENTIFIC BASIS

Our understanding in chronic venous disorders (CVDs) and varicose veins is increasing but still incomplete. Both macro- and microcirculatory alterations are involved, including venous reflux and venous hyperpression, apparently consecutive to inflammatory damage of the venous wall and valve leaflets. CVD can be asymptomatic or may be accompanied by so-called venous symptoms, such as heaviness, pain, sensation of swelling, tiredness, throbbing, itching, paresthesiae, and more debatably restless legs and night cramps. CVD is not a pure cosmetic concern but a medical one as it degrades the patient's quality of life [9] and can lead to more severe troubles, defined as chronic venous insufficiency (CVI): edema, stasis dermatitis, pigmentation, atrophie blanche, lipodermatosclerosis, and venous ulcers. Varicose veins are also a risk factor for deep vein thrombosis [10].

Major therapeutic targets are suppression of the reflux, either at the junction or on segmental dilatation, and removal of the damaged vein. Conservative treatments, such as compression and venoactive drugs (VADs), are effective on symptoms and complications, but cannot afford healing or long-term relief of CVD. Therefore, ablation of varicose veins is an essential step in treating venous disorders. Ablation may be chemical (sclerotherapy, cyanoacrylate glue), thermic (endovenous laser, radiofrequency, or steam), or surgical (flush ligation of the junction and perforators, stripping, and phlebectomy). When indicated, phlebectomy is a safe and effective technique for removing varicose veins, with excellent long-term results [5,7] that are better than those obtained with liquid sclerotherapy [11].

INDICATIONS

AP is indicated in almost all patients, including the elderly. Most of the procedures are performed in truly ambulatory patients, but the technique may also be used in conjunction with other surgical procedures or chemical ablation (in particular, echosclerotherapy of intrafascial insufficient venous pathways).

Merely all types of varicose veins may be treated with AP, including the removal of incompetent saphenous veins (except saphenofemoral and saphenopopliteal junctions and saphenous intrafascial pathway), their major tributaries, perforators, and reticular veins, the feeding veins of telangiectasias, or even blue telangiectasias. AP may also be used in varicophlebitis and superficial phlebitis or for veins in other locations, for instance, dilated periorbital, temporal, or frontal venous networks, as well as venous dilatation of the abdomen, arms, or dorsum of the hands (Table 28.1).

The goal of AP is to secure definitive treatment of the varicose veins, once the underlying cause of reflux has been treated and eliminated. Therefore, a thorough examination of the patient, including ultrasound, is mandatory.

In some cases, the goal may be only partial or a short-term improvement. Examples include avulsion of a single painful varicose vein in a young mother unwilling or unable to consider more extensive treatment or, in an elderly patient, removal of a single symptomatic varicose segment or of a feeding vein causing skin changes (eczema, leg ulcer).

CONTRAINDICATIONS

They are rare or relative: critical arterial ischemia, infections, allergy to local anesthetics, bedridden status, and impaired blood clotting or immunity.

Arrhythmias and heart disease may be a contraindication to local anesthesia.

AP is usually not performed during pregnancy or immediately postpartum as varicose veins frequently regress spontaneously after delivery.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Table 28.1 General Indications for AP

- Saphenous and saphenous collateral varicose veins
- Varicose veins of the lateral aspect of the leg
- Reticular varicose veins
- Perineal varicose veins
- Veins of the dorsal aspect of the foot
- Perforators (with some limits)
- Varicose pearls (small prominent ampullary dilatations at the distal part of the leg, covered with thin skin, prone to hemorrhages)

Phlebectomy of an isolated portion of a saphenous vein should not be conducted if the junction is insufficient. Phlebectomy of the perforators is to be envisaged with caution. The results are good if the hook is used to remove the medial perforators of the thigh and small perforators of the lateral surface of the legs. The results may be mediocre when treating the medial perforators of the lower leg.

Other indications:

- Curettage of telangiectasias
- Aesthetic indications: facial, palpebral, arm, and hand veins

PREOPERATIVE REQUISITES

Every patient should be carefully interviewed and examined in the supine position, with investigations including at least a continuous wave Doppler but preferably duplex ultrasound (DUS) in order to select the most appropriate procedure. Side illumination (episcopy) is a useful tool for detecting reticular varicose veins and feeding veins associated with overlying telangiectasias [5,12].

Before any intervention, the patient should be informed of the modalities and risks of the procedure, including the preliminary steps of the procedure: shaving (otherwise depilating the leg the day before), marking the varicose pathways, infusing anesthesia, operating, and bandaging.

PROCEDURE

Marking of Varicose Veins

Marking (indelible pen) is performed on a standing patient. Side illumination permits accurate visualization of the superficial course of a varicose vein prior to extraction (Figure 28.1a and b). Marking may also be facilitated by echography to detect nonpalpable venous networks between the visible varicosities (Figure 28.2). Special pencils are helpful to draw a preliminary marking on the wet skin when using echography gel. Take care not to erase preoperative marking when disinfecting the leg.

Local Anesthesia

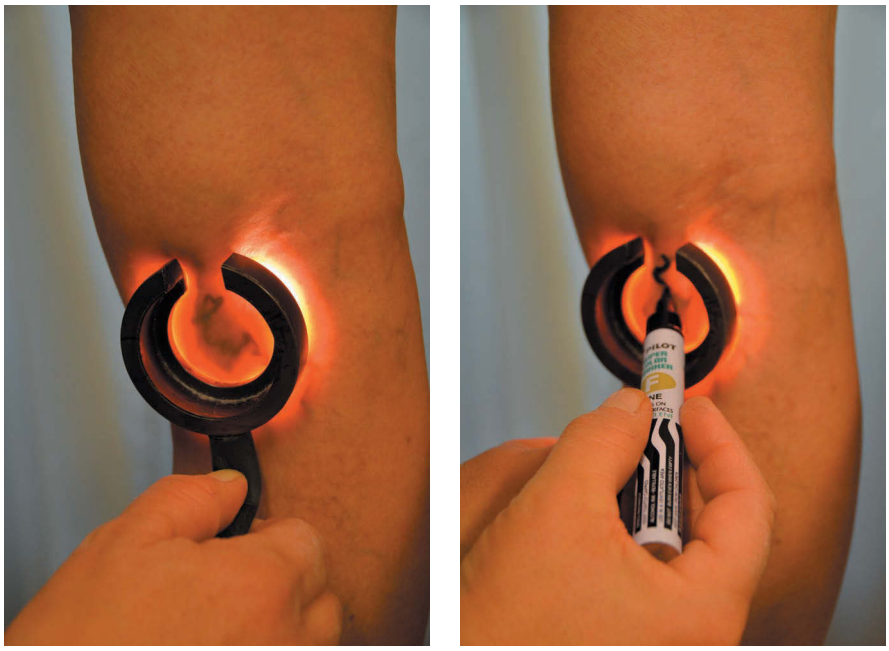
Buffered lidocaine with epinephrine diluted in saline or Ringer's solution (Table 28.2) is injected along the venous pathway according to the tumescent technique (Figure 28.3) [5].

Advantages of this procedure are enumerated in Table 28.2.

Complications of local anesthesia are exceptional. However, resuscitation equipment should be immediately accessible.

Preoperative/Peroperative Sclerotherapy of Telangiectasias

To ensure a rapid cosmetic result, sclerotherapy should be performed immediately before or during the anesthesia procedure. The high intratissular compression induced by tumescent



(a) (b)

Figure 28.1 (a) Episcopy (side illumination) permits accurate visualization of the superficial course of a varicose vein. (b) Marking of a superficial varicose vein before anesthesia and phlebectomy.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 28.2 Marking of a nonvisible varicose vein with echography. Special pencils are helpful to draw a preliminary marking on the wet skin when using echography gel (Prismalo®, by Caran d'Ache, Geneva, Switzerland).

Table 28.2 Tumescence Local Anesthesia

- Lidocaine (1%)–epinephrine: 50 mL
- 8.4% sodium bicarbonate: 5 mL
- Normal saline or Ringer's solution: 500 mL

Advantages of tumescent anesthesia:

- Virtually painless injection
- Low risk of toxicity even with high amounts of liquid
- Hydrodissection of the vein by paravascular injection
- Compression of engorged neighboring tissues that decreases bleeding and prevents hematoma
- "Rinsing" of any blood collection as the solution drips out through incisions during the hours following the operation
- Prolonged analgesic effect

Note: Klein's formula, modified.

anesthesia increases the effectiveness of sclerotherapy. This is the principle of the START technique (sclerotherapy in tumescent anesthesia of reticular veins and telangiectasias), which is quite effective in treating refractory telangiectasias [13,14]. We mostly use polidocanol (Aethoxysklerol 0.25% and 0.5%, liquid or foam) or in some cases chromated glycerin.

Instruments and Equipment

Phlebectomy hooks are essential to perform the procedure. Different models have been developed. In our opinion, the ideal hook should have a sharp harpoon to grip the adventitia of the vein (Figure 28.4), allowing its removal through minimal incisions. A comfortable grip prevents fatigue. Two sizes of hook are enough to perform all types of phlebectomies. A large

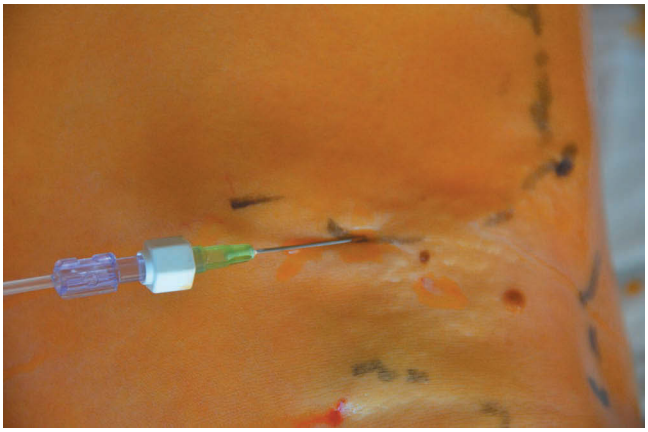


Figure 28.3 Tumescent anesthesia. The subcutaneous infiltration of a large volume of highly diluted buffered lidocaine and epinephrine in saline or Ringer's solution causes firm swelling (tumescence) of the targeted tissue. In this picture, the injection is performed with an electrical pumping device. Injection is then more rapid and more effective and induces less pain.

hook with a thicker stem is indicated in extraction of saphenous tributaries and perforators. A thinner hook is necessary to remove reticular venous network and to perform curettage of thick telangiectasias.

A cylindrical shape of the grip permits a gentle rolling of the hook between the fingers, diminishing the amount of rotation of the wrists and minimizing wrist and hand stress during the procedure. The hook stem should be short: this allows precise and close work as well as vigorous traction [5,15].

Few other instruments and equipment are requested: No. 11 straight blade scalpel, 18 gauge needle, 1–2 mm punch, mosquito hemostat forceps, sterile gauze pads, sterile gloves, mask, and dressing material (gauze pads or other absorbent pads to be placed over operative sites, elastic bandage).

Operation

Areas in which hemostasis is more difficult to achieve with the dressing (popliteal folds, thighs, groin, major perforators) are surgically removed first, the clot developing, while the patient remains supine.

Skin incisions made with the tip of the scalpel (Figure 28.5), or using a needle, are oriented along the long axis of the leg, except at the knee and the ankle where they should be perpendicular to the axis. For larger varicose veins, incision with a 1–2 mm punch is an elegant alternative (Figure 28.6) with minimal residual scarring [16].

The hook is gently inserted into the subcutis to dissect the venous pathway with the stem of the hook. Then, the hook is inserted again, the sharp edge is facing downward and is rotated under the vein, with an ample movement. The aim is to cross the varicosity and to harpoon the adventitia with the barb of the hook. The vein loop is exteriorized and grasped with a mosquito hemostat held in the left hand (Figure 28.7). Then, the vein is gently pulled out, the hemostat regularly advanced along it to prevent its premature tearing. The traction is maintained to guide the operator to the next incision.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

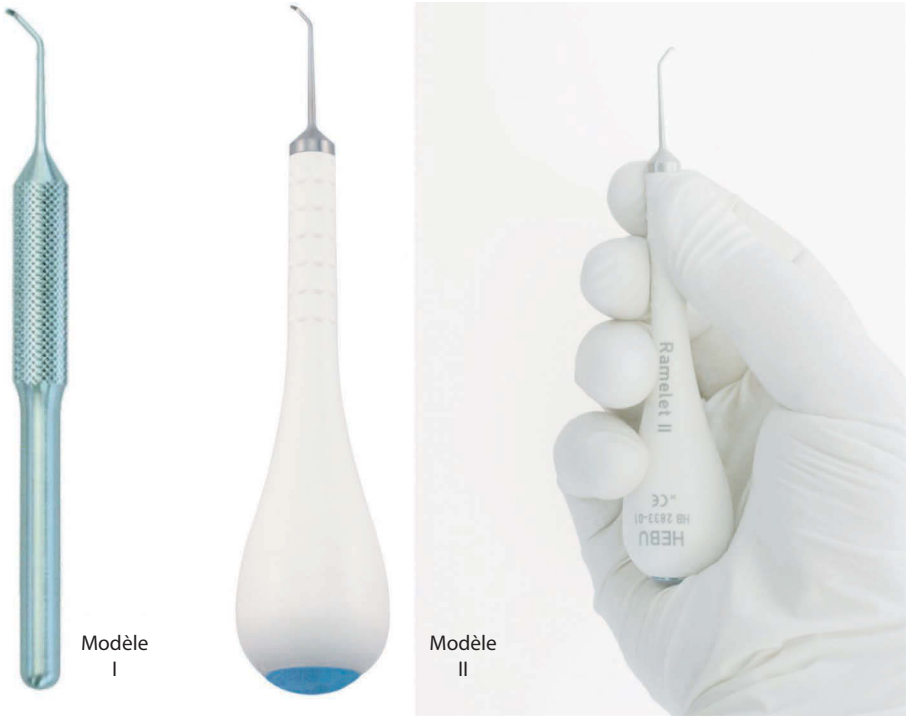


Figure 28.4 Hooks according to Ramelet. (Model 1 by Maillefer, Salzmann MEDICO, Rorschacher Strasse 304, CH-9016 St. Gallen, medico.order@salzmann-group.ch; model 2, by HEBUmedical GmbH, Badstrasse 8, D-78532 Tuttlingen, www.HEBUmedical.de; reproduced by permission.)

Figure 28.5 Skin incisions made with the tip of the scalpel.

Figure 28.6 Skin incisions made with a 1 mm punch.

The vein's entire course is removed by sliding the divided incompetent vein from one incision to the other (Figure 28.8). Neither venous ligation nor sutures of the skin are required.

Perforators are extirpated by gentle and regular traction (Figure 28.9a and b).

Larger telangiectasias may also be destroyed by gentle subcutaneous curettage with the harpoon of the hook, debris of venectasias being removed through tiny incisions.

Hemostasis is secured by compressing the bleeding point with the left hand or by an assistant in difficult cases.

No sutures are required. Incisions may be sealed with Steri-Strips.

Dressing

At the end of the operation, the leg is carefully cleansed with hydrogen peroxide (H_2O_2).

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 28.7 The barb of the hook harpoons the vein. The mosquito hemostat is ready to grasp the vein.

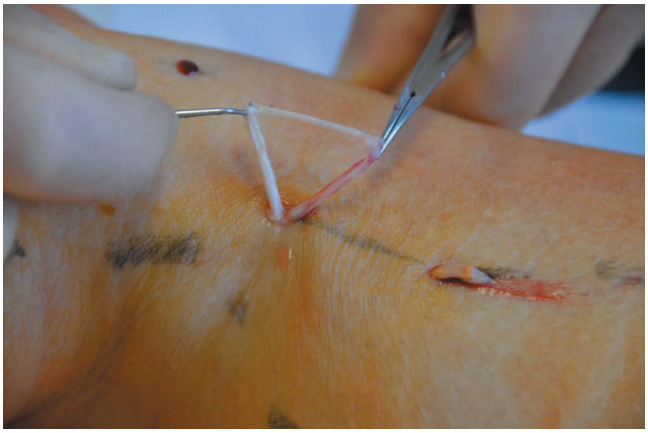


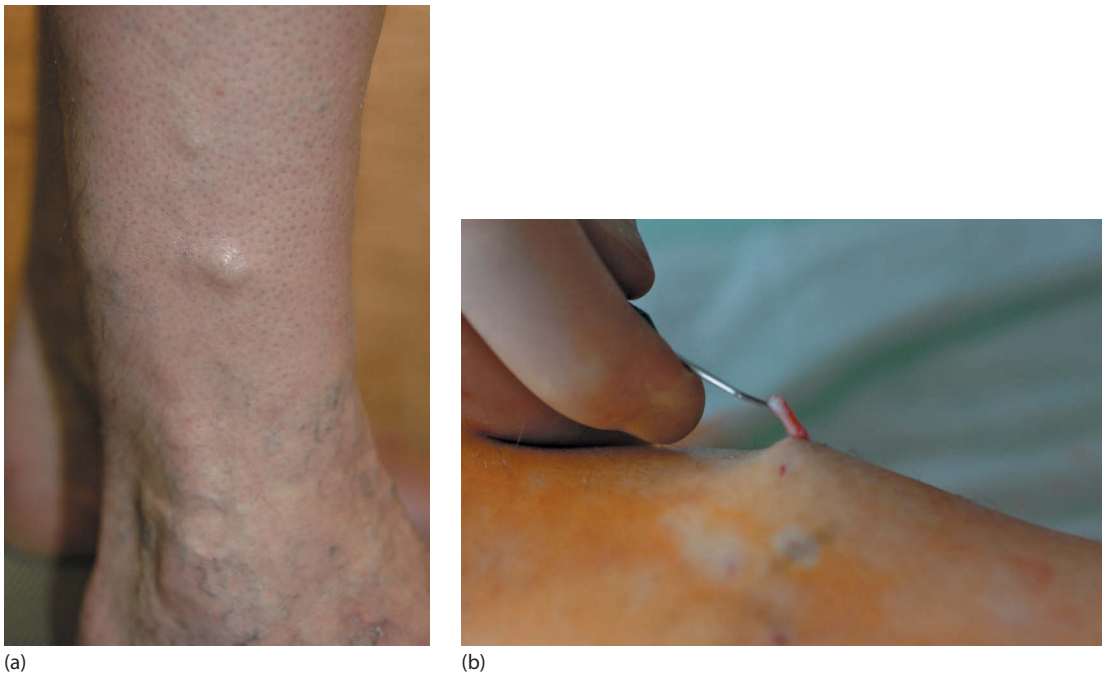
Figure 28.8 The vein loop is exteriorized and grasped with a mosquito hemostat held in the left hand.

An adequate dressing is an essential step in the procedure. Absorbent sterile dressings are applied to the incisions and covered by a tubular knit stocking (Figure 28.10). The malleoli, retromalleolar gutters, and popliteal fossa may be protected by placing packing cotton rolls. A second dressing with a long-stretch bandage achieves compression along the whole leg, from the toe joints (even if only the thigh has been operated upon) extending up proximally to operated areas. This dressing prevents postoperative hemorrhage, pain, and complications. It may be loosened during the night if too tight and replaced before getting up in the morning.

Postoperative Course

Movement is essential. The patient must regularly walk. He is also allowed to work, but driving an automobile should be avoided in the ensuing few hours postoperatively since the motor nerves may not be functioning properly due to prolonged anesthesia, particularly when operating in the popliteal fold [17,18].

Postoperative pain is rare, especially after tumescent anesthesia. Light analgesic (paracetamol) may be prescribed. Prophylactic anticoagulation is not indicated as the patient moves during the operation and walks immediately after the phlebectomy with a compression bandage. It may be considered



(a) (b)

Figure 28.9 (a) Perforator of the lateral aspect of the leg. (b) Phlebectomy of the perforator with a Ramelet's hook.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 28.10 Absorbent sterile dressings applied to the incisions.

in exceptional cases (morbid obesity, postthrombotic syndrome, thrombophilia).

Dressings are changed after 24 or 48 hours, and the wounds cleansed with antiseptic and sprayed with a protective film. No further dressings are needed at this point if the incisions' size is minimal, but compression therapy (elastic bandages or compression stockings) is recommended for 3–21 more days, depending on the size of the removed veins, degree of treated reflux, and local traditions [17,19]. Short showers are allowed 3 days postoperatively. Sun exposure should be avoided until scars have faded.

RESULTS

An experienced practitioner may achieve excellent results if all steps of the procedure are correctly respected, including preoperative assessment, marking, and skill (Figures 28.11 through 28.13).

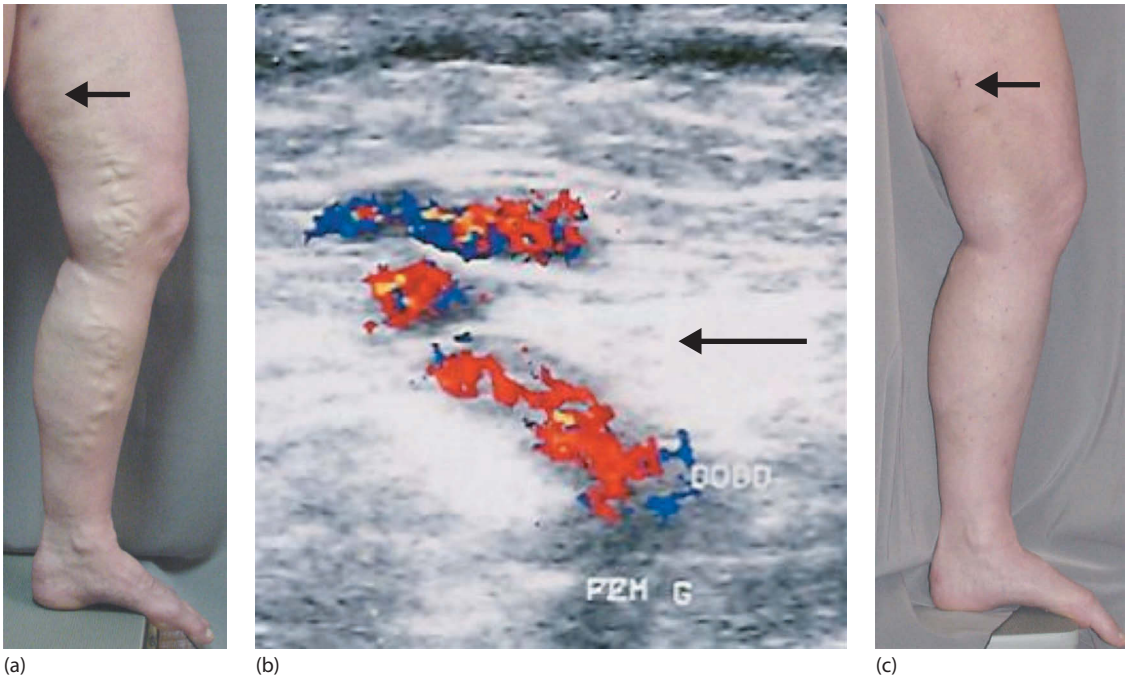
Transitory scars are visible in younger patients and in pigmented skin and may remain for several months.

ADVERSE REACTIONS

Hematomas are a usual side effect of any surgical procedure. The use of tumescent anesthesia dramatically reduces the extent of hematomas as does an adequate compression bandage.

Occasional complications of AP [5,17,20,21] may be as follows:

- Cutaneous: blisters, transitory hyper- or hypopigmentation, and visible scars (which usually fade but are quite visible in young patients during the months following the procedure). Wound infection, keloid formation, Koebner phenomenon (psoriasis, lichen planus, and vitiligo), and tattooing are exceptional complications.
- Vascular, as postoperative bleeding, or a major concern, matting. Telangiectatic matting is not rare after phlebectomy, stripping, or sclerotherapy. It may remit spontaneously after a few months or persist. Further sclerotherapy or laser treatment may be effective in its treatment. In some cases, matting is due to the persistence of a small perforator, which may be removed with a second phlebectomy. While telangiectatic matting is not rare, it is quite troublesome as the aim of phlebectomy is often to improve cosmetic appearance.



(a) (b) (c)

Figure 28.11 (a) Varicose vein along a superficial tributary of the great saphenous vein (relapse after stripping). (b) Echographic visualization of an insufficient Dodd perforator before phlebectomy of the whole varicose pathway. (c) Results 6 weeks later.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 28.12 (a) Pretibial varicose vein (saphenous tributary). (b) Result 6 weeks after phlebectomy.

Superficial thrombophlebitis is exceptional, occurring mainly if a venous segment has been missed during the operation. It may be treated by gentle incision with a No. 11 blade. Ascending thrombophlebitis may be associated with—or induce—deep venous thrombosis (a quite exceptional complication of phlebectomy). Echography is then imperative to exclude the involvement of deep veins. Treatment includes incisions (see in the succeeding text), local and systemic nonsteroidal anti-inflammatory drugs (NSAIDs) for 1 week, and anticoagulation, if the phlebitis extends close to the junction. More rarely, one may observe lymphatic pseudocyst (in particular on the dorsum of the foot and pretibial) [22], lymphorrhea, and postoperative edema (dorsum of the foot). Major hematomas are exceptional. One case of compartment syndrome has been recently published [23].

- Neurological: occasional transient or definitive damage to sensory nerves due to the procedure or due to a badly adapted compression. Transitory drop foot has been observed after anesthesia in the popliteal fold, but in our experience, this complication is prevented by the use of tumescent anesthesia [17,18]. Compartment syndrome also may occur after a poorly fitted bandage [24].
- General: malaise resulting from local anesthesia or vasovagal reaction is no longer observed since the introduction of the tumescent technique. Allergy to anesthetics or preservatives is extremely rare. Resuscitation equipment, including oxygen, must always be available.

As with any therapeutic procedures, the patient has to be warned about possible poor results and potential complications; this is particularly important when the aim of the treatment is cosmetic improvement.

WHAT TO AVOID

Most bad results are avoidable, as they are principally consecutive to

- Insufficient diagnostic capacities. The operator must respect proper indications (in particular, suppression of underlying venous reflux).
- Insufficient skill. Inappropriate incisions, traumatisms of the subcutis and of the wound edges cause pain, and increase the risk of infection and undesirable scars.

(a) (b) (c)

Figure 28.13 (a) Refractory telangiectasias, with an underlying feeding perforator. (b) Phlebectomy of the perforator. Note that the vein is fibrous as a consequence of previous ineffective sclerotherapy. (c) Excellent results 6 weeks later.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

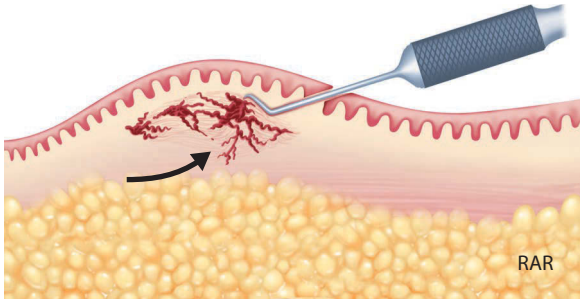


Figure 28.14 Larger telangiectasias may be destroyed by gentle subcutaneous curettage with the sharp harpoon of No. 1 Ramelet's hook. Peroperative sclerotherapy is well tolerated and improves results of one single session.

- The dorsum of the foot and the pretibial area are at risk of lymphatic damage. Incisions should be large enough to avoid hurting these delicate structures.
- Badly adapted bandage and compression may induce pain, edema, and more severe complications such as necrosis or compartment syndrome.

SPECIAL INDICATIONS

Curettage of Telangiectasias

The treatment of telangiectasias may be quite disappointing. Feeding veins should be removed by AP or treated with sclerotherapy in order to diminish the risk of recurrence of telangiectasias. Unfortunately, feeding veins are not always easily detectable, and episcopy (side illumination) may be needed to identify them. Larger telangiectasias may be destroyed by gentle subcutaneous curettage with the sharp harpoon of the No. 1 Ramelet's hook (Figure 28.14), with the resulting debris being removed through tiny incisions. This technique is not yet in widespread use, but an experienced phlebologist may achieve quite good results, even in difficult cases (Figure 28.15a and b).

Superficial Thrombophlebitis

Phlebectomy can also be used as an immediate treatment for small segments of superficial thrombophlebitis. The intravascular coagulum is expressed (Figure 28.16), and the involved vein segment can be extracted through the same incision. The patient is very rapidly relieved of discomfort, and the underlying vein is eliminated in one step.

Veins in Other Locations

AP may be used in other anatomical regions than the legs [25,26]:

- Dilated periorbital, temporal, or frontal venous networks.
- Venous dilatation of the chest and abdomen (if the veins in question are not directly associated with a deep venous obstruction).
- Dilated veins of the arms, dorsum of the hands (Figure 28.17a and b), or penis may also be removed with AP. However, ablation of functional veins for purely aesthetic reasons remains highly controversial (Figure 28.18).

Other Uses of Hook Technique

Ramelet's hook has also been used to remove implanted drug delivery systems, such as Norplant, with minimal scarring [27].

(a) (b)

Figure 28.15 (a) Telangiectasias. (b) Eight weeks after curettage and peroperative sclerotherapy (one session).

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

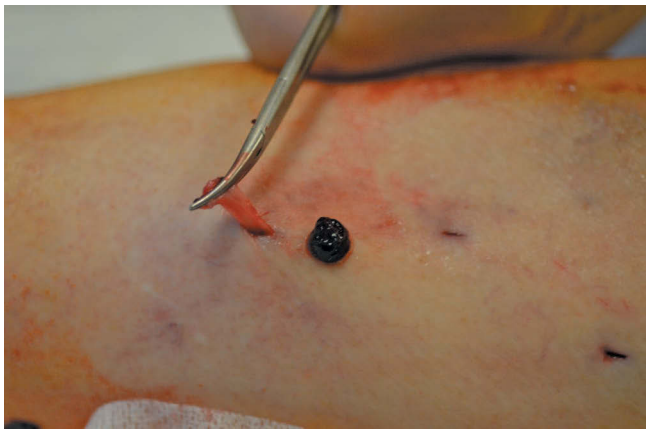


Figure 28.16 Superficial thrombophlebitis. Incision in local anesthesia, expression of the clots, and removal of the underlying thrombotic varicose veins.

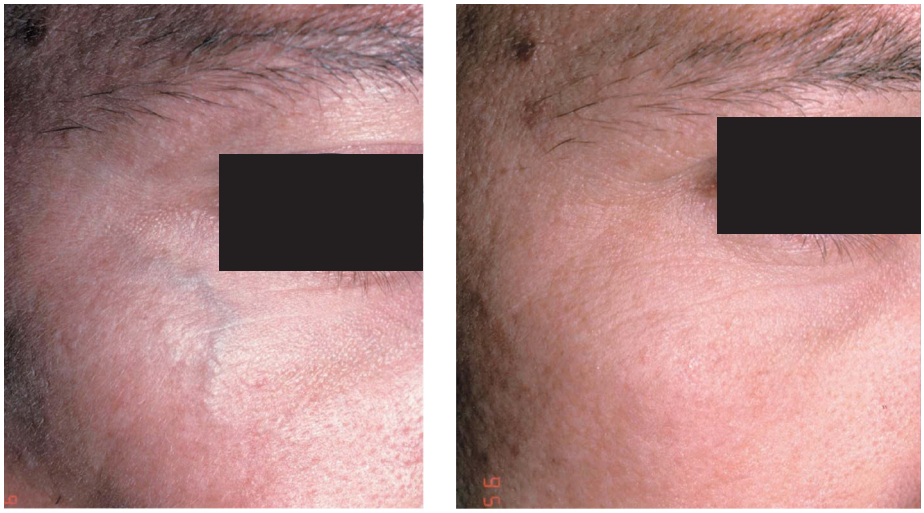
Vein biopsy may also be performed according to the AP procedure [28], such as removal of the venous lake of the lip [29] or of steatocystoma multiplex and cutaneous cysts [25,26,30].

CONCLUSIONS

An experienced phlebologist can achieve excellent and long-lasting functional results when handling phlebectomy correctly with an appropriate technique and with well-defined indications, after the exclusion/suppression of underlying venous reflux.

Disclosure of Interest

The author has no conflict of interests in this paper. They do not get any royalties or advantages with Ramelet's phlebectomy hooks.



(a) (b)

Figure 28.17 Posttraumatic dilatation of an orbital vein in a young man, (a) preoperative; (b) results 6 weeks later.

(a) (b)

Figure 28.18 Dilated veins of the dorsum of the hand, (a) preoperative; (b) results 6 weeks later.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

REFERENCES

1. Muller R. Traitement des varices par la Phlébectomie ambulatoire. *Bull S Fr Un Phlébol* 1966; 19(4):277–279.
2. Muller R. La Phlébectomie Ambulatoire. *Phlébologie* 1978; 31(3):273–278.
3. Olivencia JA. Interview with Dr. Robert Muller. *Dermatol Surg* 1998; 24:1147–1150.
4. Darcin OT, Andac MH. Surgery on varicose veins in the early Ottoman period performed by Serefeddin Sabuncuoglu. *Ann Vasc Surg* 2003; 17(4):468–472.
5. Ramelet AA. Ambulatory phlebectomy. In: Alam M, Silapunt S, eds. Treatment of leg veins, 2nd ed. Philadelphia, PA: Elsevier, 2010.
6. Ramelet AA. La phlébectomie selon Muller, description de la technique sous sa forme actuelle. *Phlébologie* 2004; 57:309–317.
7. Muller R. Mise au point sur la phlébectomie ambulatoire selon Muller. *Phlébologie* 1996; 49(3):335–344.
8. Ramelet AA, Perruchoud D-L. Phlebektomie nach Muller. *Phlebologie*. 2014; 43(6):326–333.
9. Darvall KA, Bate GR, Adam DJ, Bradbury AW. Generic health-related quality of life is significantly worse in varicose vein patients with lower limb symptoms independent of CEAP clinical grade. *Eur J Vasc Endovasc Surg* 2012; 44(3):341–344.
10. Muller-Buhl U, Leutgeb R, Engeser P, Achankeng E, Szecsenyi J, Laux G. Varicose veins are a risk factor for deep venous thrombosis in general practice patients. *Vasa* 2012; 41(5):360–365.
11. de Roos KP, Nieman FH, Neumann HA. Ambulatory phlebectomy versus compression sclerotherapy: Results of a randomized controlled trial. *Dermatol Surg* 2003; 29(3):221–226.
12. Ramelet A-A. Phlébologie esthétique. Varices tronculaires et réticulaires. *Cosmétologie et Dermatologie esthétique*. Paris, France: EMC (Elsevier Masson SAS), 2010.
13. Ramelet AA. Sclerotherapy in tumescent anesthesia of reticular veins and telangiectasias. *Dermatol Surg* 2012; 38(5):748–751.
14. Ramelet AA. La technique START (Sclerotherapy in Tumescent Anaesthesia of Reticular Veins and Telangiectasias). *Phlébologie* 2012; 65(2):13–17.
15. Ramelet AA. Muller phlebectomy. A new phlebectomy hook. *J Dermatol Surg Oncol* 1991; 17(10):814–816.
16. Gajraj H. Phlebectomy without surgical scars: A new technique. *Phlebology* 2011; 26(6):263.
17. Ramelet AA, Monti M. *Phlebology, the Guide*. Paris, France: Elsevier, 1999.
18. Otters EF, van Neer PA. Drop foot, a rare complication following Muller's phlebectomy. *Phlebology* 2012; 27(6):303–304.
19. de Roos K, Bruins F, Neumann H. Compression therapy following ambulatory phlebectomy. A prospective study. *Phlebologie* 2008; 37:3–6.
20. Ramelet AA. Complications of ambulatory phlebectomy. *Dermatol Surg* 1997; 23(10):947–954.
21. Olivencia JA. Complications of ambulatory phlebectomy. Review of 1000 consecutive cases. *Dermatol Surg* 1997; 23(1):51–54.
22. Elvy M. Post ambulatory phlebectomy: Chronic peripheral lymphocoele. *Phlebology* 2010; 25(3):158–160.
23. Malskat WS, De Maeseneer MG. Extensive hematoma in the superficial posterior compartment with threatening compartment syndrome after ambulatory phlebectomy. *Dermatol Surg* 2012; 38(12):2035–2037.
24. Hinderland MD, Ng A, Paden MH, Stone PA. Lateral leg compartment syndrome caused by ill-fitting compression stocking placed for deep vein thrombosis prophylaxis during surgery: A case report. *J Foot Ankle Surg* 2011; 50(5):616–619.
25. Ramelet AA. Phlébectomie: indications en dehors des membres inférieurs. *Phlébologie* 2012; 65(3):9–14.
26. Ramelet AA. Phlébologie esthétique: phlébectomie hors membres inférieurs. *Cosmétologie et Dermatologie esthétique*. Paris, France: EMC (Elsevier Masson SAS), 2011.
27. Lam M, Tope WD. Surgical pearl: Phlebectomy hook Norplant extraction. *J Am Acad Dermatol* 1997; 37(5 Pt 1):778–779.
28. De Roos KP, Neumann HA. Vein biopsy. A new indication for Muller's phlebectomy. *Dermatol Surg* 1995; 21(7):632–634.
29. Fays-Bouchon N, Fays S. Un traitement simple, efficace et esthétique de l'angiome sénile: l'exérèse au crochet de phlébectomie de Muller. *Nouv Dermatol* 1997; 16:117–118.
30. Lee SJ, Choe YS, Park BC, Lee WJ, Kim do W. The vein hook successfully used for eradication of steatocystoma multiplex. *Dermatol Surg* 2007; 33(1):82–84.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Nail surgery

Eckart Haneke

The beauty of the nail is defined by its size, shape, sheen, consistency, and integrity of the periungual skin in relation to a well-formed distal phalanx and the entire hand. Many of these criteria of nail beauty, such as consistency, sheen, or the aesthetic balance of the nail and digit, cannot be approached surgically. Purely aesthetic surgery of the nail unit is therefore rarely performed, but one of the most important principles of surgery of the tip of the digit is that it be done according to the rules of aesthetic surgery in general.

BASIC ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

The nail unit is an integral part of the tip of the digit [1,2]. It is functionally and anatomically linked to the other constituents of the distal digital phalanx [3]; surgery of the nail is surgery of the distal phalanx and vice versa. Anatomically, the nail is very closely located to the extensor tendon and the lateral ligaments that together form the dorsal aponeurosis of the distal interphalangeal joint, to the joint itself and the synovial membrane, as well as the periungual connective tissue (Figure 29.1). The nail apparatus consists of the proximal and the two lateral nail folds. The proximal nail fold is a narrow piece of tissue overlying most of the nail matrix. Its dorsal surface has normal epidermis and eccrine sweat glands but is devoid of pilosebaceous follicles. Its free margin is acutely angled and has the cuticle on its end. It is firmly attached to the underlying nail plate and seals the nail pocket. Most of the cuticle is derived from the horny layer of the ventral surface of the proximal nail fold, which firmly adheres to the underlying nail plate and is drawn distally with the growing nail (Figure 29.2). Thus, nails not growing anymore such as in the yellow nail syndrome lose their cuticle spontaneously and the free margin of the nail fold rounds up. However, the cuticle is also lost when the free margin of the proximal nail fold is thickened, e.g., due to chronic paronychia. In the depth of the nail pocket, or cul-de-sac, the apical matrix begins (Figure 29.3). It turns around to the bottom of the nail pocket and is responsible for the most superficial layer of the nail plate. This gives the nail its shine; thus, any damage to the apical matrix results in a rough lusterless nail. The bulk of the matrix forms the middle nail plate layers. Disturbance of the physiologic keratinization causes leukonychia, nail brittleness, or nail destruction. Distal to the matrix is the nail bed, which in contrast to the milky-white matrix is seen as the pink area adjacent to the lunula. The nail bed is very firmly attached to the nail plate and gives rise to a very thin horny layer that allows the nail plate to slide over the nail bed without being detached from it. The most distal nail bed forms a granular layer and is called the nail isthmus (Figure 29.4). Distal to it is the hyponychium that marks the physiologic separation of the nail from the nail bed. Like the cuticle, it is a crucially important structure to seal the virtual space between the nail and the nail bed. The lateral nail folds are elevated soft tissue bulges giving the nail stability to both sides. The matrix and nail bed are richly innervated and contain a large number of specified nervous end organs thus making the nail not only an instrument for defense and protection and a most useful tool but also an aid to the sensory functions of the tip of the digit. Moving two-point discrimination of the nail plate is clinically identical to that of the finger pulp [4]. The blood supply comes from the paired volar and dorsal digital arteries, which merge just proximal to the distal interphalangeal joint and form three arterial arcades that give rise to vertically running arteries between them and innumerable small vessels at the very tip (Figure 29.5). The distal arcade is protected by the interosseous ligament, a unique structure bridging the lateral condyles of the distal phalanx and the lateral extensions of the corona unguicularis. The venous and lymphatic reflux are less complex.

The matrix is the sole structure to form nail plate keratin. A fingernail grows roughly three times faster than a toenail, with the nail of the dominant middle finger growing fastest with about 3–4 mm per month (Figure 29.6). The big toenail takes approximately 18 months to fully grow out. However, after nail avulsion, the nail growth rate is slightly faster. It is also faster during the warm summer period and due to physical activity and certain drugs, such as azole antifungals and some retinoids; it grows slower during winter, in high altitude, in physically inactive subjects, and under cytotoxic chemotherapy.

It cannot be stressed enough that a normal matrix and firm nail attachment to the nail bed are prerequisites for a healthy nail. Any disturbance of this balance will result in a defective nail.

AESTHETIC NAIL SURGERY

Patient Selection

As mentioned earlier, only a limited proportion of unsightly nail conditions are amenable to surgical improvement. Thus, the patient has to be examined before surgery, including a whole body checkup for systemic and cutaneous diseases. The disturbing condition has to be discussed and realistic goals to be defined. It is essential to explain that the final result of most nail surgeries can only be evaluated after 1 year for finger and 2 years for toenails. Rough and brittle nails cannot be improved by surgery.

Patient Preparation

Optimal blood supply is a prerequisite for good wound healing; thus, the patient has to abstain from smoking for at least 2 weeks prior to surgery and during the entire healing

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

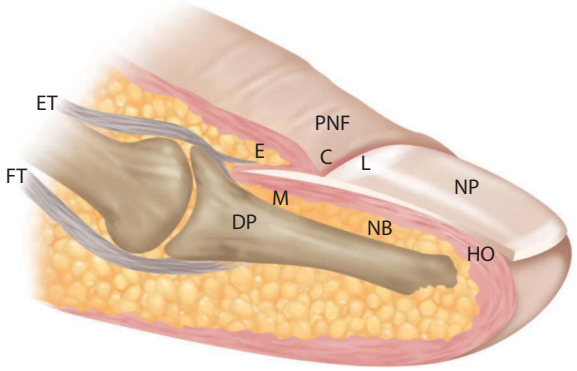


Figure 29.1 Schematic illustration of a sagittal section through the distal phalanx of a finger. C, cuticle; DP, distal phalangeal bone; E, eponychium; ET, extensor tendon; FT, flexor tendon; HO, hyponychium; L, lunula; M, matrix; NB, nail bed; NP, nail plate; PNF, proximal nail fold. (Copyright E. Haneke.)

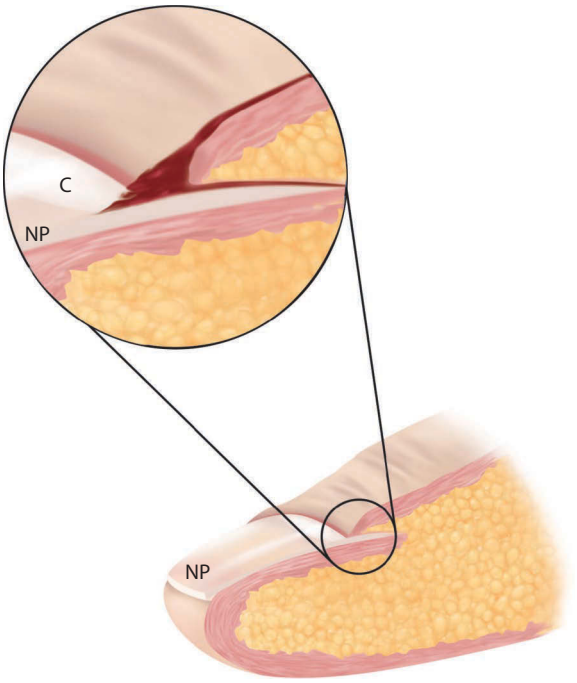


Figure 29.2 Formation of the cuticle. The growing nail pulls the attached horny layer of the ventral surface of the proximal nail fold distally and contributes approximately 75% of the cuticle. C, cuticle resulting from eponychium (ventral aspect of the proximal nail wall) and the stratum corneum of the dorsal aspect of the PNW; NP, nail plate.

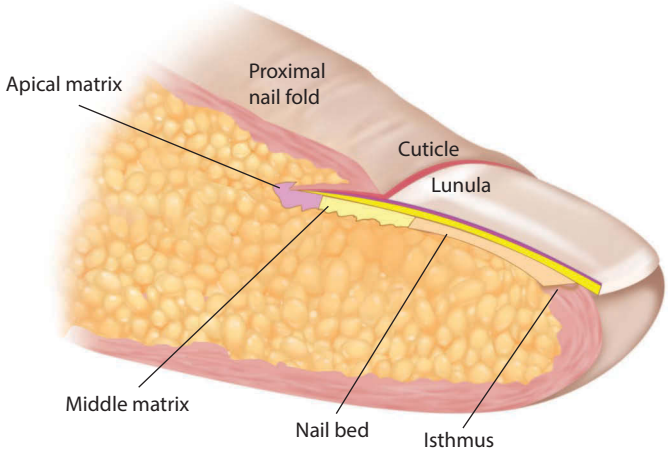


Figure 29.3 The matrix and the nail layers arising from it. The apical matrix produces the most superficial layer of the nail plate. Any change here will be visible as nail surface alteration; destruction will finally result in a pterygium.

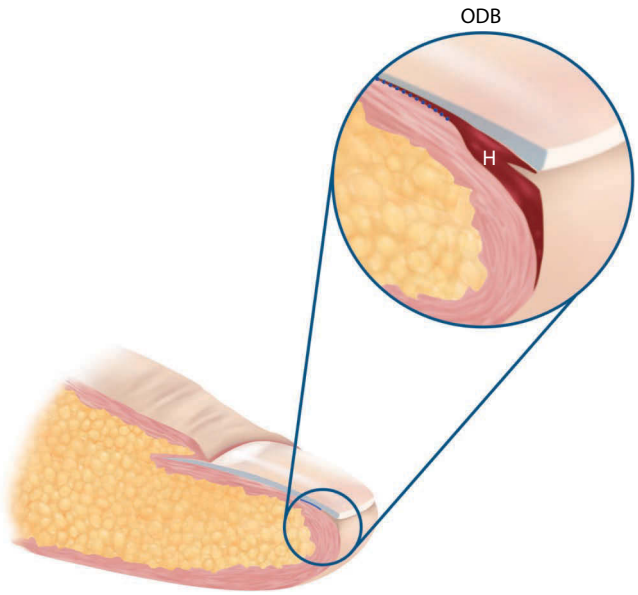


Figure 29.4 The hyponychium and nail isthmus. The hyponychium seals the virtual space under the most distal part of the nail plate. It is formed by the isthmus (blue) and the epidermis of the distal sulcus. ODB onychodermal band histologically referring to the isthmus.

period [5]. Patients claiming not to be able to stop smoking are no candidates for aesthetic nail surgery although any indicated surgery may be performed with the explicit explanation to the patient of the risk of delayed and/or suboptimal healing.

Asepsis is another prerequisite for optimal healing. The patient is told to brush the hand or foot the evening and the morning before operation with soap like a surgeon. Generous disinfection is carried out before and after injection of the local anesthesia. Cleaning the surgical field during surgery with 3% hydrogen peroxide both removes blood and acts as a powerful disinfectant.

Anesthesia of the Nail Unit

Complete anesthesia is a must for nail surgery. It has to be given early enough that the surgeon does not start when the patient still feels pain. However, some deep sensation remains so that the patient will realize that "something is done." The type of local anesthetic depends on personal preferences; however,

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

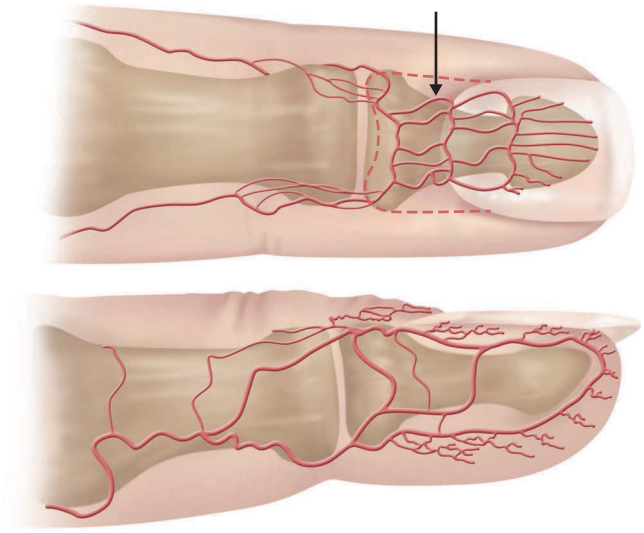


Figure 29.5 Arterial blood supply of the nail unit. Three arcades are supplying arterial blood. The ligamentum interosseum is marked by the arrow.

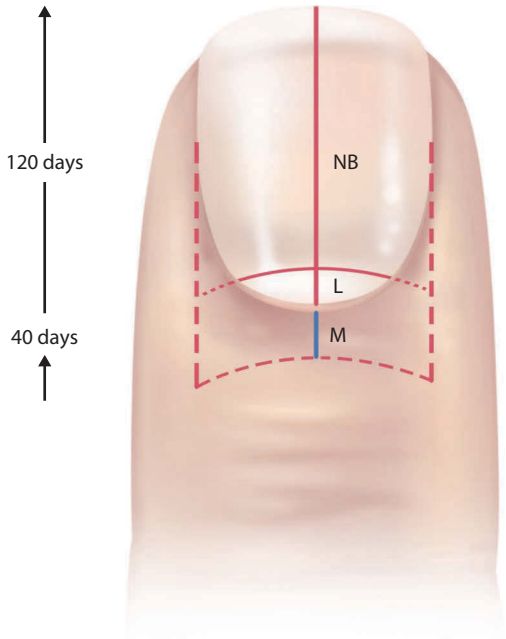


Figure 29.6 Schematic illustration of the nail growth. L, lunula; M, matrix; NB, nail bed.

we have used ropivacaine with great success since more than 15 years as it has a rapid onset and a duration of 8–12 hours. As the surgery is almost always performed with a tourniquet, no adrenaline is needed although it may be used in a fixed dilution of 1:200,000 in persons with normal peripheral blood circulation. Alternatives to ropivacaine are lidocaine, mepivacaine, prilocaine, articaine, or any other local anesthetic agent. The concentration is 1%–2%, with the higher concentration giving a long-lasting anesthesia. The same is true for the amount given. Block anesthesia techniques are most commonly used and take advantage of the particular innervation of the digits (Figure 29.7). Whereas we prefer the proximal digital block for the thumb, little finger, and toes and the transthecal block for the index, middle, and ring finger [6], other authors prefer a distal anesthesia (Figure 29.8) [7]. If neighboring digits have to be operated, a metacarpal or metatarsal block may be used to numb the opposing sides. Sterile prepping is performed.

Tourniquet

Aesthetic nail operations invariably require a bloodless field. This may be achieved for the finger with a sterile surgical glove. This is donned after anesthesia and final disinfection, and a tiny hole is cut in the tip of the respective finger, which is then pulled over the digit tip and rolled down to the base giving a perfect exsanguination. In general, a finger tourniquet should be released after 20 minutes, which is easily done by rolling the finger back to the tip of the digit. An alternative to the glove tourniquet is a Penrose drain or another sort of elastic band.

When releasing the tourniquet, bleeding is the rule. After toenail surgery, it may be advisable to keep the patient stretched out for at least half an hour to allow for spontaneous reduction of bleeding.

Postoperative Care

At the end of the surgery, a thick padded dressing is recommended that both takes up blood and absorbs shock. The operated extremity should be kept up for 24–48 hours. For toenail surgery, the patient should be instructed to bring a large open shoe and take care of the transport home. Postoperatively, analgesics are given. Paracetamol is usually sufficient, but some operations require stronger pain killers.

Surgical Procedures

Racket Nail

A classical aesthetic nail operation is narrowing the racket nail. It is characterized by a disproportionally short and wide nail, which is usually very flat but may become overcurved with age and cause discomfort and even severe pain. A lateral longitudinal nail biopsy is performed on both sides of the nail (Figure 29.9). The proximal portion of this excision is slightly slanted laterally in order to get the entire lateral matrix horn included into the surgical specimen. The proximal nail is sutured without taking the matrix. The lateral nail folds that are characteristically flat in most cases of racket thumbs are recreated by backstitches that elevate the tissue [8]. A simple stitch is performed at the hyponychium region.

This surgical intervention is rather painful after the local anesthesia has waned off and adequate postoperative pain management has to be performed.

Double Nail

The double nail of the little toe could be dismissed as a negligible minute anomaly if it were not for the pain that the condition often causes after the age of 40 years [9]. The lesion is usually overlooked as it only occurs as an abnormally wide fifth toenail or is mistaken as a corn. However, close inspection reveals that there is either a notch between the medial wider portion and the narrower lateral one or that a second nail emerges from under the common nail fold. The extra nails may catch and ladder the tights, which is felt very annoying; in fact, there is whole

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

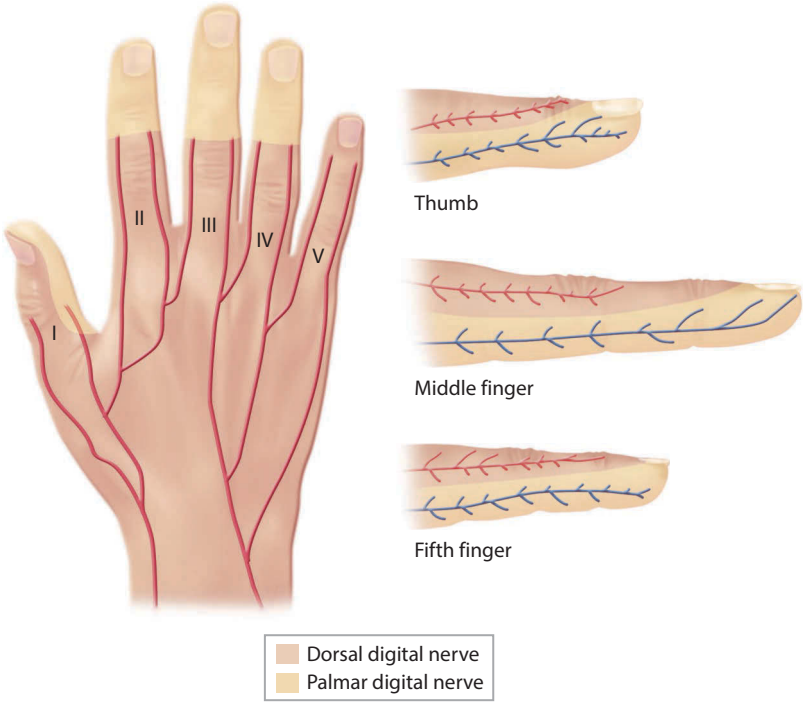


Figure 29.7 Innervation of the nails. The nails of digits 2–4 are innervated by the volar nerves, which is the anatomical basis for the transthecal block (see Figure 29.8c).

website conversation lasting over more than 4 years concerning the "split pinky toenail." When the patient has a spread foot, there is inward rotation of the big and outward rotation of the little toe. This causes the little nail to stand almost vertical and act like a painful corn. Sometimes, female patients complain of the unsightly aspect. The lesion is genetically determined with variable expression and penetrance [10,11]. Radiographs may show a tiny spiky exostosis corresponding to the double nail; hence, the condition is probably not simply a split nail but a subclinical hexadactyly.

Treatment is by selective matricectomy of the accessory nail. This can be done by segmental excision (Figure 29.10) or selective matrix removal by chemical or radio-frequency cautery or laser ablation [11].

Vertically Implanted Nail

Occasionally, a little toenail almost vertically growing out is seen. It is unsightly and disturbing as it catches socks and tights. As this nail is normally virtually unseen, it can be removed by total nail ablation [12,13]. Complete chemical matricectomy is an alternative. A wedge excision as performed for the treatment of a distal nail fold is usually not effective as the bone is pointing upwards (Figure 29.11).

Trapezoid Nail

Trapezoid nails are very wide distally, but their proximal lateral portions are hidden by lateral nail folds that stretch from a narrow proximal nail fold over the nail to the free margin (Figure 29.12). They often tend to grow in distally–laterally and are unsightly because of their width and shortness. This is easily treated by a beveled excision of the proximal–lateral portions of the nail folds [13].

Congenital Malalignment of the Big Toenail

This condition is not known by most pediatricians and many dermatologists, although it is far from being exceptionally rare. The children are either born with a lateral deviation of the long axis of the big toenail or this develops within the first 2 years of life. The nails are thick, discolored, triangular, and sharply bent on their medial side, the surface is oyster shell–like, and there is a high degree of onycholysis. The nails appear as if they do not grow and most mothers complain that they do not have to cut the nails. However, when doing so, the nails break in arciform lamellae. The condition is not painful and that is why medical help is often only sought when the child, mostly girls, complains because of the unsightly aspect of these nails. Unfortunately, this is often too late for a successful treatment. Physical examination usually shows a lateral deviation of the hallux nails and in addition a lateral deviation of the entire distal phalanx. Radiographs show that there is a tendency to hallux valgus with an internal deviation of the first metatarsal bone and a lateral deviation of the proximal and distal hallux phalanges. The proximal bone core of these two phalanges does not have a symmetrical lenticular shape but is cuneiform with its wide base medially. Further, the distal extremity of the terminal phalanx often shows upward reflecting the false distal nail fold, which is due to the lack of an attached nail plate. When this is diagnosed early, it can be corrected conservatively by taping the entire great toe. This also improves the condition of the toenail. However, when this is not diagnosed, the malformation of the first ray of the foot will be fixed by growth and ossification and tendon pull will exaggerate the condition.

Surgery is most efficient when done before the age of 2 years. The most important prognostic factor is the degree of onycholysis as this is decisive for the fate of the nail bed and

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

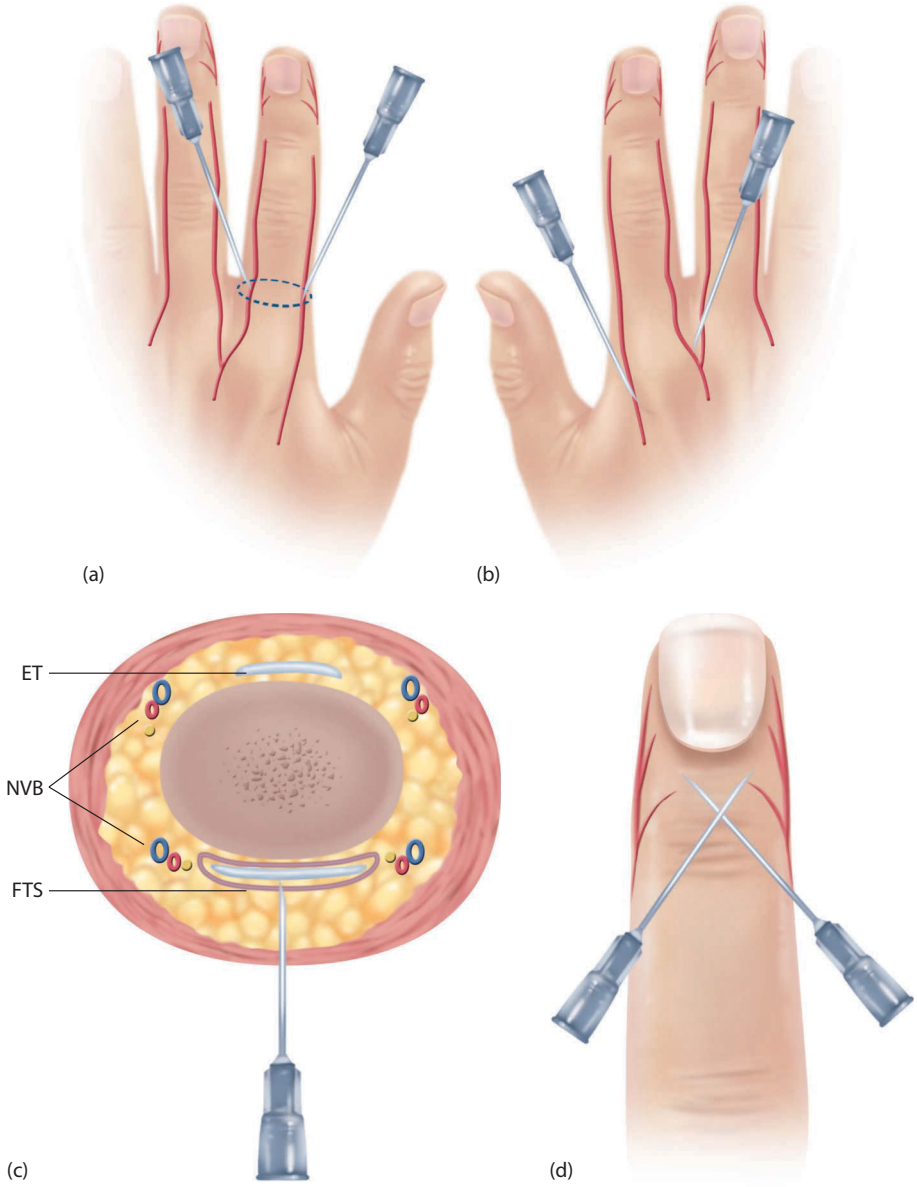


Figure 29.8 Anesthesia for nail surgery. (a) Proximal distal block. (b) Metacarpal block. (c) Transthecal block for anesthesia of the nails of digits 2–4. The anesthetic diffuses from the tendon sheath to the neurovascular bundle. (d) Distal anesthesia, also called "wing block."

the future adherence of the nail after surgery to correct the axis of the nail. When the nail is shortened during the operation, a deep impression of the overcurved medial nail margin into the mediodorsal aspect of the toe is commonly seen. The nail bed is markedly shrunk to the degree of a so-called disappearing nail bed. This toe tip lacks the counterpressure of the nail plate when the child walks and runs so that its soft tissue is gradually dislocated dorsally creating a false distal nail fold. The nail bed is seen as a tiny deeply depressed field just in front of the matrix. As the bone is still malleable at this age, the soft tissue anchoring to the distal dorsal tuft pulls the tip of the bone up, which is easily seen on lateral view radiographs.

Surgery is aimed at correcting the malpositioned long axis of the nail plate and reattaching the nail to the nail bed as only an intact matrix plus a fully functioning nail bed can guarantee a normal nail. An incision is carried around the distal phalanx approximately 6–8 mm below the level of the nail bed and a second incision starting and ending at the same point performed to yield a crescentic wedge of soft tissue, which is larger medially than laterally. The entire nail apparatus is gently dissected from the bony phalanx taking care not to penetrate the nail bed. This is most difficult at the level of the lateral matrix horns that have to be completely freed from the condyles of the base of the distal phalanx. Only then can the nail apparatus be rotated into its correct axis (Figure 29.13). When the bone shows a dorsal extension, this has to be flattened allowing the nail unit to be resutured to the tip of the toe in its orthograde direction. The stitches are left in place for 15–20 days. Although this is big surgery for the toe, the little children rarely complain of excessive postoperative pain.

In our experience, the success depends on the ability of the nail bed epithelium to recover and reattach the nail plate. In order to support this, fixation of the nail to the nail bed with circular tape

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

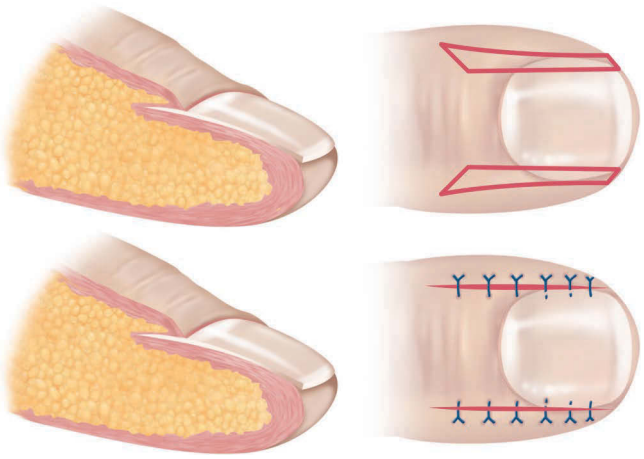


Figure 29.9 Schematic illustration of narrowing a disproportionately wide racket nail. Two lateral longitudinal excisions narrow the nail.

and forceful taping with longitudinal taping from the distal nail bed over the pulp to the proximal phalanx and midfoot's medial margin is necessary. Nevertheless, the nail does not recover in all cases. In recent years, we have therefore combined surgery with prior correction of the toe position by taping of the entire toe to the midmetatarsal bone as shown in Figure 29.14. To our surprise, this improved the nail's appearance in many cases.

If the malalignment of the big toenail is not corrected, an onychogryphosis-like condition will develop in early life. This can no longer be successfully treated except with definite nail eradication.

Split Nail Deformity

A split in the nail is embarrassing both functionally and aesthetically. In most cases, it is due to a trauma that caused a cicatricial pterygium or to lichen planus. The reason is a wound through the undersurface of the proximal nail fold and the matrix–nail bed so that these structures heal together obstructing the nail pocket. No nail can be formed in this area.

Two different techniques are recommended: either scar excision and direct suture (Figure 29.15) for narrow splits or scar excision and matrix graft for wide splits [14].

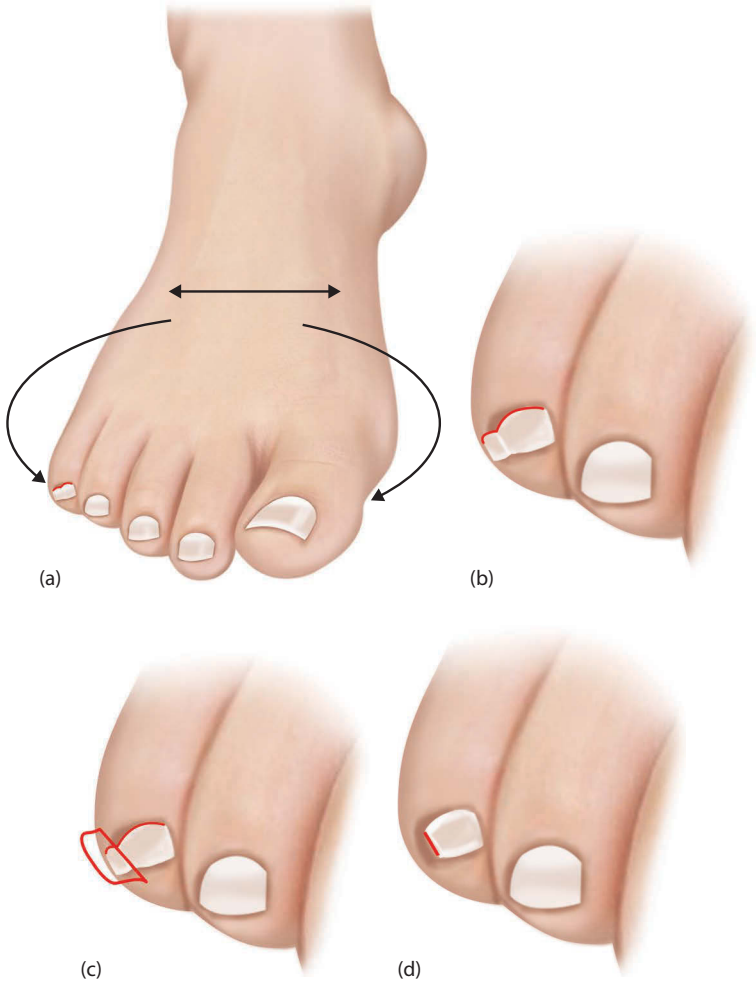


Figure 29.10 Surgery of a double little toenail ("split pinky toenail"). (a) With outward rotation of the little toe, the nail stands more and more vertically giving rise to pain similar to a corn. (b) Close-up shows the divided nail with an extra arch of the cuticle. (c) Excision of the accessory nail marked. (d) After surgery. (Copyright E. Haneke.)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

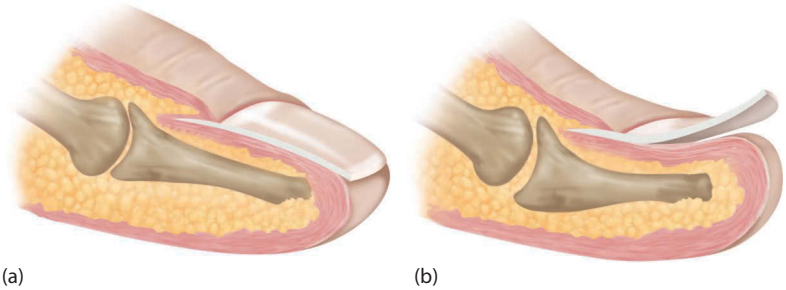


Figure 29.11 Schematic demonstration of a vertically implanted toenail. (a) Normal nail. (b) The "vertically implanted" nail points upward due to an upward direction of the distal phalanx.

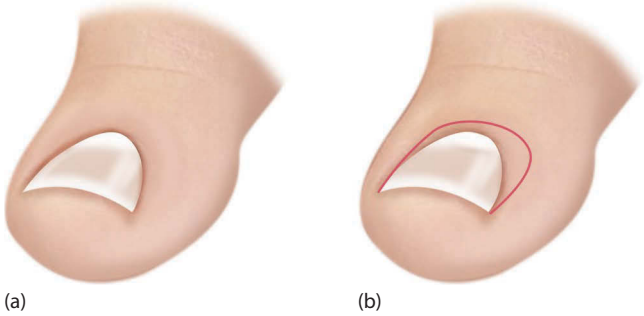


Figure 29.12 Trapezoid nail surgery. (a) Trapezoid nail. (b) Excision line drawn. (Copyright E. Haneke.)

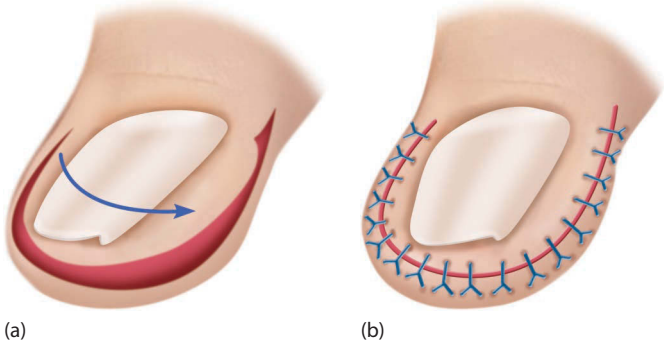


Figure 29.13 Congenital malalignment of the big toenail. (a) Delineation of incisions. (b) End of surgery.

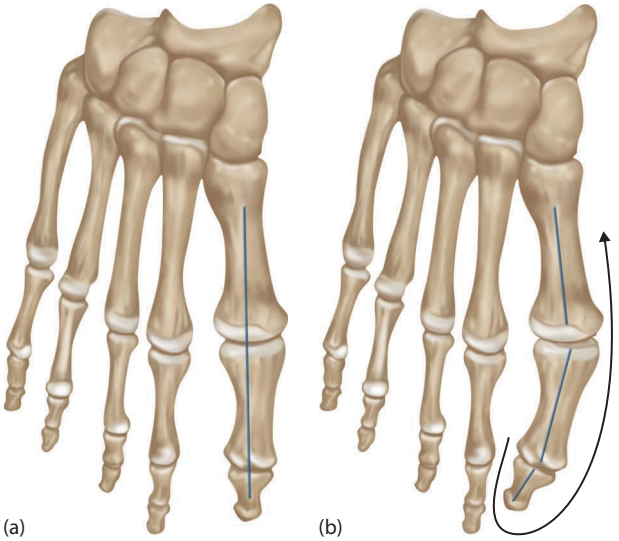


Figure 29.14 Forefoot bone alterations consistently seen in congenital malalignment of the big toenail and their correction with taping. Blue lines: Axis of the metatarsal, proximal, and distal phalanges of the first ray of the foot. (a) Normal. (b) As seen in congenital malalignment.

The nail is gently detached from the overlying proximal nail fold on both sides of the split in order to identify the pterygium or scar area. This is excised down to the bone as a longitudinal biopsy tapering distally. Both side of the matrix and nail bed wound are generously undermined with curved pointed scissors or a scalpel. The two margins of the defective nail plate are cut lengthwise in order to widen the nail defect. The wound margins are meticulously sutured edge to edge with 6-0 absorbable stitches; double or triple stitches are preferred as they can take more tension while being knotted (see Chapter 28). Then the widened split of the nail plate is sutured with 4-0 stitches, thus supporting the sutures of the matrix and nail bed. These stitches are removed after 2–3 weeks. Healing is uneventful. However, the method has the disadvantage that there is again a longitudinal scar in the matrix though much narrower that causes a slight thinning of the plate. Further, either intact nail plate or a thin silicone sheet has to be inserted into the depth of the nail pocket in order to prevent readherence of its roof and bottom.

In case the split is so wide that the wound margins after scar excision cannot be coapted properly, a matrix graft is indicated. The pterygium is cut horizontally and excess scar tissue removed. When the scar is on one side of the matrix, a thin slice of matrix epithelium with approximately 0.7 mm of matrix dermis is taken and placed on the excised scar site, paying attention to the correct direction of the graft, and sutured with 6-0 or 7-0 absorbable material. When the remaining intact

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

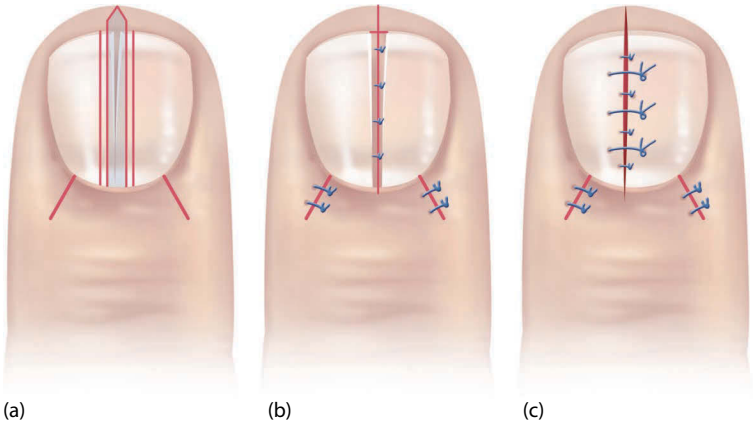


Figure 29.15 Scar excision and suture to correct a split nail. (a) The split of the nail is widened and the longitudinal scar is cut out. (b) The matrix–nail bed defect is sutured with 6-0 stitches. (c) The nail plate is finally stitched with a 4-0 suture material.

matrix is not large enough for a graft, this may be taken from the great toenail matrix. The nail is gently avulsed, and an area of matrix corresponding to size of the scarry defect is superficially incised, then horizontally excised, and transferred to the defect where it is sutured in. The big toenail may be taken as a splint for the matrix graft after being trimmed to the size of the recipient nail. It is also fixed to the recipient digit with some stitches. These are removed after 3 weeks. Both the donor and the recipient nail usually heal primarily without a nail dystrophy although a slight irregularity of the surface may occur.

Ingrown Nails

Both toenails and rarely fingernails may grow in, usually laterally. Ingrown big toenails are a common ailment of school children, adolescents, and young adults. Almost all patients have a pronounced curvature of their big toenail, and many youngsters tend to have hyperhidrosis pedum. More than a hundred different surgical methods have been described for their cure, giving evidence that the one approach fitting all cases does not yet exist [15].

Mild and moderate cases may be treated conservatively with packing of cotton under the ingrowing edge of the nail (Figure 29.16a), pulling the lateral nail fold away from the ingrowing nail edge by taping (Figure 29.16b), applying an artificial nail to thicken the lateral nail edge, or using a shape memory alloy clip, superelastic wire, or orthonyxie to unbend the nail. Gutter treatment is a semiconservative method as it requires local anesthesia and some surgical skills to move the gutter over the lateral nail edge deep into the nail pocket (Figure 29.16c). When these surgical methods fail, surgery is indicated.

Depending on whether the nail or the nail fold is thought to be at fault, different approaches are used; each of which has its advantages and disadvantages.

When a hypertrophic nail fold is held to be responsible for the onychocryptosis, it is removed leaving the matrix

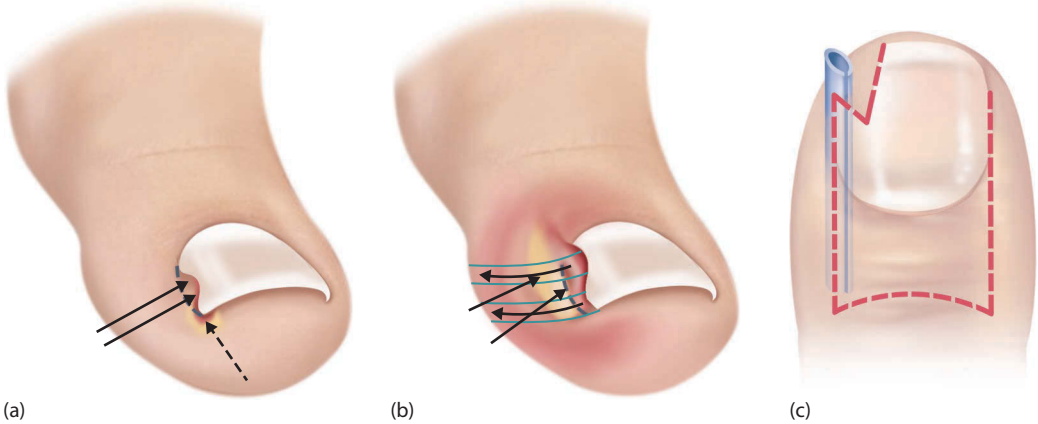


Figure 29.16 Ingrown nail treatments. (a) Packing with a wisp of cotton. The cotton is pushed under the lateral–distal edge of the nail plate to prevent the nail corner from digging into the skin. (b) Taping to pull the lateral nail fold away from the offending nail. Tape is applied to pull the swollen lateral nail fold away from the offending nail margin. (c) Gutter treatment to protect the lateral nail sulcus from the offending lateral nail edge.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

completely untouched. The lateral nail fold removal may be limited to just the area inflamed or may reach from deep into the proximal nail fold to the tip of the toe including one third of the hyponychium. This Vandenbos operation (Figure 29.17) takes several weeks to heal but is said to have no recurrences and the nail itself is not narrowed. A technique called super-U removes both the lateral nail folds and the entire hyponychial area, treating at the same time a distal nail fold (Figure 29.18). These techniques are associated with severe and long-time morbidity but have a high cure rate and good cosmetic result.

When there was a long-standing ingrown nail, the lateral nail fold may be hypertrophic and sclerotic. A fusiform excision from the lateral aspect of the toe may reduce this unsightly condition (Figure 29.19).

When the nail is believed to be at fault, it is narrowed [16]. Many techniques have been described and some of those that are pathogenetically wrong are still widely performed. Wedge excisions that may in principle cure the ingrown nail are rarely executed correctly and have recurrence rates of 20% to over 60% (Figure 29.20a). In addition, the toe is mutilated and the big toenail often does never grow normally again. This is a severe aesthetic handicap, particularly for young ladies. Therefore, wedge excisions have to be considered obsolete. The method of choice is the selective lateral matrix horn resection [17]. This can be done by surgical dissection (Figure 29.20b), laser vaporization, radio-frequency ablation, or chemocautery with liquefied phenol (Figure 29.20c) or 10% sodium hydroxide solution. Whichever technique is used does not matter as long as no viable epithelium is left in the lateral matrix horn. We prefer liquefied (88%) phenol for three reasons: Phenol is a very effective protein coagulant securely necrotizing the matrix epithelium; it is an excellent disinfectant thus obviating the need for antibiotic treatment; and it has a local anesthetic effect highly welcomed by the patients. The lateral ingrown strip of nail plate is cut longitudinally and avulsed. A tourniquet is applied and a tiny cotton wool applicator soaked with liquefied phenol is vigorously rubbed in the bloodless matrix three times for 1 minute each. The tourniquet is opened and a thick dressing with tulle gras and plenty of an antibiotic ointment is applied for 24–48 hours. The patient is asked to keep the foot elevated during this time. The dressing is removed after 1 or 2 days with a foot bath to remove any blood remnants, an ointment is applied, and the dressing is covered with an adhesive tape. This is changed twice a day with rinsing the little wound under a jet of tap water to prevent scab formation and retention of secretion from the chemical wound. Healing is complete within 2–3 weeks, but physical activity can be resumed after 2 days. The nail is slightly narrowed, which is barely visible as the ingrown nail is always strongly curved, and it is the vertically positioned lateral nail portion, which is not seen anyhow, that is lacking. There is no soft tissue wound or defect, no toe mutilation, and no nail deviation as seen after wedge excisions.

Figure 29.17 Vandenbos technique of generous excision of the lateral nail folds without touching the nail matrix. The excision comprises the entire lateral nail folds together with a portion of the proximal nail folds and one quarter to one third of the hyponychium on each side.

Figure 29.18 The super-U technique of treating hypertrophic nail folds. The super-U technique removes the lateral nail folds plus the entire hyponychium region.

Overcurvature of the Toenails

Overcurvature of the nails, also called pincer nails, omega nails, tubed nails, trumpet nails, ungues constringentes, etc., is a frequent ailment. Different types have to be distinguished: genetic, due to foot malformation, due to dermatoses, and fingernail overcurvature mainly due to distal interphalangeal degenerative osteoarthritis with Heberden nodes. The genetic type is by far the most common and almost always symmetrical on both big toenails associated with a lateral deviation of the distal phalanx and the nail plate. When lesser toenails are affected, their involvement is also symmetrical and they show a medial deviation. Radiographs invariably show that there is an asymmetrical distal phalanx with a higher medial than lateral condyles, which in addition often shows a hooklike exostosis pointing distally; it is probably the proximal insertion of the interosseous ligament. The diaphysis of the distal phalanx sits lateral from the median line of the epiphysis. The nail itself is wide proximally and rolls inward from the matrix toward the nail bed, giving rise to a distally increasing overcurvature, which may reach 360° or even more. Particularly, when the curvature is not too extreme, the lateral nail margins may press into the nail sulci and cause pain. The nail bed is pinched at the nail's free margin. Surgery is aimed at relieving the pain and improving the cosmetic aspect. In mild cases, narrowing the nail by bilateral selective matrix horn removal is often effective.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

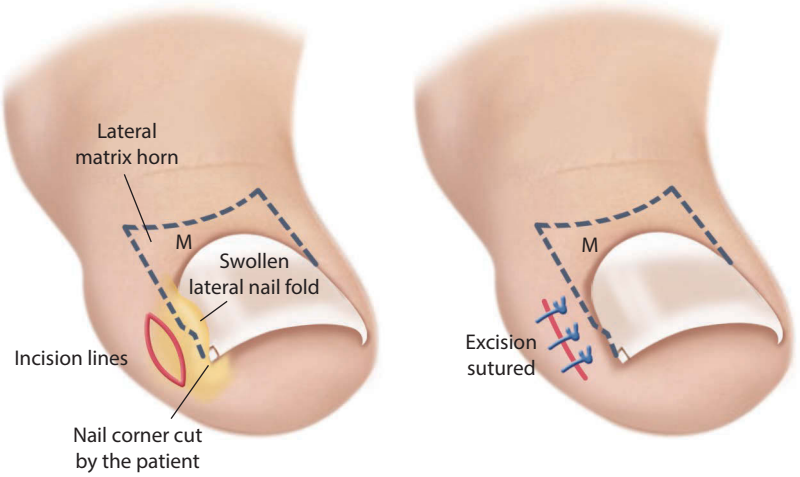


Figure 29.19 Fusiform excision from the lateral aspect of the toe to treat a sclerotic hypertrophic lateral nail fold.

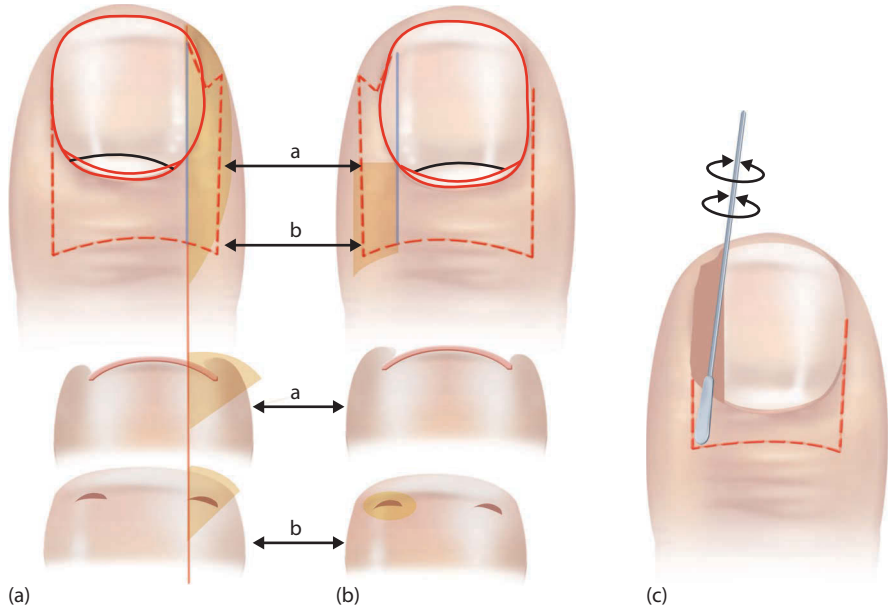


Figure 29.20 Treatment of ingrown nails with matrix excision. (a) Wedge excision as it is most commonly performed: it leaves the tip of the matrix horn *in situ* giving rise to a nail spicule or recurrence. This technique is obsolete because of its very high recurrence rate and very frequent mutilation of the toe. (b) Selective segmental matrix horn excision leaving the lateral nail fold and the toe shape completely intact. (c) Matrix horn phenolization cauterizing the matrix epithelium.

In pronounced cases, this has to be completed with a nail bed plasty aimed at flattening the pinched bed. After partial or total nail avulsion, a longitudinal median incision is carried out from the distal matrix to the hyponychium. Shortly before the end of the hyponychium, a small hump is felt with the scalpel blade representing a traction osteophyte of the distal dorsal tuft. It is generously removed. The entire nail bed is dissected from the underlying bone until it is completely freed and can then be extended and flattened. The median incision is sutured with 6-0 absorbable stitches and reversed tie-over sutures are used to keep the lateral nail folds apart (Figure 29.21). They are removed after 2.5–3 weeks. A slightly narrower but considerably less curved nail regrows.

Retronychia

This recently described condition is a painful retrograde ingrowing of the nail, mostly the big toenail but sometimes also other toe- and fingernails [18]. Clinically, the proximal nail fold is swollen and red. With light pressure on the nail, granulation tissue comes out from under the nail fold. The nail is markedly onycholytic allowing it to be moved backward with walking and other sport activities. This leads to incomplete horizontal

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

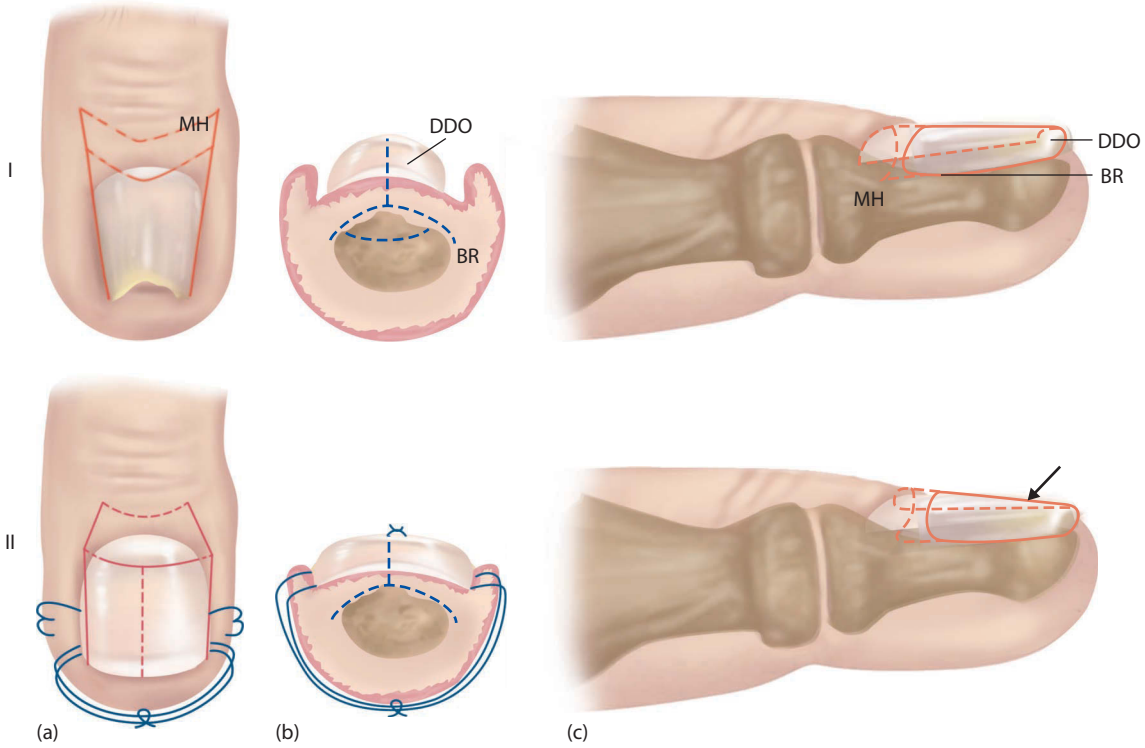


Figure 29.21 Overcurvature of the big toenail and its treatment. BR, level of bone resection; DDO, distal dorsal traction osteophyte; MH, matrix horn. The matrix horns are resected to narrow the nail, the nail bed is incised longitudinally, and the nail bed is dissected from the underlying bone allowing it to be spread. It is kept in place by reverse tie-over sutures. (a) Dorsal view. (b) Transverse section. (c) Longitudinal section. Upper row: before surgery. Lower row: after surgery.

rupture at the level of the basal compartment and keratogenous zone of the matrix. A new nail is beginning to be formed under the old one, giving rise to several layers of nail in the proximal plate. The uppermost layer has a very hard and sharp proximal margin, which virtually cuts into the ventral surface of the proximal nail fold (Figure 29.22). Careful proximal nail avulsion is usually curative [19].

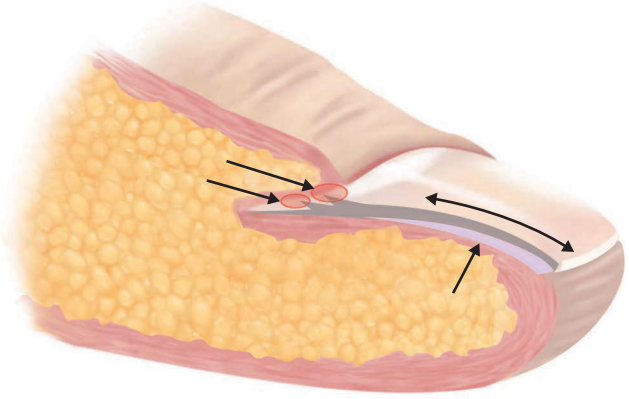


Figure 29.22 Schematic illustration of the pathogenesis of retronychia.

A chronic latent form of retronychia was called the horseshoe crab nail [20]. The nail is usually markedly overcurved and highly onycholytic. There are many transverse nail ridges running parallel to the lunula border, giving it the appearance of the back of a horseshoe crab (Figure 29.23). This condition is due to repeated retrograde pressure and was also termed "compression nail."

Common Warts

Viral warts of the nail unit are mainly in periungual, rarely in subungual location. The latter may cause pain like a corn. All are unsightly and the patients seek rapid and effective treatment.

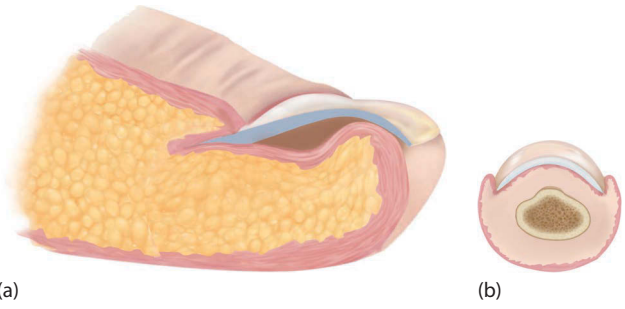


Figure 29.23 Horseshoe crab nail deformity. (a) Sagittal section, (b) transverse section through the nail.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

However, although being banal viral warts are notoriously resistant to most treatments, surgery is occasionally demanded. We strongly discourage invasive surgery for ungual warts as this usually leaves scars that may also be unsightly. When the common wart remedies do not work, aggressive keratolysis with high-percentage salicylic acid or 40% urea paste is used to remove the hyperkeratosis and then 5% imiquimod is applied daily under occlusion. This off-label use may lead to intense inflammation, which is almost invariably a sign that the treatment works.

Laser treatment is another option [21]. The carbon dioxide laser was used to ablate warts. This has to be done with care in order to prevent scarring. Gently heating the wart with neodymium:YAG [22] and drying up the wart with a pulsed dye laser [23] are other possibilities. As wart virus DNA can be found up to 15 mm around warts, recurrence is possible and close follow-up recommended.

Ungual Fibrokeratoma

Ungual fibrokeratomas are garlic clove or sausage-like tumors of the nail folds, matrix, or nail bed. Depending on the exact localization within the nail apparatus, different nail changes are seen. When they erupt from the apical matrix region, they lie on the nail causing a longitudinal depression in the plate. Origin in the middle of the matrix gives rise to an intraungual lesion, from the nail bed to a subungual fibrokeratoma. Multiple fibrokeratomas, also called Koenen tumors, are a sign of tuberous sclerosis. Treatment of solitary fibrokeratomas is usually not challenging. In prolongation of the sausage-like tumor, an incision is made around the base down to the bone (Figure 29.24) and the lesion dissected with pointed sharp iris scissors. The defect is left for second intention healing. In most cases, a normally looking nail regrows. In case of multiple Koenen tumors, they are excised at a level slightly below the surrounding epithelium. However, these patients often come very late and a cosmetically satisfactory result can no longer be achieved.

Myxoid Pseudocyst

This frequent lesion of the middle aged and elderly is known under several other names: dorsal finger cyst, distal dorsal interphalangeal ganglion, mucus cyst, etc. In type A, a dome-shaped, skin-colored to grayish-glassy lesion is seen on the proximal nail fold with a longitudinal depression in the nail plate that reflects the pressure on the matrix by the lesion (Figure 29.25a). In type B, the proximal nail fold appears swollen and its free margin is rounded; the nail plate shows irregular depressions in longitudinal arrangement due to repeated rupture of the lesion with release of the content into the nail pocket, which leads to temporary reduction of the pressure on the matrix with flattening of the nail depression. Type C is the less frequent subungual pseudocyst. Histologic and electron microscopic investigations have shown that it is not a true cyst and does not have a synovial lining; instead, it starts with a myxoid degeneration of the connective tissue of the proximal nail fold similar to a nodular mucinosis. With time and more mucin production, a lake of mucin develops that finally pushes the margin together mimicking a fibrous cyst wall. In the fingers, the lesion is very often associated with degenerative distal interphalangeal arthritis and Heberden nodes. Often, a secondary connection with the underlying joint develops, which can be visualized using intra-articular injection of a mixture of hydrogen peroxide and sterile methylene blue through the volar crease of the joint. Many treatments have been recommended, most of them with a high recurrence rate. Repeated needling and expression, injection of a sclerosant or corticosteroid, cryotherapy, heat destruction with infrared coagulation or lasers, and various cold steel extirpation techniques, from simple excision to complete dissection and flap repair, have been described. Hand surgeons sometimes only remove the bony excrescences of the Heberden nodes.

Our approach is the complete removal of the degenerated tissue. Depending on the quality of the overlying skin, either a broad-based U-shaped flap is raised over the lesion (Figure 29.25b) or, when the skin is too thin, an incision is carried around the pseudocyst and the lesion is completely dissected from the underlying dorsal aponeurosis. Intra-articular methylene blue injection often, but not always, stains the myxoid tissue light blue and marks a potential connection with the joint as a deep blue dot; sometimes more than one connection is seen [24]. These are ligated using 6-0 absorbable stitches such as 6-0 polyglactane. The U-shaped flap is reclined or a transposition flap is created from the neighboring skin to cover the primary defect (Figure 29.25c). The secondary defect is reduced in size by double stitches (see Chapter 28). A thick padded dressing with tulle gras and plenty of ointment is applied and changed the next day. The skin stitches are removed after 10–12 days. No splint is necessary. Healing of the secondary defect is rapid and usually complete after 2–3 weeks. The scars on the proximal nail fold are barely visible after 6 months. In contrast to the bone resection technique, this operation has virtually no risk of permanent joint stiffness.

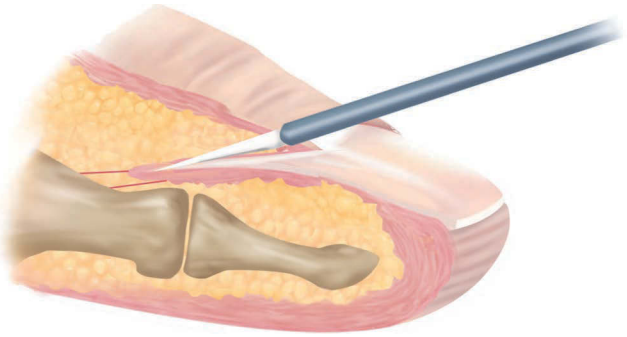


Figure 29.24 Excision of an ungual fibrokeratoma. This epiungual fibrokeratoma causes a longitudinal depression in the nail plate. A fine pointed scalpel blade is led around the fibrokeratoma down to the bone allowing the base to be dissected from the bone with fine pointed scissors.

Longitudinal Melanonychia

A brown streak in the nail may be the sign of a nail melanoma, particularly when it is acquired in patients aged 30 years and above. Most nail melanomas occur between the age of 40 and 60 years, but they were also seen in young children and in old persons aged 90 years and above. Large cohorts of more than 100 nail melanoma patients have shown mean Breslow thickness of more than 4 mm with an associated very poor prognosis. This is due to late diagnosis because of both patients' and physicians' neglect and fear of taking a biopsy because this may cause some discomfort and postbiopsy nail dystrophy. However, some patients are considerably embarrassed by such a colored band in the nail and come for its removal.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

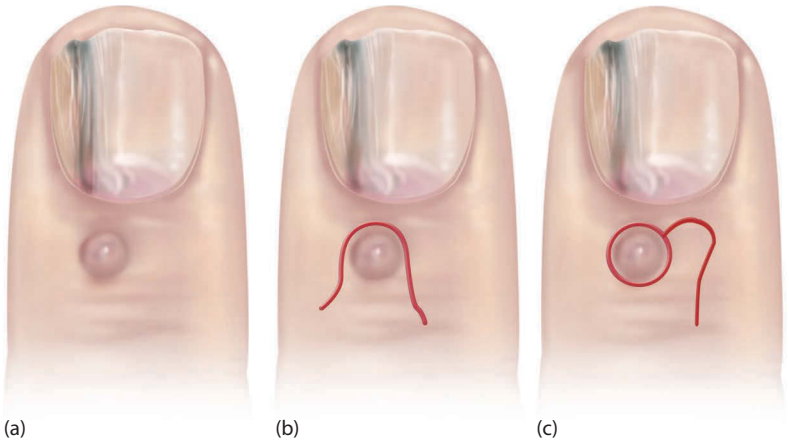


Figure 29.25 Myxoid pseudocyst. (a) Type A myxoid pseudocyst with longitudinal depression in the nail. (b) Removal of a myxoid pseudocyst with normal overlying skin. A U-shaped flap is raised over the lesion allowing it to be dissected and resected. (c) Removal of a myxoid pseudocyst with a very thin overlying skin. As the overlying skin cannot be saved, a U-shaped transposition flap is raised to cover the primary defect; the donor defect is left for second intention healing. (Copyright E. Haneke.)

We have developed a technique that allows the histopathological diagnosis to be made without postoperative nail dystrophy and that is also curative in the majority of benign longitudinal melanonychias (Figure 29.26). The proximal nail fold is detached from the underlying nail plate and retracted. When the band reaches under the nail fold, the proximal nail fold is incised on both sides and reflected in order to visualize the origin of the brown band. The nail plate is detached from the matrix on one side and cut transversely at approximately the border between the proximal and middle third and opened in a trapdoor manner. This exhibits the melanocyte focus in the matrix, which is usually oval in longitudinal direction and larger than the brown streak in the nail plate. Using a #15 scalpel blade, a shallow incision with a safety margin of 2–3 mm is performed around the lesion, which is then tangentially removed with sawing back-and-forth movements. The specimen should be around 0.7–0.8 mm thick; this is achieved when one can still see the scalpel blade through the specimen. This is stretched out on filter paper, fixed in 4% formalin, and submitted to the histopathology laboratory with a drawing from where the specimen was taken and how it has to be cut. Hematoxylin and eosin as well as immunohistochemistry stains can be performed to reach the correct diagnosis. The nail plate is laid back and fixed with a stitch as is then the proximal nail fold. In more than 60 own cases, there was only one discrete nail dystrophy. In case of *in situ* or early invasive melanoma, a complete extirpation of the nail unit with a 6 mm safety margin is performed sparing the bone and finger pulp, thus keeping a fully functioning digit though without a nail.

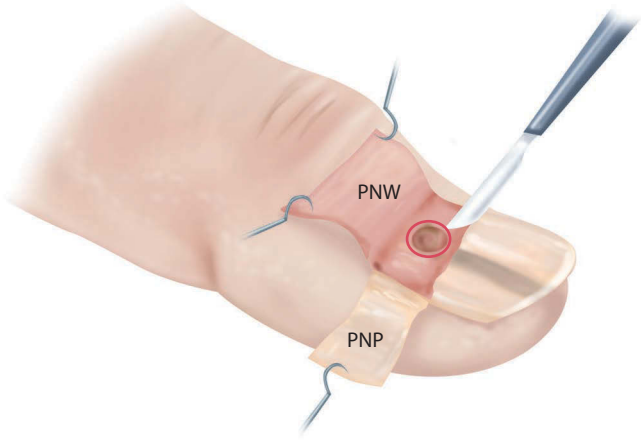


Figure 29.26 Horizontal (tangential) excision of a matrix melanocyte lesion for the diagnosis of a longitudinal melanonychia. PNW, proximal nail wall; PNP, proximal nail plate portion.

Onychopapilloma

This nail-specific lesion was only recently identified as an entity. It originates from the distal lunula where it is seen as a narrow pink wedge, which continues in the nail bed with a yellowish to light-brown or red streak of 2 to maximally 6 mm in width and is seen under the free nail margin as a keratotic rim. There is often a V-shaped distal onycholysis and the nail margin tends to split. This can be fortified using an artificial nail. However, when there is bacterial or fungal infection, this will be aggravated by artificial nails and surgery is recommended. The nail is gently separated from the nail bed on the affected side, and the lesion is tangentially removed from the lunula till the hyponychium. The nail plate is laid back and fixed with two or three stitches that can be removed after 2–3 weeks. Healing is uneventful without any nail dystrophy.

Laterally Localized Tumors

Tumors of the lateral nail fold and bed can be excised using the technique of the lateral longitudinal nail biopsy. Up to 20% of the nail bed can thus be removed and sutured directly. A wider defect or one including the lateral nail fold requires a flap repair. Our best experience is with a flap created by performing a relaxing incision over the finger pulp. This leaves a bridge of tissue both proximally and distally. The skin from the lateral aspect of the distal phalanx is dissected down to

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

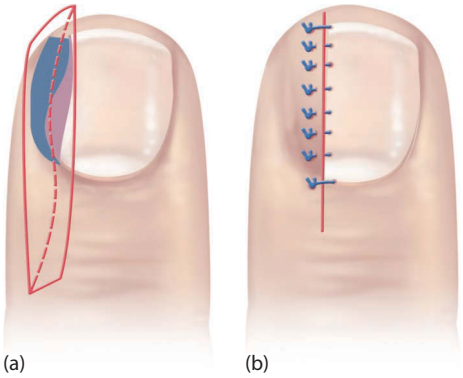


Figure 29.27 Backstitches to elevate the lateral aspect of the distal phalanx to recreate a lateral nail fold. This illustration shows the lateral nail fold and nail bed excision for Bowen's disease with closure by a bridge flap raised from the lateral aspect of the distal phalanx. (Copyright E. Haneke.)

the ligamentum interosseum allowing it to be raised up into the defect. Backstitches elevating the lateral wound margin recreate the lateral nail fold (Figure 29.27). The stitches can be removed after approximately 12–14 days. Up to one-half of the nail or finger tip circumference, respectively, can thus be repaired with excellent functional and very good aesthetic results [25].

Benign Tumors of the Proximal Nail Fold

The proximal nail fold is important for the cosmetic appearance of the finger tip. Any irregularity is immediately seen and embarrassing. Tumor removal must therefore respect the integrity of its margin.

For small- to medium-sized tumors of the free margin of the nail fold, a wedge-shaped excision is performed with the base being at the margin. Two longitudinal incisions are performed on both sides of the excision, and the resulting flaps are detached from the underlying nail plate. They are moved toward each other and sutured leaving two narrow secondary defects that rapidly heal without obvious scarring (Figure 29.28a) [26]. For wider defects, two rotation flaps are created that are moved toward each other and sutured (Figure 29.28b). The secondary defects may be narrowed with a stitch, but within a few days, there is a spontaneous reduction in their size and the scars are barely visible after 6 months [27].

Chronic Paronychia

Long-standing paronychia often leads to a thick proximal nail fold; the free margin of which is detached from the underlying nail plate and cannot produce a cuticle. This may be very unsightly. When conservative treatment does not improve the aesthetic aspect, the nail fold may be excised in a half-moon shape. The excision is drawn and the scalpel is held obliquely so that a beveled excision results (Figure 29.29). There is very little postoperative pain and healing is complete within 2–3 weeks. With the acute angle of the margin of the nail fold, a new cuticle can form again.

This technique can also be used for crescentic excisions for other indications, for example, very distally located myxoid pseudocysts.

Nail Avulsion

Unfortunately, for many physicians, avulsing the nail is their only nail surgery. In most cases, nail avulsion does much more harm and it is almost never a treatment *per se*, except in retronychia and compression nails. There are different techniques available to remove the nail, and again unfortunately the crudest method is still performed by most surgeons: the branch of a sturdy hemostat clamp is run under the nail on one side and then under the proximal nail fold, and the nail is firmly grasped and torn out by turning the clamp. This tears off much of the nail bed epithelium and may be very harmful for the nail unit as it may cause nail bed scarring and permanent onycholysis. If a nail has to be avulsed in order to institute a treatment or get access to a subungual tumor, the distal and the proximal approach are available.

Distal Nail Avulsion

For this technique, a nail elevator is used. This is a slightly bent instrument, which is gently inserted under the nail with

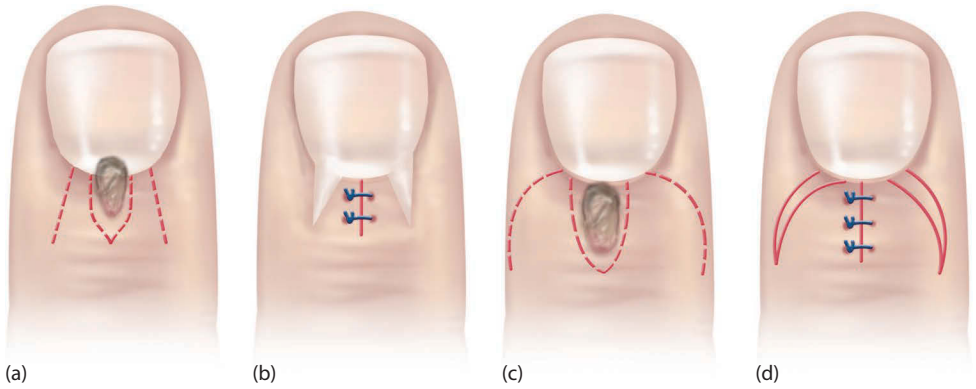


Figure 29.28 Defect repair after tumor excision on the proximal nail fold. (a) A narrow defect can be closed with two flaps from the adjacent skin (b). (c) A wider defect requires rotation flaps for defect closure (d). A narrow tumor can be closed with two flaps brought together in the median line (a, b), whereas a wider tumor requires flaps with a wider base (c, d).

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

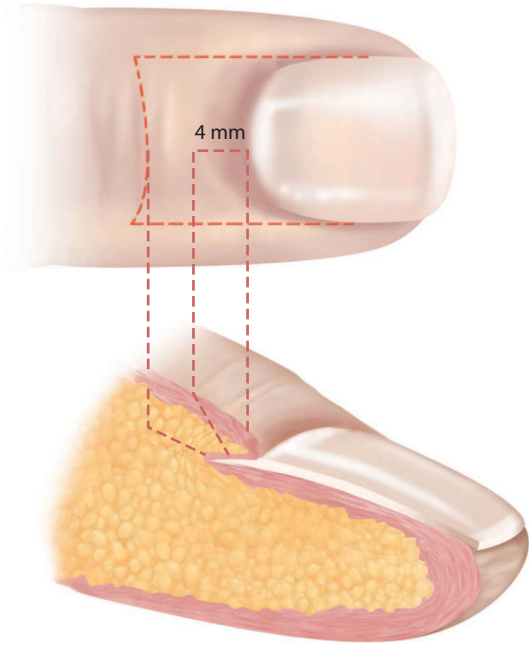


Figure 29.29 Surgical treatment of chronic paronychia. A hallmark of chronic paronychia is a thickened proximal nail fold without a cuticle and with loss of attachment of the undersurface to the nail plate.

its curvature showing up to the nail plate. With forth-and-back movements, it is led from one side to the other until the nail plate is completely detached from the nail bed and matrix. Then the elevator is taken out, turned 180°, and pushed under the proximal nail to gently detach it from the nail (Figure 29.30a). The nail can finally be taken out of the pocket with a forceps. This technique is much less traumatizing than the nail avulsion using a hemostat clamp or a nail avulsion pince.

Proximal Nail Avulsion

The elevator is inserted under the proximal nail fold to detach it from the nail. Then the elevator is flipped approximately 145° around to allow its tip to be slipped under the proximal end of the nail where it is pushed forward to separate the nail from the matrix and nail bed (Figure 29.30b). This proximal approach is even less traumatizing than the distal one.

When the nail was avulsed to permit a subungual lesion to be taken out, it is usually laid back both as a physiologic dressing and as a splint. It protects the matrix and nail bed from exsiccation and allows much faster healing with considerable less postoperative discomfort. It also prevents one of the most frequent untoward sequelae of nail avulsion, the formation of a distal nail fold. When the nail was avulsed for the treatment of retronychia, the tip of the toe should be taped in order to prevent it from becoming dorsally dislodged.

Traumatically Damaged Nail

Trauma can considerably damage the nail. Immediate repair is usually done in the emergency room by surgeons whose willingness and competence to sacrifice enough time to study the injury and its sequelae are sometimes limited. Therefore, patients often come with a distorted nail since years. It has to be admitted that it is then often not possible to fully repair such a nail. However, sometimes definitive removal is a better aesthetic solution and should be discussed with the patient. Another option may be a toe-to-finger transfer or a free graft provided an adequate donor toe is available. Too wide a nail unit can be trimmed in a second-stage operation. Many patients ask for artificial nails. Although this may be an option on fingers, it is rarely possible for the big toe as this requires a very firm connection. A nail can, however,

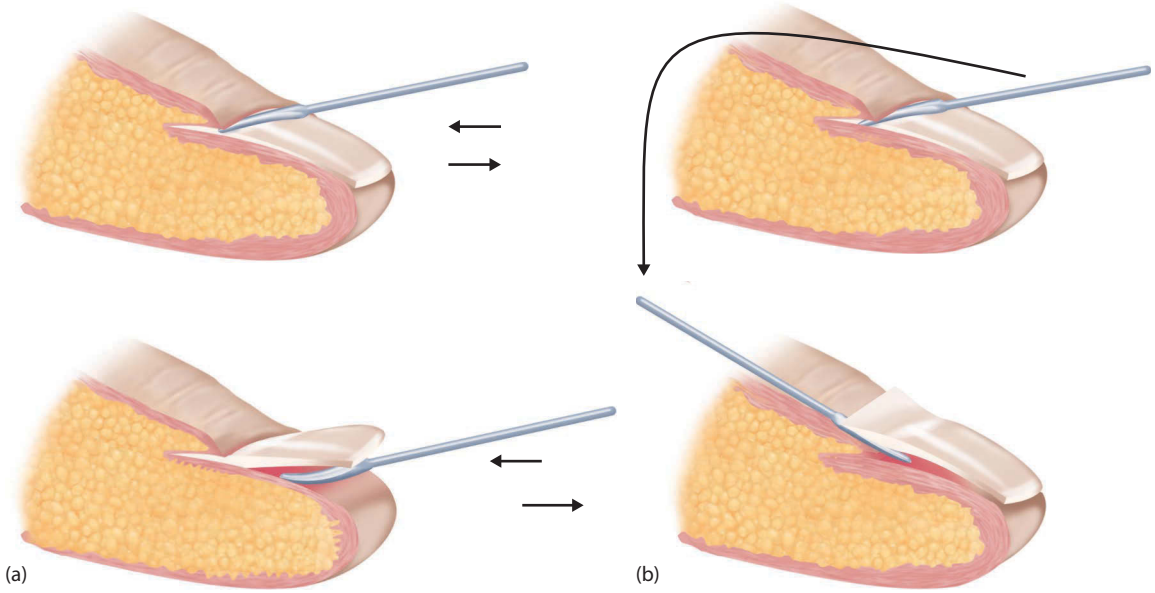


Figure 29.30 Preferred methods of nail avulsion. (a) Distal approach. Upper left: Detachment of the proximal nail fold's undersurface from the underlying nail plate. Lower left: The elevator is inserted under the distal edge of the nail to free it from the nail bed and matrix. (b) Proximal approach. (b) Upper right: After detachment of the proximal nail fold, the nail elevator is turned around to allow its tip to be slipped under the proximal margin of the nail plate. Lower right: The elevator then separates the nail plate from matrix and nail bed from proximal to distal.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

be painted with lacquer on the tip of the digit, which is only noticeable at a very short distance.

Even more frequently seen than traumatically damaged nails are those due to poor ingrown nail surgery. Wedge excisions are still widely performed and the results are more often than not an aesthetic catastrophe. The lateral nail folds are gone; the nail bed is too short; a large distal nail fold is present; the remaining nail plate is thick, discolored, onycholytic, malpositioned; and nail spicules grow out at the lateral margins. These nails are definitely destroyed and no surgery can improve them anymore. Again, camouflage with nail lacquer may be an option.

CONCLUSION

Cosmetic–aesthetic nail surgery is an underdeveloped field of dermatologic surgery. Many more conditions than briefly described earlier can be operated on with very good functional and cosmetic results. Camouflage using nail varnish and artificial nails can be used when surgery is no longer possible. Nail prostheses are now so perfect that they completely mimic the tip of the digit [28].

REFERENCES

1. Morgan AM, Baran R, Haneke E. Anatomy of the nail unit in relation to the distal digit. In: Krull EA, Zook EG, Baran R, Haneke E, eds. *Nail Surgery: A Text and Atlas*. Philadelphia, PA: Lippincott Williams & Wilkins, 2001, pp. 1–28.
2. Haneke E. Surgical anatomy of the nail apparatus. *Dermatol Clin* 2006; 24:291–296.
3. Langner I, Krüger P-C, Evert K, Zach A, Hadlich S, Ekkernkamp A, Eisenschenk A, Hosten N, Langner S. MR microscopy of the human finger and correlation with histology—A proof-of-principle study. *Clin Anat* 2013; 26:719–727.
4. Seah BZ, Wu CC, Sebastin SJ, Lahiri A. Tactile sensibility on the fingernail. *J Hand Surg Am* 2013; 38:2159–2163.
5. Goldminz D, Bennett RG. Cigarette smoking and flap and full-thickness graft necrosis. *Arch Dermatol* 1991; 127:1012–1015.
6. Chiu DT. Transthecal digital block: Flexor tendon sheath used for anesthetic infusion. *J Hand Surg Am* 1990; 15:471–477.
7. Richert B. Anesthesia of the nail apparatus. In: Richert B, Di Chicacchio N, Haneke E, eds. *Nail Surgery*. London, U.K.: Informa Healthcare, 2010, pp. 24–30.
8. Haneke E. Reconstruction of the lateral nail fold after lateral longitudinal nail biopsy. In: Robins P, ed. *Surgical Gems in Dermatology*. New York: Journal Publishing Group, 1988, pp. 91–93.
9. Haneke E. Therapie von Nagelfehlbildungen. In: Landthaler M, Hohenleutner U, eds. *Fortschritte der operativen Dermatologie*. Berlin, Germany: Blackwell Wiss.-Verl, 1997, Vol. 12, pp. 180–187.
10. Chi CC, Wang SH. Inherited accessory nail of the fifth toe cured by surgical matricectomy. *Dermatol Surg* 2004; 30:1177–1179.
11. Haneke E. Double nail of the little toe. *Rom J Morphol Embryol* 2014; 55:235–256.
12. Baran R, Haneke E. Matricectomy and nail ablation. *Hand Clin* 2002; 18:693–696.
13. Richert B, Choffray A, de la Brassinne M. Cosmetic surgery for congenital nail deformities. *J Cosmet Dermatol* 2008; 7:304–308.
14. Haneke E. Advanced nail surgery. *J Cutan Aesthet Surg* 2011; 4:167–175.
15. Haneke E. Controversies in the treatment of ingrown nails. *Dermatol Res Pract* 2012; 2012:1–12.
16. Haneke E. Surgical treatment of ingrowing toenails. *Cutis* 1986; 37:251–256.
17. Haneke E. Segmental matrix excision for the treatment of ingrown toenails. In: Robins P, ed. *Surgical Gems in Dermatology*. New York: Journal Publishing Group, 1988, pp. 94–95.
18. de Berker DA, Richert B, Duhard E, Piraccini BM, André J, Baran R. Retronychia: Proximal ingrowing of the nail plate. *J Am Acad Dermatol* 2008; 58:978–983.
19. Baumgartner M, Haneke E. Retronychia: Diagnosis and treatment. *Dermatol Surg* 2010; 36:1610–1614.
20. Kowalzick L, Schell B, Eickenscheidt L, Ziegler H. Pfeilschwanzkrebs-Onychodystrophie. *Akt Dermatol* 2008; 34:26–28.
21. Kimura U, Takeuchi K, Kinoshita A, Takamori K, Suga Y. Long-pulsed 1064-nm neodymium:yttrium-aluminum-garnet laser treatment for refractory warts on hands and feet. *J Dermatol* 2014; 41:252–257.
22. Pfau A, Abd-el-Raheem TA, Bäumler W, Hohenleutner U, Landthaler M. Nd:YAG laser hyperthermia in the treatment of recalcitrant verrucae vulgares (Regensburg's technique). *Acta Derm Venereol* 1994; 74:212–214.
23. El-Mohamady AE, Mearag I, El-Khalawany M, Elshahed A, Shokeir H, Mahmoud A. Pulsed dye laser versus Nd:YAG laser in the treatment of plantar warts: A comparative study. *Lasers Med Sci* 2014 May; 29(3):1111–1116.
24. Haneke E. Operative Therapie der myxoiden Pseudozyste. In: Haneke E, ed. *Gegenwärtiger Stand der operativen Dermatologie*. Fortschritte der operativen Dermatologie 4. Heidelberg, Germany: Springer, 1988, pp. 221–227.
25. Haneke E. Epidermoid carcinoma (Bowen's disease) of the nail simulating acquired ungual fibrokeratoma. *Skin Cancer* 1991; 6:217–221.
26. Haneke E. Cirugía dermatológica de la región ungueal. *Monografias de Dermatología* 1991; 4:408–423.
27. Haneke E, Richert B, Di Chiacchio N. Surgery of the proximal nail fold. In: Richdert B, di Chiacchio N, Haneke E, eds. *Nail Surgery*. London, U.K.: Informa Healthcare, 2010, pp. 42–54.
28. Pillet J, Didierjean-Pillet A. Les prothèses unguéales. In: Dumontier C, ed. *L'Ongle. Monographie de la Société Française de Chirurgie de la Main*. Paris, France: Elsevier, 2000, pp. 242–246.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Superficial and medium-depth chemical peels

Nicolas Bachot, Christopher M.E. Rowland Payne, and Pierre André

The aim of this chapter is to present the basic principles of use that the various superficial and medium-depth chemical peels have in common and to help the physician to choose the right peel for each indication.

A chemical peel consists of applying to the skin a caustic formula that creates a limited destruction of the epidermis and/or the dermis in order to improve pathological and aesthetic disorders.

Chemical peels are among the oldest techniques of skin rejuvenation. They are customarily classified into three categories, superficial, medium, and deep peels, based on the depth of the procedure. This classification is restrictive but provides a useful well-defined framework.

Skin regeneration takes place from residual keratinocytes, in the case of a superficial peel, and from keratinocytes and cutaneous adnexae (pilosebaceous units), in the case of a medium or deep peel.

Regeneration of the skin depends on the number of pilosebaceous units, which varies in different body areas. (The face has a great number of pilosebaceous units and heals faster than the back of the hands where the adnexae are fewer.)

The healing phase is essentially characterized by the production of new collagen, elastic fibers, and glycosaminoglycans (GAGs).

HISTORY

Peels are a very ancient technique, as caustic preparations were used in Egypt and described on Ebers papyrus (3500 BC) and also by the Greeks, the Romans, the Turks, the Gypsies from Hungary who have transmitted their recipes over many generations. Since 1800 dermatologists have used peels to treat sunspots and melasma, based on Hebra's studies from Vienna.

In 1882, Unna, a German dermatologist, described the properties of salicylic acid, resorcinol, phenol, and trichloroacetic acid (TCA). In 1952, George MacKee reported the use of a phenol solution for the treatment of acne scarring [1]. In 1961, Thomas Becker described his formula and established the procedure scientifically [2]. In the 1980s, superficial peels with alpha-hydroxy acids (AHAs) (notably glycolic acid) were described perfectly and became very popular.

Since then, all these procedures have been improved, thanks to many scientific works and histological studies.

Currently, more than 50 commercial peels are available in Europe.

INDICATIONS

Skin aging and particularly photoaging: Peels may improve solar lentigines, actinic keratoses, textural aspects, fine lines, and wrinkles. With superficial and medium peels, the action is essentially on the epidermis and the papillary dermis. With phenol peels, the dermis will also be tightened and the result will last many years.

Hyperpigmentations: Melasma, lentigines, freckles, and postinflammatory hyperpigmentation (PIH). The treatment of melasma is always risky in darker phototypes and the patient must be fully advised that PIH may appear.

Acne: Superficial peels may help to clear the skin more quickly.

Acne scars: Peeling is not the best way, but repeated sessions may improve them. Some combinations (e.g., TCA or carbon dioxide) are more successful.

CONTRAINDICATIONS

Contraindications depend on the type of peel used.

With superficial peels, there is no contraindication, except skin infection and unrealistic expectations.

With medium and deep peels, it is mandatory to explain to the patient that there is a notable downtime and that postoperative treatment must be carried out perfectly to achieve the best outcome.

Patients with poor general health, e.g., unstable angina, poorly controlled diabetes, immunosuppression, and mental illness, must be rebutted.

Patients who have taken isotretinoin within the last year are best not be treated with medium or deep peels because of the risk of poor healing due to the atrophy of sebaceous glands.

Patients suffering from herpes simplex infection should receive prophylactic antiviral treatment (e.g., acyclovir, valacyclovir, famciclovir).

CHOOSING THE RIGHT PEEL

The peel selected depends on the indication, the patient's phototype, and the physician's expertise.

The indications (see earlier text).

The phototype, according to Fitzpatrick's classification.

Some body areas are risky, e.g., the neck and the back of the hands, and can only tolerate less aggressive peels.

Superficial peels: Superficial peeling may be achieved by a wide variety of agents, including AHAs, TCA 10%–25%, resorcin, Jessner's solution, and cryopeeling. Each of them includes a desquamation of the epidermis with consequent hastening of the cell cycle. They act essentially on the epidermis and/or on the papillary dermis. They treat superficial pigmentation and

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

other superficial defects of the skin. Healing time depends on which superficial peel is used. There is no downtime after glycolic acid peel. Downtime lasts a few days after Jessner's solution and resorcinol.

Medium-depth peel: w/v TCA 30%–50% produces epidermal and dermal necrosis without systemic risk. The action is deeper, targeting dermoepidermal structures, according to the percentage of TCA. The best indication is rejuvenation of fair skin with photoaging and fine wrinkles. Healing time varies from 7 to 10 days.

Deep or phenol peel: Phenol formulas have been used extensively for facial rejuvenation. Phenol coagulates proteins and acts more deeply than TCA 50%.

Clinical studies have reported startling results on skin texture and wrinkles, and a tightening effect has also been described.

During a full-face phenol peel, the application procedure must be followed very carefully to avoid systemic adverse effects, including cardiac arrhythmia. A preoperative ECG is also advisable.

Because the postoperative appearance is appalling, patients must be very well informed preoperatively. Healing time varies from 10 to 12 days. Hypopigmentation may occur, sometimes developing up to 18 months later.

For treating wrinkles of the upper lip, it is one of the best treatments.

Peeling is very technique dependent. A superficial peel may become a medium-depth peel, dependent on the precise technique used: relative vigor of prepeel degreasing the surface of the skin, number of coats of Jessner's solution of weak TCA, and duration of application of a glycolic acid peel whether or not a phenol peel is occluded.

It remains true that peels have a well-deserved place in the antiaging therapeutic armamentarium. They are well established. Superficial peels present minimal risk. Medium and deep peels need much more expertise and should only be performed by well-trained physicians.

HOW TO PEEL

There are three phases in a peel: the *prepeel*, the *peel*, and the *postpeel*.

Prepeel: Preparation of the skin may be essential, depending on the type of peel and the type of skin to be peeled. Photoprotection and application of a bleaching agent, for 1 month before the procedure, diminish the risk of PIH. Application of retinoic acid decreases epidermal thickness, facilitates the penetration of the peeling agent, and also stimulates keratinocyte turnover.

Prior to a phenol peel, there is no need for any prepeel care (other than warning the patient of the postpeel experience).

Before medium and deep peels, in patients with recurrent herpes simplex, it is safer to begin 5 days of antiherpetic prophylactics (acyclovir, valacyclovir) on the day of the procedure.

Peel: The technique of each particular peel is described in each particular fraction.

Postpeel: In the case of medium or deep peels, apply twice a day an antiseptic agent, followed by a moisturizing cream or ointment. Avoid the development appearance of thick crusts, which otherwise increase the duration of wound healing and increase the chance of secondary infection.

In the case of all peels, as epidermal skin thickness is reduced, melanocytes are more exposed to solar irradiation with a concerned risk of PIH. Good photoprotection is required, i.e., sun exposure is avoided using sunscreen.

COMPLICATIONS

The incidence of adverse events is high, but they are most usually correctable.

The deeper the peel, the higher the risk.

Complications will be described in detail in each corresponding section.

The patient must be informed of all of them before starting the procedure.

CONCLUSION

Of all the many cosmetic procedures, peels are among the most efficacious and rewarding. Choosing the right peel and obtaining a good result needs a great deal of expertise, particularly with medium and deep peels.

Global support of the patient before, during, and after the procedure facilitates the best outcomes.

SUPERFICIAL PEELS

Definition

Superficial peeling is a technique of exfoliation of the epidermis, which uses chemical or physical agents to obtain a limited and controlled destruction of the superficial skin layers. They are generally performed multiple times to achieve the desired result. Classically, these peels do not breach the basal skin layer. However, they may act on the papillary dermis and induce formation of new collagen, elastic fibers, and GAGs. These peels include desquamation of variable intensity followed by regeneration of the skin from residual keratinocytes. Superficial peels can be used on various areas of the body, even the most risky areas, including the neck or the décolleté.

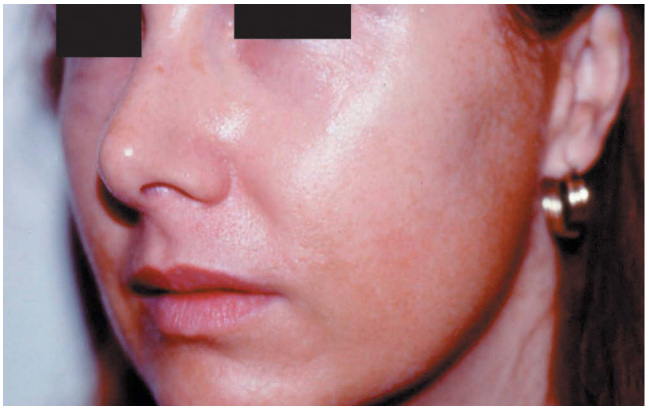
Why Choose a Superficial Peel?

To improve the signs of photoaging [3–6]: By eliminating dead keratinocytes and irregular pigmentation, the superficial peel will enhance the skin glow. A dull complexion with enlarged pores may also be improved. Fine lines are improved but not deep wrinkles or rhytides, which require a medium or a deep peel.

To treat melasma (Figure 30.1): For epidermal melasma (confirmed by Wood's lamp), the association of superficial peeling and Kligman's trio gives the best result [7]. Several sessions (e.g., with glycolic acid peels) are needed at 1- to 2-week intervals. In the case of mixed melasma, the result is only partial as the action of both the peel and Kligman's formula is essentially epidermal.

Combined within some glycolic acid peels, there is a bleaching agent (kojic acid, hydroquinone, azelaic acid), which is supposed to offer a better bleaching effect [8].

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a)

(b)

Figure 30.1 (a) Before glycolic acid peel and (b) after six sessions of glycolic acid peel.

The improvement obtained after treatment does not prevent recurrences. A follow-up treatment, including sunscreen and bleaching agents, is therefore essential.

To treat PIH: Glycolic acid peels and bleaching agent give the best result [9].

To treat acne: Superficial peels are proposed as an adjuvant to acne treatment. Similar results are obtained with salicylic acid, glycolic acid, or Jessner's solution [10]. These peels can be used on all skin types and help reduce blackheads, papules, and pustules as well as pore size. They help expel microcyst and comedone. This treatment is well tolerated and as far as 5.6% of patients suffer unwanted effects [11]. Several sessions are needed for good improvement.

Temporarily PIH may occur but will disappear progressively.

These peels also improve excoriated acne and may help patients physically and psychologically during their treatment [12].

Results on acne scars are disappointing despite some favorable reports. For scars, it is better to choose a combined medium-depth peel with carbon dioxide or a phenol peel.

TCA, 10%–30%

TCA has long been used and is well known.

TCA is a chlorinated derivative of acetic acid (CC1-COOH), which is available in the form of colorless crystals. It is soluble in water, ether, and alcohol. Because alcoholic solutions do not penetrate the skin, aqueous solutions must be used for dermatologic use. It is prepared by mixing crystals, measured in grams, and distilled water, measured in milliliters (e.g., TCA 20% = 20 g TCA + 100 ml water). The preparation obtained is not light sensitive. It may be stored at room temperature, longer in a specific plastic container (>2 years) than in a glass bottle (6 months). However, the activity of the solution alters with time. It is advised to write the date of mixing on the bottle.

Reaction and penetration vary with different regions of the body skin.

Penetration is not always homogenous, hence the importance of skin preparation. Some authors prefer to add glycerin or saponin in order to obtain a greater control of the ideal depth.

TCA acts by precipitating epidermal proteins and causing necrosis and sloughing. It has no systemic toxicity and is not allergenic.

Technique

Superficial peels do not require anesthesia.

Before starting the procedure, the skin must be washed and gently degreased (with ether or acetone), and then the TCA is applied over the whole face with cotton-tipped applicators or gauze. Two or three coats may be needed to achieve an even redness and a slight whitening of the skin (the frost) (Figure 30.2). After several minutes, the frosting clears leaving redness in its wake. During the application, the patient first feels prickling and then a sensation of intense burning during around 2–3 minutes. TCA is not neutralizable, but the cold compresses are applied to decrease the burning sensation and a large fan close by is very helpful.

TCA on the eyelids: Take a single cotton-tipped applicator, which must be nearly dry to avoid unwanted drips. Inform the patient that in case the agent gets into the eye, it will sting but tears will immediately dilute it and protect the eye from damage. Nevertheless, flood the eye with saline. Therefore, have a 5 or 10 mL syringe of saline in hand during the procedure.

Figure 30.2 The frost after TCA peel.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Histological Aspects

Used at a low concentration (<30%), TCA provokes skin cleavage on the third day, with a very weak skin inflammation. After 30 days, a thickening of the skin has been described.

Different Brands of TCA

Obagi Blue Peel Obagi Blue Peel [13] is applied in coats.

TCA combined in a clay vehicle. The paste is spread onto the skin in one coat. After 2–3 minutes, a small opening is made on the forehead in order to check the effectiveness. If the whitening is judged sufficient, the mask is washed off with humid sponges, if not, it is left on a few minutes longer.

Unna's Paste Unna described the use of resorcinol as a peeling agent in the late 1800s. Resorcinol (dihydroxybenzene) is structurally and chemically related to phenol. It is an irritant and a keratolytic agent.

Serge Letessier [14] modified the formula by adding axungia and ceyssatite for homogeneity.

Letessier's formula	
Resorcin	40 g
Zinc oxide	10 g
Ceyssatite	2 g
Benzoin axungia	28 g

Technique A skin test must be performed behind the ear to detect resorcinol allergy.

The patient lies supine. The paste is applied to the whole face and left on for 30 minutes on the first day (Figures 30.3 and 30.4). A second application is made the next day. After 30 minutes, the paste is wiped off using a tongue depressor and then with a dry gauze to leave a gray resorcin membrane. No topical care is needed until epidermal renewal occurs, which takes 7 days.

The application should not be done on a large body area and/or repeated too many times to avoid inducing dizziness or hypothyroidism.

Jessner's Solution Jessner's solution was described by Max Jessner, in New York, around the 1960s. It was based on Unna's studies. It is a combination of different agents, which, in combination, reduce their toxicity (salicylic acid and resorcinol) and enhance their keratolytic effect.

The solution must be kept in a dark bottle.

Salicylic acid	14 g
Resorcinol	14 g
Lactic acid (85%)	14 g
Ethanol (95%) q.s. ad	100 mL

Jessner's solution or Coombs' formula, which is very similar, associates different keratolytic agents in alcohol.

Action This solution acts by potentiating the effects of different activities by decreasing the toxicity of resorcinol and salicylic acid. It permits a very progressive application. The peel may be made more or less potent, depending on the application technique and the number of layers. It can be used alone or added to other peels as an adjuvant. In this case, it is applied first in order to prepare the skin to favor a more homogeneous and more complete penetration of the next agent (e.g., glycolic acid, TCA).

Technique The application may be done with cotton-tipped applicators, cotton balls, a paintbrush, or gauze.

The effect may be more or less potent depending on the number of coats and the pressure or friction with which it is applied.

An interval of 10 minutes is required between each coat. Up to three coats may be applied in one session. Increasing the number of coats applied and the pressure increase the reaction produced.

No neutralization or dilution is needed.

The patient feels a burning sensation for a few minutes. Flaking follows for 5–7 days.

Several repeat sessions may be undertaken every 3 weeks.

Indications It is excellent for acne patients and mild photoaging.

Figure 30.3 Unna's paste and hands.

Figure 30.4 Unna's paste and the face.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Contraindications Allergy to resorcinol: A skin test behind the ear may be proposed before the procedure.

To avoid systemic adverse effects of salicylic acid, this peel should not be used on large body areas (on the whole face and neck, but not on the back at the same time).

Salicylic Acid Swinehart's technique consists of using 50% salicylic acid ointment under occlusion to peel the skin from the back of the hands and forearms [15]. The dressing is removed 48 hours later. The healing phase lasts a few weeks.

This peel is not used anymore since the discoveries of new rejuvenating techniques, such as laser and intense pulsed light.

AHA Peels

These are naturally occurring organic acids that contain hydroxy group in the alpha position. The principal one used is glycolic acid, which is derived from sugarcane. Others include lactic acid from sour milk, citric acid from citrus fruits, malic acid from apple, tartaric acid from grapes, and phytic acid from rice. As several AHAs are derived from fruits, they are called fruit acids.

AHAs induce exfoliation and speed the cell cycle. They have a strong influence on the keratinization process. They act just above the granular layer, where they reduce corneocyte cohesion. Prolonged application may cause epidermolysis. Otherwise the stratum corneum becomes thinner and the cell cycle, which is slowed in aged skin, speeds up.

History

AHAs have been used in an empirical way over the years. It is known that Cleopatra used to take baths in donkey's milk (lactic acid) and that before the French revolution, women at the court liked to apply wine on their faces (tartaric acid). In the West Indies, it is still common to apply lemon for a better complexion. In 1984, Van Scott and Yu published the results of the application of AHAs to the skin when treating dry skin or keratin disorders [16]. Glycolic acid has known a rapid expansion since the beginning of the 1990s, thanks to the work of Van Scott, Yu, Mene, Moy, Smith, and Rubin.

Histology

Glycolic acid peels induce an increase in skin thickness and production of new collagen, elastic fibers, and GAGs in the dermis [17]. Some studies have reported either *in vivo* or *in vitro* activation of fibroblasts as well as collagen production [18].

Indications

Indications are those of a superficial peel.

Acne, photoaging, melasma, and PIH are the best indications.

Benefits are progressive, which is why several sessions are performable at 1 or 2 weekly intervals.

Fundamentals of AHA Peel

There are many AHA peels on the market and each one is different. Usually a glycolic acid peel is performed. The concentration (varies usually from 20% to 70%), the pH (the lower it is, the more acid is the peel), and the vehicle can increase the penetration or decrease the sensitivity to the acid.

When the pH is high, the peel is less aggressive. Some formulations are "buffered" with a base, such as sodium bicarbonate, to increase patient tolerability. They are also less active and require a longer application time to obtain good results.

AHA peels may be neutralized to stop the action and to avoid epidermolysis, which is always uneven. Sodium bicarbonate neutralizes AHAs. Some practitioners prefer to dilute the AHA peels in water, which enables the peel to act a little more strongly.

Some other acids may be added to AHAs, such as kojic acid or pyruvic acid, to increase the efficacy or the bleaching effect.

A low pH is recommended for acne or photoaging. A higher pH is recommended for melasma to avoid PIH.

Technique

Once the first consultation has happened and the procedure has been well understood by the patient, the prepeel phase must be explained.

This phase is important to prepare the skin.

Retinoic acid or glycolic acid creams may be applied 2 weeks beforehand to homogenize the stratum corneum, which facilitates AHA action. If the skin is very irritated, it is safer to wait a few days before peeling, as the action may otherwise be too strong and induce epidermolysis.

Sunscreen and bleaching agents are applied for 3 weeks before application to reduce melanocyte activity and help avoid PIH afterward.

Once the skin has been cleaned of all makeup, it is gently degreased either with ether or acetone or a specific solution.

If a solution is used, the application is done with a brush or a gauze compress. Application time depends on the patient, the indication, and the characteristics of the chosen formula (a 70% solution acts more quickly than a 30%, a low pH solution faster than a high pH).

The patient feels a slight burning or prickling.

When redness appears, it is safe to neutralize or to dilute with water (which can increase the burning sensation for a few minutes before it settles); otherwise epidermolysis (uneven whitening of the skin) (Figure 30.5) occurs with a concomitant risk of PIH (Figure 30.6), dyschromia (Figure 30.7), and even scarring.

It is useful to apply a moisturizing cream immediately after the session.

Usually there is just a slight redness the next day. In the case of epidermolysis, it is important to avoid formation of crust

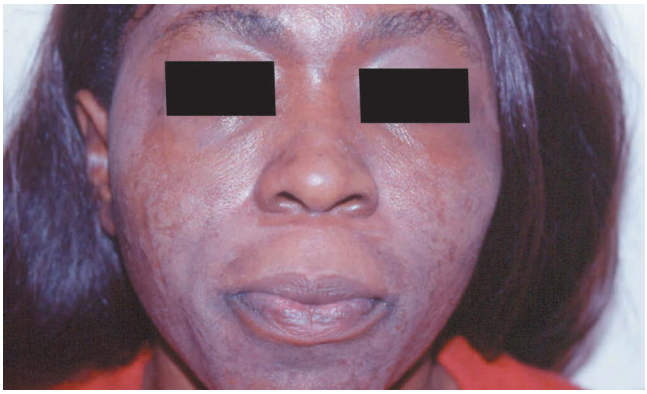


Figure 30.5 Uneven epidermolysis after a 70% glycolic acid peel.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

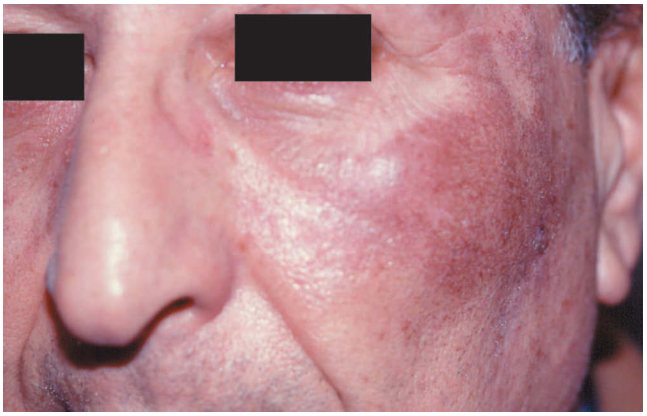


Figure 30.6 PIH after glycolic acid.

Figure 30.7 Dyschromia after 70% glycolic acid peel.

by applying, several times a day, a greasy ointment, such as white soft paraffin, until complete healing occurs.

To obtain a good result, 4–6 sessions are required at 1–2 weekly intervals.

Between sessions, sun exposure is avoided as sunscreen is used.

PHYSICAL PEELS

Dry Ice (Carbon Dioxide Snow)

This is done by maintaining on the skin a mixture of acetone and ice in chamois leather or by using a *Lortat–Jacob* cold probe. The mixture is applied in slow movements on the skin in order to obtain erythema without going as far as the icing of the skin. The day after, the skin becomes pigmented and peels the following days.

This is an old technique, which is operator dependent, but helps to brighten up a complexion and to improve acne scars.

Liquid Nitrogen

This is an excellent technique, especially for brown spots in Fitzpatrick skin types I and II. It can be applied with cotton buds or with a cryogen spray. The application is done in the same way as for dry ice. Indications and healing are identical.

The procedure is unpleasant rather than painful.

These physical techniques are commonly used in Northern Europe but less commonly in Southern Europe because of the risk of dyschromia.

Complications

Superficial peels are the least risky of the peels. Nevertheless, many side effects may occur.

PIH is probably the most frequent side effect, particularly in dark skin, hence the importance of sun avoidance and skin preparation.

With resorcinol, allergy and dizziness may occur possibly by transcutaneous systemic absorption. Scarring and hypochromia are rare but may occur after a strong application of Jessner's solution or glycolic acid.

Herpes simplex may occur. It can be prevented by antiherpetic drugs.

Conclusion

Superficial peels are cheap and easy to perform by a well-trained practitioner. Superficial peels are a marvelous procedure in cosmetic dermatology.

Even though their use seems easy, the learning curve is long in order to get best results.

MEDIUM-DEPTH PEELS

TCA Peel >30%

Summary

TCA peel has been widely used for many years in the treatment of photodamaged skin (especially actinic keratoses and wrinkles), hyperpigmentation, and some acne scars. Selecting patients, preparing the skin, mastering the technique, and managing a good recovery will optimize the result and reduce the risk of complications.

TCA >30% is a baseline medium-depth peel in dermatology.

It is used mainly on the face but also on other body areas.

Why Choose a Medium-Depth Peel?

The indications are the same as for superficial peels.

To improve the signs of photoaging: TCA improves not only the epidermal lesions and the glow of the complexion but also the dermal alterations, the wrinkles, and the deep rhytides. Even though TCA 40% or 50% may improve deep wrinkles of the upper lip, it is not the best treatment. It is better done by mechanical dermabrasion or an ablative laser resurfacing or a deep phenol peel. The association of phenol peel around the mouth and TCA over the whole face gives a marvelous result without the systemic risk of a full-face phenol peel (Figure 30.8). A tightening effect of lax photodamaged skin is also observed (more after phenol than TCA).

To treat melasma (Figure 30.9): But only in fair skin because of the risk of PIH in dark skin.

To improve depressed acne scars: The best result is obtained in combination with solid carbon dioxide (CO_2) application.

For patients who are well informed about the healing phase and who understand and accept the risks.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

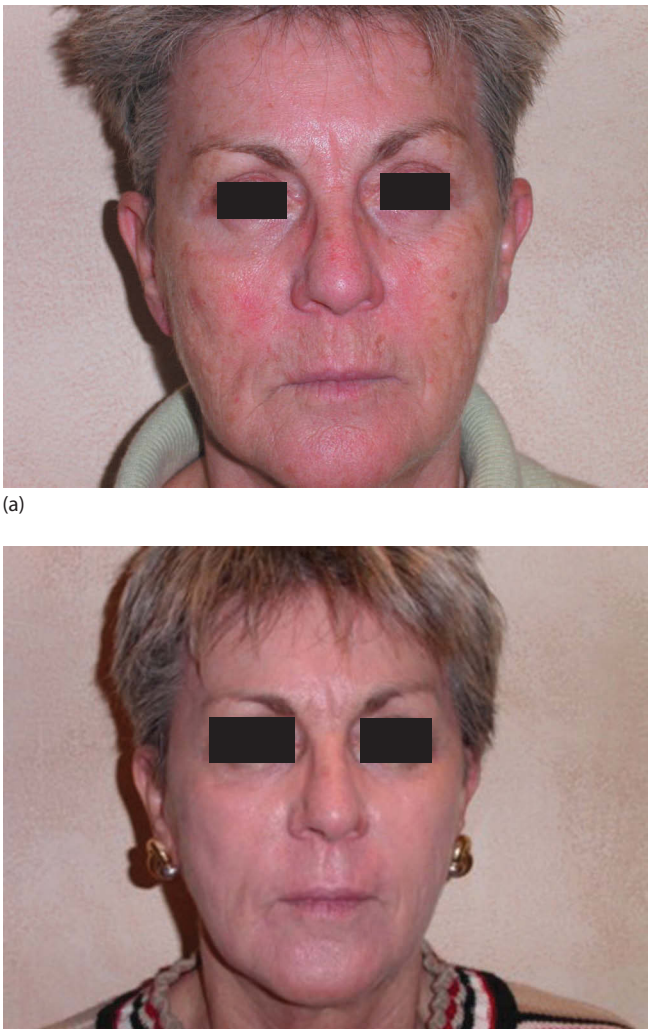


Figure 30.8 (a) Before perioral phenol peel combined with 40% TCA of the face. (b) Two months after perioral phenol peel combined with 40% TCA of the face.

Contraindications

Relative

Fitzpatrick types IV and V
Lifestyle (sun exposure)
Some photosensitizing medications
Smoking
Unrealistic expectations
Recurrent herpes simplex (patients must receive prophylactic antiherpetic drugs)

Absolute

Pregnancy
Poor general health (unstable angina, unbalanced diabetes, and immunosuppression)
Mental illness
Isotretinoin treatment within the last year
Keloid formers

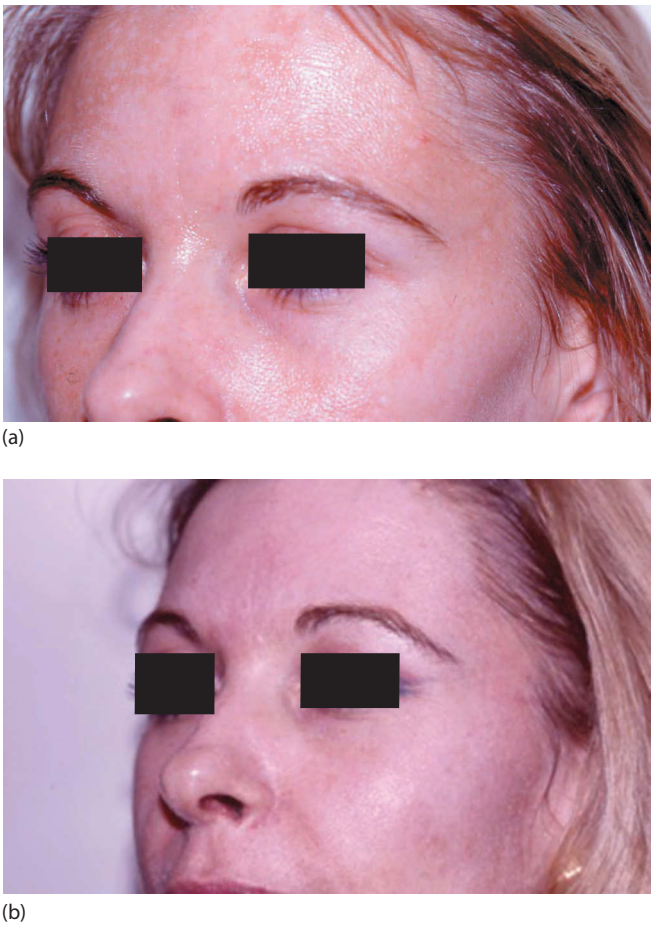


Figure 30.9 Melasma (a) before and (b) after TCA peel.

History

Described by the German dermatologist, Unna in 1882, many publications on TCA in the 1990s have given full and precise explanations of their uses [19–22].

Preparation (See Earlier Text)

The most important is to always use the same formula and to specify it when publishing.

Action

TCA >30% provokes a precipitation of skin proteins with epidermal and dermal necrosis.

100% TCA is more caustic than pure phenol. Concentrations above 50% are avoided because of the risk of scarring. 50% TCA must be used with precaution (risks of keloid, especially around the mouth).

TCA 35%–45% is the standard solution for medium-depth peels.

Application of successive coats of TCA increases the depth of the peel.

TCA cannot be neutralized but it can be diluted with water in order to stop its action.

An occlusive dressing does not increase the action of TCA. Perhaps this is because occlusion prevents transepidermal water loss and so increases interstitial fluid content that dilutes TCA. Neither does application of a greasy cream or other modern dressings modify the depth of the peel [23].

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Technique

Prepeel Once the patient has been carefully examined and the procedure explained in detail, informed consent must be signed.

Photography beforehand is necessary.

The application of sunscreen and bleaching agents for 3 weeks before the procedure is important to avoid PIH (especially in dark skin).

The application of retinoic acid cream for 2–3 weeks before the procedure may homogenize the epidermis and speed the healing phase [24].

Peel A medium-depth peel is painful but bearable.

Topical anesthesia with Emla® cream (lidocaine 2.5%, prilocaine 2.5%) applied 1 hour before the peel does not modify the outcome of the peel [25]. A nerve block around the mouth is suitable in the case of localized peel. General anesthesia is never recommended.

The procedure starts by washing and degreasing the skin (with ether or acetone).

A fan close by is helpful. Sometimes with fearful patients, it is useful to give sublingual diazepam or bromazepam, knowing that if the patient trusts you "vocal anesthesia" works well!

The application is the same as for a superficial TCA peel (see above). The frosting is more intense, *like a ghost*, and stays longer before returning to red.

Protect the eyes with a compress and wipe away any tears, which can run onto the surrounding skin. Tears may dilute the TCA and decrease its efficacy, leaving streaks.

The appearance of a demarcation line must be avoided by feathering at the margins, so peel just under the jawline. Peel also the earlobe and the tragus.

The burning sensation is much more intense and is alleviated by cold compress or a cold gel pack.

Postpeel Within an hour, the frosting changes to erythema and progressively the skin turns a brownish hue (Figure 30.10). Considerable redness and edema categorized the next day as *red and swollen like a microwaved tomato* is present for 48 hours. It is better to sleep on the back and to avoid excessive facial expressions. After a few days, the skin "cracks like a crocodile" and then, a day or two later, "peels like a snake," and cracks may appear. It is important to apply twice daily an antiseptic solution and a soothing and moisturizing ointment. The appearance of crusts should be avoided to decrease the risk of infection and scarring.

Healing is usually completed by days 7–10, leaving new skin "clear like a baby's bottom."

Slight edema and erythema will last for a few weeks, particularly in fair skin. PIH may occur around the third week of treatment, hence the importance of sunscreen and sun avoidance.

Makeup is possible once the healing is completed; sun protection is required for 6 months.

As patients do not always do their own care well, it is better to ask them to come back to the office on the 3rd and 10th days.

In the case of a very anxious patient, it is reassuring that they may call the office at any time.

Histological Aspects

TCA induces epidermal necrosis, papillary edema, and a slight lymphocytic infiltrate in the midreticular dermis. Three months later, the papillary dermis is thicker with a band of new collagen, elastic fibers, and a greater quantity of GAGs. The thickness of this band depends on the strength of the wounding agent [26].

Complications [27]

Many side effects may occur, but most of them are manageable with time and treatment.

During the healing phase: Any infection must be confirmed and rapidly treated by topical and/or systemic antibiotics. In case of pain, suspect the occurrence of herpes simplex and treat it systemically by acyclovir or valacyclovir or even a secondary bilateral infiltration that would require flucloxacillin. In the case of a burning sensation or itching, suspect contact dermatitis (Figure 30.11).

After complete healing: The most common side effect is color change. PIH appears usually around the third week and disappears in a few weeks; sometimes it persists for many months or years (Figure 30.12) and requires bleaching treatment. It is much more frequent in Mediterranean or Asiatic skin.

Figure 30.10 Brownish hue and desquamation after a few days.

Figure 30.11 Contact dermatitis after topical treatment.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 30.12 PIH in asiatic skin after TCA peel.

Figure 30.14 Textural anomalies and redness after TCA peel.

Figure 30.13 Textural anomalies and achromia after TCA peel.

Figure 30.15 Hypertrophic scar after TCA peel.

Hypopigmentation is rare with medium-depth peels but may occur 6 months later (Figure 30.13); if it occurs, it is most usually permanent but sometimes improves with sun exposure. The demarcation line is another potentially unsightly drawback, which depends on the application technique.

Persistent erythema is more frequent in fair skin and may highlight textural anomalies or scarring (Figures 30.14 and 30.15). Topical corticosteroid or vascular laser (pulsed dye laser) may help to clear it.

Scarring is infrequent but always hard to treat. Persistent erythema with itching may herald textural anomalies and hypertrophic scars and is best treated with high-potency topical corticosteroids. Hypertrophic scars most likely occur on the upper lip or at the angle of the jawline, *the line of regret*; it either disappears spontaneously within 6 months or becomes a keloid.

High-potency topical corticosteroid, silicone gel, intralesional triamcinolone acetonide, or bleomycin will usually improve such scars. Vascular lasers, such as pulsed dye or Nd:YAG, are helpful. Such scars are mostly resolved.

Ectropium of the lower lid may occur in patient with a skin of poor elasticity.

Telangiectasia may develop.

Perioral dermatitis may occur if corticosteroid cream is used for a long period (Figure 30.16).

Different Brands of TCA

Many companies have launched their own ready-to-use TCA. The percentage of TCA may change following the dilution of crystals: w/v versus w/w (see above). Some add bleaching agents such as kojic acid and phytic acid.

Obagi [13] reported a new technique, attempting to standardize TCA peeling to provide indicators of peel depth. This TCA is mixed with glycerin, saponin, and a blue color base. Multiple coats are applied, and the intensity of the frost, the blue color, and the skin wrinkling, when the skin is pinched, facilitate an estimation of the depth of the peel.

TCA may be combined into a clay mask (see above) [28].

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 30.16 Perioral dermatitis due to corticosteroid applications.

Body Peels

Apart from peeling of the face, TCA may be applied to other body areas.

Because nonfacial skin is less rich in sebaceous glands, healing is slower and more hazardous.

TCA is used on the back to improve acne scars and on the back of the hands to remove solar lentigines and actinic keratosis.

Conclusion

Medium-depth peels with TCA allow facial rejuvenation with amazing result. Even today, since the development of new technologies (lasers, flashlamps), it maintains a very rewarding place in the cosmetic arsenal.

The procedure is simple but the learning curve is long in order to obtain the best outcomes.

REFERENCES

1. Mackee GM, Karp FL. The treatment of post acne scars with phenol. *Br J Dermatol* 1952; 64:456–459.
2. Baker TJ, Gordon HL. The ablation of rhytides by chemical means: A preliminary report. *J Fla Med Assoc* 1961; 48:451.
3. Newman N, Newman A, Moy LS et al. Clinical improvement of photoaged skin with 50% glycolic acid. A double-blind vehicle-controlled study. *Dermatol Surg* 1996; 22:455–460.
4. Berson DS, Cohen JL, Rendon MI et al. Clinical role and application of superficial chemical peels in today's practice. *J Drugs Dermatol* 2009; 8:803–811.
5. Okano Y, Abe Y, Masaki H et al. Biological effects of glycolic acid on dermal matrix metabolism mediated by dermal fibroblasts and epidermal keratinocytes. *Exp Dermatol* 2003; 12(Suppl. 2):57–63.
6. Mangat DS, Tansavatdi K, Garlich P. Current chemical peels and other resurfacing techniques. *Facial Plast Surg* 2011; 27:35–49.
7. Gupta AK, Gover MD, Nouri K et al. The treatment of melasma: A review of clinical trials. *J Am Acad Dermatol* 2006; 55:1048–1065.
8. Cohen JL, Makino E, Sonti S et al. Synergistic combination of an in-office procedure and home regimen for the treatment of facial hyperpigmentation. *J Clin Aesthet Dermatol* 2012; 5:33–35.
9. Callender VD, St. Surin-Lord S, Davis EC, Maclin M. Post-inflammatory hyperpigmentation: Etiologic and therapeutic considerations. *Am J Clin Dermatol* 2011; 1:87–99.
10. Kim SW, Moon SE, Kim JA et al. Glycolic acid versus Jessner's solution: Which is better for facial acne patients? A randomized prospective clinical trial of split-face model therapy. *Dermatol Surg* 1999; 25:270–273.
11. Cassano N, Alessandrini G, Mastrolonardo M et al. Peeling agents: Toxicological and allergological aspects. *J Eur Acad Dermatol Venereol* 1999; 13:14–23.
12. Wang B, Carey WD. Chemical peeling as adjuvant therapy for facial neurotic excoriations. *J Am Acad Dermatol* 1994; 30:669–670.
13. Obaji ZE, Obaji S, Alaiti S et al. TCA-based blue peel: a standardized procedure with depth control. *Dermatol Surg* 1999; 25:773–780.
14. Letessier SM. Chemical peel with resorcin. In Roenigk RK, Roenigk HH, eds. *Dermatologic Surgery*. Marcel Dekker Inc.: New York, 1989, p. 1017.
15. Swinehart JM. Salicylic acid ointment of the hands and forearms: Effective non surgical removal of pigmented lesions and actinic damage. *J Dermatol Surg Oncol* 1992; 18:495–498.
16. Van Scott EJ, Yu RJ. Hyperkeratinization, corneocyte cohesion and alpha hydroxy acids. *J Am Acad Dermatol* 1984; 11:867–879.
17. Ditre CM, Griffin TD, Murphy GF et al. Effects of alpha hydroxy-acids on photoaged skin: A pilot clinical, histologic, and ultrastructural study. *J Am Acad Dermatol* 1996; 34:187–195.
18. Kim SJ, Park JH, Won YH et al. Increased in vivo collagen synthesis and in vitro cell proliferative effect of glycolic acid. *Dermatol Surg* 1998; 24:1054–1058.
19. Brody HJ, Hailey CW. Medium-depth chemical peeling of the skin: A variation of superficial chemosurgery. *J Dermatol Surg Oncol* 1986; 12:1268–1275.
20. Bridenstine JB, Dolezal JF. Standardizing chemical peel solution formulations to avoid mishaps: Great fluctuations in actual concentration of trichloracetic acid. *J Dermatol Surg Oncol* 1994; 20:813–816.
21. Coleman WP, Brody HJ. Advances in chemical peeling. *Dermatol Clin* 1997; 15:19–26.
22. Dinner MI, Artz JS. The art of the trichloracetic acid chemical peel. *Clin Plast Surg* 1998; 25:53–62.
23. Peikert JM, Kaye VN, Zachary CB. A reevaluation of the effect of occlusion on the trichloroacetic acid peel. *J Dermatol Surg Oncol* 1994; 20:660–665.
24. Hevia O, Nemeth AJ, Taylor JR. Tretinoin accelerates healing after trichloroacetic acid chemical peel. *Arch Dermatol* 1991; 127:678–682.
25. Koppel RA, Coleman KM, Coleman WP. The efficacy of EMLA versus ELA-Max for pain relief in medium-depth chemical peeling: A clinical and histopathologic evaluation. *Dermatol Surg* 2000; 26:61–64.
26. Nelson BR, Fader DJ, Gillar M et al. Pilot histologic and ultrastructural study of the effects of medium-depth chemical facial peels on dermal collagen in patients with actinically damaged skin. *J Am Acad Dermatol* 1995; 32:472–478.
27. Nikalji N, Godse K, Sakhiya J et al. Complications of medium depth and deep chemical peels. *J Cutan Aesthet Surg* 2012; 5:254–260.
28. Chiarello SE, Resnik BI, Resnik SS. The TCA masque: A new cream formulation used alone or in combination with Jessner's solution. *Dermatol Surg* 1996; 22:687–690.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Deep peels

Nicolas Bachot, Philippe Evenou, and Pierre André

The benefits of the phenol peel have been known for a long time. It is the deepest peeling and the one that gives the most dramatic results, but is also the most dangerous, requiring a good knowledge of the skin and healing, and must be performed only by a well-trained practitioner.

It penetrates into the reticular dermis and corrects most severe skin damages. Its indications are precise and limited to cases that cannot be treated by other peels. Severe photoaging (Figure 31.1) with phototypes I, II, and III is the main indication.

HISTORY

In 1882, PG Unna, a German dermatologist, described the properties of resorcinol, salicylic acid, trichloroacetic acid (TCA), and phenol. During World War I, the French doctor La Gassé treated gunpowder burns with phenol. His daughter Antoinette moved to the United States and practiced lay peeling near Los Angeles in the 1930s. At the same time, in Florida, Francis and Miriam Mascheck opened lay peeling salon.

In 1952, Mackee reported his clinical study with phenol for acne scars. At this time, lay peelers use many different phenol formulas until the late 1950s when detailed studies on phenol toxicity and histological aspects are reported [1].

In the early 1960s, T Baker and H Gordon reported their personal experience with their formula. From that time, the interest of physicians for phenol started [2]. A mass of publication essentially by American surgeons and dermatologists permitted clear understanding of the mechanisms that lie behind the excellent result achieved with today's phenol peels [3–5].

PHENOL CHARACTERISTICS

Phenol is obtained by hydrolyzing chlorobenzene.

Liquefied phenol consists of 88% solution in water.

Most commercial phenol has a purity of 98% C_6H_5OH (carbolic acid).

Phenol is bacteriostatic up to a strength of 1% and is bactericidal above 1%.

Phenol crystals are white or pink with a characteristic smell.

It is soluble in oils and fats, and 50% alcohol may remove it rapidly from the skin.

PHENOL TOXICITY

Phenol is poisonous.

Ingesting more than 10 g of phenol is enough to lead to death by immediate collapse.

Phenol is rapidly absorbed by the skin and mucous membranes that can lead to systemic toxicity. Cardiac arrhythmia is the more commonly reported symptom, but hepatorenal and central nervous system depression and cardiorespiratory failure have also been reported.

In a recent study [6] on 181 patients with full-face phenol peel, 12 cases of arrhythmias (6.6%) were detected through cardiac monitoring. Diabetes, arterial hypertension, and depression were risk factors for arrhythmia. A spontaneous resolution arose in 4 cases. In 8 other cases, the intravenous injection of 100 mg of lidocaine allowed the correction of arrhythmia. This toxicity is proportional to the treated surface, the duration of the application, and also the used formulation. Kidneys eliminate 75% of phenol and the remaining 25% is metabolized into water and carbon dioxide directly through the lungs [7].

The application of phenol on small areas (around lips or eyes) has never entailed cardiac arrhythmia. Phenol elimination is carried out within 15 minutes, and it is mandatory to wait for this deadline between every area to be treated.

Before doing a full-face application, it is necessary to check on the renal and the hepatic functions. Usually, hydration with 500 cc of lactated Ringer's solution prior to the procedure and 1000 cc during the peel ensures a good renal function and prevents phenol toxicity. Some formulas prove the absence of systemic toxicity, but anyway cardiac monitoring is safer to perform during the procedure and 30 minutes later (the procedure lasts for approximately 90 minutes).

CROTON OIL

Croton oil is an irritant that accelerates epidermolysis and increases the cutaneous penetration of phenol and inflammation. Croton oil is a cocarcinogen [8]. It seems that a single application of a phenol formula containing 1% or 2% croton oil has never caused skin tumor. On the contrary, long-term histological studies show that phenol (even when the formula contains croton oil) has a protective effect against skin cancers [9].

PROPERTIES AND HISTOLOGY

It is important to understand that pure 88% liquefied phenol is less strong than diluted phenol to approximately 50%–60%. Pure phenol acts more as a medium-depth peel than as a deep peel.

This paradoxical effect is due to the fact that at a concentration higher than 80% phenol causes immediate coagulation of epidermal keratin proteins. Phenol precipitating the skin proteins creates a biological barrier, which prevents a deeper penetration. Reducing the concentration (from 50% to 60%) of a phenol solution can therefore make it more dangerous, both locally and systemically [10].

Septisol is a surfactant, which reduces the surface tension and promotes a more even peel.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 31.1 Type IV Glogau's classification.

Occlusion can be used to increase the depth of action of a phenol peel when the practitioner wants the penetration to be deeper in the reticular dermis. Occlusion with an occlusive dressing at the end of the procedure increases humidification that facilitates phenol penetration.

Unoccluded Baker's formula may produce an excellent result on patients with less photoaging signs and is much more comfortable.

Many histological studies have shown dermoepidermal changes [11–13].

Immediately after application, there are signs of necrosis along the entire epidermis and signs of changes of the papillary and reticular dermis dependent on the levels of the formula.

After 1 month, the epidermis is thickened; the superficial dermis contains new collagen forming a thick horizontal band. There is a synthesis of new collagen to 120 days [14].

After 1 year, there is still a dense horizontal arrangement of new collagen [15]. The fibroblasts are strongly stimulated and secrete all the components of the extracellular matrix (ground substance, collagen, elastin) [16]. These histological results have been confirmed after 15–20 years [12].

DIFFERENT FORMULAS

Pure 88% phenol may serve as a medium-depth peel; it could be useful around the eyes and on groups II and III of the Glogau classification.

Many different phenol formulas have been proposed to strengthen the action of pure phenol. Some are more active, some must be prepared just before the procedure, some are stable, and some have less systemic toxicity. Anyway, it is better to use always the same formula to be sure to know well its properties.

Baker–Gordon: 48.5%

Liquid phenol USP[a] 88%	3 mL
Distilled water	2 mL
Croton oil	3 drops
Septisol®	8 drops

It is the most used formula.

(*Continued*)

Litton: 50%

Phenol crystals	1 lb[b]
Distilled water	8 mL
Glycerine	8 mL
Liquefied phenol	4 oz[c]
Croton oil	1 mL
Distilled water	4 oz[c]

It takes longer to prepare, but the emulsion may be stored in an amber glass bottle for a long time.

Venner–Kellson: 67%

Concentrated Lysol®	1 oz[c]
Olive oil	0.5 oz[c]
Distilled water	1.5 oz[c]
Croton oil	10 drops
Melted losses phenol crystals	8 oz[c]

The stability of the formula is very long.

Truppman–Maschek: 53%

The stability is very long but contains less croton oil than Litton's formula.

Fintsi (Exoderm*)

Unknown formula. It claims no systemic toxicity.

Gradé: 49.5%

Croton oil	12 drops
Olive oil	3 drops
Phenol crystals	4 oz[c]
Distilled water	4 oz[c]

Mix in a glass bottle and wait for 6 weeks before use.
The stability is long.

Soria: 44%

Phenol	44%
Glycerol	1 tablespoon
Croton oil	14 drops
Dimethyl sulfoxide (DMSO)	5–10 drops
Distilled water	q.s. ad[d] 100%

Hetter's formulas

Medium-light formula

Phenol 88%	4 mL
Water	6 mL
Septisol®	16 drops
Croton oil	1 drop

Very light formula

Take 3 mL of the aforementioned mixture and add 2 mL 88% phenol and 5 mL water.

Heaviest formula	3 mL
88% phenol	2 mL
Water	8 drops
Septisol®[e]	3 drops
Croton oil	

This formula corresponds to Baker–Gordon and must be used with caution in very precise cases (around lips, phototypes I, II, and III).

[a]USP: U.S. Pharmacopeia.
[b]One livre (lb) corresponds to 453.59 g.
[c]One ounce (oz) corresponds to 28.35 g.
[d]q.s. ad = quantity sufficient to add up to.
[e]Septisol® is a hexachlorophene soap used widely as a wetting agent in phenol peel formulations.

INDICATIONS

Phenol peel is the deepest peel. Its indications are precise and limited to cases that cannot be treated by other peels. The main indication for phenol peel is severe photoaging with deep

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

wrinkles (types III and IV of Glogau's classification and phototypes I, II, III).

Administration of phenol peel to patients with phototypes IV, V, and VI is risky, and they may develop postinflammatory hyperpigmentation (PIH) and/or visible demarcation line. They are not good candidates.

It can be used in a localized way: around the mouth and eyes or on a full face [17,18].

Acne scar treatment is another indication, even if it is less effective than dermabrasion.

CONTRAINDICATIONS

Pregnancy, systemic diseases, unbalanced diabetes, severe cardiovascular disease, immunosuppression, patients under isotretinoin, keloid formers, and mental illnesses are absolute contraindications.

Patients suffering from recurrent herpes simplex must be treated before the procedure by antiherpetic drugs (acyclovir, valacyclovir).

Smokers may have delayed healing, and excessive mouth movements contribute to the risk of scarring.

Medications, which interfere with the coagulation, should be avoided.

At last, feared patient with unrealistic expectation should be turned away.

THE PRE-PEEL

The patient's inquiry must check for face-lift (be cautious with the undermined areas) and blepharoplasty (check for small ectropion, which can be increased by the peel).

After scrutinizing the patient, you need to inform him or her of all the risks and complications. At this time, pictures are taken and an informed consent must be signed.

Lifestyle is important, particularly sun exposure, which must be excluded for 6 months.

In case of phototype III or IV, it is safer to ask the patient to apply bleaching cream and sunblock for 3 weeks before the pre-peel.

Vitamin A acid cream application for 3 weeks before may homogenize the epidermis and speed the healing phase. Usually, it is not used before phenol, as it is with TCA.

THE PEEL

The procedure is done (in a sitting position) preferably in the morning, which prevents patients suffering at night, always more anxious time. The burning sensation lasts for 6 hours. The patient must buy his pain medicine before the procedure.

In case of treating the whole face, intravenous fluids and sedation are administered.

The patient is administered with 500 cc of lactated Ringer's solution before the procedure and 1000 cc during the procedure (to prevent any systemic toxicity).

Sedation is made either by mouth (diazepam, bromazepam), intramuscular, or intravenous. Nerve blocks may also be used. A cardiac monitoring equipment and a pulse oximeter are mandatory.

In case of localized treatment (Figure 31.2) (perioral, periorbital), there is no systemic risk and neither hydration nor cardiac monitoring is useful. Sedation around the mouth is made by a nerve block (infraorbital, mental). Lidocaine without epinephrine (to avoid cardiac arrhythmias) is the best choice for anesthesia.

Figure 31.2 Protect nostrils from phenol vapor.

Then the skin is shaved (if necessary) and cleansed and an antiseptic is applied. The whole area is carefully degreased with a swab lightly soaked in acetone (or ether).

The patient is placed in a comfortable position in a room that is properly ventilated (to eliminate phenol vapors). A surgical skin marker is then used to draw the line marking the lower limits of the peel. The line will be hidden in the shadow of the jaw in a sitting position to minimize a possible demarcation line.

If under local anesthesia, it is best to prepare the patient with anxiolytics (diazepam, bromazepam) and/or analgesics (paracetamol, buprenorphine). Facial nerve blocks are quick and easy for a full-face anesthesia (frontal and upper eyelid block, infraorbitary, mental).

The full-face phenol peel is divided into 5 cosmetic units: forehead, cheeks, perioral, periorbital, and nose areas. Each area is treated separately and 10–15 minutes is expected before processing the next (to allow the phenol elimination). The procedure takes about 90 minutes.

The application is done with a cotton-tipped applicator. The applicator must be rolled over the skin; the left hand stretches the skin to obtain a homogeneous frosting. To avoid creating a visible demarcation line between the skin of the forehead and the hair, the solution should be feathered into the anterior hairline. The assistant should be ready to sponge away any reflex tears as soon as they appear to prevent any diluted phenol dripping onto the face (otherwise there are streaks). The ear lobes are peeled also. When treating the upper lip, do not forget to feather the solution on the vermillion.

The upper and lower eyelids have a very thin skin, which do not require a deep peel, but rather a medium-depth peel (pure phenol or TCA).

Once the peel was applied, the most common technique involves the occlusion for 24 hours (Figure 31.3). The assistant prepares the strips of occlusive tape, cutting it to the right size (1.5–4 cm long) so that the occlusive mask can be applied immediately. Micropore®, or equivalent (the choice of the tape is dependent on the practitioner), is applied in two layers to improve phenol efficacy by maceration. All the face is covered, except the eyelids.

Some practitioners prefer to use petrolatum or other specific ointment instead of tape. Even if the result is less dramatic on strong photoaging, it is much more comfortable for patients.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 31.3 Occlusion after perioral phenol peel.

Figure 31.4 After removing the tape.

THE POST-PEEL

Pain lasts for 6 hours after the procedure, and the patient needs pain medication.

Severe edema occurs quickly after phenol has been applied; corticosteroids can be administrated during the procedure to reduce it.

For the first 48 hours, the patient must eat and drink with a straw and sleep in a semireclining position.

It is often easy and relatively painless to remove the mask after 48 hours.

After removing the mask (Figure 31.4), the face is very swollen and looks severely burnt, coated in a thick liquid. At this time, the patient does not feel much pain.

Unlike ablative laser, a peel does not physically remove the skin, even though it devitalizes the skin completely. The skin can be considered as the base of a moist dressing using antiseptic and moisturizing creams. Avoiding scabs by repeating the application of emollient is fundamental to reduce risk of infection and scars. Do not pick at the crust!

We use water pulverization, disinfection with aqueous chlorhexidine, and fairly application of ointment with zinc oxide and copper sulfate.

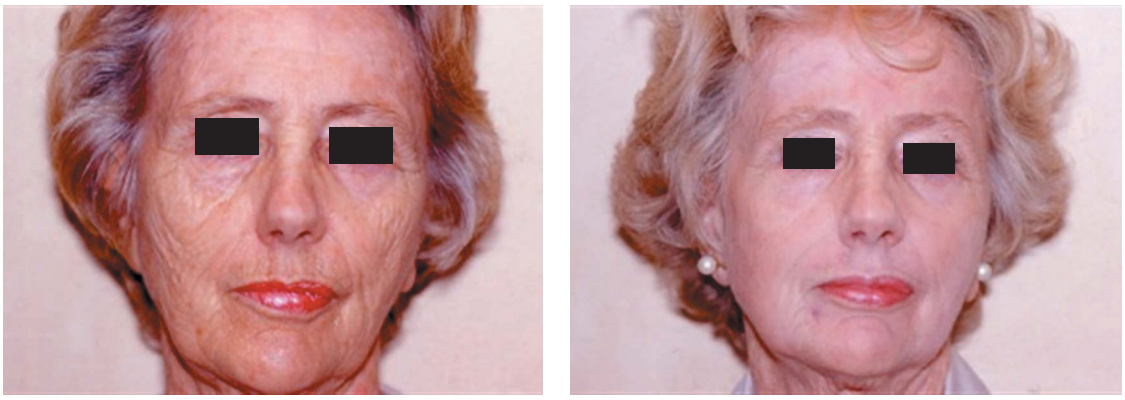
The epidermal layer returns to normal in 8–10 days. The patient may apply makeup to hide the very pinkish color of the skin as soon as the crusts have disappeared. Complete sun avoidance and effective sun protection is a must for 3 or even 6 months.

The patient should be observed regularly at the beginning of the treatment and at 3 months for the final result (Figures 31.5 and 31.6).

The spectacular clinical changes last for a long time. In histological sections taken 15 years after a phenol peel, the difference between the treated and nontreated skin is incredible. For 3 months, patients should actively protect their "new skin," but outdoor activities can be resumed. It is wrong to claim that never again can the skin get a tan.

COMPLICATIONS

A thorough knowledge of the symptomatology, rules of application, and post-peel care, with no place for improvisation, is essential to reduce complications. In our practice, complications are rare, but can nevertheless be linked to the invasive nature of the procedure [19,20]. Complications are more frequent with the Baker–Gordon formula.



(a) (b)

Figure 31.5 (a) Before phenol peel. (b) After phenol peel.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 31.6 (a) Before phenol peel. (b) After phenol peel.

Pigmentary Changes

Phototypes IV, V, and VI carry a much higher risk to develop PIH 2 or 3 weeks after the peel. Avoiding sun exposure and effective sun protection must be used, eventually a bleaching agent and topical corticosteroids. This reaction is generally considered to last for 3 months at the most.

In general, a slight loss of pigment should be considered as normal and not as a complication. The risk of depigmentation can pose a problem with dark-skinned patients. As yet, there is no effective treatment to return the color of the skin that has been lost.

The risk of a demarcation line is higher in phototypes IV and V, therefore the importance of feathering the borders.

Hypo- and hyperpigmentation are rarely associated.

Prolonged Erythema

Erythema is normal after a deep peel and will disappear progressively in 3 months. Sometimes, it persists for years (Figure 31.7) and needs a specific treatment (vascular laser), which does not work always well. It is more frequent in fair skin.

Scarring

Any previous surgical face-lift, peel, and isotretinoin use may be the risk factors for scarring.

Figure 31.7 Persistent erythema after years.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 31.8 Scarring of the upper lip.

Textural anomalies may essentially occur on the eyelids or the temples; they cause usually hypertrophic scar. Severe itching and intense redness may cause hypertrophic scarring, which must be treated by topical corticosteroids.

Hypertrophic scar is more frequent on darker skin and on the upper lip (Figure 31.8).

In this case, topical corticosteroid or intralesional injection of diluted triamcinolone, eventually combined with application of silicone plaque or silicone gel all day, is useful.

Pulsed dye laser, but also YAG long pulse or intense pulsed light, may improve the redness and flatten the scar.

Hypertrophic scar may transform into keloid after 6 months, which is much more difficult to treat.

Ectropiun can develop if the peel is performed after a lower blepharoplasty, which needs surgical treatment.

Infections

Infection is rare since phenol is bactericidal.

The presence of crusts favors infection. The best deterrent to infection is to minimize crusting by applying a smooth and greasy ointment, several times a day.

After full-face phenol, pseudomonas infection and toxic shock syndrome have been reported.

A culture for identification and sensitivity is performed to give the patient the suitable antibiotic treatment.

Herpes simplex flare-up is no more seen since patients are preoperatively treated by antiherpetic drug [21].

Contact Dermatitis

Related to the used products, which are applied onto the face, pruritus, redness, and delayed healing are suggestive signs.

Cardiac Arrhythmias

Phenol is cardiotoxic, but if the application rules are observed, there is no trouble.

CONCLUSION

Phenol peel has been performed for a long time, and many clinical and scientific reports have been published.

This is a marvelous technique, which must be performed by a well-trained practitioner.

Its application on the whole face is more risky than localized treatment (perioral or periorbital); this is why a combined procedure with TCA is easier and safer to perform.

To treat the deep upper lip wrinkles, it is as effective than laser resurfacing but much cheaper.

REFERENCES

1. Brody HJ, Monheit GD, Resnik SS, Alt TH. A history of chemical peeling. *Dermatol Surg* 2000; 26:405–409.
2. Baker T, Gordon H, Mosienko P, Sekinger D. Long-term histological study of skin after chemical face peeling. *Plast Reconstr Surg* 1974; 53:522–525.
3. Alt TH. Occluded Baker Gordon chemical peel: Review and update. *J Dermatol Surg Oncol* 1989; 15:980–993.
4. Brody H. Update on chemical peel. *Adv Dermatol* 1992; 7:275–289.
5. Edison RB. Phenol peeling: New standards of excellence. *Aesthet Plast Surg* 1996; 20:81–82.
6. Landau M. Cardiac complications in deep chemical peels. *Dermatol Surg* 2007; 33:190–193.
7. Koopman C. Phenol toxicity during face peels. *Otolaryngol Head Neck Surg* 1982; 90:383–384.
8. Bertolini TM. Is the phenol-croton oil peel safe? *Plast Reconstr Surg* 2002; 10:715–717.
9. Baker TJ. Is the phenol-croton oil peel safe? *Plast Reconstr Surg* 2003; 112:353–354.
10. Stone PA. The use of modified phenol for chemical face peeling. *Clin Plast Surg* 1998; 25:21–44.
11. Giese SY, McKinney P, Roth SI, Zukowski M. The effect of chemosurgical peels and dermabrasion on dermal elastic tissue. *Plast Reconstr Surg* 1997; 100:489–498.
12. Kligman A, Baker T, Gordon H. Long-term follow-up of phenol face peels. *Plast Reconstr Surg* 1985; 75:652–659.
13. Nelson B, Fader D, Gillard M. Pilot histologic and ultrastructural study of the effects of medium-depth chemical facial peels on dermal collagen in patients with actinically damaged skin. *J Am Acad Dermatol* 1995; 32:472–478.
14. Stegman S. A comparative histologic study of the effects of three peeling agents and dermabrasion on normal and sun damaged skin. *Aesthet Plast Surg* 1982; 6:123–135.
15. Ayres S. Dermal changes following application of chemical cauterants to aging skin. *Arch Dermatol* 1960; 82:578–585.
16. Bell E, Sher S, Hull B. The reconstitution of living skin. *J Invest Dermatol* 1983; 81:2–10.
17. André P. Peeling au phénol de la région péri-buccale. *J Méd Esthét Chir Dermatol* 1995; 87:161–167.
18. Baker T, Gordon H. Chemical peeling as a practical method for removing rhytides of the upper lip. *Ann Plast Surg* 1979; 2:209–212.
19. Alt TH. Avoiding complications in dermabrasion and chemical peel. *Skin Allergy News* April 1990; 2.
20. Maloney BP, Millman B, Monheit G, McCollough EG. The etiology of erythema after chemical peel. *Dermatol Surg* 1998; 24:337–341.
21. Prekins SW, Sklarew EC. Prevention of facial herpetic infections after chemical peel and dermabrasion: New treatment strategies in the prophylaxis of patients undergoing procedures in the perioral area. *Plast Reconstr Surg* 1996; 98:427–433.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Combination chemical peels

Philippe Deprez and Evgeniya Ranneva

TYPES OF COMBINATION

Penetration Enhancement Combinations

Definition: To make a deeper penetrate, a peeling solution is associated with another technique or another peeling.

Mosaic Peels and Pixel Peels

Definition: A combination of different depths of peelings during the same session.

Mosaic peel: Different types of peeling are used on the same area: a focal deep peeling is done very locally, together with a lighter peeling around it to make the result more uniform.

Pixel peel: The skin is microperforated before the application of peeling solution, in order to deepen the penetration of the acids, so achieving better results without using more acids.

Some areas will be deeply treated, mainly for removing local wrinkles or deep lentigines, whereas other areas will be treated more superficially at the same time, during the same peeling session, mainly for balancing the result on photoaged skin. If an area is severely touched by wrinkles when the rest of the face is relatively good appearing, it is not necessary to impose to the patient a full-face deep peeling because a local deep peeling can be sufficient, only locally, to resolve the problem. When some large lentigines stain a skin, it is not always necessary to perform a medium or deep peel on the whole face, décolleté, or hand, and it can be safer to use the "pixel peel" or the "mosaic peel" technique. This allows to deeply treat a lentigine very locally and to apply a uniformization peeling all around the deeply treated area.

Combination between Peelings and Other Nonabrasive or Perforating Aesthetic Procedures

Fillers, mesotherapy for biorevitalization, botulinic toxin, and many more methods can be combined with some peelings.

PENETRATION ENHANCEMENT COMBINATIONS

The corneal layer is the main barrier for any product applied on the skin and also for penetration of wounding agents: removing, damaging, or multiperforating the horny layer induces a faster and deeper peeling agent penetration. I am used to compare corneocytes with the plasticized cover of a book that protects the internal pages—keratinocytes, in this comparison—against external aggressions. The literature first described techniques that combined one of the weak wounding agents (alpha hydroxyl acid [AHA] or salicylic acid) in order to increase the permeability of the epidermis and allow a deeper penetration of a stronger peeling agent, trichloroacetic acid (TCA), applied after the injury.

Association of AHA and TCA

The most efficient and shortest AHA is the well-known glycolic acid. Glycolic acid can be used at several concentrations and at several pH. The strength of a glycolic acid peel depends on the concentration and pH, but its action also depends on the application protocol.

Indications

The combination peel (glycolic + TCA) allows a quite good result on fine lines, freckles, lentigines, and keratoses, when a peeling such as a 20%–25% W/W TCA solution (e.g., Unideep 23% w/w TCA—Skin Tech, Spain) is used after 70% native glycolic acid peel. Freckles, little lentigines, keratoses, and epidermal and "grenz zone" pigmentation are largely improved when a peeling such as Easy TCA (15% w/w TCA—Skin Tech Spain) is used after glycolic acid.

Acne scars, deep wrinkles, folds, and sagging skin are not good indications for this technique since these pathologies need a reticular dermis deep peel to be treated.

How to Apply Glycolic Acid

Glycolic acid 70%, not buffered (native pH: 1), is segmentally applied on the skin using a cotton ball or any convenient applicator. Depending on the thickness and oiliness of the skin, several coats might be needed to induce the first erythema, which is a sign of epidermal action of glycolic acid and end point of this part of the peeling.

Rinse the Glycolic Acid

As soon as erythema is seen, glycolic acid has to be rinsed with a large quantity of water, but should not be neutralized. Indeed, the use of a neutralizer would transitorily modify the skin pH and "preneutralize" the TCA that will be applied just after the AHAs. Rinse until the patient declares that he or she does not feel any burning sensation anymore. Be cautious if some frosting points have appeared: the TCA penetration will be faster on this area. After rinsing, dry the skin using soft gauzes that do not induce any mechanical abrasion.

How to Apply the TCA Solution

After rinsing the AHA peel and depending on the needed peel depth, I will possibly combine two different TCA peels with standardized W/W concentrations: Skin Tech Easy TCA 15%,

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

normally used for inducing a peeling up to the basal layer or the "grenz zone," or Skin Tech Unideep 23%, usually applied when a peel up to the papillary dermis is needed. For non-facial skin (including the neck), 15% TCA is preferentially used, since the body's skin could show unexpected reactions when combining higher concentrations. The face tolerates a 20%–25% TCA (W/W) after glycolic acid. Application should be very careful, in any case, only after checking individual responses on little areas. The depth of skin injury and regeneration depends on the transepidermal penetration (how the skin is permeable) and also on the number of coats that are applied: more coats giving a deeper peel. Knowing that a previous application of glycolic acid will deepend on the TCA penetration, the selected TCA peel will be applied the same way as usual but waiting for another end point compared to the usual one: for example, after few minutes, the first coat of Easy TCA will easily induce a peel up to the grenz zone (end point; frosting clouds), and Unideep will induce a uniform pink white frosting.

What to Do at the End of TCA Application

During peels, mainly during TCA application, patients experience a burning sensation, which is stronger after Skin Tech Unideep 23% than after Skin Tech Easy TCA 15%. Classical technique recommends using a fan or applying cold packs to relieve the burning or stinging pain, but many patients do not feel any relief by using these methods. Fortunately, both these peels (Easy TCA and Unideep) come together with a "post-peel mask" cream that is applied on the face immediately after the frosting has appeared and that nearly immediately suppresses the pain and inflammatory reaction. Post-peel mask has to be applied once only, by the MD, immediately at the end of the peel. It is not a neutralizer and stays on the skin until the next morning, when it is washed.

Post-Peel Treatment

See general recommendations, depending on the depth of combined peel.

Association of Carbon Dioxide Application Followed by TCA Peel

Carbon dioxide applied on the skin disrupts its natural permeability and allows TCA solutions to penetrate deeper and faster. The depth of the wound caused by the cold directly depends on the contact time: a contact duration of 2–5 second is considered as grade 1 (2 seconds on thin skin and 5 seconds on thick skin), a contact duration of 4–8 seconds as grade 2, and 9–15 seconds as grade 3.

Technique

Skin disinfection (alcohol) and degreasing (acetone).

Carbon dioxide exists under pressure in special canisters from which it is easy to extract a pencil-shaped solid block. Carbon dioxide would stick with the skin if directly applied on it. Therefore, it is usual to dip the block in a solution (2/3 acetone + 1/3 alcohol) so that it will be possible to make it slip on the skin. A fan is appreciated by the majority of the patients, since it, at least, evaporates uncomfortable acetone and alcohol vapors faster. One paracetamol + codeine tablet can be taken 30 minutes before the procedure to reduce discomfort.

Carbon dioxide will be mainly applied specifically on little areas, where we need a deeper TCA penetration. We never use carbon dioxide on large areas, since we actually have at our disposal fractional lasers, skin abrasive techniques, or microneedling devices that can substitute this technique, with many advantages.

Carbon Dioxide Contact Duration

Acne scars: grade 3 application (insisting even on the edges of scars to smooth it)
Seborrheic/actinic keratoses: grade 2 application
Perioral wrinkles: grade 2 application
Periocular wrinkles: grade 1 application

TCA Application

After the application of carbon dioxide, the skin is dried with a gauze and TCA is applied uniformly. We are used to apply TCA soaked on 2 cotton buds. Easy TCA (15% w/w) or Unideep (23% w/w) can be safely applied after carbon dioxide. The depth of the peel reaches, papillary and reticular dermis, respectively. Higher concentrations should be used very cautiously (mainly in case of deep acne scars or thick keratoses) since the risk of scarring (that would be mainly hypertrophic, since atrophic scars only would occur for still deeper wounds) increases with the TCA concentration. We prefer to apply TCA in two passes rather than increase the TCA concentration.

Association of Jessner Peel Followed by TCA Peel or by AHA Peel

Jessner's solution formula (in the United States, also called Combe's solution)

Resorcinol	14 g
Salicylic acid	14 g
Lactic acid	14 g
Ethanol 95% ad	100 mL

Jessner's solution should be stored in a brown glass sealed vial. It can be stored in the refrigerator for more than 2 years. The oxidation of the solution gives a pinkish color. Contact of Jessner's solution with nails can discolor it and give a yellow-orange color. The depth of Jessner's solution is modulated by the number of coats. One coat only induces a very superficial peel, while 3 or 4 coats can remove the full epidermal thickness.

Jessner before an AHA Peel

Usual AHA peels are known for not having a uniform penetration. Jessner peels would uniformize and improve the penetration of AHAs through the skin. Moy described the following technique: After preparation and conventional cleaning of the skin, apply Jessner's solution up to the "level 1"; only one coat is applied. A rash appears accompanied by at most a few points of localized "frosting." In case of thick and oily skin, several coats can be applied using a brush, cotton buds, or any applicator that suits the MD. Allow 5 minutes between each layer possible. Apply the final coat. No neutralization is needed, but salicylic acid creating a white coat on the skin can be gently removed or washed with water before drying the skin and applying TCA solution. Jessner's solution will disrupt the epidermal impermeability and allow a faster and deeper pass of the AHA solution. Selection of glycolic acid concentration (from 50% up to 70%; from pH 1 up to pH 2.5) follows the security rules described earlier in this chapter. Then, apply uniformly

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

the glycolic acid solution until erythema. Neutralize. The problem of this combination is that, classically, glycolic acid should be neutralized as soon as erythema appears. Unfortunately, preexisting erythema due to Jessner's solution does not allow to correctly estimate the evolution of AHAs, and frosting with unexpected overruns is common. This technique is more difficult and could be used in the treatment of very oily and thick skin, which are resistant to significant concentrations of AHA left in place for long periods before neutralization.

Note: In our practice, we stopped using this difficult technique and replaced it by the use of Easy Phytic solution, which is a 60%, pH:1 mixture of lactic, glycolic, and mandelic acids, together with phytic acid. The solution is slowly released, allowing the progressive and harmless actuation of 100% of the molecules of the peeling solution. The solution is also self-neutralizing, avoiding any mistake about the right moment to neutralize. Application protocol, linked to clinical signs, allows an easy penetration up to the basal layer in every skin type, without any possibility of mistake. In the case of Easy Phytic solution, no prepeel conditioning should be done, since the full integrity of horny layer is needed for allowing the slow release penetration. Removing the full stratum corneum would induce a very fast penetration of this specific solution, increase the risk of side effects, and impose a neutralization that is normally not needed.

Jessner before a TCA Peel

Jessner's solution can be used as preparation for a TCA peel. Monheit describes the following technique: After preparation and conventional cleaning of the skin (alcohol and acetone), apply Jessner's solution up to the "level 1"; only one coat is applied. A rash appears accompanied by at most a few points of localized "frosting." In case of thick and oily skin, several coats can be applied using a brush, cotton buds, or any applicator that suits the MD. Allow 5 minutes between each layer possible. Apply the final coat. No neutralization is needed, but salicylic acid creating a white coat on the skin can be gently removed or washed with water before drying the skin and applying TCA solution. Jessner will disrupt the epidermal impermeability and allow a faster and deeper pass of the TCA solution. Following the same logic as for TCA combined with glycolic acid, we will select Easy TCA 15% or Unideep TCA 23% depending on the final depth desired by the MD.

Apply the selected TCA solution that penetrates faster—and more evenly when a thick oily skin is treated—due to the rupture of the effectiveness of the epidermal barrier. Penetration will be felt more painful than usual. This technique could be used in patients with oily and thick skin in which we want better penetration of TCA.

Immediately after the frosting of TCA peel has appeared, apply the "post-peel mask" that can be found in the peel kit of Easy TCA or Unideep, in the needed quantity (see dosing card) to relieve pain and inflammatory reaction. Post-peel mask stays acting on the skin until the next morning, and then it is washed and emollient or nourishing or depigmenting creams are applied.

Note: We stopped using this technique many years ago since easier and safer techniques actually exist.

"Laser Pixel Peel" or "Fraxpeel": Association of Fractional Laser and TCA

Definition

The risk of unwanted adverse reaction, such as long-term residual erythema, postinflammatory hyperpigmentation, pain, infection, and scars, made ablative lasers much less attractive. Technical advances that made lasers more like the microneedling technique then made possible the launch of the "fractional laser" possible: The laser beam is divided into many narrow beams, and this pixelated ablation does not remove a large surface of skin but induces deep and narrow wells of coagulation. As long as a large surface of skin is not ablated, skin regeneration is much faster and gives much less problem. At the same time, dermal stimulation and therefore skin tension occur all around the penetration wells. The same happens when using the "Pixel Peel" technique, which will be described later.

Anyway, fractional laser has revolutionized skin resurfacing treatment: significant clinical results (but not as good as full ablative techniques) could be obtained, with lower (but not absent) risk of side effects. Erbium-doped yttrium aluminum garnet (Er:YAG) fractional laser appears to be the actual best laser for wrinkle and pore size reduction, skin texture, and acne scar improvement. Hyperpigmented lesions do not seem to be a good indication for fractional laser, since the melanocytes that have not be killed in the "penetration well" are stimulated by the temperature shock and the subsequent inflammation and could trigger postinflammatory pigmentation. The "Pixel Peel" technique has then been adapted to Er:YAG fractional laser. Dr. Han (Korea) proposed a combination treatment of Er:YAG fractional laser (Dermablate Effect) and Easy TCA peel (Skin Tech), taking advantages of the unique features of each treatment method: deep laser stimulation wells done with Er:YAG fractional laser are combined to a "basal layer" (frosting point) peeling using Easy TCA (Figure 32.1). The post-peel mask of Easy TCA was clearly stopping very quickly posttreatment pain, inflammation, and erythema. Not only the results of this combination therapy were better, but also the risk of side effects has been much reduced, even on Asian skin.

How to Combine Er:YAG Fractional Laser with Easy TCA Peel

Laser treatment is done first, in conformity with usual rules. Easy TCA peel is applied immediately after fractional laser. The acid will penetrate into the tiny holes induced by the fractional laser and create wells of "secondary" proteocoagulation (Figure 32.2). "Primary coagulation" has been made by the laser beams. In case an anesthetic cream, such as eutectic mixture of local anesthetics (EMLA), has been applied before laser treatment, it should be carefully removed before peeling application since its basic pH (9.4) would neutralize the TCA peel at the same time as its application. EMLA should therefore be removed with water and soap. Then the skin pH should be balanced again using a Skin Tech cleanser foam (pH: 5.5), before applying the TCA peel.

Immediately after fractional laser application, the skin has been multiperforated, forming numerous wells made of dead cells that do not give the skin its physiologic impermeability, focally. The Easy TCA solution will pass easily through these wells of hyperpermeability, creating secondary protein coagulation in the proximal neighborhood of the well created by laser. At the same time, the full epidermis is treated by TCA that induces a stimulation of epidermal renewing and epidermal turnover. This is the way the result is enhanced compared to laser application only.

Fortunately, Easy TCA comes together with a post-peel mask that controls the post-peel inflammation and, in this specific case, will control the post-combined treatment inflammation. Immediately at the end of the peel, the practitioner should then apply the "post-peel mask," which will very quickly remove the posttreatment pain, inflammatory sensation, and redness.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 32.1 (a) Before and (b) after session of fractional laser followed by Easy TCA peeling. (Courtesy Dr. Han, Korea.)

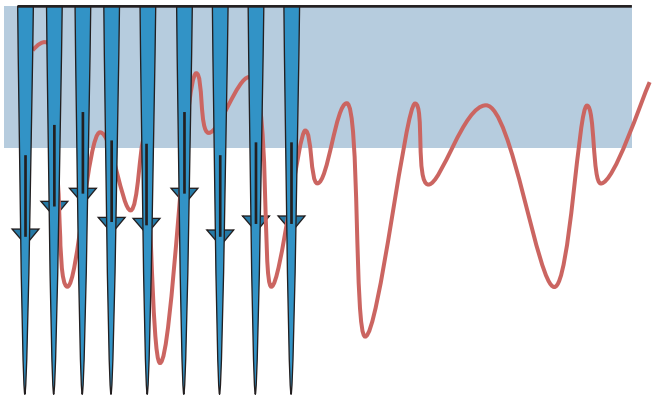


Figure 32.2 Fractional laser opens holes through epidermis. Peeling, normally intended to perform a basal layer peel (Easy TCA), will penetrate deeper, in a pixelated way, down to the dermis. Easy TCA post-peel mask will also immediately control the post-treatment inflammation.

Post-peel mask should be applied once only and left in place until the next morning; then, it is washed with a soft cleanser and post-peel daily home care can begin: blending bleaching cream in case of post inflammatory hyperpigmentation (PIH) risk, tensing cream with dimethylaminoethanol (DMAE) for sagging skin, etc.

Sunscreen is mandatory after the treatment.

The combination of Er:YAG fractional laser and Easy TCA results in a better outcome, in a much lower posttreatment inflammation and pain, that reduces the risk of side effects.

"Microneedling Pixel Peel": Microneedling and TCA Peeling

Definition

"Microneedling Pixel Peel" is a recently emerging method that consists in microperforating the skin with a handpiece terminated by a "roller" supporting needles, or a "stamp" (for very small areas) immediately before applying a TCA peeling solution (Figure 32.3). The peeling solution will penetrate through

Figure 32.3 Aesthetic Dermal® AD ROLL TD® Specific microneedling (copyrighted) device, 600 needles, with a "stamp" included into the handpiece to allow small-area microneedling (around eyes, lips, around ears, etc.). Needle length can be selected by the user.

the little wells produced by the needles at a depth depending on the length of the needles. We hence take advantage of the stimulation induced by the microneedling itself, which will be enhanced by the TCA penetration. At the difference of a conventional peeling where the acid has to penetrate evenly through the skin, up to the desired depth, Pixel Peel allows some kind of "deep microtower peel," by coagulation of the walls of the wells done by the needles. It results in a deeper fibrosis induction, and therefore a better skin tension, without significant increase of epidermal damage and, if the needles are short, without a long social eviction. That's the peeling corresponding to actual fractional lasers.

Selection of Needle Length

Needle length selection will depend on the depth we want the acid to penetrate. Let's consider that the usual epidermal thickness is 0.5 mm. A 0.25 mm long microneedling device will create wells inside of the epidermis, allowing the TCA to easily penetrate up to the basal layer. A 0.5 mm long needle device will perforate the full epidermal thickness, bringing the acids up to the level of grenz zone. Longer needles penetrate deeper into the skin, stimulate deeper layers, and theoretically allow a deeper penetration of the acid. We can nevertheless speculate

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

that the depth of acid penetration will not exactly follow the length of the needles. In reality, when TCA penetrates into the tiny wells, it induces a proteocoagulation of the walls of the well that will not allow a full penetration up to the bottom of the hole. We will therefore take advantage of two types of stimulation: the one induced by the needle itself, which is deeper, and the one induced by the combination of the needle and the TCA.

Indications and Needles' Length Selection

The main indication is skin antiaging treatment, since the needling associated with the peeling will induce a strong dermal stimulation. Indication depends on the needle length: A 0.25 mm needle will be useful for treating epidermal problems, 0.5 mm needles will be useful for treating problems that need an action at the level of the basal layer or grenz zone, 1 mm needles will be used for stimulating the papillary dermis, and longer needles will be useful for stimulating the papillary and reticular dermis.

Microneedling is a perforating treatment that can be quite aggressive when needles are longer than 0.25 mm. The device should be therefore sterile. We strongly recommend, for evident reasons, using the microneedling device only once and to discard it after use.

The face as well as the body can be treated. There is no limitation in surface, as long as no potentially toxic product is used after microneedling. Pixel Peel is therefore an interesting option for treating neck, arms, legs, and abdomen skin laxity.

How to Do the Treatment

After careful skin disinfection, pass the microneedling device 4 times in 4 different directions. The pressure to be applied is similar to the one of a scratching. The "roller" has to be lifted from the skin at each passage to avoid repeating the same holes on each occasion, which would reduce the final number of efficient punctures. The use of 0.25 and 0.5 mm needles usually does not induce any bleeding, except if 0.5 mm is used on thin skins, but bleeding points occur when longer needles are used. Bleeding is not a problem at all. The use of 0.25 mm needles is not really painful and 0.5 mm is bearable. Longer needles could induce quite a lot of pain, in direct relation with the length of the needles. The use of 2.5 mm needles is more painful compared to 1 mm. The microneedling treatment fortunately allows an easy topical anesthesia: creating holes through the stratum corneum allows an anesthetic solution to easily pass the basal layer of the epidermis and papillary dermis, which are found to be sensitive nervous terminations. When the Pixel Peel technique is used, we therefore recommend to pass the roller on the skin superficially for a few times, in order to microperforate the corneal layer and to apply, directly on the micropunctured area, a gauze soaked with a 2% adrenalinated lidocaine solution. Anesthesia occurs in parallel with vasoconstriction that stops an eventual bleeding. Longer needles or deeper pressure can then be applied without inducing local pain. At the same time, further application of TCA will not be painful, the skin being under local anesthesia (Figure 32.4).

Knowing that the holes done by the needles have a fast natural tendency in closing, thanks to the skin's elastic properties, I recommend treating sequentially the area: the microneedling device is passed on the first area (for example, 50% of the forehead) and the TCA peel is applied immediately after microneedling, when the holes are still open. The next area is then treated the same way. We usually apply Easy TCA peel (15% w/w—Skin Tech) for this combined treatment. The number of TCA coats depends on the symptoms visually appearing few minutes after the acid application: the end point should be the appearance of white or grey white frosting points at the level of every skin perforation. Then, "post-peel mask" is applied (Easy TCA post-peel mask has a strong anti-inflammatory efficacy, limiting side effects).

Post-Peel

The post-peel of the Pixel Peel technique done with short needles (0.25 mm) is identical to the one of a peeling done without microneedling. When microneedling is done using 1 mm to 2.5 mm needles, the post-peel shows a dark crusting at day 3 or 4, but a fast skin healing at the end of the first week (Figure 32.5).

Should the Pixel Peel technique be used to reach the reticular dermis, then we recommend to cover the skin with a product called "Yellskreen" (Skin Tech SL, Spain) that contains bismuth subgallate powder, which is a disinfectant and speeds up skin healing.

At day 3, sterile petrolatum jelly should be applied on the edges of the treated area to avoid creating inflammation between the crust and the skin surrounding it. At day 6,

Figure 32.4 (a) Before and (b) after pixelated penetration of Easy TCA peel applied immediately after 2 mm microneedling. Indication: large lentigine (which will disappear) surrounding verruca seborrhoica (which will not disappear).

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 32.5 (a) Immediate post-peel: apply a thick coat of the post-peel mask, included in Easy TCA peeling kit. (b) At day 4, scabbing has a normal aspect.

petrolatum jelly should be applied on the whole scab to unstuck it and make it fall down at day 7 without finger manipulations. The general post-peel recommendations listed in the introduction of this chapter have to be respected.

Abrasive Techniques associated with Peelings

Definition

Acne scars and striae distensae are common problems for which the treatment has often been considered as disappointing (Figure 32.6).

Pike acne scars are not easily treated by chemical peels. Deep phenol peels are not always giving good results, due to a lack of penetration of the peeling solution up to the bottom of scars, even if a small cotton bud or a wooden toothpick is used to try reaching it. Chemoabrasive techniques allow getting a satisfying result, using a controllable—even if difficult—technique.

Striae distensae are also not easily treated by chemical peels. Lasers are also largely disappointing in this indication.

Figure 32.6 Frosting during deep phenol peel done for treating acne scars. Phenol visibly did not penetrate up to the bottom of acne scars. Result will be insufficient, even if some yellowish spots show that phenol penetration was maximal.

Anterior chemoabrasion can give an interesting solution to very old, atrophic, and large stretch marks and allow up to 75% enhancement of the situation.

Anterior chemoabrasion is contraindicated in case of local infections, insulin-dependent diabetes, immunodeficiency, skin infections, autoimmunity diseases, etc.

Abrasive techniques can be combined with peelings in order to improve the results, in case of deep problems.

We distinguish the following:

1. The "posterior" chemoabrasion: A peeling is done and an abrasion is performed immediately after the peeling. This abrasion can be done immediately after TCA or phenol peels.
2. The "anterior" chemoabrasion: An abrasion is done at a selected depth (usually grenz zone or—as maximum—papillary dermis), and one coat only of Easy TCA peel (Skin Tech SL, Spain) is applied immediately after abrasion. Abrasion can be performed using a sterile sandpaper sheet or, deeper, a diamond drill. We used only Easy TCA peel after abrasion because of the strong protective anti-inflammatory effect of the post-peel mask that allows a smooth post-peel period and a lack—up to date—of side effects, when the technique is strictly respected. Attention! The anterior abrasive technique is the deepest way of performing peelings and should be used by skilled and trained professionals only.

Caution: Anterior chemoabrasion cannot be done using a TCA concentration of higher than 15% w/w. Anterior abrasion cannot be done before phenol peelings for toxicity reasons: abrasion would allow a very fast penetration of phenol into the skin and blood circulation that would overpass the detoxification potential of the body, and there would be a high risk of general toxicity and eventually death of the patient.

Anterior Chemoabrasion

The sand abrasion kit of Skin Tech (abrasion with sandpaper) includes

1. Single-use sandpaper, sterilized by gamma rays (P220 grain, wet or dry type)
2. Bismuth subgallate, healing and disinfectant powder, presented in a jar for medical use and small envelopes to be used by the patient, as part of the post-peel daily care during the next days after the abrasion procedure

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Using the Sandpaper Combined with Easy TCA Disinfect the skin with alcohol and degrease with acetone.

Preparing and Performing the Abrasion Procedure Roll a sheet of sandpaper around a rounded object to take it firmly between fingers. Stretch the skin with one hand and rub the whole area gently and carefully back and forth with the sandpaper. This type of sand abrasion renders the skin permeable by removing the stratum corneum and some keratinocyte layers.

After sand abrasion, the course of action will depend on the chosen protocol:

1. *Protocol without acid*: More superficial and less risky (treatment of the décolleté). Apply the post-peel mask directly after abrasion, without acid solution, followed by occlusion.
2. *Protocol with acid*: Deeper. Topical anesthesia to be administered before applying the Easy TCA peel solution. An occlusion (treatment of striae) can be used for deepening the action of the peeling.

Protocols without occlusion are possible.

How to Select the Right Depth

Grade 0 Sand Abrasion
Subjectively: The patient feels no pain.
Objectively: Touching the epidermis conveys a sensation of "corneocytary palpation"—that is, the finger slides over the surface layers of dehydrated and dead corneocytes. If sand abrasion is limited to this level, the anesthesia will be of poor quality and the peeling too superficial and thus insufficient. No blood drop can be seen.

Grade I Sand Abrasion
Subjectively: The patient notices the abrasion as uncomfortable but experiences no pain.
Objectively: Epidermal palpation still conveys a sensation of "corneocytary palpation." If sand abrasion is limited to this level, the anesthesia will be insufficient and the peeling superficial. No bleeding can be seen.

Grade II Sand Abrasion: The desired level for stretch marks treatment
Subjectively: The patient feels the first pain from the abrasion and the very first points of bleeding appear; the abrasion must usually be stopped at this point, although the pain threshold does vary from one patient to another (hence the importance of touching).
Objectively: Epidermal palpation gives a sensation of "keratinocytary palpation": the finger feels a slowing sensation as it passes over the living, well-hydrated keratinocytes revealed by the abrasion, when compared with the dehydrated and slippery corneocytes of the adjacent, nonabraded skin.
Keratinocytary palpation: The finger slides over the dehydrated corneocytes of the nonabraded skin and is halted on the well-hydrated keratinocytes revealed by the abrasion.

Apply the Easy TCA solution and the post-peel mask or the post-peel mask only, according to the chosen protocol; then occlude if the chosen protocol so suggests.

Grade III Sand Abrasion: If the abrasion is continued after the grade 2
Subjectively: The patient perceives the abrasion as painful. Proceed with caution: the abrasion is reaching the papillary dermis.
Objectively: Much more drops of blood appear, uniform bleeding. The abrasion should have been stopped before this point. Application of Easy TCA acid after a grade 3 abrasion can be harmful.

Occlusion The occlusion of the peeling solution and the post-peel mask stimulate the atrophic areas, while the abrasion procedure causes a resurfacing effect of the normal skin between striae.

Using Bismuth Subgallate The bismuth subgallate facilitates the post-peel and prevents patients from having to perform complex local care. Sprinkle the powder on the moist, deepidermized areas. Spread using a cotton bud or finger with glove. Reapply powder on the moist areas over the first 2 days. Patients must refrain from scratching the area. Protect the treated zones with a dressing that does not adhere to the wounds (e.g., Melolin by Smith and Nephew). Around the sixth day, apply Vaseline to assist desquamation and prevent pruritus.

Follow with the prescribed daily care cream.

Anterior Chemoabrasion with Easy TCA for Striae Treatment

The peeling must be performed by experienced physicians only. Physicians must monitor patient progress carefully. Strict observation is required.

Prepeel Skin Conditioning Two weeks before the procedure, use blending bleaching cream twice a day to avoid post-peel PIH.

Prescribe a Painkiller: Patients could take codeine + paracetamol 1 hour before and some hours after the striae procedure.

Skin Preparation Cleanse (Skin Tech's prepeel cleanser); disinfect with alcohol; leave to dry; degrease with acetone; leave to dry; and divide the area to be treated into subareas of 10 cm × 10 cm.

Abrasion with Sandpaper Wear gloves while working. Roll up the sandpaper around a plastic bottle. Carry out painless, slow, gentle, and uniform sand abrasion on the whole area. Perform grade II abrasion.

Grade II Abrasion The sandpaper provides a more uniform abrasion than the coridon grains or the erbium laser, but coridon grains and erbium laser can eventually replace the sandpaper for this purpose.

Carry out the sand abrasion just until the very first points of blood show up. Stop sand abrasion at this moment.

Anesthesia The sand abrasion procedure is not painful. However, applying an acid peeling solution on a previously sandbraded area will be very painful, so anesthesia is required. Anesthetize by applying gauze soaked in 2% lidocaine with adrenaline (about 5 cc per 10 × 10 cm area). Leave it on for about 10–15 minutes under plastic film. Vasoconstriction will take place when the anesthesia begins to work.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Applying Easy TCA Apply the Easy TCA peeling solution as follows: Apply one coat of Easy TCA, using circles application. Thanks to the topical anesthesia, the application of the Easy TCA peeling solution should not produce pain or discomfort, except in the surrounding areas where there is not enough anesthesia working.

A light pink-white frosting is generally obtained quickly. It usually appears only on the normal (not atrophic) skin between the striae. The combination of the Easy TCA peeling and the abrasion procedure gives rise to a resurfacing effect on the normal skin between the striae. This stimulates the growth of remaining normal keratinocytes and stimulates the regeneration of a normal looking skin.

Applying the Post-Peel Mask and Occlusion Apply about 0.5 g of post-peel mask (use the "blue card" in the Easy TCA kit) per 10 × 10 cm surface area. Let the post-peel mask work between 6 and 24 hours, under plastic occlusion. The post-peel mask under occlusion will cause significant but controlled inflammation at the bottom of the atrophic striae. This can stimulate dermal cellular division and increase metabolism of dermal cells. Physicians should remember that the peeling procedure gets deeper when the occlusion takes longer: a longer occlusion means a deeper peeling.

How to Select the Right Depth

The depth of the peeling will depend on different factors:

1. *The abrasion depth*: The peeling procedure gets deeper depending on the abrasion depth. A deeper abrasion means a deeper peeling procedure. Be conservative: start with a superficial treatment. When in doubt, choose a superficial treatment.
2. *The number of coats of Easy TCA peeling solution*: Look at the frosting. For superficial nonatrophic striae, the frosting should be a uniform pink-white color. For deep and atrophic striae, the frosting should appear only on the normal skin between the striae; it must be pink-white, never pure white. For patients with thin skin, apply just the post-peel mask (no Easy TCA acid) and occlusion, as in the décolleté protocol.
3. *The occlusion duration*: Occlude using an impermeable plastic film (cling film). Remove the plastic after a period of 6–24 hours: 6-hour occlusion, superficial treatment (but gives more PIH); 12 hour occlusion, medium-depth treatment; and 24 hour occlusion, deep treatment. Avoid deep treatment on the breasts or the upper thighs.

Cares after Removing Occlusion Should epidermal liquefaction occur after a 24 hours occlusion, dust the area with bismuth subgallate, continuing as long as the skin remains moist (usually 48 hours). Cover with a dressing that will not adhere to the wounds (e.g., "Melolin" by Smith and Nephew) so as to prevent the dressing from sticking to the skin.

When the skin and the powder have dried, wait 24 hours before applying Vaseline (petrolatum), used to assist desquamation and prevent pruritus. From day 4–5 to day 7, Vaseline should be applied to assist desquamation.

Table 32.1 Frequency of Treatment and Number of Sessions

	Striae type	Number of sessions
Once a month	Small superficial striae	1–3
Once a month	Atrophic, old, wide, deep striae	2–5

How It Works

1. Easy TCA + sand abrasion cause significant stimulation of the growth of the normal keratinocytes between atrophic bottom of striae. This gives skin a smoother look, making it progressively more even and softer to the touch.
2. Post-peel mask under occlusion causes strong dermal stimulation. This makes flaccid skin look fresher and improves its tonicity. Physicians must monitor patient progress carefully. Strict observation is required.

PIH Prevention before and after the Peeling Procedure Always administer preventive treatment for PIH: Apply the blending bleaching cream twice a day, 2 weeks before the peeling procedure.

Continue with the blending bleaching cream for at least 6 weeks after the peeling procedure. Apply the blending bleaching cream twice a day. Avoid exposure to the sun. Hydroquinone-based cream can be used if needed.

Useful Tips Avoid infection and prolonged erythema (survey and IPLASE cream use after first week). If local erythema is longer than 15–21 days, prescribe a topic corticoid. Prescribe a painkiller to ease pain on the first day. Avoid contact with water during the first week. (It could cause pain and infection). Administer antibiotics if necessary. Avoid sunlight during the 3-month post-peel. Be cautious of the Koebner phenomenon (psoriasis, vitiligo).

Complications usually increase with the depth of the peeling. Always start with a superficial protocol and then gradually work deeper. The deeper the peeling, the more expert and careful the physician must be. Patients must always be informed of the type of post-peeling treatment they will undergo. Do not treat patients with "cutis laxa."

Table 32.1 sets out the variables in treatment, depending on the type of striae.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

33

Dermabrasion

Anthony V. Benedetto

HISTORY

Since the time of the Egyptians, man has used different abrasive implements such as pumice and alabaster to remove different types of scars and blemishes from the surface of the skin [1,2]. At the turn of the twentieth century, Kromayer described using cylindrical knives, rasps, and burrs attached to a motor-driven dental instrument with either a clockwise or counterclockwise rotation to remove scars [3]. Iverson reported on successfully removing traumatic tattoos with sandpaper in 1947, which occasionally resulted in foreign body silica granuloma [4]. Dermabrasion, as we know it today, was originally developed by Kurtin and Robbins in 1952 [5]. They attached a wire brush onto a motor-driven rotary dental apparatus, and with the aid of a refrigerant spray for anesthesia, they were able to remove the surface of the skin by sanding or planing. Thus, dermabrasion can be described as the mechanical planing of the surface of the skin to remove the epidermis and upper dermis with either a wire brush or a diamond fraise [6–8].

The wire brush used in dermabrasion is a 3.0 × 17.0 mm wheel composed of a circular array of beveled strands of stainless steel wire that protrude at an angle from the center of the wheel. A diamond fraise is a stainless steel wheel of similar dimensions and of various shapes that has multiple fragments of diamond chips of different coarseness bonded to its surface.

Current indications for the treatment of dermabrasion are defects of the epidermis and papillary dermis that can be modified or removed by planing, including facial scars due to acne, varicella, and any other disease process that scars or blemishes the surface of the skin (Table 33.1) [9,10]. Benedetto et al. also described dermabrasion as a preventive and therapeutic means to inhibit continued development of premalignant and malignant lesions of the face [11]. Soon others followed with similar observations [12]. Other indications for dermabrasion include the resurfacing of traumatic and surgical scars, especially to reduce the irregular surface of a sutured flap or graft [13–15]. Dermabrasion has been used to rejuvenate the skin of the face by planing away moderate to deep rhytides produced by solar elastosis and photodamage [16,17]. Both traumatic and decorative tattoos also have been removed by wire brush or diamond fraise dermabrasion [18,19].

SCIENTIFIC BACKGROUND

The beneficial effects produced by the resurfacing of the epidermis and upper levels of the dermis by the mechanical planning of dermabrasion result from the microcellular mechanisms of second intention wound healing that replace old and degenerative collagen, elastin, and ground substance with new healthy tissue. Aged and sun-damaged epidermal tissue is replaced by new epithelial cells migrating from adjacent, intact adnexal appendages. Solar elastotic papillary dermis is replaced with a widened Grenz zone of more abundant, new, thicker collagen bundles aligned horizontally, parallel to the surface of the skin along with the eventual reappearance of finely branching elastic fibers. These post-treatment histologic observations of dermabraded skin are similar to those found in non-sun-damaged healthy skin [11]. Nelson et al. found significant amounts of increased type I procollagen, type III procollagen, and transforming growth factor β1 in the papillary dermis after wire brush and diamond fraise dermabrasion when analyzed by immunohistologic and biochemical methods. These findings along with the subsequent increase in papillary dermal collagen I and collagen III deposition were felt to be responsible for the clinical improvements seen on the skin after dermabrasion [17]. Furthermore, this increase in fibroblast activity also was thought by Harmon et al. to be promoted by the upregulation of tenascin expression throughout the papillary dermis after dermabrasion [20]. This altered localization of tenascin expression within the wound bed appears to coincide with a modified and more dispersed expression of α6/β4-integrin subunits throughout the epidermis as detected by immunohistochemical and ultrastructural evaluation. Harmon et al. concluded that these findings pointed to an alteration in epidermal cell-to-cell interaction and dermal cell-to-matrix interaction that might result in a decrease in the potential for scar formation. This modification of dermal extracellular ligand expression and reorganization of the underlying connective tissues can be clinically appreciated especially when dermabrasion is performed to diminish the appearance of a fresh scar [13,20].

GENERAL USE

Dermabrasion has proven to be beneficial in the reduction of scars caused by acne, varicella, trauma, and surgical procedures [13,21]. Dermabrasion can be used to diminish the obtrusive appearance of scars that result from suturing [14,20]. This is a remarkably useful adjuvant procedure after full-thickness grafting anywhere on the face and body, but in particular on the nose and cheeks [15]. Prior to the advent of ablative laser surgery, dermabrasion also was used to resurface and rejuvenate photodamaged facial skin [11,12,16,17]. In fact, for some, wire brush dermabrasion is still used to remove the bulk of elastotic, sun-damaged, and wrinkled skin in conjunction with ablative CO_2 or Er:YAG laser resurfacing to obtain a more complete removal of the photodamaged skin, which cannot be accomplished by fractionated or non-fractionated ablative laser resurfacing alone [6].

Other reported uses of dermabrasion are found in Table 33.1. Of these indications, the phymatous changes of the face, e.g., rhinophyma, gnathophyma, and metophyma, are the third most common disorders treated by wire brush dermabrasion [22]. In fact, dermabrasion is the best means of completely

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Table 33.1 Indications for Dermabrasion

Acne rosacea	Keloids
Actinic keratosis	Lentigines
Actinically damaged skin	Lichenified dermatoses
Active acne	Linear epithelial nevus
Age- and sun-related wrinkle lines	Melasma
Amateur-type tattoos (India ink)	Molluscum contagiosum
Angiofibromas of tuberous sclerosis	Multiple trichoepitheliomas
Basal cell nevus syndrome	Neurotic excoriations
Blast tattoos	Porokeratosis
Chicken pox scars	Porokeratosis of Mibelli
Chloasma	Postacne scarring
Chronic radiation dermatitis	Postoperative scarring
Colloid milium	Pseudofolliculitis barbae
Darier's disease	Resistant or chronic acne
Decorative tattoos	Rhinophyma
Dermatitis papillaris capillitii	Seborrheic keratoses
Elevated recipient sites of hair transplantation	Smallpox scar
	Solar elastosis
Favre–Racouchot syndrome	Telangiectasia
Fox–Fordyce disease	Traumatic scarring
Freckles	Traumatic tattoo
Hailey–Hailey disease	Multiple trichoepithelioma
Hidradenitis scars	Verrucous nevus
Hypertrophic suppurativa	
Hypertrophic scars	

Sources: Adapted from Roenigk HH Jr, *J Dermatol*, 1(2), 72, July 2002; Lawrence N et al., *Dermatol Surg*, 26, 95, 2000.

resurfacing rhinophymatous skin with minimal attendant adverse events when performed properly [23].

The popularity of dermabrasion has waned with the advent of AIDS and the recognition of the dangers of aerosolized viral particles of HPV, HSV, HIV, HBV, HCV, and other types of viruses and prions. In reality, universal precautions against such infections must be taken during any form of patient management and care, be it during a surgical or ablative laser procedure or during postoperative or routine daily nursing care of any patient. Customarily, during a dermabrasion procedure, the surgical team should wear protective gowns, gloves, face masks, and shields [6]. Furthermore, the proper evaluation and selection of patients for a dermabrasion procedure is of the utmost importance.

There are other types of conditions and situations that may require either a temporary delay or exclusion from a dermabrasion procedure, which should be identified during the preoperative evaluation, some of which are listed in Table 33.2.

With the introduction of tumescent anesthesia, many procedures that were routinely done in the hospital operating room setting can now be performed in an ambulatory or outpatient office setting, including extensive excisional surgical procedures, liposuction, and dermabrasion [24]. Tumescent anesthesia has reduced the amount of bleeding and tissue splatter during a dermabrasion procedure, minimizing the total amount of environmental aerosolization of potentially harmful tissue products [25].

For those patients who have been treated with a course of oral isotretinoin, at least 6 months must elapse before any dermabrasion procedure can be considered so as to prevent the eventuality of compromised healing and inadvertent, unpredictable scarring [26,27]. The same can be said for patients who have recently undergone any surgical procedure that requires extensive tissue undermining, e.g., face-lift surgery or a flap or graft reconstructive procedure.

Table 33.2 Details of a Patient's History to Identify Prior to Performing a Dermabrasion of the Face

- Isotretinoin therapy within past year
- Face-lift or other major flap surgery
- Prior facial resurfacing: dermabrasion, laser ablation, or chemical peeling
- X-radiation therapy for acne or other cutaneous disorder
- Chronic steroid use
- Immune status: presence of diabetes mellitus, atopy, or immunosuppressive medications
- Koebnerizing conditions, e.g., lichen planus, psoriasis, vitiligo, chronically active eczema, etc.
- Keloid formation
- History of HPV, HSV, HIV, hepatitis (HAV, HBV, HCV)

Table 33.3 Laboratory Studies Obtained Prior to Full-Face Dermabrasion

- Full-blood count with differential and platelets
- Complete metabolic panel
- HIV
- Hepatitis panel
- ANA
- Urinalysis

Table 33.4 Postoperative Medications

Antibiotic	Cephalosporins or quinolones 1 g per day starting 1 day before surgery, for 7–10 days
Somnifacient	Lorazepam 1 mg once a day starting the night after surgery as needed for 5 days
Analgesic	Opiate or opioid derivative starting the day of surgery as needed for 5 days
Antiviral	Thymidine kinase inhibitor at a therapeutic dose starting 2 days before surgery, for 15 days
Anti-inflammatory	Prednisolone 20 mg mane for 5 days only

Once a patient is deemed to be a good candidate for dermabrasion, preoperative medical clearance for surgery and blood chemistry evaluation must be obtained at least 4–6 weeks prior to the dermabrasion (Table 33.3). The patient is then given pre- and postoperative prophylactic medications, which must include antibiotics, antivirals, analgesics, somnifacients, and anti-inflammatory medications (Table 33.4).

In preparation for surgery, anesthesia utilizing nerve blocks of the supraorbital, supratrochlear, zygomaticofacial, zygomaticotemporal, infraorbital, mental, and greater auricular nerves along with a paranasal ring block in combination with tumescent anesthesia of the cheeks is ideal and recommended for complete facial anesthesia prior to a full-face dermabrasion [25] (Table 33.5).

Table 33.5 Preoperative Medications and Anesthesia (Nerve Blocks and Tumescent Anesthesia) in Preparation for Full-Face Dermabrasion

- Ketorolac 60 mg im or diclofenac 100 mg pr
- Lorazepam 1 mg SL
- For nerve blocks: In 10 mL syringes (4 syringes)
  - 6 mL of 2% lidocaine with epinephrine plus
  - 4 mL of normal saline
- For tumescence: In 10 mL syringes (4 syringes)
  - 4 mL of 1% lidocaine with epinephrine plus
  - 6 mL of normal saline
- Topical anesthesia: Lidocaine-based cream to be applied the day of surgery as needed

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

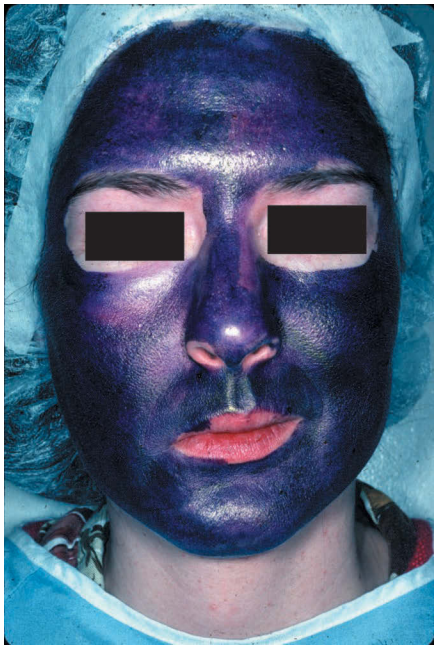


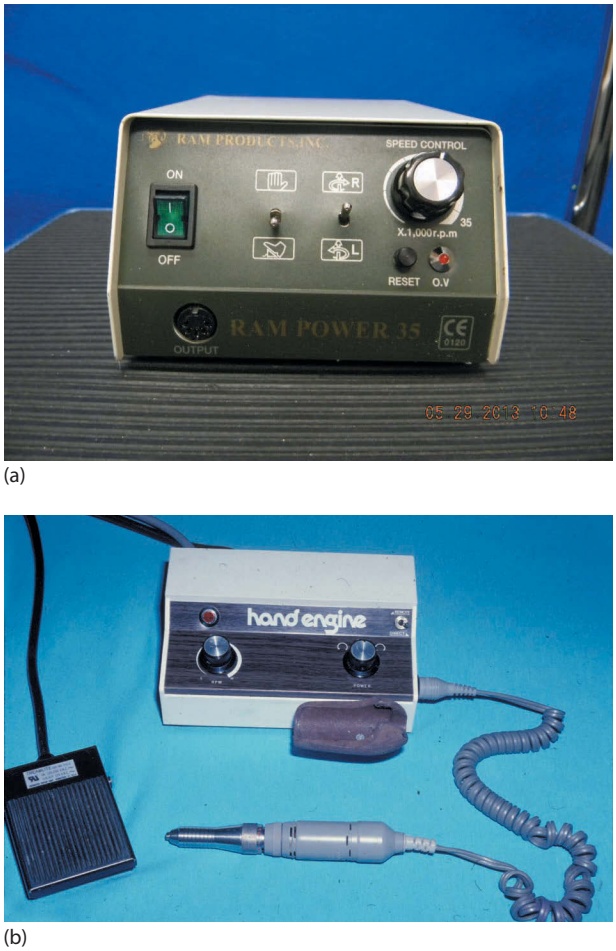
Figure 33.1 Preoperative view of a patient painted with gentian violet prior to a full-face dermabrasion.

Prior to the advent of tumescent anesthesia, a refrigerant spray containing Freon 114 (Frigiderm™) was typically used to anesthetize and solidify the surface of the skin immediately prior to planing it [28]. Especially now with the universal ban on hydrofluorocarbons, those Freon-containing products are no longer necessary particularly when tumescent anesthesia is used.

The entire skin surface to be dermabraded is then painted with gentian violet [6]. This stains the tissue to be treated, identifying at what depth the dermabrasion can be completed and allowing for intraoperative clear visualization of a potentially bloody field (Figure 33.1). Petrolatum (e.g., Aquaphor, Eucerin) and KY jelly, or a similar preparation, can be applied along the hairline and over the eyebrows to prevent the entanglement of strands of hair around the spinning dermabrasion tip.

Once the entire face has been anesthetized and the preoperative medications have taken effect, planing of the skin surface can commence using an electrically powered, high-torque rotary apparatus (e.g., Bell Hand Engine® [Bell Handengine, Inc., Grants Pass, Oregon] or RAM® engine [Rampower, Inc., East Brunswick, NJ]) (Figure 33.2). Wire brushes are shaped only as wheels and come in various widths, whereas diamond fraises come in different shapes and degrees of coarseness (Figure 33.3).

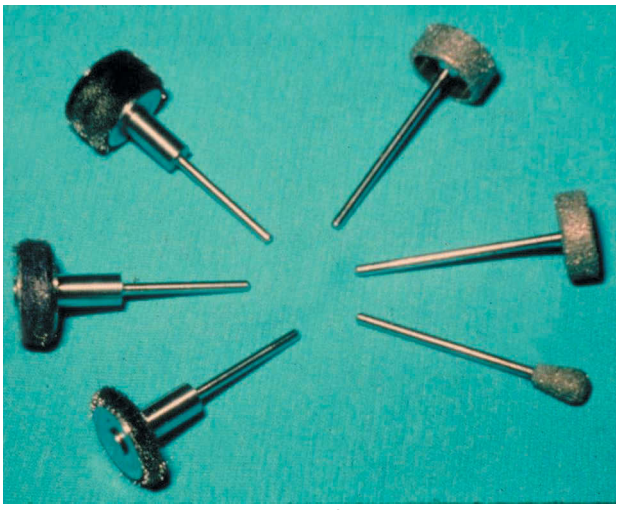
The proper technique of planing or sanding the surface of the skin during a dermabrasion procedure is performed with back-and-forth movements perpendicular to the direction of the rotation of the dermabrader handpiece and tip, be it a wire brush or a diamond fraise. The revolutions per minute (RPMs) of the rotating engine can be set at approximately 20,000–30,000 RPMs. Diamond fraises can be used with the rotating head spinning clockwise or counterclockwise. However, a wire brush is composed of multiple radiating stainless steel wire bristles and can be used with or against the angle of the radiating bristles. The aggressiveness of planing and depth of tissue removal with



(a)

(b)

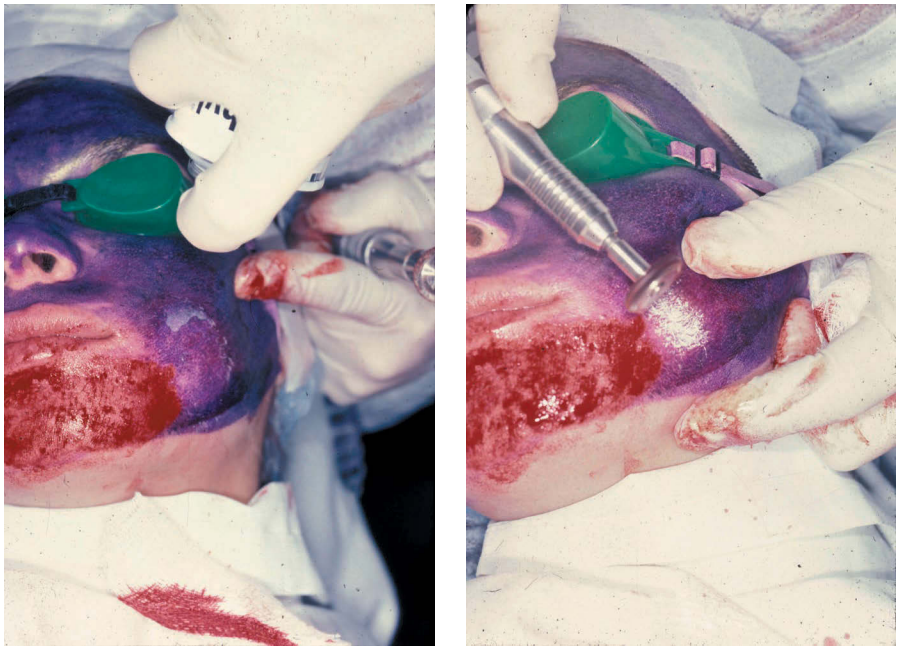
Figure 33.2 (a) Ram Power 35 and (b) Bell Hand Engine rotary dermabrasion machines used to power a wire brush or diamond fraise used in dermabrasion.



(a) (b)

Figure 33.3 Dermabrader tips of different widths, shapes, and coarseness. (a) Wire brushes on the left. (b) Diamond fraises on the right.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b)

Figure 33.4 (a) Intraoperative wire brush dermabrasion without tumescent anesthesia, using Frigiderm™ to anesthetize and solidify the surface of the skin. (b) Note the frost and excess bleeding on the skin surface during the dermabrasion procedure.

each pass over the skin surface are predicated upon the direction of the spin of the wire brush. Clockwise rotation of a wire brush (i.e., against the angle of the radiating bristles) planes the skin more aggressively and deeply, while a counterclockwise rotation (i.e., with the angle of the radiating bristles) planes the skin less aggressively and more shallowly.

The depth of planing is determined and controlled visually. The elimination of the gentian violet–stained skin is the first indication that the proper depth of tissue removal has been reached (Figure 33.4). Another visual clue that indicates that the proper depth of tissue removal has been reached is the appearance of punctate bleeding. This identifies the level of the papillary dermis. When strands of frayed dermal tissue (i.e., collagen bundles) are exposed along with more profuse bleeding, entry into the upper reticular dermis is achieved and planing over the area should stop immediately (Figure 33.4). The skin adjacent to the area where wire brush dermabrasion is taking place should be stretched tautly to avoid the rotating wire brush accidently lacerating or gouging a deep wound into the skin surface (Figure 33.5). This is less likely to happen when a dermabrasion is performed with a diamond fraise or when skin refrigerants were used to solidify the surface of the skin. Once surgery is complete, bleeding subsides within a few minutes, thanks to the vasoconstrictive properties of tumescent anesthesia (Figure 33.6a). Wound dressings are customarily applied with absorbent, nonstick sterile surgical dressings, the types of which are usually selected according to the preferences of the operating surgeon and nursing staff [29–31] (Figure 33.6b).

Additional adjuvant surgical techniques that can be performed prior to a full-face dermabrasion are subcision [32] and

Figure 33.5 Intraoperative view of the patient undergoing a full-face wire brush dermabrasion with tumescent anesthesia. Note the lack of bleeding.

punch grafting [33]. Subcision of small but deep facial scars is usually completed approximately 2–3 months prior to a full-face dermabrasion. Subcision is performed with a 16- or 18-gauge NoKor needle that is inserted through the skin surface down into the mid to deep dermis (Figure 33.7). Back-and-forth cutting movements parallel to the surface of the skin with the triangulated blade tip of the NoKor needle release the collagenous

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 33.6 (a) Patient immediately after a full-face wire brush dermabrasion by tumescent anesthesia. (b) Same patient immediately after full-face dermabrasion and with postoperative dressings in place.

Figure 33.7 NoKor needle, 16 gauge and 18 gauge.

adhesions and contractures that tether tiny zones of the surface of facial skin downward forming the typical boxcar and rolling scars [34] resulting from bouts of severe papulopustular and cystic acne and varicella infections [32] (Figure 33.8).

Punch grafting of ice pick scars [35,36] is also completed 2–3 months prior to a full-face dermabrasion. The narrow but deep ice pick scars (Figure 33.9a and b) are punched excised (Figure 33.10a), and the full-thickness defect is replaced with a cylinder of full-thickness normal skin usually harvested from hairless retroauricular skin from the mastoid area (Figure 33.10b). The donor punches should be approximately 0.5 mm wider in diameter than the recipient defects. This larger and wider full-thickness punch graft fits tightly into the recipient site and helps prevent accidental fallout because the donor grafts are held in place postoperatively only with Steri-Strip® dressing tape (Figure 33.11). There is minimal, if any, loss of the grafts with this technique, which are ready to be dermabraded along with the rest of the facial skin surface after approximately 2 or 3 months (Figure 33.12a through c).

Postsurgical scar revision by dermabrasion, known as "scarabrasion" [37], with a wire brush or diamond fraise is still frequently performed to diminish the obtrusiveness of scars, particularly those on the face. An example of this technique is best realized after a full-thickness skin graft on the nose (Figure 33.13).

Dermabrasion can be used as an adjunctive modality in tattoo removal. Depending on the depth of the particles of the foreign body material of a traumatic tattoo or the pigment of a decorative tattoo, dermabrasion down to the upper reticular dermis can aid and even hasten the transepidermal elimination of the pigment and foreign body particles that are resistant to laser tattoo removal. If the tattoo is deeper than the upper reticular dermis, dermabrasion should not be attempted down to this depth because postdermabrasion scarring will probably occur.

POSTOPERATIVE CONSIDERATIONS AND ADVERSE REACTIONS

When the patient is sufficiently prepared preoperatively with antivirals and antibiotics, the postoperative course should proceed uneventfully. However, close and frequent observation in

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

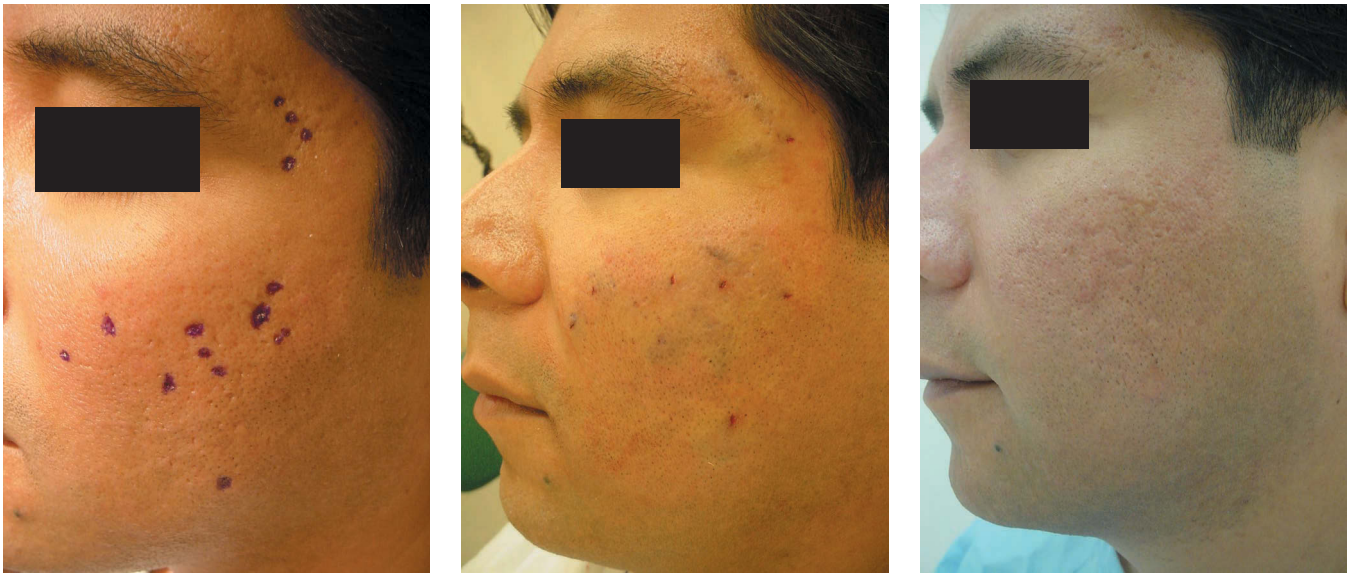


Figure 33.8 (a) Boxcar and rolling type scars presubcision with gentian violet markings. (b) Same patient immediately after subcision with red NoKor needle puncture marks caused by NoKor needle piercing the skin surface and (c) 8 weeks after subcision and just prior to a full-face dermabrasion.

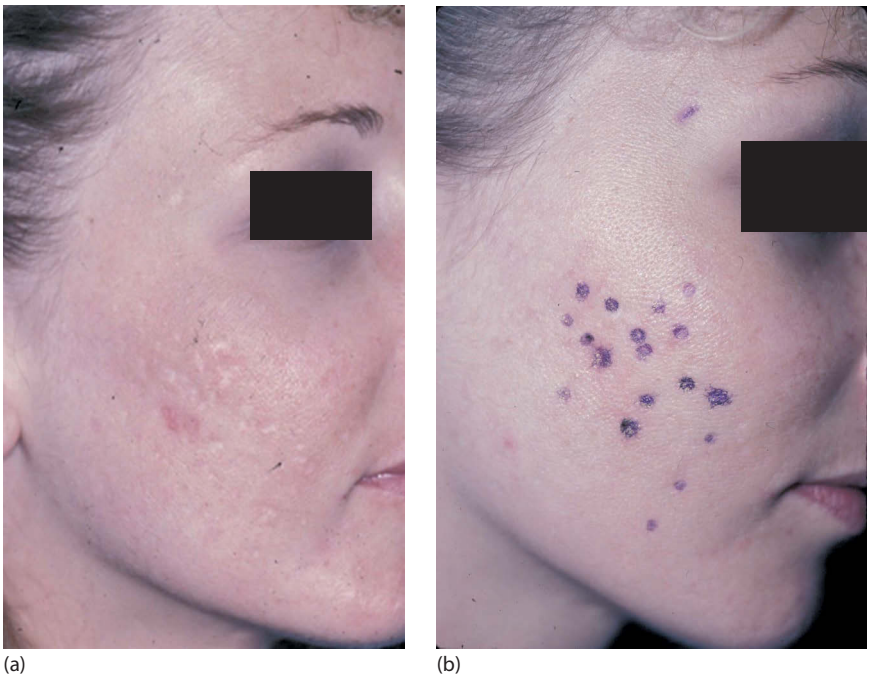
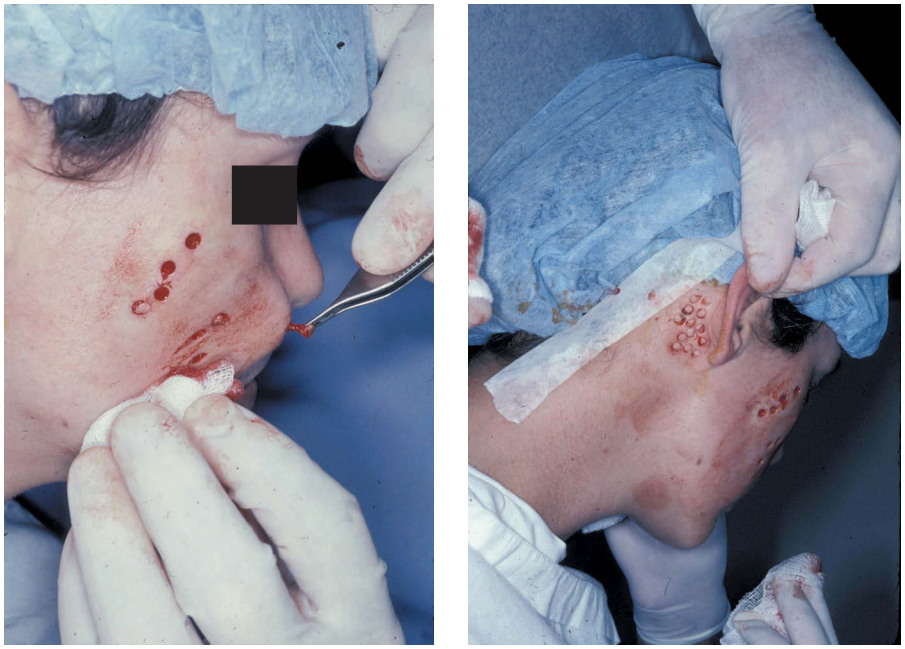


Figure 33.9 (a) Preoperative view of ice pick and boxcar scars just prior to punch grafting without and (b) with gentian violet markings.

the postoperative period is imperative. Reepithelialization usually occurs within 7–10 days after a deep full-face dermabrasion.

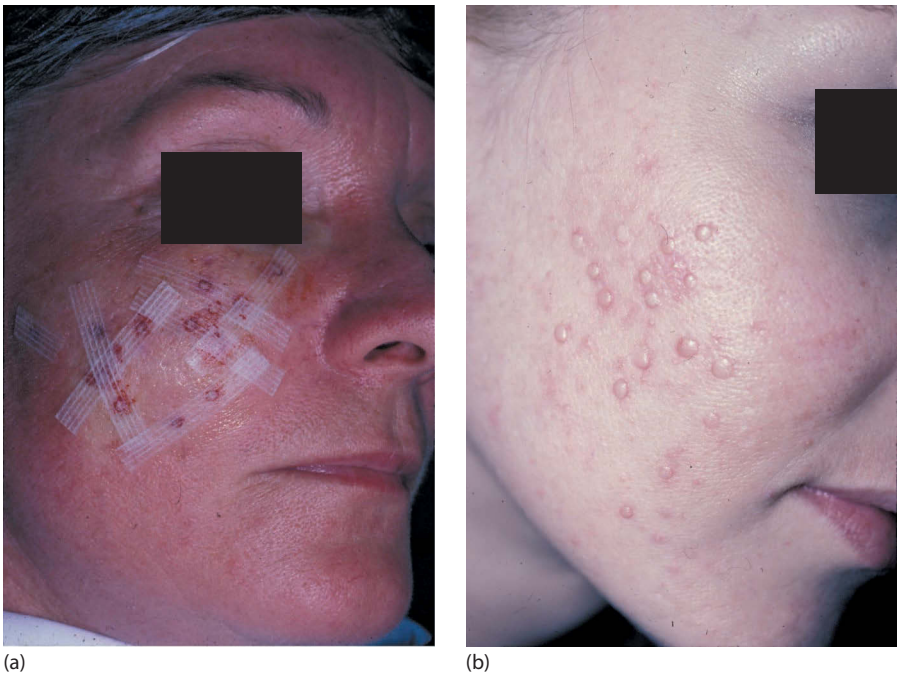
The patient should continue to take both antibiotics and antivirals for at least 14 days after surgery. For some patients who are predisposed to candidal infections, a 10- to 14-day course of an antibiotic can induce not only a superinfection of mucosal candidiasis but also an acute yeast infection on the surface of the dermabraded areas of the face. This can be characteristically seen as progressive and increasingly painful erythema with punctate pustules and micropapules on the skin

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b)

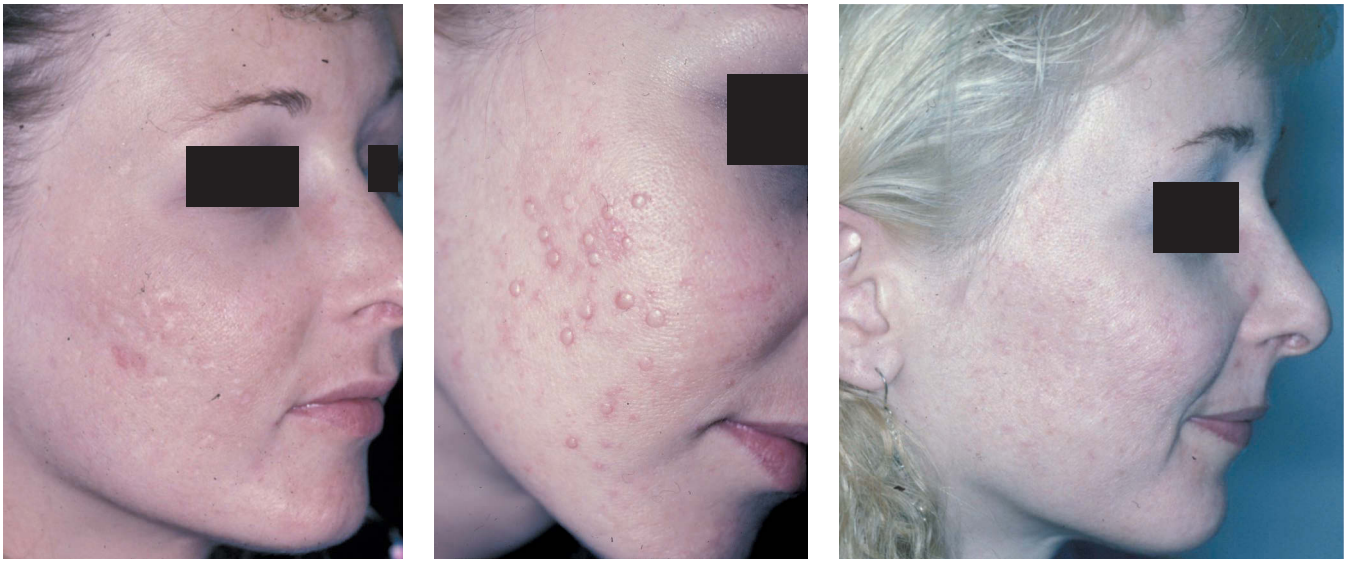
Figure 33.10 (a) Full-thickness punch excision of ice pick scars. (b) Full-thickness donor punches prior to transplantation.



(a) (b)

Figure 33.11 (a) Patient immediately after punch grafting with donor punches in recipient sites and Steri-Strip® dressings in place. (b) Another patient with donor punches in recipient sites 10 weeks after transplantation and just prior to a full-face wire brush dermabrasion.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b) (c)

Figure 33.12 (a) Preoperative view of ice pick and boxcar scars just prior to punch grafting. (b) Same patient 10 weeks after punch grafting and just prior to a full-face dermabrasion. (c) Same patient 6 months after full-face wire brush dermabrasion.

surface within the dermabraded areas and surrounding skin, along with an exudative, eczematous golden-yellow discharge (Figure 33.14). Immediate intervention with oral and topical anticandidal medications will prevent deep erosions and subsequent scarring. Likewise, diffuse deep figurate scarring can also occur if the patient develops an HSV infection. Deep erosive HSV ulcers also can quickly disseminate over the entire non-epithelialized dermabraded skin (Figure 33.15); hence, the reason to continue a therapeutic dose of antiviral medication for 2 weeks or at least 5 days after all the dermabraded facial skin has completely reepithelialized [38].

When bright red, shiny (atrophic) erythema persists over bony prominences or areas of thin skin, in particular over the border of the mandible, 3–4 weeks postoperatively, this may indicate that planing was too deep and excessive in these areas and postoperative hypertrophic scarring is imminent

(a) (b)

Figure 33.13 (a) Patient after Mohs excision for a recurrent basal cell carcinoma on the dorsum of the nose. (b) Same patient with full-thickness skin graft in place. (*Continued*)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(c)

(d)

(e)

Figure 33.13 (*Continued*) (c) Same patient 1 year after the full-thickness skin graft and prior to dermabrasion. (d) Same patient just after a wire brush dermabrasion. (e) Same patient 4 months after dermabrasion.

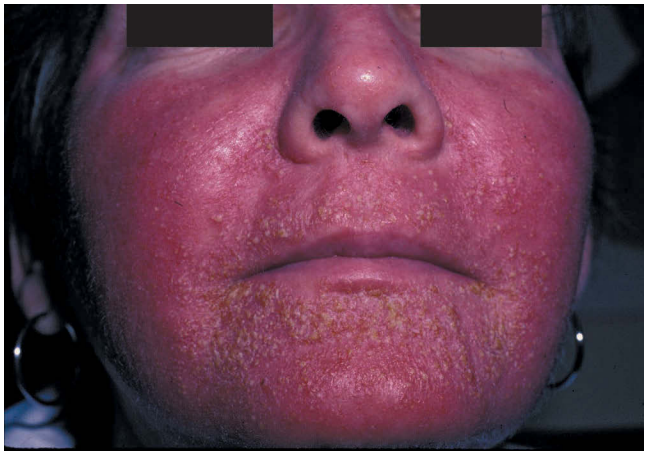


Figure 33.14 Patient 10 days after a full-face wire brush dermabrasion, developing signs and symptoms of candidiasis. The patient was prediabetic.

(Figure 33.16). In such situations, the application of high-potency topical corticosteroids and intralesional injections of dilute corticosteroids is mandatory to avert progressive scarring.

Whether or not erythema persists, treatments with a 585 nm or 595 nm pulsed dye laser can help reduce recalcitrant erythema and the possible sequel of resultant scarring [39].

Attendant adverse effects of any resurfacing procedure, including ablative laser treatments and chemical peelings, include persistent light-colored, pink erythema for 2 and up to 6 months postoperatively [40]. The more heat generated and conducted during a resurfacing procedure, the longer the persistence of postoperative erythema and the more likely is the

Figure 33.15 Patient in 1980 prior to the existence of any antiviral medication developed severely painful erosive ulcers diffusely spread over the entire area of non-epithelialized dermabraded facial skin. Only symptomatic treatment was available at the time, the infection eventually left multiple, irregular atrophic and hypertrophic scars over her entire face.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

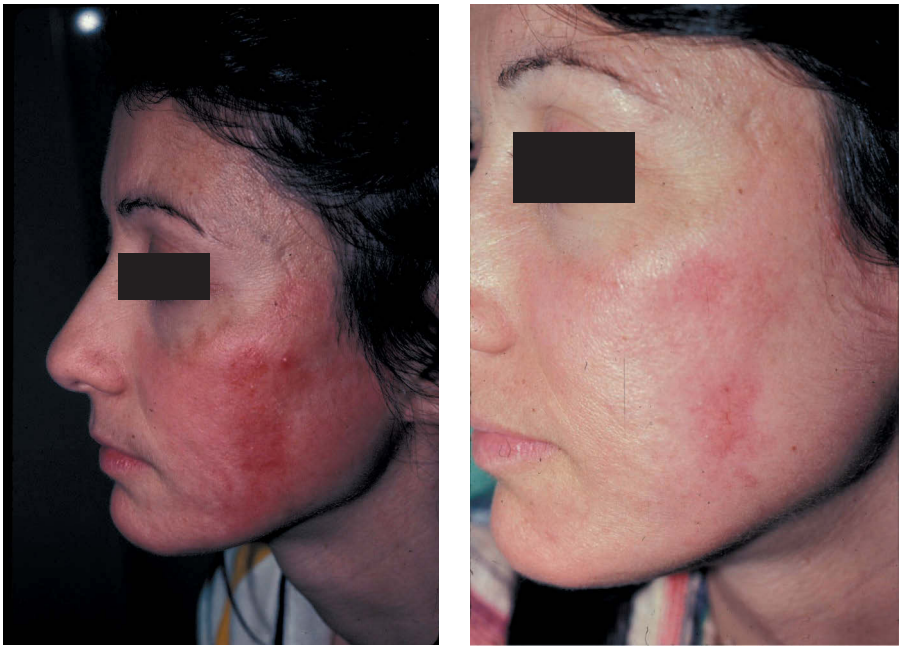


Figure 33.16 (a) Persistent redness 4–5 weeks after a wire brush full-face dermabrasion heralds. (b) Incipient hypertrophic scarring.

occurrence of early postoperative postinflammatory hyperpigmentation, which inevitably leads on to hypopigmentation, usually 12–18 months postprocedure. This is probably due to the near total destruction and elimination of melanocytes by heat conduction during the resurfacing procedure. In the case of postinflammatory hyperpigmentation, symptomatic bleaching regimens can be initiated with different available topical medications. In the case of postinflammatory hypopigmentation, treatments with the 308 nm excimer laser seems promising at reestablishing skin color to match the normally pigmented surrounding skin [41].

Pruritus can occur over the dermabraded areas within days of total facial reepithelialization. Symptomatic treatment with oral or topical antipruritic medication is helpful. Also, within 4–6 weeks postoperatively, susceptible patients can develop multiple crops of milia diffusely over the entire areas dermabraded. Only in rare instances do these need active, symptomatic treatment because they usually spontaneously resolve within 4–6 weeks from the time of their appearance (Figure 33.17).

Along with the effacement of various scars of different origins (Figure 33.18) and the resurfacing of photodamaged, wrinkled, aged skin (Figure 33.19), the reduction of phymatous facial skin (e.g., rhinophyma and metophyma) is the next most common condition best treated by dermabrasion (Figure 33.20).

CONCLUSION

In the hands of a competent and skilled, physician dermabrader, a full-face resurfacing procedure performed by wire brush dermabrasion is comprehensively therapeutic and minimally invasive. There is no other resurfacing technique that is so thoroughly beneficial and long lasting in effect. Of all the resurfacing procedures currently in use today, wire brush dermabrasion remains the prototypical resurfacing procedure that is the standard by which all other resurfacing procedures are measured.

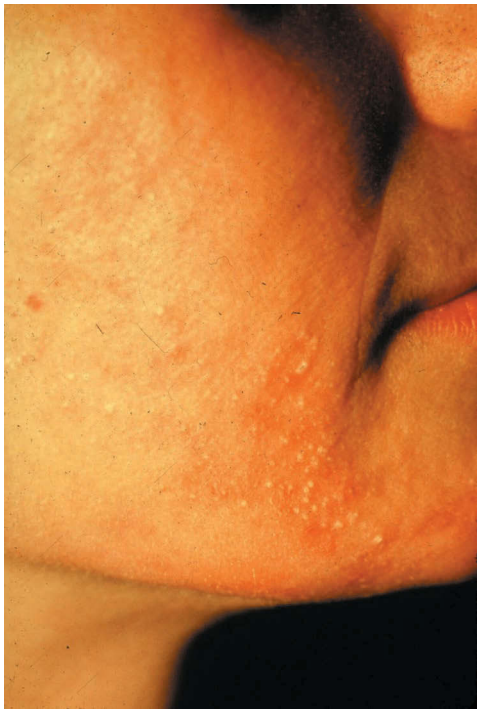


Figure 33.17 Patient 5 weeks after a full-face wire brush dermabrasion developing crops of milia that remitted spontaneously 4–6 weeks later. Note the presence of postinflammatory hyperpigmentation that also remitted after a course of topical hydroquinone.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 33.18 Wire brush dermabrasion of acne scars (a) before and (b) 6 months after subcision, punch grafting, and a full-face dermabrasion.

(a) (b)

Figure 33.19 Full-face wire brush dermabrasion for facial rejuvenation (a) before and (b) 1 year after.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

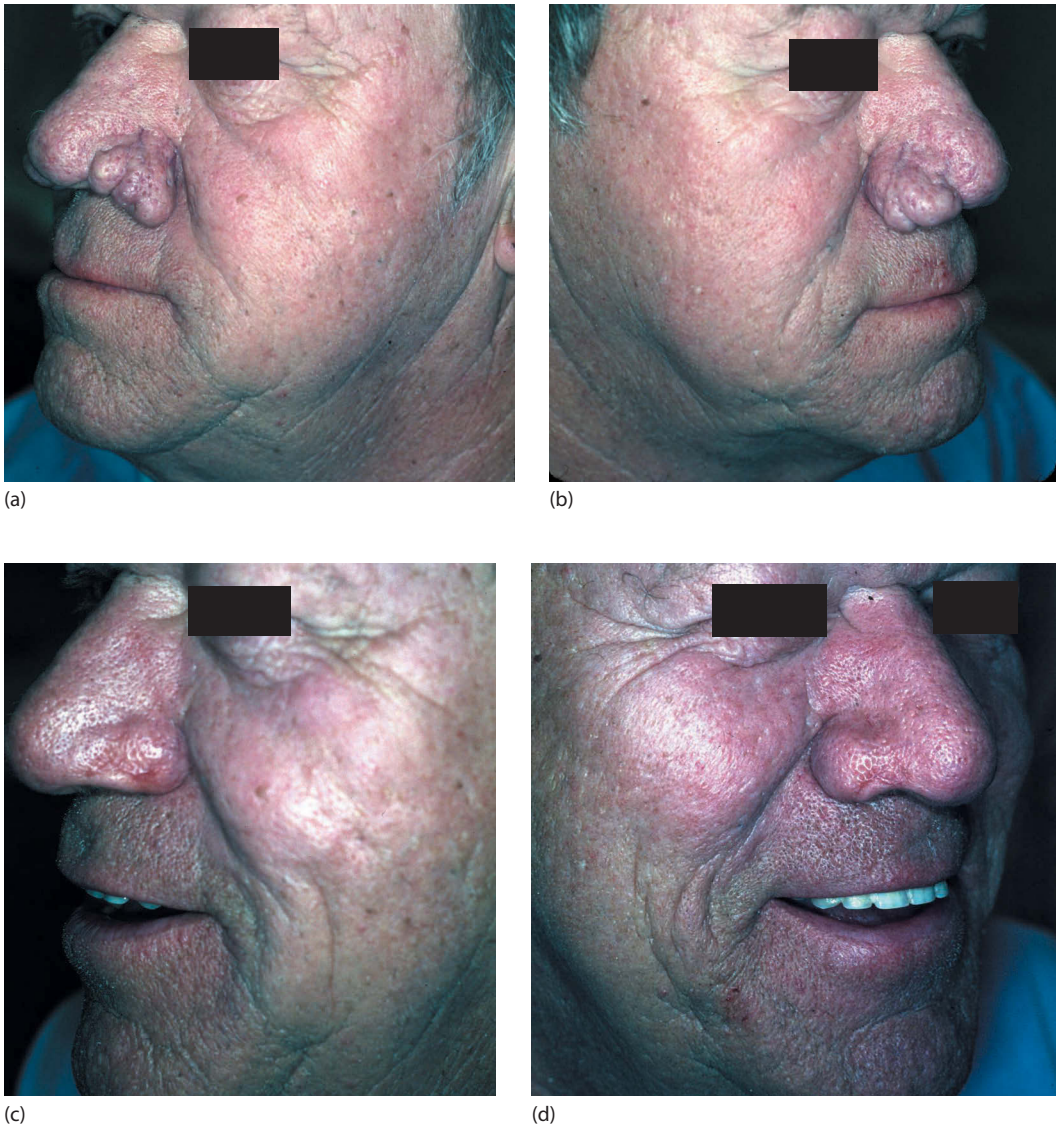


Figure 33.20 Wire brush dermabrasion of rhinophyma (a, b) before and (c, d) 2 months after.

REFERENCES

1. Ebell B. (Trans.). *The Papyrus Ebers: The Greatest Egyptian Medical Document*. Copenhagen, Denmark: Levin & Munksgarrd, 1937.
2. Lawrence N, Mandy S, Yarborough J et al. History of dermabrasion. *Dermatol Surg* 2000; 26:95–101.
3. Kromayer E. Rotationsinstrumente; Ein Neus Technisches Verfahren in der Dermatologischen Kleinchirurgie. *Dermatol Z* 1905; 12:26.
4. Iverson PC. Surgical removal of traumatic tattoos of the face. *Plast Reconstr Surg* 1947; 2:427.
5. Kurtin A. Corrective surgical planning of skin. *Arch Dermatol Syphil* 1953; 68:389–397.
6. Roenigk HH Jr. Dermabrasion: State of the art 2002. *J Dermatol* 2002 July;1(2):72–87.
7. Yarborough JM. Dermabrasion by Wire Brush. *J Derm Surg Oncol* 1987 June; 13(6):610–615.
8. Alt T. Facial dermabrasion: Advantages of the diamond fraise technique. *J Derm Surg Oncol* 1987; 13:618.
9. Goodman G. Treating scars: Addressing surface, volume, and movement to optimize results: Part 1. Mild grades of scarring. *Dermatol Surg* 2012; 38:1302–1309.
10. Goodman G. Treating scars: Addressing surface, volume, and movement to expedite optimal results. Part 2: More-severe grades of scarring. *Dermatol Surg* 2012; 38:1310–1321.
11. Benedetto AV, Griffin TD, Benedetto EA, Humeniuk HM. Dermabrasion: Therapy and prophylaxis of the photoaged face. *J Am Acad Dermatol* 1992; 27:439–447.
12. Coleman WP III, Yarborough JM, Mandy SH. Dermabrasion for prophylaxis and treatment of actinic keratoses. *Dermatol Surg* 1996; 22:17–21.
13. Yarborough JM Jr. Ablation of facial scars by programmed dermabrasion. *J Dermatol Surg Oncol* 1988; 14:292–294.
14. Collins PS, Farber GA. Postsurgical dermabrasion of the nose. *J Dermatol Surg Oncol* 1984; 10:476–477.
15. Robinson JK. Improvement of the appearance of full-thickness skin grafts with dermabrasion. *Arch Dermatol* 1987; 123:1340–1345.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

16. Nelson BR, Majmudar G, Griffiths EM et al. Clinical improvement following dermabrasion of photoaged skin correlates with synthesis of collagen I. *Arch Dermatol* 1994; 130:1136–1142.
17. Nelson BR, Metz RD, Majmudar G et al. A comparison of wire brush and diamond fraise superficial dermabrasion for photoaged skin: A clinical, immunohistologic, and biochemical study. *J Am Acad Dermatol* 1996; 34:235–243.
18. Clabaugh W. Removal of tattoos by superficial dermabrasion. *Arch Dermatol* 1968; 98:515–521.
19. Notaro WA. Dermabrasion for the management of traumatic tattoos. *J Dermatol Surg Oncol* 1983; 9:916–918.
20. Harmon CB, Zelickson BD, Roenigk RK et al. Dermabrasive scar revision. immunohistochemical and ultrastructural evaluation. *Dermatol Surg* 1995; 21:503–508.
21. Burks JW. Abrasive removal of scars. *South Med J* 1955; 48:452–459.
22. Jansen T, Plewig G. Clinical and histological variants of rhinophyma, including nonsurgical treatment modalities. *Facial Plast Surg* 1998; 14(4):241–253.
23. Rohrich R, Griffin J, Adams W. Rhinophyma: Review and update. *Plast Reconstr Surg* 2002; 110(3)860–869.
24. Coleman WP III, Klein JA. Use of the tumescent technique for scalp surgery, dermabrasion, and soft tissue reconstruction. *J Dermatol Surg Oncol* 1992; 18:130–135.
25. Goodman G. Dermabrasion using tumescent anesthesia. *J Dermatol Surg Oncol* 1994; 20:802–807.
26. Rubenstein R, Roenigk HH Jr, Stegman SJ, Hanke CW. Atypical keloids after dermabrasion of patients taking isotretinoin. *J Am Acad Dermatol* 1986; 15:280–285.
27. Roenigk HH Jr, Pinski JB, Robinson JK et al. Acne retinoids and dermabrasion. *J Dermatol Oncol* 1988; 11:396.
28. Hanke CW, O'Brien JJ, Solow EB. Laboratory evaluation of skin refrigerants used in dermabrasion. *J Dermatol Surg Oncol* 1985; 11:45–49.
29. Pinski JB. Dressings for dermabrasion: Occlusive dressings and wound healing. *Cutis* 1986; 37:471–476.
30. Mandy SH. A new primary wound dressing made of polyethylene oxide gel. *J Dermatol Surg Oncol* 1983; 9:153–155.
31. Mandy SH, Gross KKG, Yarborough JM. Guidelines of care for dermabrasion. *J Am Acad Dermatol* 1994; 31:654–657.
32. Alam M, Omura N, Kaminer MS. Subcision for acne scarring: Technique and outcomes in 40 patients. *Dermatol Surg* 2005; 31:310–317.
33. Lowenthal L. Punch biopsy with autograft. *Arch Dermatol Syphil* 1953; 67:629–631.
34. Jacob CF, Dover JS, Kaminer MS. Acne scarring: A classification system and review of treatment options. *J Am Acad Dermatol* 2001; 45:109–117.
35. Solotoff S. Treatment for pitted acne scarring-postauricular punch grafts followed by dermabrasion. *J Dermatol Surg Oncol* 1986; 12:1079.
36. Johnson W. Treatment of pitted scars: Punch transplant technique. *J Dermatol Surg Oncol* 1986; 12:260.
37. Katz BE, Oca AG. A controlled study of the effectiveness of spot dermabrasion ("scarabrasion") on the appearance of surgical scars. *J Am Acad Dermatol* 1991; 24:462–466.
38. Silverman AK, Laing KF, Swanson NA, Schaberg DR. Activation of herpes simplex following dermabrasion: Report of a patient successfully treated with intravenous acyclovir and brief review of the literature. *J Am Acad Dermatol* 1985; 13:103–108.
39. Alster T. Laser scar revision: Comparison study of 585-nm pulsed dye laser with and without intralesional corticosteroids. *Dermatol Surg* 2003; 29:25–29.
40. Stegman SJ. A comparative histologic study of the effects of three peeling agents and dermabrasion on normal and sundamaged skin. *Aesthetic Plast Surg* 1982; 6:123.
41. Grime PE, Bhawan J, Kim J et al. Laser resurfacing-induced hypopigmentation: Histologic alterations and repigmentation with topical photochemotherapy. *Dermatol Surg* 2001; 27:515–520.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

41-Laser dermatology

Serge Mordon and Geneviève Bourg-Heckly

INTRODUCTION

Since their invention in 1960, lasers have emerged as potentially interesting light sources for medicine because they possessed three characteristics that set them apart from conventional sources: directivity, the ability to operate in pulsed mode with very short pulses, and monochromaticity. This latter property is without doubt the least useful in medicine because biological molecules have an extended absorption spectrum and their activation does not require a source that is spectrally very narrow.

Dr. Leon Goldman was the first dermatologist to use the ruby laser in 1963 [1]. The carbon dioxide (CO_2) laser, introduced by Polanyi in 1970 [2] and Kaplan in 1973 [3] had been first of all proposed to surgeons with the concept of an "optical" scalpel. It has since been implemented in very numerous applications, most especially in dermatology.

Therapeutic applications of lasers exploit a certain number of effects that can be produced by the action of a light beam on a biological tissue. Whatever the effect utilized, the mechanism of action always starts with a transfer of energy carried by the light beam to the tissue. Four effects are usually considered:

- *The thermal effect*: Energy is transformed locally into heat.
- *The photoablative effect*: Energy absorbed by the tissue causes the rupture of a certain number of molecular bonds.
- *The photochemical effect*: Light energy is absorbed by an exogenous chemical agent rendered thus active and capable of inducing cytotoxic chemical reactions.
- *The electromechanical effect*: Energy is transported by very short light pulses that induce the formation of a plasma at the origin of a shock wave, which leads to a mechanical disruption of the tissue structure.

INTERACTION OF LIGHT WITH BIOLOGICAL TISSUES

Understanding and mastering the therapeutic effect at a given location in a tissue requires knowing the amount of energy that has been deposited by the laser beam. However, this depends at the same time on both irradiation parameters characterizing the laser source (power, beam diameter, wavelength, repetition rate, and energy per pulse for a pulsed laser) and the optical properties of the tissue. If the user knows and controls well the characteristics of the available laser sources, it is not the same for the optical properties of tissue that are difficult to reach.

Indeed, tissues are complex environments, highly heterogeneous, composed of scattering and absorbing structures and organelles. Their optical properties not only vary from one tissue to another but can also vary within the same tissue because of local inhomogeneities. As with any material medium, the light–tissue interaction involves three different phenomena: reflection, absorption, and scattering. These phenomena are described quantitatively with the help of parameters that together constitute the optical properties of the medium.

Reflection

Let us first recall some basic notions on the phenomenon of reflection. The refractive index of a material medium, denoted n, is defined as the ratio of the speed of propagation of light in a vacuum to the speed of the light in the medium under consideration:

$$n = c/v$$

Depending on the nature of the surface, smooth or rough, the reflection will be specular or scattered (Figures 34.1 and 34.2).

The reflection is specular (Figure 34.1) if the surface is optically smooth, i.e., if the height of irregularities is less than $\lambda/10$. A light beam incident on an optically smooth surface separating two media with different refractive indexes n_1 and n_2 undergoes a partial reflection; i.e., a fraction R of the incident energy flux is sent back to the first medium, the remaining fraction passing into the second medium.

The relationships between the angles of incidence i, of reflection r, and of transmission t are given by the following laws ascribed to Descartes:

- The angle of the reflected ray relative to the normal is equal to the angle of the incident ray i = r.
- The angles of incidence and transmission satisfy the following relationship:

$$n_1 \sin i = n_2 \sin t$$

The value of the coefficient of reflection is as follows:

$$R = \text{reflected energy flux/incident energy flux}$$

which depends on

- The angle of incidence
- The ratio of the indices of the two media

For an unpolarized light, R is given by the Fresnel formula:

$$R = \tfrac{1}{2}\{[\mathrm{tg}^2(i - t)/\mathrm{tg}^2(i + t)] + [\sin^2(i - t)/\sin^2(i + t)]$$

Consequently, for an air–glass reflection at normal incidence ($n_1 = 1$; $n_2 = 1.5$), R = 0.04, 4% of the incident flux is reflected.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

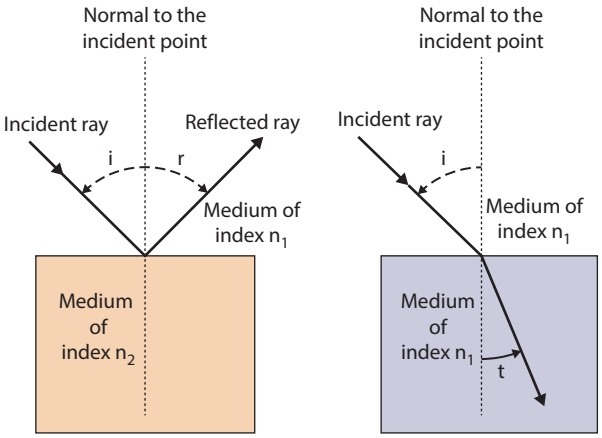


Figure 34.1 Specular reflection. The law of Snell–Descartes for reflected and refracted rays ($n_2 > n_1$).

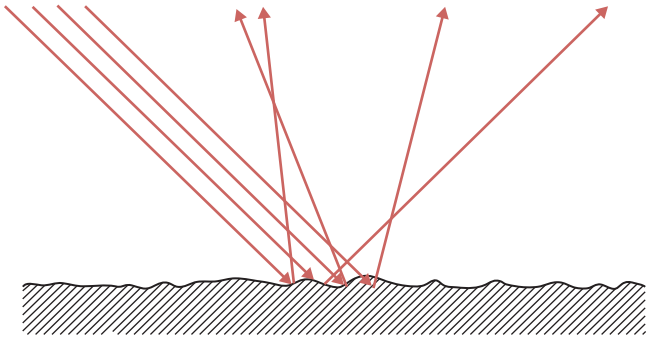


Figure 34.2 Scattering reflection.

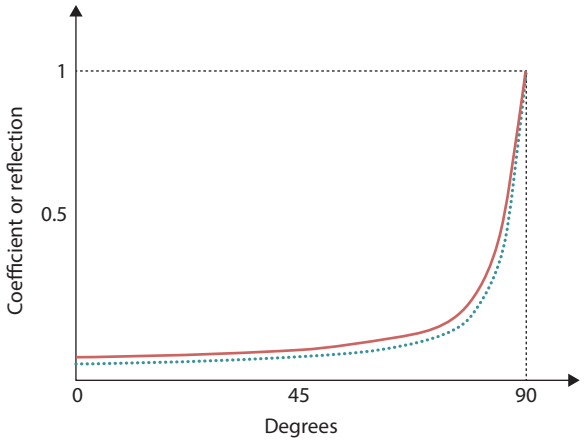


Figure 34.3 Variation of the coefficient of reflection as a function of the incident angle for an air–water interface (n_2 = 1.33 in the dashed line) and an air–glass interface (n_2 = 1.5 in the solid line).

The higher the index gap, the higher the coefficient of reflection R.

Figure 34.3 gives the variation of R with the angle of incidence for an unpolarized light beam: the larger the angle of incidence, the more significant the fraction of the incident flux that is reflected.

In the case where the interface presents irregularities with a dimension larger than λ/10, the reflection is said to be scattered (Figure 34.2) because for the same incident direction, the light is reflected in numerous directions.

The refractive index of biological tissues varies between 1.35 and 1.45; and its value depends principally on their water content whose index is equal to 1.33. For a completely dehydrated tissue, the index is of the order of 1.55. Table 34.1 gives typical values of the refractive index measured in the visible for some types of biological molecules and cellular organelles. It should be noted that at the cellular level, the refractive index varies greatly from one organelle to another.

Plasma membranes have an index practically equal to that of lipids of which they are predominantly constituted, while the index of cytoplasm is close to that of water. As with other material media, the refractive index of tissue depends on the wavelength and decreases with it. For example, for measurements performed on beef muscle, the refractive index changes from 1.43 at a wavelength of 390 nm to 1.38 at a wavelength of 710 nm.

Table 34.1 Refraction Indices of Some Biological Molecules and Cellular Organelles

Medium	Index
Water	1.33
Proteins	1.6
Lipids	1.46
Melanin	1.7
Cytoplasm	1.37
Membranes	1.46
Nucleus	1.39

If the light source is collimated and perpendicular to the tissue, the coefficient of reflection at the air–tissue interface is of the order of 4%–7% between 300 and 3000 nm. For an isotropic and scattering point source, it is approximately 8%–10%.

We should point out that for skin in a nonlubricated state, the condition of specular reflection is not fulfilled; for a wavelength of 600 nm, it is necessary that the height of irregularities should be less than λ/10 or 60 nm, whereas the dead cells

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

of the *stratum corneum* have a typical thickness of 600–800 nm. Reflection is therefore scattered, which explains the matt appearance of skin. On the other hand, in the case of moist mucosa, the irregularities are reduced and reflection can be considered to be specular.

Absorption

Fundamentals

Absorption plays a major role in laser therapy, since it is the first step in transferring light energy to the tissue.

A molecule can only exist in a certain number of discrete energy states corresponding to given electronic configurations. A schematic representation of these levels is given in Figure 34.4, called the Jablonski diagram.

There are two types of electronic states:

1. States of multiplicity 1, called singlet states, designated by S in which all the electrons are paired, i.e., arranged in pairs of opposite spins. The total spin of the molecule is therefore zero (S = 0).
2. States of multiplicity 3, called triplet states, designated by T, in which there are two unpaired electrons having a spin in the same direction.

In a given electronic state, the molecule possesses many degrees of freedom corresponding to the vibrations and rotations of nuclei, each vibrational–rotational state is characterized by an energy level; the energy gaps between rotational levels are small compared with the differences between vibrational levels, and the latter are themselves small compared with the differences between electronic levels (Table 34.2).

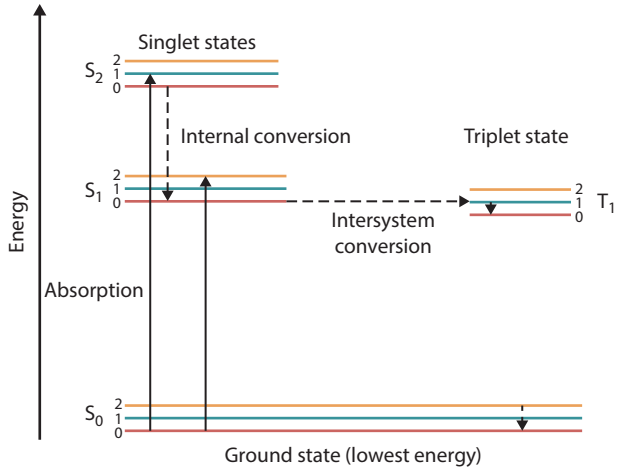


Figure 34.4 Jablonski diagram of the energy levels of a molecule and the mechanism of absorption.

Table 34.2 Energy Gaps between the Different Levels of Energy of a Molecule

	Energetic gaps between levels	Wavelength domain
Rotational	Around 10 J/mole	Microwaves
Vibrational	1–40 kJ/mole	Infrared
Electronic	150–600 kJ/mole	UV–visible

Each electronic state is therefore divided into very close vibrational levels, which are themselves divided into rotational levels. Inside an electronic level, different vibrational levels are defined by their vibrational quantum numbers v = 0, 1, 2, …, where v = 0 corresponds to the lowest vibrational energy state. When the molecules are in a condensed phase, very strong interactions between them exist, which cause an enlargement of the vibrational levels. Consequently, there is a significant overlap of these levels, and the sequence of discrete energy levels, which constitutes the structure of an electronic level, becomes a *continuum* that is designated by the name band.

The electronic state corresponding to the lowest energy is called the ground state. In the majority of cases, it is a singlet state that is denoted by S_0. At room temperature (300 K), all molecules are found in the lower vibrational levels of the ground state.

A photon of frequency $\nu_a = c/\lambda_a$ will be able to be absorbed by the molecule if its energy $h\nu_a$ is equal to the difference in energy between the lower vibrational levels of the S_0 state and one of the level of the excited singlet states (Figure 34.4). Numerous vibrational levels of the electronic state S_1 (or S_2) can be reached from the same ground state; therefore, the molecule will not absorb a single frequency but will present several absorption lines. In the condensed phase, the vibrational levels of each state S form a practically continuous band, with the result that the molecule will be able to absorb a continuous domain of wavelengths called absorption bands. The absorption bands located in the visible and the ultraviolet (UV) (between 100 and 750 nm, corresponding to energy transitions from 12 to 1.7 eV) correspond to transitions between the electronic level S_0 and the level S_1 or S_2. Transitions between vibrational levels, which require a low energy, of the order of a few hundredths of an electron volt are at the origin of the absorption bands observed in the infrared. A given molecule therefore presents several absorption bands that characterize it.

If we consider now a homogeneous, absorbing, and nonscattering medium, containing n identical molecules per unit of volume, a light beam whose wavelength belongs to an absorption band of the molecule will, by propagating in this medium, give up a fraction of its energy. Indeed, a certain number of the photons of the beam are going to be absorbed by the molecules according to the quantum process described in the previous paragraph, and the macroscopic effect of all these absorptions will be a diminution in the intensity of the beam as its propagation into the medium progresses. Let us consider a monochromatic beam of irradiance I (W/m^2) propagating along the z-direction and entering the medium at z = 0 (Figure 34.5).

The decrease in intensity dI caused by the crossing of the layer of thickness dz is proportional to the intensity I(z) incident on this layer and to the number of molecules present in the layer, namely, n dz.

It therefore becomes

$$dI = -\sigma I(z) n\, dz$$

The coefficient of proportionality denoted here by σ is characteristic of a given molecule and is dependent on the wavelength. It is called the efficiency absorption cross section and has the dimension of a surface. By integration, we obtain the

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

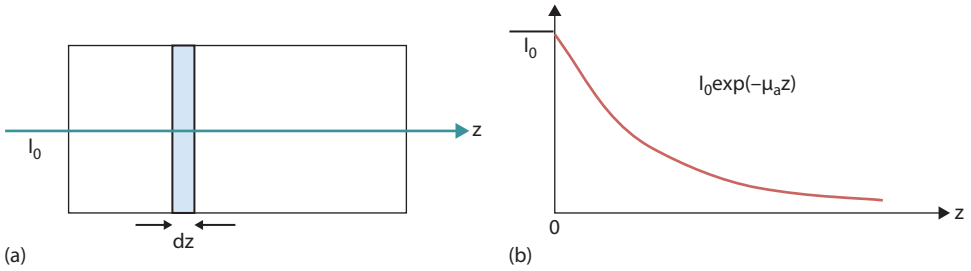


Figure 34.5 The Beer–Lambert law: (a) monochromatic beam of irradiance I (Watts m^{-2}) propagating along the z-direction and entering the medium at z = 0, (b) intensity decrease as a function of z.

residual intensity after passing through the thickness d, which is written by putting $I(z = 0) = I_0$:

$$I(z = d) = I_0 \exp - \sigma nd = I_0 \exp - \mu_a d$$

where $\mu_a = \sigma n$ defines the linear coefficient of absorption, whose dimensions are the inverse of a length and are generally expressed in cm^{-1} or mm^{-1}.

The intensity therefore decreases exponentially as a function of z (Figure 34.5b). This law is called the Beer–Lambert law. The penetration depth is defined as the depth at which the incident intensity I_0 has been divided by e, in other words, the depth at which it remains at 37% of the initial intensity.

The Beer–Lambert law is very often expressed in the form

$$I(z = d) = I_0 10^{-\varepsilon Cd}$$

where

C designates the concentration in mole/L
d is the thickness traversed in cm
ε is the molar absorption coefficient at a given wavelength, which is expressed in mole/L/cm

The comparison between the two expressions of intensity I shows that μ_a and ε are linked by the relationship $\mu_a = 2.3\varepsilon C$.

The absorption spectra are presented in graphics, either with the absorption coefficient μ_a or with the molar extinction coefficient ε as a function of wavelength λ or wavenumber $1/\lambda$.

Absorption of Light by Biological Tissues

Compounds that absorb light are called chromophores. Knowledge of the absorption spectra of different endogenous biological chromophores of tissues is essential because it allows us to determine which type of wavelength, i.e., which laser to use, depending on the designated target. Figure 34.6 presents the absorption spectra of the principal chromophores of the tissue.

Absorption in living tissue depends principally on the water of which it is primarily composed (the brain contains 85%, the muscles 75%, the kidneys 82%, and the bones 22%), as well as the hemoglobin contained in the blood vessels. It is necessary to add the melanin for which the absorption spectrum extends from the UV up to the near infrared. In the UV, for wavelengths less than 290 nm, absorption is owing to proteins (amino acids), to DNA bases, and to water. Proteins exhibit an

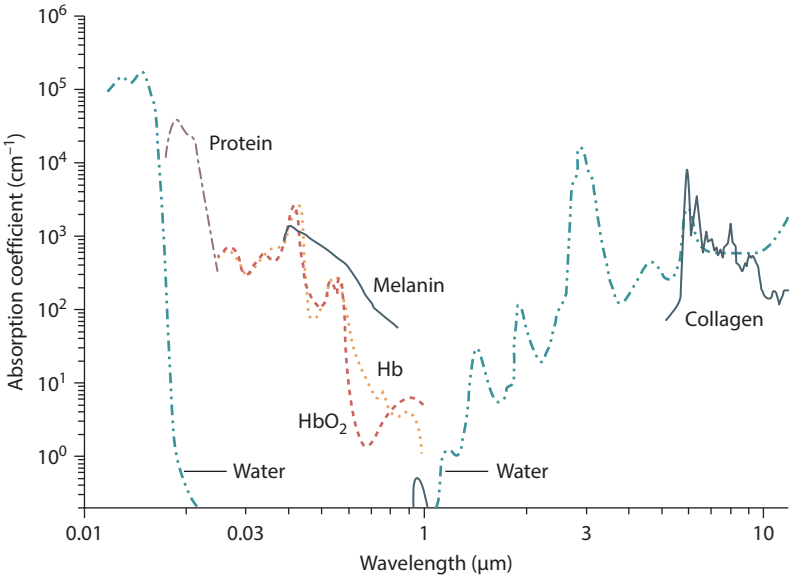


Figure 34.6 Absorption spectra of the principal tissue chromophores. (From Vogel A and Venugopalan V, *Chem Rev,* 103(2), 577, February 2003.)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

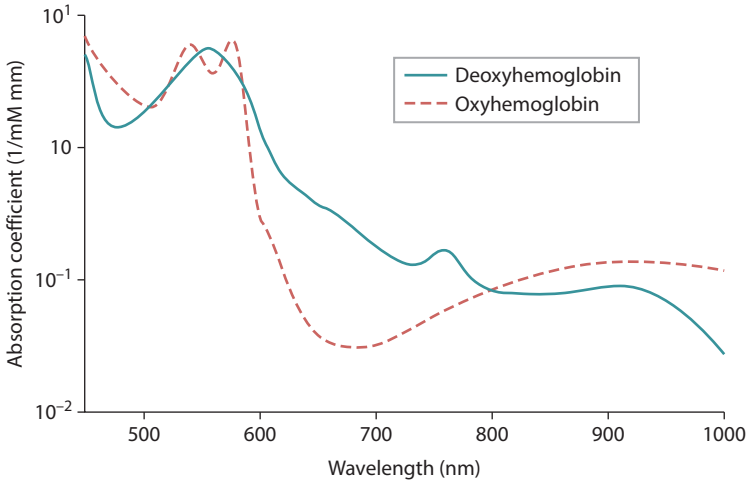


Figure 34.7 Absorption of oxyhemoglobin and deoxyhemoglobin from 450 nm to 1000 nm. (From Mordon S, La physique des lasers, in Dahan TM, ed., *Les Lasers en Dermatologie*, 2nd ed., Doin, Paris, France, 2006, pp. 3–32.)

absorption peak around 280 nm. In general, the majority of large organic molecules have a strong absorption in the UV and in the domain of short wavelengths of the visible spectrum (from purple to green). The more significant the absorption, the more rapidly the light energy is "consumed" and therefore the weaker the penetration. As a result, the penetration depths in the UV are extremely low, of the order of a few micrometers.

The principal chromophores responsible for absorption in the visible domain are hemoglobin and melanin.

Deoxyhemoglobin (Hb) and oxyhemoglobin (HbO_2) present a major peak of absorption in the blue around 415 nm, which explains the red color of blood. Their absorption coefficients then decrease strongly with the wavelength, but there is still a nonnegligible absorption as far as the near infrared around 1000 nm (Figure 34.7).

The absorption spectra of deoxyhemoglobin and oxyhemoglobin differ significantly, particularly in the red and near-infrared region, and this feature is exploited in oximetry, particularly in the pulse oximeter that measures oxygen saturation. The difference of absorption between the two species explains the bright red color of arterial oxygenated blood, saturated at 98%, and the darker venous blood, saturated at around 75%. When heating the blood, to about 50°C, deoxyhemoglobin and oxyhemoglobin transform into methemoglobin (Met-Hb) produced by the oxidation of ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}). The absorption spectrum of methemoglobin differs from that of hemoglobin, with, in particular, a much larger absorption around 1000 nm. This property can be exploited in heat treatment with a Nd:YAG laser emitting at 1060 nm [6].

Melanin is a protein produced by melanocytes at the end of the basal layer of the epidermis and then transferred to adjacent cells in the form of small pigments called melanosomes whose size is of the order of micrometers. The absorption spectrum of melanin extends from UV as far as the near infrared, and its absorption coefficient decreases monotonically with wavelength from 200 to 1300 nm.

In the infrared domain, water is the predominant chromophore (Figure 34.8). Practically transparent in the visible, water absorption is important in the infrared and increases from the near infrared and to the far infrared with two sizeable

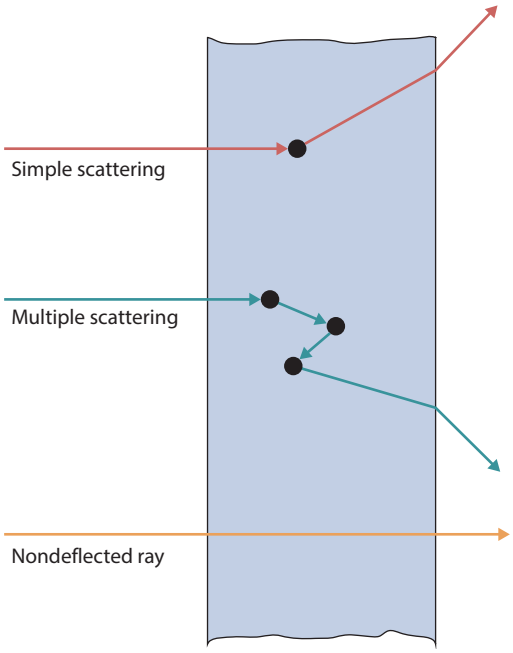


Figure 34.8 Schematic representation of the phenomenon of scattering.

peaks around 2000 and 3000 nm. The presence of these peaks is at the origin of the interest shown in the holmium:YAG laser (λ= 2120 nm; δ ~ 400 µm) and the erbium:YAG laser (λ = 2940 nm; δ ~ 1 µm).

The absorption coefficient of water increases by a factor of 1,000 between 1,300 and 10,000 nm going from μ_a = 1 cm^{-1} for 1,000 nm to μ_a = 1,000 cm^{-1} for 10,000 nm. It follows that at a wavelength of 1,300 nm, a thickness of 10 mm of water is necessary for the incident irradiance to be reduced to 37% of its initial value, whereas at 10,000 nm, a thickness of 0.01 mm is sufficient. This enormous difference between the value of the absorption

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

coefficients explains why, although both operating in a mode of thermal action, the effects of Nd:YAG laser (1,060 nm) and the CO_2 laser (10,000 nm) on tissues differ considerably.

Scattering

The phenomenon is represented schematically in Figure 34.8. Let us consider an inhomogeneous medium consisting of a collection of identical particles, with index n_s, of any shape, randomly distributed in a transparent medium, homogeneous and isotropic with index n_m. If the size of particle is less than or of the same order of magnitude as λ, we observe that a light beam of wavelength λ falling on this medium can

- Either propagate itself in the medium following its initial direction
- Or be deflected once (simple scattering) or several times (multiple scattering) from its initial direction

The deflection of the beam, which takes place without loss of energy, i.e., without changing the frequency of the radiation, constitutes the phenomenon of elastic scattering. It results from the interaction between the electromagnetic light wave and the charges of the particle: under the influence of the electric field of the incident wave, the charges of the particle begin to oscillate, transforming themselves into oscillating dipoles that emit radiation in all directions of space at the same frequency as the incident wave. The particle then behaves like a secondary light source; the emitted light power and its angular distribution in space depend on the wavelength of the incident radiation, the size, and the geometric shape of the particle.

Tissues are very heterogeneous and are composed of numerous scattering particles of various sizes and refractive indices: cells and subcellular organelles such as nuclei and mitochondria and blood vessels. The subcellular organelles, with a size of the order of magnitude of a few micrometers, produce Mie scattering, whereas membranes, whose thickness ranges from a few nanometers to about ten nanometers, molecular aggregates, and collagen fibrils generate Rayleigh scattering. Figure 34.9 illustrates the hierarchy of scattering structures, and Table 34.3 presents some scatterers of the human skin.

For a given tissue, each of the scattering structures that are present there contributes to its overall properties of scattering, as a function of its individual scattering parameters (μ_s and g) and of its relative concentration. To describe this global scattering, we will consider that the tissue is equivalent to an assembly of scatterers exhibiting an average scattering coefficient and an average phase function of radial symmetry p(cos θ), which represents the average angular distribution of scattering events.

The angular distribution of the scattered light exhibits a strong anisotropy. For the majority of human tissues, the anisotropy factor g = <cos θ>, the average value of the scattering angle, comprises values between 0.7 and 0.97, which signifies that the scattering will "point" toward the front. As a result, the irradiated volume exhibits an oblong shape, progressively taking the appearance of a flame with the increase of g (Figure 34.10).

The tissue scattering coefficient μ_s decreases with the wavelength. In the visible and the near infrared between 400 and 1200 nm, μ_s varies between 5 and 20 mm^{-1}; therefore, an average distance traveled by a photon between two scatterings comprises values between 0.2 and 0.05 mm. We can therefore consider that in the majority of tissues, all photons that reach

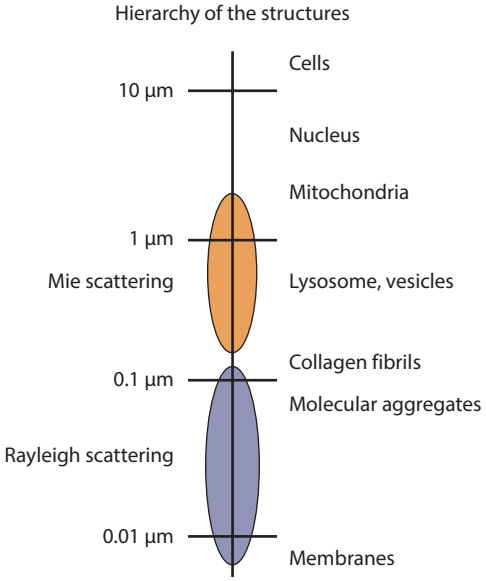


Figure 34.9 Tissue scattering structures. (From Jacques S and Prahl S, Optical properties, 1998. Available from: http://omlc.ogi.edu/classroom/ece532/class3/index.html. Accessed 2012.)

Table 34.3 Some Scatterers of Human Skin

Scattering structures	Size in micrometers (µm)
Cells of stratum corneum nuclei of cells	Thickness, 0.6–0.8
Melanin granules of the epidermis	0.3–0.8
Collagen fibrils of the dermis	0.02–0.1
Eythrocytes	7–8
Leukocytes	9–40
Platelets	1–3

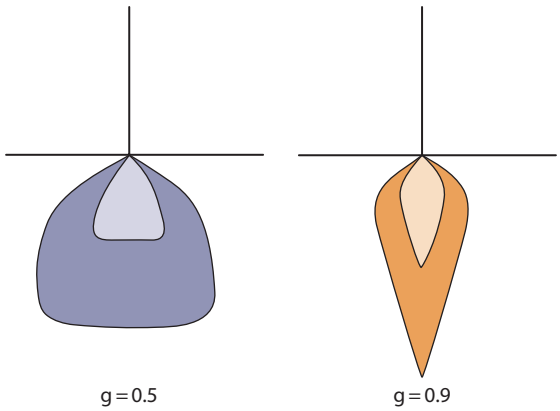


Figure 34.10 Influence of the value of the coefficient g on the shape of the irradiated volume.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Table 34.4 Values of Optical Coefficients for Some Tissues

Tissue	Wavelength (nm)	Absorption coefficient μ_a (cm^{-1})	Scattering coefficient μ_s (cm^{-1})	Anisotropy coefficient g
Epidermis	337	32	165	0.72
Epidermis	577	10.7	120	0.78
Epidermis	633	4.3	107	0.79
Dermis	337	23	227	0.72
Dermis	577	3.0	205	0.78
Dermis	633	2.7	187	0.82
Blood	450	381	2940	0.997
Blood	665	1.30	1246	0.995

Source: Extracted from Tuchin V, Chapter 1: Optical properties of tissues with strong (multiple) scattering, in Tuchin V, ed., *Tissue Optics: Light Scattering Methods and Instruments for Medical Diagnosis*, SPIE, Bellingham, WA, 2007.

a depth greater than a few tenths of a millimeter have been the object of multiple scatterings. Table 34.4 gives the values of μ_a, μ_s, and g measured *in vitro* for some tissues.

The reader will find in the reference [8] a collection of measurements of tissue optical coefficients performed on numerous types of tissue at various wavelengths. It is essential to know that, for the same tissue at a given wavelength, the values of these coefficients can differ significantly from one publication to another; indeed, they are derived indirectly from measurements carried out using different methods with the help of analytical or numerical expressions. Finally, the physiological state of the tissue may vary from one experiment to another.

From μ_s and g, one forms a new quantity, the reduced scattering coefficient μ_s' defined by

$$\mu_s' = \mu_s(1-g)$$

The coefficient μ_s' is a fundamental parameter involved in the theory of the propagation of light founded on the scattering approximation.

Its inverse $l_s' = 1/\mu_s \times (1 - g) = l_s/(1 - g)$ is the transport mean free path. It represents the distance at the end of which a photon has undergone such a large number of scatterings that it has lost the memory of its initial direction; this distance is typically of the order of 500 µm for biological tissues. Beyond a depth equal to l_s', the propagation of the light can be considered to be isotropic, but with a mean free path of scattering l_s'. In other words, there is then equivalence between an anisotropic propagation characterized by the mean free path of scattering l_s and the anisotropy coefficient g and an isotropic propagation characterized by the transport mean free path l_s' and g = 0. By way of an example, Figure 34.11 illustrates this equivalence for g = 0.9, i.e., a mean free path of transport of $l_s' = 10\ l_s$. Between two scatterings, the direction of the photon varies little because g is high. After having traveled ten mean free paths, the photon has lost the memory of its initial direction; its overall trajectory is equivalent to steps of length l_s' with a random scattering between two steps. As shown in Figure 34.11, a very large number of small steps in anisotropic scattering are then equivalent to a much smaller number of steps in isotropic scattering.

Penetration of Light in Biological Tissues

The simultaneous action of absorption and scattering determines a spectral range comprising values between 600 and 1200 nm, which is called the therapeutic window, where the transmission in the tissues is at maximum and the penetration of a light beam could reach several millimeters. For example, Figure 34.12 shows the light transmitted through a human hand illuminated by a pocket light.

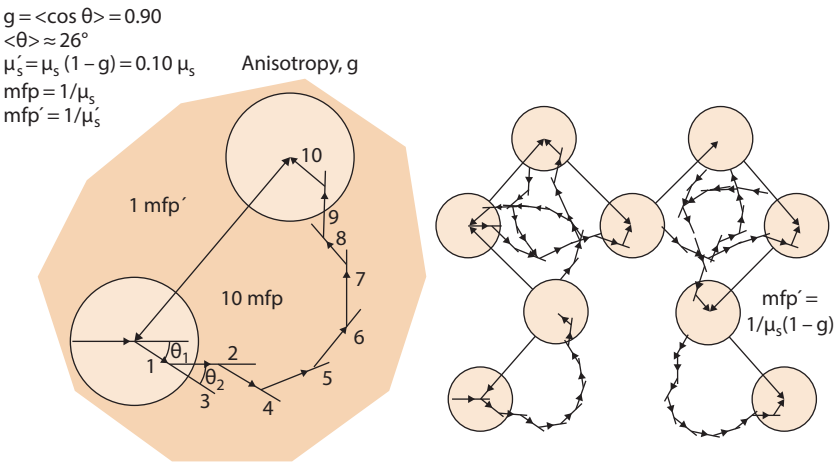


Figure 34.11 Scattering and transport mean free path. (From Jacques S and Prahl S, Optical properties, 1998. Available from: http://omlc.ogi.edu/classroom/ece532/class3/index.html. Accessed 2012.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 34.12 Transmission of white light from a pocket light through a human hand.

Below 600 nm, the depth of penetration is always less than one millimeter. Above 1100 nm, the penetration is limited by the absorption of water. By way of an example, Figure 34.13 gives the depth of penetration of the light into the skin as a function of the wavelength.

In the range stretching from red to the near infrared (600–200 nm) where the global absorption of tissue is low, with typical values for μ_a comprising values between 0.01 and 1 mm^{-1}, the scattering is much greater than the absorption and therefore plays a dominant role. As a result, the spatial distribution of the light in the tissue is going to differ significantly from that which would be produced by a purely absorbing medium. If a tissue displayed only absorption, a collimated beam falling on it would remain collimated and would propagate by attenuating itself exponentially following the Beer–Lambert law. Owing to scattering, the beam is going to be "uncollimated," the lateral scattering of photons expanding the section of the irradiated volume in relation to the initial geometry of the beam (Figure 34.14).

Finally, if simple scattering is highly anisotropic and exhibits a strong component in the direction of the incident beam, multiple scattering has a tendency to render the spatial distribution of photons more and more isotropic as the light proceeds to penetrate into the tissue.

When scattering greatly outweighs absorption ($\mu_a \ll \mu_s$)—the case of the therapeutic window between 600 and 1100 nm—and for a depth l greater than the transport mean free path l'_s ($l > l'_s$), scattering can be considered isotropic. The propagation of light in the tissue can then be treated as a diffusion

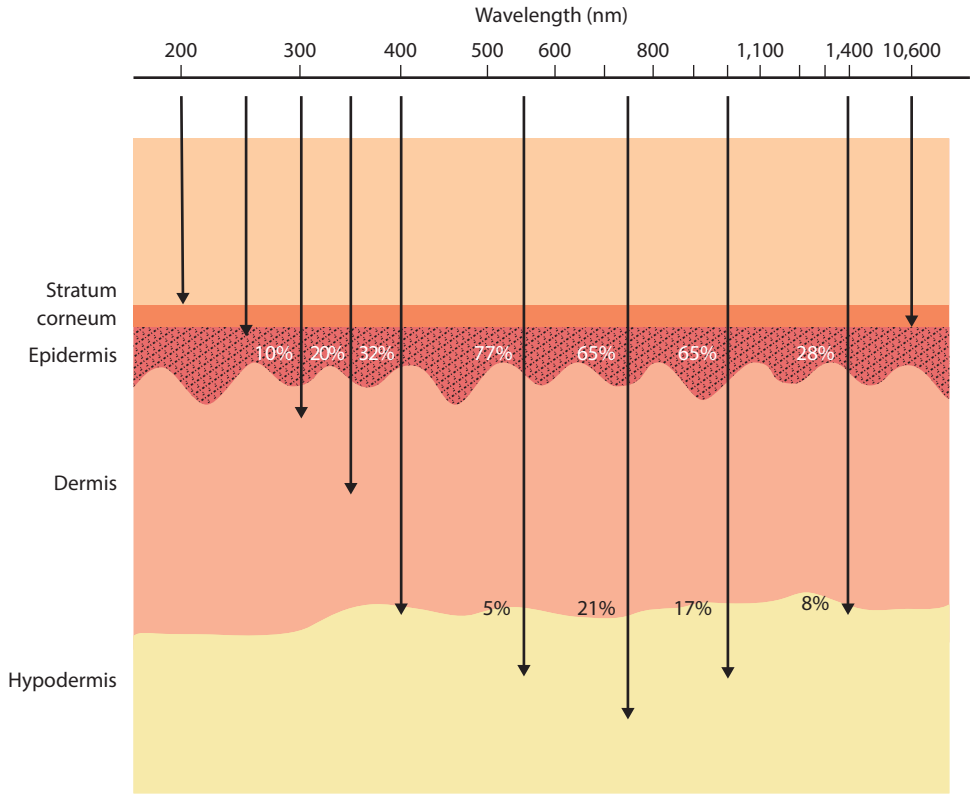


Figure 34.13 Depth of penetration in the skin as a function of the wavelength. (From Mordon S, La physique des lasers, in Dahan TM, ed., *Les Lasers en Dermatologie*, 2nd ed., Doin, Paris, France, 2006, pp. 3–32.)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

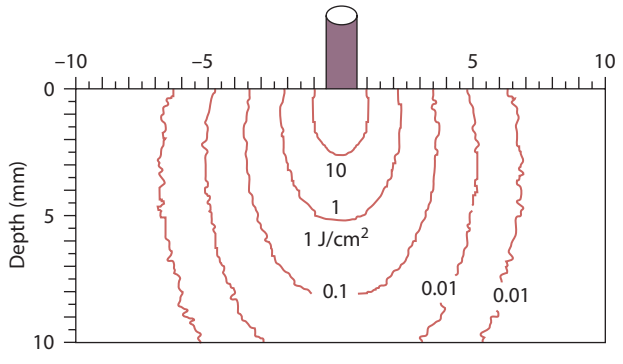


Figure 34.14 Isofluence contours (J/cm²) inside a tissue obtained by Monte Carlo simulation for an exposure to a collimated light beam with diameter of 1.2 mm. Optical proprieties of the tissue: $\mu_a = 0.1\ mm^{-1}$, $\mu_s = 1\ mm^{-1}$, g = 0.9, n = 1.33. (From Jacques S and Prahl S, Optical properties, 1998. Available from http://omlc.ogi.edu/classroom/ece532/class3/index.html. Accessed 2012.

process—the term diffusion being taken in the sense that we understand when we speak of the diffusion of heat, for example. We can show that the evolution of the fluence rate ϕ as a function of the depth z is governed by the parameter μ_{eff}, which is called the effective attenuation coefficient, defined by

$$\mu_{eff} = [3\mu_a(\mu_a + (1-g)\mu_s)]^{1/2} = [3\mu_a(\mu_a + \mu_s')]^{1/2}$$

The fluence rate along the z axis passing through the center of the beam is then given by

$$\phi(z) = A \exp(-\mu_{eff}\, z)$$

It should be noted that the constant A is not equal to the initial irradiance I (z = 0). The effective penetration depth μ_{eff}, defined by $\mu_{eff} = 1/\mu_{eff}$, is often used as a reference to provide an estimate of the depth of penetration of light into a tissue.

THERAPEUTIC EFFECTS OF LASERS

It is possible to classify the interaction between the laser light and biological tissue according to four types of effects as a function of the applied irradiance and the duration of exposure used (Figure 34.15):

- Electromechanical effect (disruptive action), obtained with pulses of 10 ps to 10 ns and irradiances of the order of 10^7–10^{12} W/cm².
- Photoablative effect, obtained with pulses of 10–100 ns. In this case, more than the irradiance, it is the spectral domain that is important for the photoablative effect, since it requires energetic photons.
- Thermal effect, obtained with pulses of 1 ms to several seconds and irradiances of the order of 10^1–10^6 W/cm².
- Photochemical effect, obtained exclusively in combination with a photosensitizer, the duration of illumination ranging from tens of seconds to tens of minutes with irradiances generally that are very weak.

Thermal Effect

The thermal effect today constitutes the predominant mode of action for therapeutic applications of lasers.

Mechanisms of Thermal Action

The thermal effect groups together a wide range of types of interaction are characterized by a significant change of temperature inside the tissue illuminated by the laser. The thermal effect can also be achieved with either a laser exhibiting a continuous emission or with pulsed lasers. The thermal effect of lasers is a complex process consisting of three phenomena: a conversion of the laser light into heat (1st stage), a transfer of heat into the tissue (2nd stage), and a tissue reaction dependent

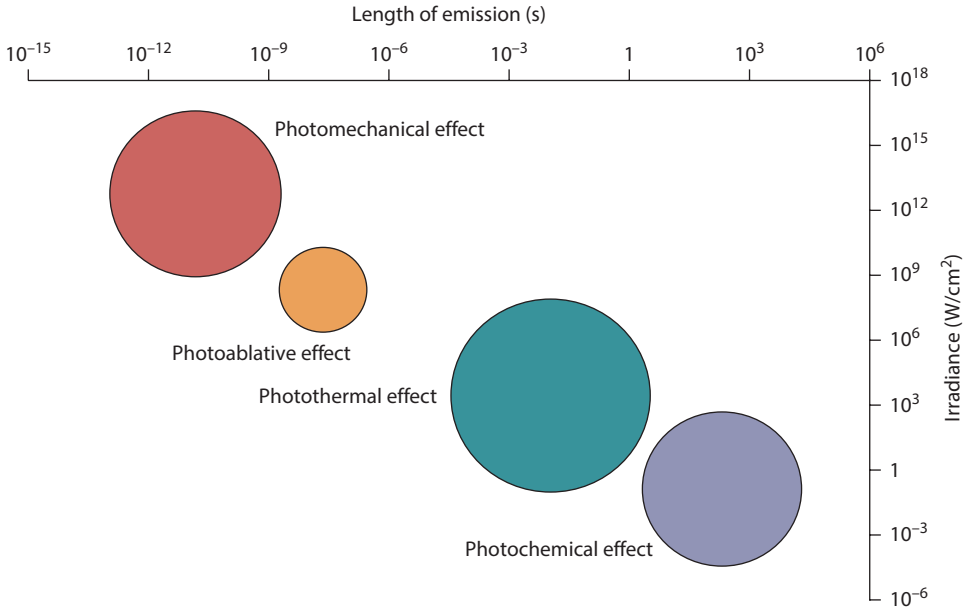


Figure 34.15 Effects produced by the laser light to a tissue, classified as a function of the irradiance and the duration of exposure. (From Mordon S, La physique des lasers, in Dahan TM, ed., *Les Lasers en Dermatologie*, 2nd ed., Doin, Paris, France, 2006, pp. 3–32.)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

on the temperature (3rd stage). Depending on the duration of the heating carried out, and also as a function of the temperature rise of the tissue, we can obtain hyperthermia, coagulation, or volatilization of a given volume of tissue [9].

First Stage: Conversion of the Light into Heat This conversion begins with the absorption of a photon by a molecule, which carries it into a vibrational excited state, followed by an inelastic collision with another molecule that produces an increase in the kinetic energy and therefore an increase in temperature. We can consider that the depth to which this conversion of light energy into heat occurs is equal to the effective penetration depth $\delta_{eff} = 1/\mu_{eff}$.

A judicious choice of the wavelength *vis-à-vis* the dimensions of the target, its position, and its optical coefficients is essential for the result of thermal action. The wavelength is selected depending on the target that we wish to reach: blue-green for hemoglobin, infrared for water (from 1000 nm); for melanin, by placing ourselves in the visible, the absorption will be more significant than in the near infrared, but the light will penetrate less deeply. If the target is perfectly determined, a deep vessel, for example, we will look for a wavelength that is well absorbed by hemoglobin but poorly absorbed by the surrounding tissue in order to obtain the best efficiency at depth.

Second Stage: Heat Transfer The second stage is the transfer of heat. This step plays an essential role because it is going to determine in large part the importance of thermal action through the creation of temperature gradients within the tissue. Indeed, living tissues are capable of transforming a large portion of energy into the form of heat because the maintenance of a specific temperature determines tissue life. There are two main mechanisms for heat transfer in biological tissues: convection and conduction. The convection of heat is achieved with the transport of mass, while the conducting heat is characterized by a transport of heat without the transport of mass.

For calculations of temperature, definition of the initial conditions requires knowledge of a mechanism that dominates transfer in living tissues. In the case of a laser irradiation, the transfer of heat *via* the blood vessels, generally considered to be an important sector for transfer by convection, does not take place if the heating is conducted for a duration of less than ten seconds, and as a consequence macroscopic convection does not appear. Cell membranes restrict heat convection at a microscopic scale. Heat conduction is therefore the predominant mechanism that takes place by the interaction of particles of tissue. This transfer is carried out randomly from the most energetic particles to those that are less energetic and depends on the thermal coefficients of the tissue. The capacity that a tissue has to transport energy by conduction is characterized by a steady state, which is the thermal conductivity, and a transient state, which is the thermal diffusivity k, expressed in cm^2/s. This last notion allows us to introduce an important term, which is the thermal relaxation time τ. This time corresponds to the duration required for the temperature at the center of the target to decrease by an amount equivalent to 50% of the maximum temperature reached and for a transfer of heat outside the target to be observed. The consequences of this phenomenon of heat transfer are therefore the cooling of the target and the elevation of the temperature of tissue adjacent to it. The thermal relaxation time depends on the dimensions of the heat source (and therefore the dimensions of the target) and on its volume (Table 34.5). It can be expressed by the following equation:

$$\tau = D^2/C \cdot k$$

where

D is the diameter of the target

k is the thermal diffusivity (1.3×10^{-3} cm^2/s for the cells of the epidermis and 1.7×10^{-3} cm^2/s for the blood)

C is the geometry coefficient of the target (sphere C = 27, cylinder C = 16, plane surface C = 4)

Table 34.5 Thermal Relaxation Time τ as a Function of the Dimension of the Target

Biological structure	Average size	Relaxation time τ[a]
Particle of carbon/ melanosome	1 μm	1–10 μs
Cell	3–10 μm	10–100 μs
Vessel	30–300 μm	1–100 ms
Hair follicle	0.3–1 mm	0.1–1 s

[a] This time is variable as a function of the diffusivity and the geometry of the target [9].

As a function of the heating time, *vis-à-vis* the thermal relaxation time, it is possible to distinguish three cases:

- The pulse duration is much shorter than the thermal relaxation time τ of the target: in this case, there is a breakdown of the target by the thermomechanical effect (Figure 34.16). This is generally the case when dealing with blood vessels. It is also known as selective photothermolysis.
- The pulse duration is similar to the thermal relaxation time τ of the target. In this case, there is a heating of the target (Figure 34.17). This heating remains confined to the target and the transfer to surrounding tissue structures is nearly nonexistent. We speak of selective photocoagulation.

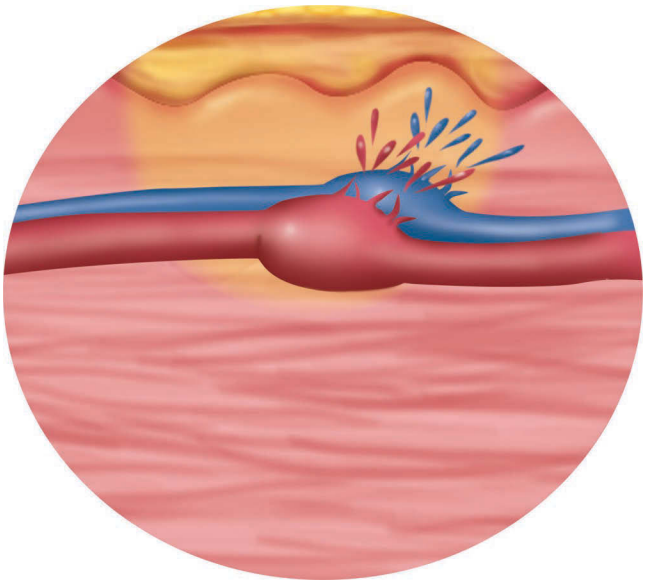


Figure 34.16 Pulse duration $\ll$ τ. Rupture of vessels by the thermomechanical effect: selective photothermolysis. (From Mordon S, La physique des lasers, in Dahan TM, ed., *Les Lasers en Dermatologie*, 2nd ed., Doin, Paris, France, 2006, pp. 3–32.)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

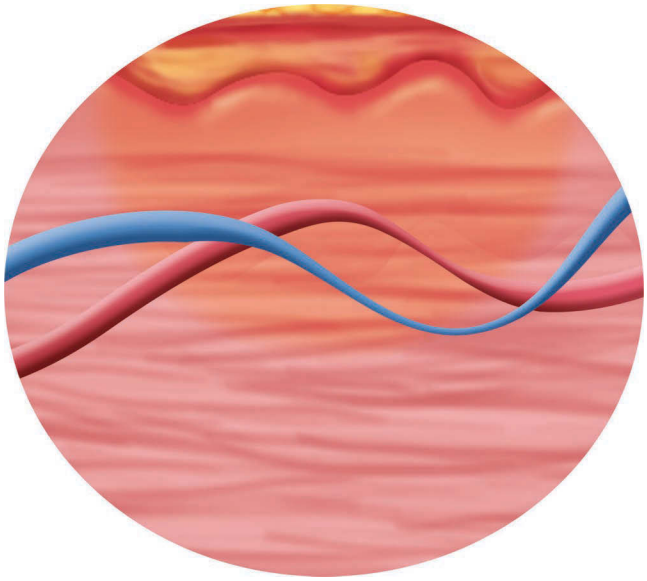


Figure 34.17 Pulse duration = τ. The heating remains confined to the vessels: selective photocoagulation. (From Mordon S, La physique des lasers, in Dahan TM, ed., *Les Lasers en Dermatologie*, 2nd ed., Doin, Paris, France, 2006, pp. 3–32.)

- The pulse time is much longer than the thermal relaxation time τ of the target. In this case, there is no more containment of the heating. The resulting thermal transfer can cause damage to surrounding tissue structures. One understands as well that an inappropriate choice of pulse duration can cause the loss of all the advantages of optical selectivity. It is necessary therefore to also have a *thermal* selectivity.

The lengthening of pulse duration beyond the thermal relaxation time can also be a good way to heat the target from a distance in order to obtain, for example, a more significant coagulation (Figure 34.18).

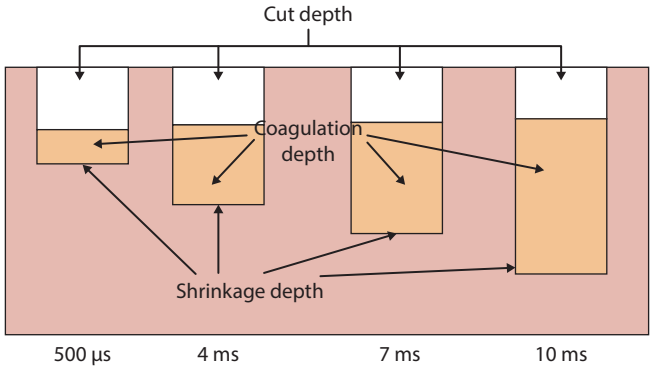


Figure 34.18 CO_2 laser used for skin resurfacing of the skin (τ = 0.8 ms). One sees in this example that the lengthening of the pulse duration up to 10 ms allows to obtain a more significant heating zone, leading to coagulation and consequently shrinkage. (From Mordon S, La physique des lasers, in: Dahan TM, ed., *Les Lasers en Dermatologie*, 2nd ed., Doin, Paris, France, 2006, pp. 3–32.)

Third Stage: Tissue Denaturation The denaturing (or destruction) of tissue, or more precisely that of its tissue constituents, is determined by the heating induced by the absorption of the laser light into the tissue. Knowledge of the kinetics of this transformation is necessary to understand the process of necrosis. The kinetics depends on the temperature in the tissue and on its temporal evolution. The speeds of tissue denaturation depend on the molecular structure of the tissues to be transformed. Owing to the large number of accessible vibrational states in the majority of molecules of biological tissues, the speeds are high, of the order of a few tens of milliseconds to a few seconds for volumes of a few cubic millimeters to a few tens of cubic millimeters.

The modification of different components of the tissue therefore requires kinetics of transformation and energies of activation, which are very different. In order to express this modification in a manner homogeneous for the different tissues involved, an equation has been proposed in order to define a state of tissue transformation as a function of both temperature and time. The greater or lesser sensitivity (susceptibility) of tissues to an elevation in temperature can also be an asset in the research of a specific thermal action.

This equation is written

$$\Omega = P \int \exp(E/R \cdot T(t)) \cdot dt$$

where

$d\Omega/dt$ is the kinetics of thermal denaturation
t is the time in seconds
R is the gas constant value = 8.3 J/K/mole
T(t) is the temperature of tissue in K, at time t and at the considered depth z
P and E are the constants evaluated from experimental data
P is defined as the thermal susceptibility of tissue in s^{-1}
E is the energy of activation per mole/molar constant of tissue in kJ/mole
E and P are determined experimentally for each tissue

This mathematical formalization allows us, on the one hand, to quantify the tissue damage and, on the other hand, to represent the thermal damage in the form of isodamage curves that can be easily correlated to the results of a histological study.

The isodamage Ω = 1 corresponds to the appearance of tissue coagulation. The role of kinetic heating on the tissue damage is detailed in Figure 34.19. The quantification of the damage shows well that there are reversible damage took place for which the time–temperature combination had not been sufficient: for example, in the case of the skin, a temperature of 45°C maintained during a period of 20 minutes, or even a temperature of 90°C applied for less than 1 ms, leads to a damage less than 1 and therefore is a reversible damage.

The heterogeneity of tissue, the presence of numerous tissue components in proportions that vary greatly from one tissue to another, makes it difficult to propose a strict classification of thermal actions of lasers. However, depending on the tissue temperature reached, some modifications of components are worth noting, which is summarized in Table 34.6.

Thus, for a heating time of the order of 5 seconds, at 50°C appear the first phenomena of vasodilation and endothelial damage that lead to cell death. At 55°C, there is a disappearance of enzymatic activity. Disruption of cellular membranes is obtained at 60°C, as well as the denaturation of certain proteins.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

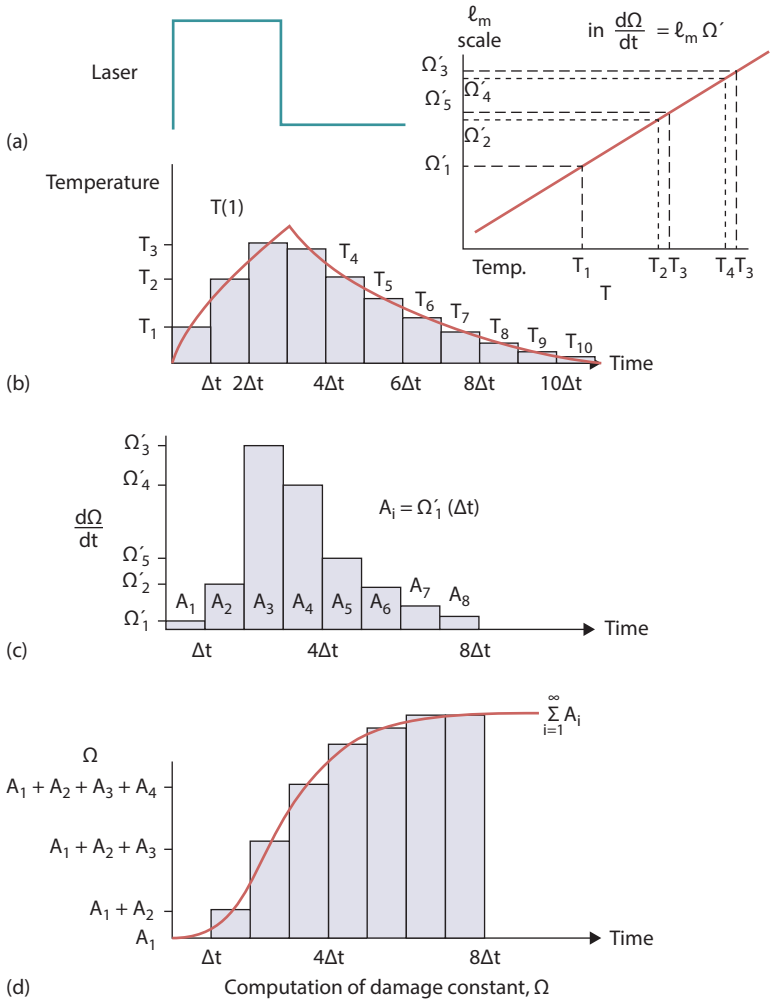


Figure 34.19 The role of kinetic heating in the denaturation of tissue. (a) For each tissue, there corresponds a curve expressing the thermal damage as a function of the temperature. (b) Temperature rise of the tissue. After stopping the pulse, the temperature decays. (c) For each temperature, one can associate a resulting damage using the curve of (a). The higher the temperature, the more important the damage. (d) The final damage is the sum of damages obtained for each temperature. One notices that the damage produced is greater after the laser has been switched off. (Illustration by Serge Mordon from Welch AJ et al., *J Biomech Eng*, 111(1), 62, February 1989.)

Table 34.6 Effect of Temperature on the Components of Tissue

Temperature (°C)	Modifications
45	Vasodilatation, endothelial damage
50	Disappearance of enzymatic activity
60	Disruption of cell membranes
	Denaturation of proteins
70	Collagen denaturation
	Permeabilization of membranes
80	Shrinkage of collagen fibers
	Coagulation necrosis
100	Vaporization of water
	Total dehydration
>100	Volatilization of organic components

Source: Mordon S, Actions thermiques des lasers, in SFLM, ed., *Encyclopédie des lasers en Médecine et en Chirurgie: Bases physiques et principes fondamentaux*, Piccin, Padoue, Italie, 1995, pp. 199–214.

Indeed, proteins are formed from polypeptide chains whose tertiary structure is defined by strong bonds (disulfide bonds) and weak bonds (hydrogen and hydrophobic bonds). The heat alters neither the disulfide bonds nor the covalent bonds, but it breaks the hydrogen bonds. Consequently, the denatured protein exhibits a higher axial ratio, therefore a more elongated structure. This renders it more viscous in solution. Plasma proteins are denatured at temperatures between 60°C and 70°C and in this way increase the viscosity of blood. These mechanisms can be obtained for shorter durations but necessitate slightly higher temperatures.

Collagen is also a protein, but its resistance to temperature is greater because its structure is more hierarchical. Procollagen displays the shape of a triple helix of polypeptide held in place by hydrogen bonds. The combination, by covalent bonds, of several units of tropocollagen forms a fibril of collagen. It is the combination of several fibrils through the intermediary of ionic and hydrogen bondings thanks to the presence of water (interstitial fluid)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

that forms a fiber of collagen. The heating produces an evaporation of water from the interstitial fluid. The hydrogen bonds of interfibers, created thanks to the presence of liquid, therefore disappear with water. Finally, the heat induces an unmasking of the reactive groups that are susceptible to form hydrophobic bonds. This implies an important increase in these hydrophobic and glycoprotein bonds that then form a "glue": the fibronectin.

Photoablative Effect

The photoablative effect, also known as ablative photodecomposition, is based on the use of photons having energy greater than the energy of the bonds of biological molecules. The photoablative process accordingly consists of a dissociation or a breakdown of the material and the expulsion of fragments at supersonic speed. Photons having energy of the order of 3–5 eV are susceptible to dissociate peptide bonds or carbon–carbon bonds of polypeptide chains. Consequently, lasers emitting in the UV such as excimer lasers (ArF, 193 nm, 6.4 eV, or XeCl, 308 nm, 4 eV) or even a frequency quadrupled Nd:YAG laser (266 nm, 4.7 eV) are well suited for laser photoablation.

This effect is particularly used in ophthalmology for the refractive surgery of the cornea where it is possible to correct myopia, mild to moderate astigmatism, and small hyperopia. The *laser-assisted in situ keratomileusis* technique has progressively replaced photorefractive keratectomy by laser, which was originally proposed. This technique consists of using a microkeratome to cut a thin flap of cornea lifted temporarily, the time to proceed with the treatment of the corneal stroma. The membrane is then repositioned above the treated area and takes the new curvature of the cornea. The end of the first decade of this millennium saw the emergence of IntraLASIK where a femtosecond laser now replaces the microkeratome.

Photochemical or Photodynamic Effect

Photodynamic therapy, commonly referred to the acronym PDT, is the destruction of diseased tissue by a photochemical reaction. The principle illustrated in Figure 34.20 is to label a pathological tissue with an exogenous chemical agent (photosensitizer) and then to illuminate it with light of an appropriate wavelength in order to induce a cascade of photochemical reactions leading to the destruction of the treated lesion. The method is based on a two-step process: (1) first, the application or injection of a photosensitizer or of a substance inducing the production of this photosensitizer allows us to achieve an accumulation of the latter in the zone to be treated, and (2) then illumination of this area is performed with a light whose wavelength is absorbed by the photosensitizer. The therapeutic effect is obtained by illumination of low irradiance (tens of mW/cm^2) and long duration (up to 10 minutes), without a thermal effect, allowing the activation of the photosensitizer and the production of cytotoxic compounds in the presence of oxygen. This is a photodynamic effect.

Principle of the Photodynamic Effect

As we have seen previously, by absorbing light in the spectral range corresponding to its absorption spectrum, the molecule is carried into different vibrational states of the excited electronic states S_1 or S_2 and consequently acquires an excess of energy relative to the ground state. The molecule deactivates itself rapidly (~10^{-12} s) by nonradiative relaxation to the low vibrational level of the excited singlet state of lowest energy S_1. This latter state, being more stable than the previous ones with a lifetime of the order of nanoseconds, can lose its energy by three processes as shown schematically in Figure 34.21:

- Releasing energy as heat to the surrounding environment.
- Emission of fluorescence (this aspect may be of interest if you want to visualize the presence of the photosensitizer in the tissue).
- Transition to an intermediate state called the triplet state. The decay of the triplet state to the ground state is much slower than that of the singlet state, the singlet–triplet transition being forbidden; i.e., it presents a very low probability. It is from the triplet state that the photosensitizer molecule will have time to interact with other molecules of the tissue medium, generating the photodynamic effect.

These chemical processes can be induced thanks to the excess of energy of the triplet state in two principal ways:

- In mechanisms of type I, the photosensitizer will chemically react with molecules in direct interaction. Oxidation–reduction reactions lead to the formation of radical species and, by complex processes involving usually oxygen, to the degradation of neighboring molecules. The photosensitizer is usually destroyed in these reactions.

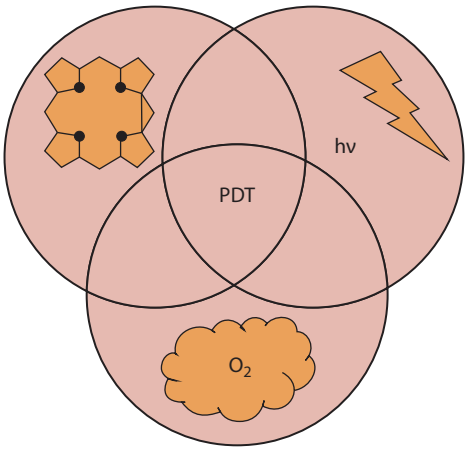


Figure 34.20 Principle of photodynamic therapy.

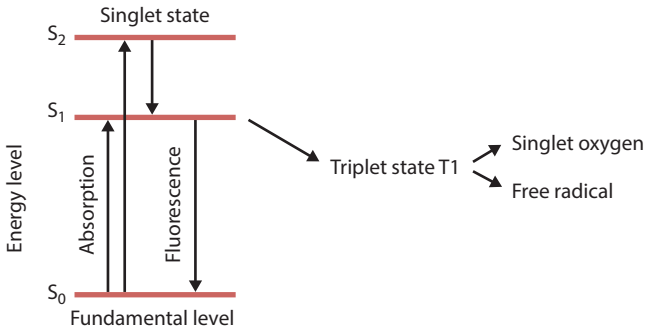


Figure 34.21 Diagram showing the energy levels of a molecule and the different pathways leading to the emission of fluorescence and to the processes of photosensitization. (From Barberi-Heyob M et al., *L'Actualité Chimique*, 308–309, 26, 2007.)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

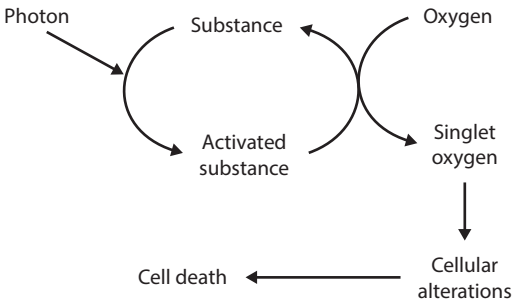


Figure 34.22 Mechanism of type II preponderant in the photodynamic processes. (From Barberi-Heyob M et al., *L'Actualité Chimique*, 308–309, 26, 2007.)

- In mechanisms of type II (Figure 34.22), a transfer of energy to oxygen sends the latter into the singlet excited state $^1O_2$. The photosensitizer returns to its ground state, ready for a new absorption of light energy. Singlet oxygen is a highly reactive species, capable of oxidizing numerous biological molecules. Amino acids, certain nucleotides, and lipid chains, which make up the membranes, are particularly sensitive to its action. Mechanisms of type II are predominant in photodynamic processes.

The main cellular targets are the cytoplasmic and mitochondrial membranes. Cell death is then induced mostly by necrosis. Oxidative stress may be relayed by a mechanism of apoptosis acting both on the cell membranes and on the mitochondria. The short lifetime of singlet oxygen limits its range of diffusion to some tens of nanometers and the effect will therefore be localized. Besides direct cellular alterations, the photodynamic effect causes a destruction of the vascular network of vessels, which induces necrosis by anoxia. Finally, the immune response to PDT results in an inflammatory reaction, which will damage the microcirculation and will contribute to vascular damage.

The photodynamic effect requires that the molecule is in the triplet state T_1; a photosensitizer is a molecule possessing a high quantum efficiency of triplet state formation. The photosensitizers currently used are porphyrin derivatives or precursors of porphyrins (aminolevulinic acid [ALA] and its derivatives). Several drugs are currently available on the market depending on the indications and medical disciplines, and other molecules are under development and are subject to clinical assessments.

The choice of the wavelength of illumination is a compromise between two requirements: irradiating in a spectral region where the absorption of the photosensitizer is significant while ensuring a sufficient penetration of light into tissue. One is consequently led to work most often in the red or near-infrared zone.

The use of a laser as a light source is justified by the need to utilize an optical fiber for endoscopic or interstitial treatments because the low divergence of the laser beam allows us to inject a higher power into the fiber. Dye lasers, employed originally, which were heavy to implement, have been replaced by diode lasers, which were compact, easy to use, and requiring a minimum maintenance. In dermatology, where illumination is directly performed, filtered lamps and LED panels have replaced lasers because, as indicated previously, irradiances required are relatively low. One of the keys to the success of PDT treatment is the respect for light dosimetry (total energy deposited per unit area of tissue); its control has necessitated the development of different types of light diffusers adapted to the morphology of the treated organ and providing a uniform light profile.

In dermatology, current indications, where the photosensitizer (derived from ALA) is applied locally as a cream, concern actinic keratoses and certain carcinomas; the results are comparable with classical techniques with superior cosmetic results. Basal cell carcinoma accounts for 75% of malignant skin tumors. Less than 1% of them are CBC giants, defined by a size greater than 5 cm in diameter and for which the risk factors include an aggressive histological type, a recurrence after treatment, history of irradiation, or neglect. Photodynamic therapy is a highly advantageous replacement

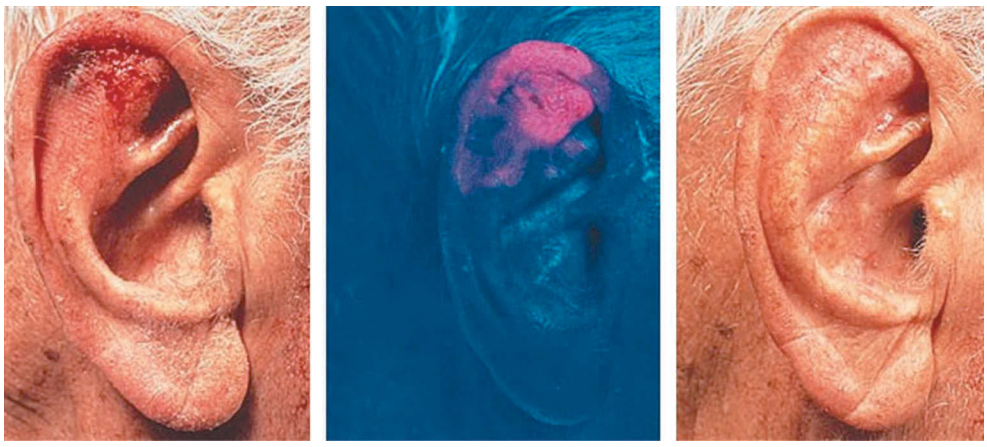


Figure 34.23 Carcinoma of the pinna in a patient of 72 years. After application of ALA and light illumination by Wood, it is possible to visualize the fluorescence of the protoporphyrin IX. On the right, an aspect obtained 18 months after three sessions (ALA then illumination with 180 J/cm² [570–750 nm]). (From Fritsch C et al., *Skin Pharmacol Appl Skin Physiol*, 11(6), 358, November–December 1998.)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

for surgical excision. As shown in Figure 34.23, PDT preserves the lobe, while the surgery would have necessitated cutting the extremity of it.

Electromechanical Effect

When an ultrashort laser pulse (ns and below) is focused on a target tissue, thereby creating high irradiances (of the order of 10^{10}–10^{12} W/cm^2), it is possible to obtain locally intense electric fields (10^6–10^7 V/m) comparable with atomic or intramolecular fields. Such fields induce an electrical breakdown of the material of the target resulting in the formation of a plasma. The shock wave associated with the expansion of the plasma generates extremely significant pressure waves and therefore a mechanical disruption of the tissue structure. This electromechanical effect is generally obtained with Nd:YAG lasers operating in Q-switched mode (ns) or locked mode (ps). It is used in ophthalmology to destroy membranules of the eye that occur in particular after the implantation of an artificial crystalline lens. In dermatology, we turn to lasers operating in Q-switched mode (ruby, alexandrite, and Nd:YAG) for the treatment of pigmented lesions and removal of tattoos. In the latter case, the large molecules of pigment (well tolerated by the skin) explode and give birth to smaller molecules that will be absorbed by the macrophages of the dermis. Furthermore, the explosion of microparticles of pigments generates microopenings in the dermis: these sluices contribute to the transepidermal elimination of part of pigment. Several sessions are generally necessary.

REFERENCES

1. Goldman L, Blaney DJ, Kindel DJ Jr, Franke EK. Effect of the laser beam on the skin: Preliminary report. *J Invest Dermatol* 1963 March; 40:121–122.
2. Polanyi TG, Bredemeier HC, Davis TW Jr. A CO_2 laser for surgical research. *Med Biol Eng* 1970 November; 8(6):541–548.
3. Kaplan I, Ger R, Sharon U. The carbon dioxide laser in plastic surgery. *Br J Plast Surg* 1973 October; 26(4):359–362.
4. Vogel A, Venugopalan V. Mechanisms of pulsed laser ablation of biological tissues. *Chem Rev* 2003 February; 103(2):577–644.
5. Mordon S. La physique des lasers. In: Dahan TM, ed. *Les Lasers en Dermatologie*, 2nd ed. Paris, France: Doin, 2006, pp. 3–32.
6. Mordon S, Brisot D, Fournier N. Using a "non uniform pulse sequence" can improve selective coagulation with a Nd: YAG laser (1.06 micron) thanks to Met-hemoglobin absorption: A clinical study on blue leg veins. *Lasers Surg Med* 2003; 32(2):160–170.
7. Jacques S, Prahl S. Optical properties. 1998. http://omlc.ogi.edu/classroom/ece532/class3/index.html. Accessed 2012.
8. Tuchin V. Chapter 1: Optical properties of tissues with strong (multiple) scattering. In: Tuchin V, ed. *Tissue Optics: Light Scattering Methods and Instruments for Medical Diagnosis*. Bellingham, WA: SPIE, 2007.
9. Mordon S. Actions thermiques des lasers. In: SFLM, ed. *Encyclopédie des lasers en Médecine et en Chirurgie: Bases physiques et principes fondamentaux*. Padoue, Italie: Piccin, 1995, pp. 199–214.
10. Welch AJ, Pearce JA, Diller KR, Yoon G, Cheong WF. Heat generation in laser irradiated tissue. *J Biomech Eng* 1989 February; 111(1):62–68.
11. Barberi-Heyob M, Frochot C, Bezdetnaya-Bolotine L et al. La thérapie photodynamique. *L'Actualité Chimique* 2007; 308–309:26–34.
12. Fritsch C, Lang K, Neuse W, Ruzicka T, Lehmann P. Photodynamic diagnosis and therapy in dermatology. *Skin Pharmacol Appl Skin Physiol* 1998 November–December; 11(6):358–373.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Surgical lasers: Ablative and fractional devices

Krystle Wang and Nazanin Saedi

INTRODUCTION

The concept of nonsurgical skin rejuvenation was born in the 1980s with the introduction of the carbon dioxide (CO_2) laser. The possibility of reversing outward signs of skin aging with minimal risk and rapid recovery inspired the field of laser skin resurfacing. With an aging population, the demand for an effective treatment modality for photorejuvenation continues to grow. Since the original CO_2 lasers were introduced, new developments, such as fractional resurfacing, have changed the playing field and hold forth the promise of impressive results with minimal adverse effects and shorter recovery times. Moreover, the indications that these lasers effectively treat in addition to photoaging continue to expand. This chapter will focus on two major modalities—ablative and fractional laser resurfacing.

ABLATIVE LASER SKIN RESURFACING

History

In the 1980s, continuous wave (CW) CO_2 lasers were first introduced. The field of skin resurfacing, traditionally limited to dermabrasion and chemical peels, was to be transformed by the advent of dermatologic laser surgery. Although the CW CO_2 lasers were effective at the gross destruction of lesions, the high rates of unpredictable scarring and dyspigmentation proved unacceptable.

The emergence of high-energy, pulsed, and scanned CO_2 laser systems led to the abandonment of CW systems. These technologies were based on Anderson and Parrish's principles of selective photothermolysis [1]. In brief, precise thermal destruction of a target chromophore could be achieved without affecting surrounding structures, if a wavelength that absorbed the specific tissue chromophore was selected. Moreover, laser pulse duration was made shorter than the thermal relaxation time (TRT) of the chromophore, where TRT was defined as the time required by the targeted site to cool to one-half of its peak temperature immediately after laser exposure. Using these principles, it became possible to reliably ablate skin layers at higher-energy densities, while still allowing for refined and controlled tissue destruction. The second generation of CO_2 lasers thus revolutionized the field of skin resurfacing.

The development of the short-pulsed erbium:yttrium–aluminum–garnet (Er:YAG) laser quickly followed. On emitting wavelengths at 2940 nm, the Er:YAG laser targeted water as a chromophore, similar to the CO_2 laser. However, the Er:YAG wavelength better approximated the 3000 nm absorption peak of water. This closer relationship permitted even more precise ablation with shallower depth of penetration and less thermal damage. Although the Er:YAG was associated with fewer adverse effects, comparative studies between Er:YAG and CO_2 lasers nevertheless demonstrated more favorable results with the latter [2,3]. As a result, the CO_2 laser arguably remained the "gold standard" for laser skin resurfacing until the advent of fractional lasers.

Mechanism

CO_2 Laser

The CO_2 laser delivers wavelengths in the far-infrared electromagnetic spectrum (106,000 nm) to water contained in target tissues. At such high wavelengths, there is minimal interaction with melanin and hemoglobin. The CO_2 laser penetrates about 20–30 μm in depth, while residual thermal damage extends a further 100–150 μm with pulse duration less than 1 ms. Calculations have shown that 5 J/cm^2 is the fluence needed to achieve tissue vaporization [4]. If a lower fluence is delivered, tissue coagulation and dessication occur instead.

Fluence is also affected by the beam diameter. Small-diameter beams (100–300 μm) can achieve high fluences, resulting in rapid tissue vaporization. Diffusion of heat and consequent tissue charring and dessication is minimized so long as the beam is moved rapidly across the skin surface. On the other hand, larger-diameter beams (>2 mm) often fail to induce rapid vaporization. There is also an increased risk of deep thermal damage using larger-diameter beams because lower fluences necessitate longer treatment durations for tissue vaporization to occur.

Based on these considerations, two CO_2 laser systems were developed to achieve tissue ablation—the high-energy, pulsed CO_2 laser system and the low-energy, rapidly scanning CW CO_2 laser. UltraPulse (Coherent Laser Corporation, Palo Alto, CA) and TruPulse (Tissue Technologies, Albuquerque, NM) were two examples of the pulsed type. The UltraPulse delivered up to 500 mJ using pulse durations less than 1 ms. A 3 mm spot size was standard, but a computer pattern generator (CPG) could be used to create various ablative patterns using 2.25 mm spots. The TruPulse used a 3 mm spot size and delivered up to 10,000 W at 90 μs and pulse energies between 250 and 500 mJ.

Low-energy scanning CO_2 laser systems, exemplified by the Sharplan FeatherTouch (Lumenis, Santa Clara, CA), used CW CO_2 with a beam delivered to the skin by a flash scanner. This scanner rapidly moved the beam in a series of patterns so that the dwell time on any given spot remained less than 1 ms.

Combining aspects of these systems led to the development of the superpulsed CO_2 lasers, such as the Luxar Nova Pulse (Luxar Corporation, Bothell, WA). Superpulses are clustered together to create short bursts lasting less than 1 ms and can deliver fluences of 7 J/cm^2. Rapid scanning over the skin is performed with a CPG.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Despite these apparent advances, however, a study comparing the 4 CO_2 lasers mentioned earlier showed equivalent clinical improvement in rhytides and scars. The overall duration of postoperative erythema was also equivalent among the 4 lasers [5]. With the advent of fractionated CO_2 lasers, traditional CO_2 lasers were largely rendered obsolete.

Er:YAG

The Er:YAG laser emits light within the mid-infrared portion of the electromagnetic spectrum at a wavelength of 2940 nm, which corresponds to the 3000 nm absorption peak of water. Compared to the CO_2 laser, energy from the Er:YAG laser is 12–18 times more efficiently absorbed by water-containing tissues [6]. As the majority of the epidermis is composed of water, the Er:YAG energy is more superficially absorbed, and a shallower zone of ablation is created compared to that generated by a CO_2 laser. The calculated tissue ablation threshold is 1.5 J/cm^2 and the pulse duration averages 250–350 µs. A single pass using the Er:YAG laser penetrates on average 2–5 µm per pulse with thermal necrosis ranging from 20 to 50 µm. A meta-analysis comparing 6 different Er:YAG lasers found equivalent clinical and histological results. All 6 Er:YAG lasers needed 3 passes to achieve total epidermal ablation [7].

Indications

Photoaging

Studies have shown the CO_2 laser achieves the most impressive results, both clinically and histopathologically, on photoaged skin. After one pass of the CO_2 laser using standard treatment parameters, epidermal ablation is achieved. However, it is the second and third passes that generate long-term collagen shrinkage and remodeling [8,9]. A retrospective study of 47 patients with perioral, periorbital, and glabellar rhytides demonstrated good to excellent cosmetic results in all areas after treatment with a CO_2 scanning device. Superficial rhytides resolved, and there was a drastic improvement in deeper rhytides. Generalized tightening of the skin was also noted [10]. Numerous other studies showed equally impressive improvements in skin tone, texture, and rhytides after CO_2 treatments [9,11]. Despite these dramatic results, the significant postoperative morbidity experienced by patients continued to dampen the enthusiasm of practitioners.

The Er:YAG laser has found a role in treating superficial and medium-depth rhytides. Studies have shown improvement in perioral, periorbital, and forehead rhytides, beginning 3 weeks after laser treatment [12,13]. Despite a reduction in morbidity, however, studies demonstrate inferior results for treating photoaged skin compared with the CO_2 laser [2,14].

The Er:YAG laser appears most useful for treating photoaging in dark-skinned patients (Fitzpatrick phototypes III and higher). After Er:YAG treatment, rhytides in 50 Asian patients showed a significant improvement in all individuals. Shorter periods for reepithelialization and resolution of erythema were observed as compared to previous reports on CO_2 laser resurfacing [15].

Treating photoaging of the neck is often avoided with CO_2 lasers due to significant concerns for scarring. The Er:YAG laser has shown good results treating this area in particular. Twenty patients treated for photoaging of the neck had improvements in both skin texture and color with minimal adverse effects [16]. Since the initial CO_2 and Er:YAG studies on photoaging, a shift toward its combined use has seen enhanced results [17–19].

The development of longer-pulsed Er:YAG lasers followed and allowed for increased dermal remodeling while still maintaining a safer side effect profile compared to the CO_2 laser [20].

Acne Scarring

Acne scarring, particularly atrophic scars, responds well to CO_2 laser treatments. A study including 60 patients with moderate to severe atrophic facial acne scores showed a significant improvement in all patients. Continued collagenesis and dermal remodeling was observed in histological specimens even at 18 months posttreatment [21]. Results for treatment of ice-pick scars from severe acne were less impressive. However, when using a combination treatment consisting of punch excisions followed by CO_2 laser treatment, ice-pick scars responded more favorably [22].

The Er:YAG laser has also demonstrated utility in treating acne scars. Studies have shown good results for atrophic and pitted scars, but side effects included acne flare-ups and postinflammatory hyperpigmentation (PIH) [23–25]. Combination treatments using the Er:YAG and CO_2 laser have also been studied. A study examining 158 Asian patients with atrophic acne scars showed more than 90% improvement in 32 patients, 80%–89% improvement in 65 patients, and 70%–79% improvement in 56 patients [26].

Other Forms of Scarring

CO_2 lasers have also been successfully used in the treatment of other types of scars, including those from surgery, trauma, and varicella. In one study, 30 subjects with postsurgical scars were treated between 4 and 6 weeks after scar formation, whereas traumatic, acne, and varicella scars were treated anywhere from 1 to 10 years after scar formation. All patients with surgical scars had greater than 50% improvement, and 20 of 24 patients had greater than 75% improvement. All 6 traumatic, acne, and varicella scars had greater than 50% improvement. The authors noted that elevated scars generally improved more so than depressed scars [27].

Data on the use of Er:YAG lasers for the treatment of other types of scars are limited. In the current literature, there exists a single randomized control trial investigating the efficacy of the Er:YAG laser in the treatment of hypertrophic scars. A moderate improvement was shown using the Vancouver burn scar assessment scale [28].

Melasma

Studies evaluating the treatment of melasma have typically shown the best results when the CO_2 laser is used in combination with the Q-switched alexandrite laser. In melasma, it is believed that abnormal melanocytes and excessive melanin are deposited within the epidermis, while melanin-laden macrophages lie in the dermis. The CO_2 laser removes pigment in the epidermis through epidermal ablation, while the subsequent Q-switched laser (QSL) treatment allows for deeper penetration of the dermis without serious side effects. A split-face study comparing the combination treatment of ultrapulse CO_2 laser with the Q-switched alexandrite laser versus the Q-switched alexandrite laser alone showed better results with the former [29]. A study evaluating the reverse—the combination of the pulsed CO_2 and the Q-switched alexandrite laser compared to the CO_2 laser alone—also showed improved results in the combination treatment [30]. In both studies, however, many patients experienced PIH.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

The treatment of melasma using the Er:YAG laser has been moderately successful with caveats similar to those when using the CO_2 laser. In a 1999 published study, 10 female patients were treated with the Er:YAG laser. Although there was marked improvement immediately after the laser surgery, all 10 patients experienced PIH between 3 and 6 weeks [31]. In a similar study, recurrence was noted starting at 3 months post-treatment [32].

Pigmented Lesions

The CO_2 laser was one of the first devices evaluated for the treatment of solar lentigines. In 1988, Dover and colleagues reported the use of the CO_2 laser in 5 patients and found substantial lightening or clearing [33]. In 1994, Fitzpatrick and colleagues found complete clearance of 83 solar lentigines after CO_2 laser treatment. In addition, this article reported a 100% clearance rate in treating 690 seborrheic keratoses on 32 patients [34].

The use of the Er:YAG laser has been described to treat café au lait macules (CALM). In 2001, Alora and colleagues described CALM in a single patient that almost completely cleared. Notably, this CALM had been resistant to several prior treatments of Q-switched ruby and Q-switched frequency doubled Nd:YAG treatments [35]. In 2005, Trelles and colleagues reported the efficacious response for the pigment removal in a Becker's nevus. They compared a single pass with the Er:YAG to 3 treatment sessions with the Nd:YAG laser. Two years after Er:YAG treatment, 54% of patients had 100% clearance of lesions and all 11 patients had greater than 50% clearance. In comparison, only 1 patient treated with the Nd:YAG laser showed greater than 50% clearance after 3 treatment sessions [36].

Congenital melanocytic nevi (CMN) have been treated using the CO_2 laser with mixed results. A 2005 study examined 12 patients with CMN after CO_2 treatments. Posttreatment, all cases had nevi that were minimally visible. Half of the patients, however, developed hypertrophic scarring. The authors concluded that this risk of hypertrophic scarring can be minimized by avoiding areas with known risk of hypertrophic scarring such as the anterior torso, flanks, and arms [37].

Combination treatment for CMN with the CO_2 laser followed by the Q-switched alexandrite laser has generally produced better outcomes. Chong and colleagues treated 11 patients with CMN using the CO_2 laser followed by a Q-switched alexandrite laser. Using a 5-point grade scale, the average posttreatment improvement ratings were 3.82 and 3.73 by physicians and patients, respectively. In this study, there were no cases of hypertrophic scarring or PIH that persisted beyond 2 weeks and no recurrences during the 2-year follow-up period [38].

Er:YAG laser treatments on CMN have yielded mixed results. A study of 10 children with CMN showed good to excellent results several weeks after Er:YAG treatment. Two patients with giant CMN, however, developed hypertrophic scars and skin atrophy. Two other patients showed repigmentation 2–3 months after treatment [38,39].

Premalignant and Malignant Skin Cancer

The CO_2 laser has seen much use in the treatment of actinic cheilitis, actinic keratoses (AKs), superficial basal cell carcinoma (BCC), and squamous cell carcinoma in situ (SCCIS). Clinical studies using the CO_2 laser to treat actinic cheilitis have shown recurrence rates varying from 0% to 14.28% for a minimum follow-up period of 11 months [34,40–42]. Treatment results for AKs using the CO_2 laser have also been mixed. One study reported no clinical evidence of residual or recurrent AKs in all 14 treated patients [43].

Another study examined the use of the CO_2 laser for the prophylaxis of AKs and BCCs with disappointing results. Five of 35 patients with extreme sun damage at baseline developed AKs or BCCs 1–6 months after CO_2 laser resurfacing [44].

Patients with nevoid basal cell syndrome have seen good results with the CO_2 laser for the treatment of numerous superficial BCCs [45]. A histopathological study concluded that 3 passes with a minimum of 4 mm margins were needed to effectively ablate superficial BCCs. However, as 3 passes did not completely ablate all the SCCIS, the authors concluded that the CO_2 laser was not a recommended modality for the treatment of thick or keratotic lesions [46].

The literature examining the efficacy of the Er:YAG laser in treating premalignant and malignant skin cancers is much more sparse compared to the CO_2 laser. A retrospective study examining 99 patients with actinic cheilitis treated with the Er:YAG laser showed an 84.8% cure rate at a mean follow-up time of 65.7 months. Over 90% of patients were satisfied with the treatment, and scarring occurred in only 5.1% of cases [47].

A much smaller study showed a decrease in the total number of clinical AKs ranging from 86% to 96% after 2–3 passes of the Er:YAG laser. However, only 5 patients were treated [48,49]. When comparing the use of topical 5-fluorouracil with Er:YAG laser for the treatment of AKs, a study found the laser to be more effective with lower recurrence rates. More side effects, however, occurred in the Er:YAG group [39].

Few studies have examined the use of the Er:YAG laser in the treatment of BCCs. A study compared the efficacy of the Er:YAG laser alone, photodynamic therapy (PDT) alone, or combination therapy in the treatment of nodular BCCs in 286 patients. Er:YAG laser treatment alone showed 91.75% efficacy. Combined therapy demonstrated the greatest efficacy at all time points, with 98.97% efficacy at 12 months after treatment. On this basis, the authors concluded that the combination of the Er:YAG laser with PDT could be a therapy of choice for the treatment of nodular BCCs [50]. No studies to date have investigated the use of the Er:YAG laser in the treatment of squamous cell carcinomas.

Rhinophyma

The CO_2 laser is still considered an excellent treatment modality for rhinophyma. A study of 124 patients produced results that were classified as good to excellent in 118 patients and poor in only 6 patients. The response was maintained at 3 months posttreatment. Scarring and hypopigmentation were seen in only 4 patients [51]. Smaller studies show equivalent success rates with follow-up periods of up to 4.5 years [52,53].

The Er:YAG laser has also been shown to be effective at treating rhinophyma [54,55].

More recently, studies examining the combined use of the CO_2 laser with other treatment modalities, including the Er:YAG laser, have demonstrated impressive results [56,57]. One report suggests that the combined use of the Er:YAG and CO_2 laser to treat rhinophyma should be considered the new gold standard. The authors argue that the CO_2 laser causes deep thermal damage to surrounding normal tissue, which often results in scarring. With the combination Er:YAG and CO_2 laser, the CO_2 laser is set to a lower power setting. This allows the CO_2 laser to coagulate instead of ablate tissue [57].

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Benign Epidermal and Dermal Lesions

The CO_2 laser has been used to successfully ablate various benign lesions, including verruca vulgaris [58–61], seborrheic keratoses [34,62], xanthelasma [63–65], adnexal tumors such as syringomas [66–68] and trichoepitheliomas [67,69–71], angiofibromas [72–74], and neurofibromas [75–77].

The Er:YAG laser has also shown efficacy in the removal of various benign lesions, including seborrheic keratoses, verrucae, xanthelasmas, hidradenomas, and fibroepithelial papillomas [78]. No studies have directly compared the efficacies between these two lasers in the removal of benign lesions.

FRACTIONAL LASER SKIN RESURFACING

History

Fully ablative laser skin resurfacing garnered popularity as the standard for facial rejuvenation in the 1990s. Despite its dramatic results, significant postoperative morbidity and complications limited its use. Ablation of the entire epidermis was associated with copious oozing and crusting and thus required a lengthy downtime for the patient. Moreover, the recovery period necessitated extensive care and follow-up. The need for frequent dressing changes, the increased risk of infection, and the risk of scarring resulted in a declining interest in the field.

In response, nonablative laser skin resurfacing became popular in the subsequent years. Dermal injury with relative sparing of the epidermis lacked many of the side effects associated with destruction of the entire epidermis, and downtime was considerably shortened. The results, however, were noticeably less impressive than those seen using ablative laser skin resurfacing.

Since the introduction of the concept of fractional lasers, it has garnered great interest in the field; laser fractionation appeared to strike a happy medium with great efficacy at the expense of more acceptable risks. In a 2004 publication, Manstein and colleagues reported on the improvement in skin texture and wrinkle appearance after treating forearm skin and periorbital rhytides with their prototype fractional photothermolysis (FP) device. By targeting a portion of the skin in a pixilated fashion, microthermal zones (MTZs) of injury were created. The use of higher dosages in comparison to those for nonablative laser resurfacing led to more impressive results, while the intervening zones of untreated skin expedited recovery and achieved increased safety [79].

Mechanism

FP is based on the use of microscopic beams of pixilated light to induce narrow zones of tissue destruction, termed "microthermal zones." Unlike ablative or nonablative lasers, which create confluent patches of tissue injury, these columns of thermal damage leave surrounding tissue unaffected. In the initial study by Manstein and colleagues, the MTZs were 100 µm in diameter and penetrated up to 400 µm into the skin [79]. Laser parameters, however, can be altered to produce columns of injury with varying shapes and depths. These MTZs create focal thermal damage or ablation, while the surrounding "skip areas" facilitate rapid healing by acting as a structural and nutritional reservoir [79].

After FP treatment, Manstein and colleagues have shown that there are both epidermal and dermal necroses within the MTZs via lactate dehydrogenase viability staining. Within 24 hours after treatment, reepithelialization is apparent through keratinocyte migration and extrusion of a collection of necrotic debris located just below the intact stratum corneum. This material was termed "microepidermal necrotic debris" (MEND) and corresponds histologically to the brown spots observed after FP treatment using epiluminescence microscopy [79]. Hantash and colleagues have since demonstrated that degenerated dermal material is also incorporated into MENDs, shuttled up the epidermis, and, finally, extruded through the stratum corneum. MENDs have also been shown to contain an abundance of melanin and are postulated to explain the efficacy behind FP in treating pigmentary disorders [80].

Although both epidermal and dermal necrosis occurred within the MTZs in the prototype FP device, histological specimens revealed an intact stratum corneum. Thus, this resurfacing was termed "nonablative" FP (NAFP) [79]. Ablative FP (AFP) devices have since been developed. In AFP, tapering microcolumns of ablation are seen instead in specimens and can vary in thickness and depth depending on the laser parameters used. These cavities lack an intact stratum corneum, are lined by a thin layer of eschar, and are surrounded by annular coagulation zones. Reepithelialization occurs within 48 hours, and collagen remodeling has been shown to persist for at least 3 months posttreatment [81,82].

Tissue injury created by FP stimulates both collagen remodeling and elastin tissue formation. Immunohistochemical studies have shown collagen remodeling markers such as heat shock proteins (47, 70, and 72), proliferating cell nuclear antigen, and alpha-smooth muscle actin in treatment areas [83]. Treated skin has also shown new collagen via procollagen III stains [84] and new elastin via antielastin stains [85].

Devices

Following the success of the prototype FP device used by Mansfield and colleagues, new devices using similar technology developed. Table 35.1 details fractional lasers that are being marketed and divides them into ablative and nonablative subcategories. This list is not meant to be exhaustive but rather provides an overview of the devices currently available.

Nonablative Systems

The 1550 nm nonablative fractional device (Fraxel re:store, Solta Medical, Hayward, CA) was the first commercially available medical laser that utilized FP. Consequently, it is the most extensively studied to date. The device uses an erbium-doped fiber laser at a nonablative wavelength of 1550 nm. The handpiece utilizes a scanning mode based on an Intelligent Optical Tracking System®. Originally, a blue optical dye was used to facilitate tracking, but advancements in technology have since eliminated this need. The Fraxel re:store device creates MTZs 100–200 µm in width and 500–1400 µm in depth. Energy levels can be adjusted from 4 to 70 mJ per MTZ. Additional nonablative fractional resurfacing (NAFR) lasers followed. However, literature comparing the different fractional nonablative devices is sparse, making it difficult to conclude which systems are more efficacious.

Ablative Systems

The emergence of ablative fractional lasers followed soon after nonablative fractional lasers. Three wavelengths—10,600 nm (CO_2 laser), 2,940 nm (Er:YAG laser), and 2,790 nm (yttrium–scandium–gallium–garnet (YSGG) laser)—were selected because their wavelengths are absorbed by tissue water.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Table 35.1 Fractional Lasers Currently Available

Device	Company	Type	Wavelength (nm)
Nonablative fractional lasers			
LuxIR fractional	Palomar	IPL powered infrared	825–1,350
Emerge	Palomar	Erbium fiber	1,410
Fraxel re:fine	Solta	Erbium fiber	1,410
Affirm	Cynosure	Nd:YAG	1,440
Clear + brilliant	Solta	Nd:YAG	1,440
Lux1540	Palomar	IPL power laser	1,540
Fraxel DUAL	Solta	Erbium fiber/thulium	1,550/1,927
Sellas1550	Benev	Erbium fiber	1,550
Ablative fractional lasers			
Pearl	Cutera	YSGG	2,790
Harmony	Alma lasers	Er:YAG	2,940
Lux2940	Palomar	Er:YAG	2,940
ProFractional	Sciton	Er:YAG	2,940
Active FX	Lumenis	CO_2	10,600
Affirm CO_2	Cynosure	CO_2	10,600
Deep FX	Lumenis	CO_2	10,600
Fraxel re:pair SST	Solta	CO_2	10,600
Juvia CO_2 fractional	Ellipse	CO_2	10,600
Mixto SX	Lasering USA	CO_2	10,600
Mosaic	Lutronic	CO_2	10,600
Pixel CO_2	Alma lasers	CO_2	10,600
SmartXide DOT	DEKA	CO_2	10,600

The Fraxel re:pair (Solta Medical Inc., Hayward, CA) was the first ablative fractional device. The device employs a 10,600 nm CO_2 laser that utilizes scanning handpiece technology. Energy and MTZ density can be adjusted. The Active/Deep FX system (Lumenis Aesthetic, Santa Clara, CA) is another well-studied ablative fractional laser device. The Active FX utilizes the original CPG handpiece with updated technology to create random patterns of injury while preventing bulk heating. The 1.3 m beam diameter creates a large but superficial spot treatment. The second technology, known as Deep FX, utilizes a narrower spot diameter (0.12 mm) but achieves greater penetration into the dermis. These two treatments together, with the first pass being the Deep FX and the second pass being the Active FX, have been collectively termed "Total FX." Unlike the scanning delivery method in the Fraxel re:pair, the Deep FX system uses a stamping method. Moreover, parameters of energy and density are not interchangeable between the two devices as the calculation with the Fraxel re:pair is based on the total area damaged (ablation and thermal coagulation), while the Deep FX density is based only on the area of vaporization.

Fractional ablative technology using Er:YAG lasers has also been developed including the Sciton ProFractional (Sciton Inc., Palo Alto, CA), the Alma Pixel (Alma Lasers, Buffalo Grove, IL), and the Palomar StarLux2940 (Palomar Medical Technologies, Burlington, MA). These devices vary from one another, but are based on the 2940 nm wavelength. This wavelength has a much higher affinity for water compared to the CO_2 10,6000 nm wavelength. Thus, cells will immediately vaporize and less thermal injury is generated. Following an Er:YAG laser treatment, decreased hemostasis often results in comparison to that seen after a CO_2 laser treatment.

The Pearl (Cutera Inc., Brisbane, CA) utilizes a 2790 nm Er:YSGG laser. The YSGG laser wavelength has an intermediate absorption coefficient of water, between that of the Er:YAG and CO_2. This allows for more collateral thermal injury than that seen following fractional Er:YAG treatment, but less than that seen following fractional CO_2 treatment.

The development of the Matrix RF (Syneron Medical Ltd., Yokneam, Israel) applied the concept of fractionation to radiofrequency (RF) for the first time. Studies have shown efficacy for skin rejuvenation [87,88].

Indications

Photoaging

In 2004, Manstein and colleagues first reported significant improvements in periorbital rhytides and skin textures of patients after treatment with their prototype nonablative device. They found a linear pattern of shrinkage related to the thermal injury. Tissue shrinkage was subsequently followed at 1 month by a relaxation period prior to a retightening at 3 months [79]. Since this initial study, numerous publications have supported this finding and continued to document improvements in photoaging using both ablative (Figure 35.1) and NAFP.

NAFP has been shown to improve photoaging on both facial and nonfacial surfaces. Photoaging changes, including those from texture, wrinkling, dyspigmentation, and telangiectasias, have been documented to improve after treatments. In 2006, Geronemus and colleagues showed improvement in the vertical lines of the upper lip [89]. Although the results were less than those expected from ablative laser resurfacing treatments, the minimal side effect profile and decreased downtime of NAFP were duly noted. Since then, studies have shown efficacy in photoaging of the hands [90] and photoaging of nonfacial surfaces [91]. For photoaging, Rahman and colleagues recommend lower surface area coverage and lower energy levels for off-face resurfacing compared to greater surface area coverage and higher energy for moderate and severe facial rhytides [92].

More recently, studies have investigated a synergistic approach, looking into combining the effects of intense pulsed

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

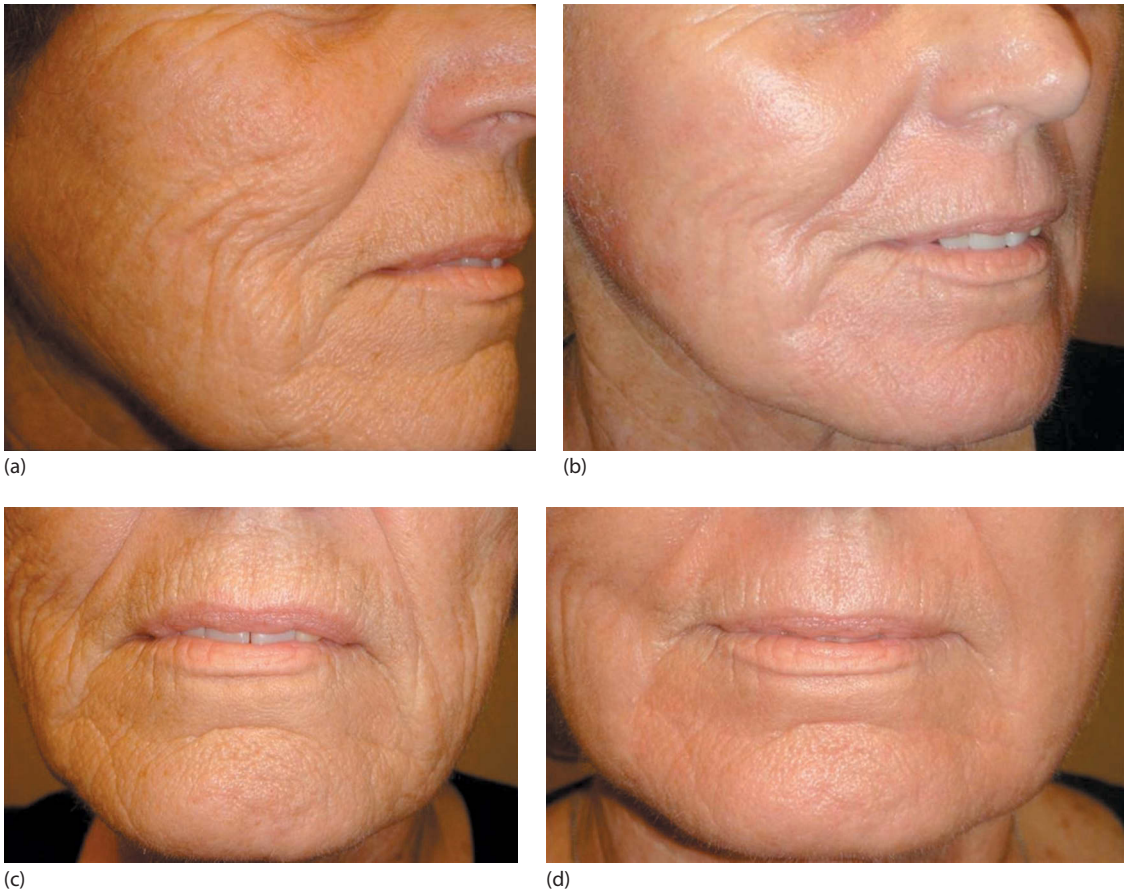


Figure 35.1 Fractionated CO_2 laser treatment (Fraxel re:pair) for photoaging. (a, b) Significant rhytides apparent pretreatment. (c, d) Improvement in texture, dyspigmentation, and rhytides 1 month posttreatment. (Courtesy of Christopher Zachary.)

light (IPL) with NAFP for photoaging treatment. Mezzana and Valeriani showed greater improvement with FP followed by IPL than with FP alone [93]. Similarly, Kearney and colleagues found a greater effect when IPL was combined with a 1550 nm FP for photoaging than either treatment alone [94]. In addition to photoaging, FP has proven to be effective in the treatment of Poikiloderma of Civatte in one case report [95].

AFP has shown significantly greater degrees of improvement in photoaging compared to NAFP. In 2007, Hantash and colleagues first described the use of a novel AFP device. Immunohistochemical stains from the initial *in vivo* studies revealed a wound remodeling response induced by adjacent intact skin that was sustained for at least 3 months posttreatment. Subsequent studies have confirmed greater clinical improvements in skin texture and wrinkling achieved with AFP than with FP. In addition to improving photoaging of the general face, perioral and periocular rhytides have shown particular promise with AFP. Recently, Tierney and colleagues studied 25 patients in a prospective, single-blinded study for lower eyelid laxity. They noted a significant improvement in skin texture, rhytides, and skin laxity after 2–3 treatments [96].

Acne Scarring

The initial studies of fractionated lasers on acne scarring were performed with NAFP devices. Patients with ice pick to boxcar and rolling scars showed mean clinical improvement from 25% to 50% as assessed using digital photography [89]. Atrophic-type acne scars similarly demonstrated improvement with NAFP [97]. Efficacy appears reliant on successive treatments as many studies have demonstrated increased clinical improvement after consecutive NAFP treatments [98–101]. Moreover, multiple laser passes seem to result in better clinical outcomes [79].

A significant improvement has been shown in acne scars treated with AFP (Figure 35.2). Between AFP and NAFP in the treatment of acne scars, AFP has demonstrated superior efficacy. A study compared nonablative 1550 nm fractional laser with a fractional CO_2 laser in 8 patients with acne scars and found more improvement when using the fractional CO_2 laser [102]. Between the two ablative fractional lasers, Er:YAG and CO_2, treatment of acne scars has been comparable, but there is more treatment discomfort with the fractional CO_2 laser [103]. Of note, effective AFP settings for acne scarring are considered to be those with high-energy, low-density laser settings as opposed to low-energy, high-density laser settings [104].

Both NAFP and AFP in the treatment of acne scarring in dark-skinned patients (Fitzpatrick skin types III–VI) have been studied. In a study with 27 Korean patients, 3–5 sessions of NAFP showed excellent or significant self-assessed improvement in 89% of patients [105]. For NAFP, it is recommended that darker skin phototypes have reduced passes and total treatment density to minimize PIH. Increasing the total number of treatment sessions is needed to achieve maximum efficacy [106].

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

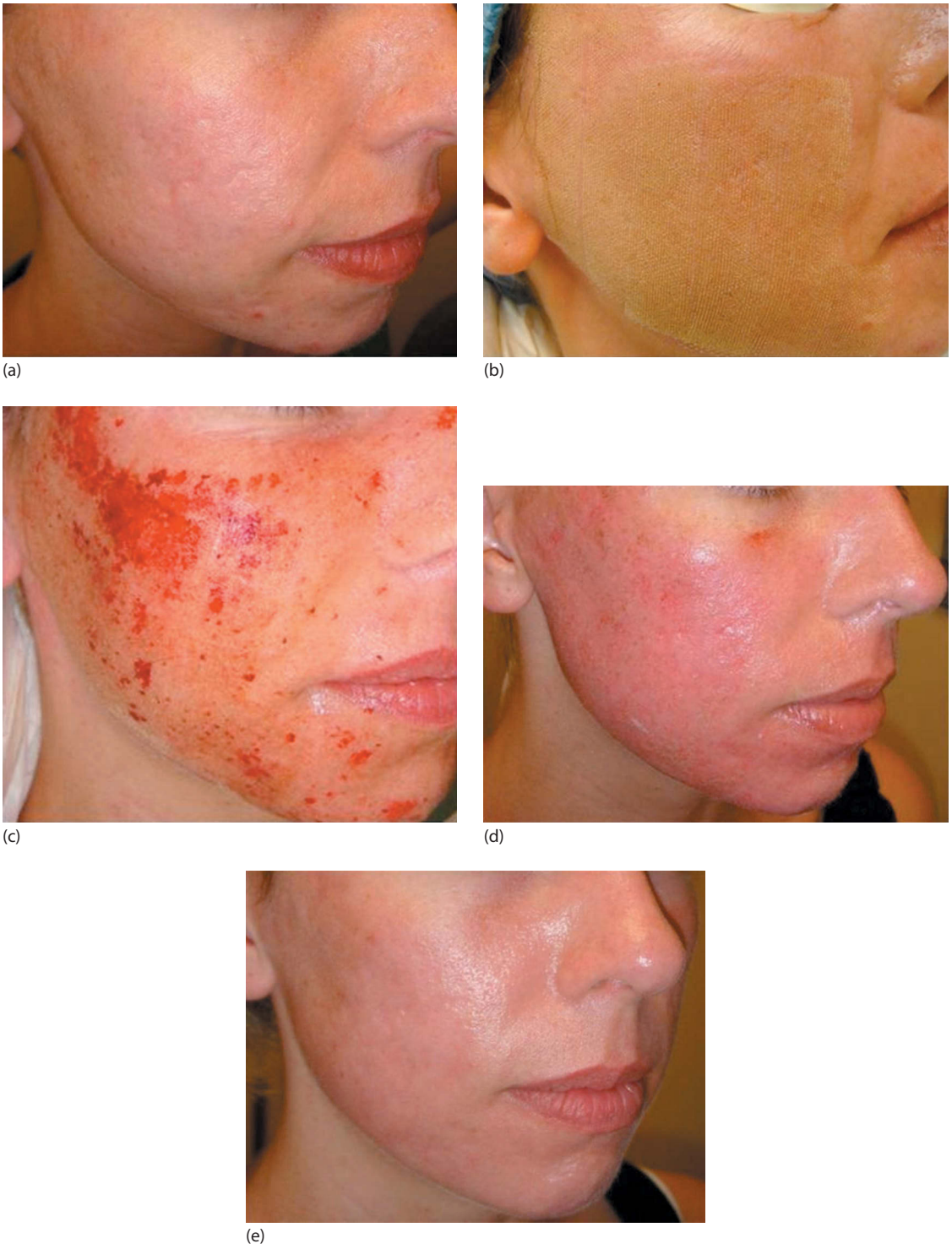


Figure 35.2 (a) Fractionated CO_2 laser treatment (Fraxel re:pair) for acne scars. (b, c) Pretreatment. (d) Visible microthermal zones (MTZs) of injury immediately following treatment. (e) 4 days posttreatment. 1 month posttreatment. (Courtesy of Christopher Zachary.)

A study using two modes of fractional CO_2 to minimize the number of treatment sessions showed a good improvement in acne scarring after one treatment session. The authors suggested that using AFP as opposed to NAFP could decrease total number of treatments, yet still achieve satisfactory results. Recently, combined use of fractional CO_2 laser and RF waves was used to treat 15 acne-scarred patients in a pilot study with promising results [107].

Acne-induced postinflammatory erythema has also shown marked improvement after one treatment session of NAFP in two patients. Continued improvement was noted after multiple treatment sessions. The authors speculate that

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

the 1550 nm wavelength, which targets tissue water, destroys blood vessels and results in improved erythema [108].

Other Forms of Scarring

Other scars, including surgical, posttraumatic scars, and striae distensae, have responded to FP. Glaich and colleagues showed improvement in long-term hypopigmented scars (5–20 years) resulting from acne and from a gas fire using the 1550 nm NAFR laser. All patients reported improvement sustained for at least 3 months. The authors postulated that the fractional resurfacing improved pigmentation by causing melanocytes from surrounding normal tissue to migrate and repopulate into the MTZs of injury [108].

Tierney and colleagues compared NAFP with pulsed dye laser (PDL) in the treatment of patients with surgical scars and found greater improvement with NAFP. They speculated that the MTZ of injury induced neocollagenesis and collagenolysis and resulted in improved scar remodeling [109]. Other studies showing promising results include treatment of CO_2 laser–induced hypopigmentation with AFP [110], thermal burns with FP [111–113], striae distensae with FP [114–117], and hypertrophic scars with NAFP. For the latter, low-density treatments appear as effective as high-density treatments, but with the benefit of fewer side effects. Study results suggest younger hypertrophic scars have more favorable outcomes [118] (Figure 35.3).

Pigmentary Disorders

Melasma treated with FP has shown efficacy with limitations. One of the initial reports on FP in the treatment of melasma was by Rokhsar and Fitzpatrick. After 4–6 treatment sessions, physician evaluation confirmed that 60% of patients achieved 75%–100% clearance [119]. Promising results included one type IV skin patient demonstrating 100% clearing of melasma on the bilateral cheeks and one type V skin patient showing 75%–100% improvement. Neither had any posttreatment hyperpigmentation or hypopigmentation [120]. However, the patients had a high recurrence rate after treatment. More recently, sustained results at 12 months were achieved using a combination of AFP and Kligman's topical formula as compared to either topical or laser alone [121]. Other pigmentary disorders reported to have been successfully treated with FP include minocycline-induced hyperpigmentation [122] and Nevus of Ota [123]. A recent study examining 40 patients with idiopathic guttate hypomelanosis treated with fractional CO_2 laser showed promising results [124].

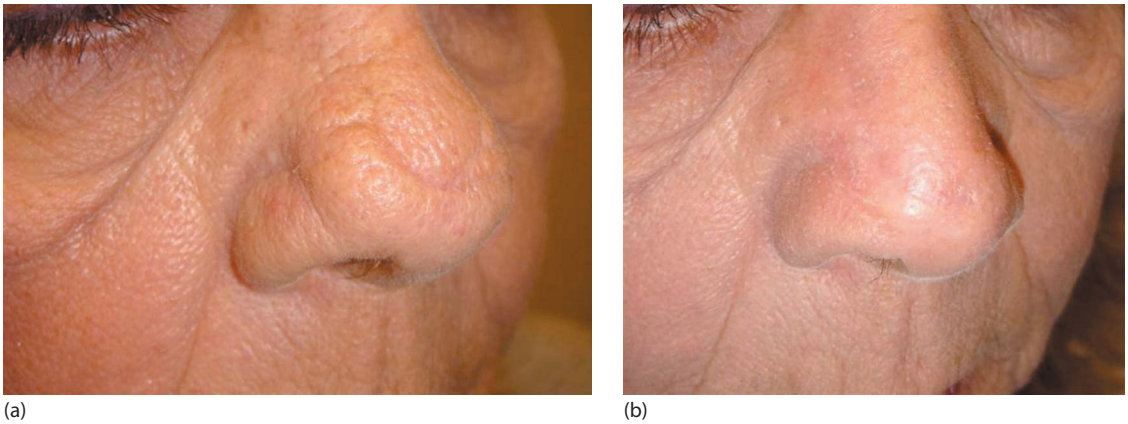
Vascular Disorders

In 2007, Glaich and colleagues reported the improvement of telangiectatic matting on a patient's right medial thigh after 5 successive monthly treatments with NAFP [108].

Similar in mechanism to improvements seen after FP treatment of Poikiloderma of Civatte and postinflammatory erythema from acne, FP is thought to specifically damage the dermal vasculature. Case reports have also shown improvements in involuted hemangioma residuum from FP treatment, specifically in the flattening of fibrofatty residual tissue and in the improvement of color and texture [125–127].

Other

The treatment of AKs with FP has recently generated interest. In 2011, Katz and colleagues reported 6-month follow-up data for facial AKs treated with a 1550 nm fractionated erbium-doped fiber laser after subjects underwent 5 laser treatments. Posttreatment biopsies suggested histological persistence of some AKs. They concluded that FP decreased the number of clinical AKs but that the use of FP as a single-treatment modality for AKs was inadequate [128]. Using FP as part of a multimodality treatment of AKs, however, appears more effective. Most recently, Togsverd-Bo and colleagues reported that ablative fractional laser resurfacing followed by PDT with methyl aminolevulinate (MAL) was more effective for AK treatment in field-cancerized skin than conventional PDT with MAL. They suggested that the increased efficacy was due to AFP creating vertical channels that facilitated MAL uptake and led to improved PDT efficacy [129]. Isolated case reports have also shown promise in FP treating granuloma annulare [130], disseminated superficial actinic porokeratosis [131], colloid milium [132], and morphea-related contracture [133].



(a) (b)

Figure 35.3 Fractionated CO_2 laser treatment (Fraxel re:pair) for surgical scars. (a) Pretreatment. (b) Posttreatment. (Courtesy of Christopher Zachary.)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

PRE- AND POSTPROCEDURE CONSIDERATIONS

Patient Selection

When determining whether a patient is a candidate for laser resurfacing, patient selection is paramount. Three areas—a complete history and physical, determination of skin type, and patient expectations—need to be thoroughly assessed. Caution should be exercised in treating those with a history of delayed wound healing (including secondary to tobacco or alcohol abuse, diabetes, or any other systemic medical conditions), history of connective tissue disease, or an immunocompromised status. Isotretinoin use in the past 6–12 months may also impair wound healing. Patients with dermatologic diseases that demonstrate koebnerization phenomenon such as vitiligo, psoriasis, and lichen planus should be avoided if possible. Special consideration should be given to any patient with active local or systemic infections and those with keloid scarring.

During the initial consultation, patient expectations should be established. Patients should also be educated appropriately regarding the different treatment options, so that they can weigh the pros and cons and make an educated decision. For instance, a single treatment with an ablative fractionated device may achieve superior results to one treatment with a nonablative fractionated device. However, the former requires significant more downtime than the latter, while the latter may necessitate multiple treatments to achieve similar results to the former. Most importantly, it should be stressed that there is individual-to-individual variability to treatment responses. Setting reasonable expectations helps to ensure better patient satisfaction.

Preoperative Management and Anesthesia

Various regimens have been suggested for preoperative management and anesthesia. Oral antivirals are generally recommended for herpes simplex virus (HSV) prophylaxis. Patients are often given antiviral prophylaxis even without documented history of an outbreak. Acyclovir or valacyclovir is typically given anywhere from 1 day prior to the morning of the treatment and continued from 5 to 14 days after the treatment. Antibacterial prophylaxis, usually in the form of penicillins or macrolides, is sometimes given as well. Less commonly, antifungal prophylaxis is provided.

On the day of the procedure, patients are instructed to thoroughly cleanse their face with soap, water, and a terry towel. For those undergoing low-energy, low-density NAFR, treatment is often initiated without anesthesia. For those undergoing ablative resurfacing, various methods are employed. Topical agents such as lidocaine, tetracaine, and prilocaine can be used. Nerve blocks also may be utilized if needed. Particularly, anxious patients may warrant additional systemic agents, including anxiolytics, anti-inflammatory agents, narcotics, or intramuscular sedation. Topical anesthesia is removed prior to the procedure, roughly 1 hour following application.

Postoperative Course

Evaluation for adverse reactions such as blistering, sloughing, or dramatic vasospasm (clinically seen as skin whitening) should be performed during and after the procedure. Topical, oral, or intramuscular steroids can be given in the postoperative period to decrease edema. Verbal and written care instructions must be provided. Consistent application of petrolatum-based emollient is usually recommended postoperatively; however, acne-prone patients are advised to use noncomedogenic products. Hydrogen peroxide or a dilute acetic acid solution can be applied to the treated area periodically to decrease crust formation and colonization with microbes. For darker skin types, many dermatologists will prescribe hydroquinone 4% after the exudative phase of recovery has stopped. For all patients, strict sun protection and avoidance is recommended. Close follow-up is key as most adverse reactions occur between 2 and 7 days following the procedure [134].

COMPLICATIONS

Infections

Although HSV reactivation is the most common type of infection to occur after fractional laser resurfacing, reported rates range from 0.3% to 2% of cases [135,136]. These rates are low, particularly when compared to those associated with NAFP, which are reported to range from 2% to 7% [137]. When antiviral prophylaxis is administered to all patients regardless of their past history, the rate of patient reactivation has been shown to be less than 0.5% in healthy individuals [136]. Interestingly, a recent paper reported the first 3 cases of varicella zoster reactivation after NAFP. None of the patients had taken HSV prophylaxis [138].

Bacterial infection after FP appears even less common; only 0.1% of all treated cases are documented to develop impetigo [135,136]. Nevertheless, caution should be exercised. One should look for signs of a bacterial superinfection as delay in appropriate management can lead to scarring. When there is a high index of suspicion, prompt wound culture should be performed, especially given the increased prevalence of methicillin-resistant *Staphylococcus aureus*. A recent case of *Mycobacterium chelonae* infection was reported after fractionated CO_2 facial resurfacing that mimicked an acneiform eruption [139].

Acneiform Eruptions

The rate of acneiform eruptions following NAFP has been reported to be between 2% and 10%, and milia development has been reported in as many as 19% of patients [136].

It is theorized that treatment causes the abnormal reepithelialization of the follicular units, which contributes to the acneiform eruptions. Occlusive dressing can further exacerbate the eruption, and noncomedogenic alternatives should be recommended if needed. A short oral course of tetracycline-based antibiotics can be prescribed for more severe cases, and patients will often be prophylactically treated prior to subsequent treatments [140].

Prolonged Erythema

Erythema immediately posttreatment is a natural process needed for wound healing. However, prolonged erythema is defined as redness that persists longer than 4 days with nonablative resurfacing and beyond 1 month with ablative resurfacing [141].

A study comparing ablative single-pass CO_2 laser versus multiple-pass Er:YAG treatment showed more postoperative erythema in CO_2 patients. From 100 treated patients, CO_2-treated patients had erythema lasting an average of 4.5 weeks versus 3.6 weeks in Er:YAG-treated patients [142]. In a study by Rahman and colleagues examining 30 patients, 33% experienced erythema 1 month postfractional CO_2 laser treatment. By 3 months posttreatment, only 7% still had erythema [143].

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Studies investigating treatments that decrease postoperative erythema include the use of a 590 nm light-emitting diode array [144] and of topical ascorbic acid [145].

Pigmentary Alteration

From a 2010 review, PIH was reported to occur in anywhere from 1% to 32% of cases, depending on the applied system and parameters and skin phototype [141] In a study examining 500 patients, hypopigmentation occurred in <1% treated with CO_2 laser skin resurfacing [137]. Higher skin phototypes have an increased risk of developing PIH. However, studies have shown that the use of higher fluencies, lower-density settings, and longer treatment intervals can minimize these effects [146,147].

To treat PIH, chemical peels and topical bleaching agents are often prescribed. Strict sun protection and, if possible, sun avoidance are usually recommended immediately prior to and after the procedure to curtail PIH effects.

Hypopigmentation appears to be an unusual posttreatment complication. A few cases have been described, including one of transient hypopigmentation occurring 15 days posttreatment and 2 within areas of laser-induced hypertrophic scarring [148,149]. Hypopigmentation, however, may have a delayed onset and may occur up to 6–12 months postoperatively.

Scarring

Several reports have documented posttreatment hypertrophic scarring, especially for ablative laser resurfacing. Most likely, these are related to a lack of technical finesse with the use of overly aggressive settings in scar-prone anatomic locations. Both vertical and horizontal bands of hypertrophic scars have been described on the neck [148]. Care should thus be taken when treating sensitive areas such as the periorbital and mandibular regions as well as the neck and chest. High-risk patients such as those who have experienced postoperative wound infection, contact dermatitis, or keloid scarring should be closely monitored. Early treatment of hypertrophic scarring in patients includes the use of topical corticosteroids, silicone gel products, intralesional corticosteroid injections, and PDL therapy [150]. Paradoxically, FP lasers often successfully treat hypertrophic scars using low-energy, low-density parameters.

Other

Ectropion has been reported after FP [134,151]. Those at greatest risk appear to be people who have had prior eyelid surgeries or less skin elasticity in the periocular area. Other reported complications after FP include eruptive keratoacanthomas [152], heat-induced recall phenomenon [153], delayed purpura [154], contact dermatitis [136], and anesthesia toxicity [155].

FUTURE TRENDS

Drug Delivery

Animal studies have shown enhanced dermal drug delivery after ablative fractional resurfacing. Treatment of skin in a porcine model that was pretreated with fractional resurfacing showed enhanced depth of PDT following porphyrin application [156]. An *in vitro* study using low-fluence fractionated Er:YAG demonstrated upward of a 125-fold increase in imiquimod delivery [157]. Clinical trials are currently underway to determine the feasibility and safety of fractional resurfacing–assisted drug uptake. This method may allow for the delivery of molecules that are unable to penetrate the intact skin. The possibility of delivering drugs, including biological peptides and vaccines, via this method appears promising.

Tattoo Removal

Recently, ablative fractional resurfacing in conjunction with the Q-switched ruby laser has shown significant promise for tattoo removal [158]. This effect is likely twofold. Microscopic zones of vaporization created by fractional lasers allow for the physical removal of tattoo ink and also provide a conduit through which ink drainage can occur after QSL treatment [158].

Ibrahimi and colleagues also recently showed successful removal of tattoos with allergic reactions using AFP. Although QSLs are considered the gold standard for tattoo removal, allergic tattoo reactions often present as a treatment dilemma. Using QSLs on these tattoos risk the release of antigenic proteins into the lymphatic circulation. In this study, however, AFP achieved not only significant lightening of the tattoos but also pruritic relief from the allergic reactions [159]. The use of fractional laser resurfacing may have a greater role in tattoo removal in the future, most likely, in combination with other lasers.

Home Devices

Home fractionated devices are becoming increasingly accessible to patients. These are low-energy and low-density devices that patients can use at home with minimal-to-no downtime. Improvement in skin texture can be seen after 4 to 6 treatments. Despite advances to make these devices available at home, they are not a replacement for the existing ablative and fractional laser devices. The technology provides improvement in skin texture, but it does not create the level of injury of those used by physicians in office settings. Still, these home devices appeal to patients who like the accessibility and convenience of treating at home.

CONCLUSIONS

Since the introduction of CO_2 lasers in the 1980s, the field of laser resurfacing has seen much improvement and continued refinement. Although ablative laser resurfacing provided excellent responses, the downtime and risk of side effects were deterrents for many. The introduction of fractional lasers paved the way for a new era of laser skin resurfacing that provides great results coupled with minimal downtime and adverse effects. This ongoing demand for great results with minimal risks will continue to drive the development of new lasers and techniques.

REFERENCES

1. Anderson RR, Parrish JA. Selective photothermolysis: Precise microsurgery by selective absorption of pulsed radiation. *Science* 1983; 220(4596):524–527.
2. Newman JB, Lord JL, Ash K, McDaniel DH. Variable pulse erbium:YAG laser skin resurfacing of perioral rhytides and side-by-side comparison with carbon dioxide laser. *Lasers Surg Med* 2000; 26(2):208–214.
3. Khatri KA, Ross V, Grevelink JM, Magro CM, Anderson R. Comparison of erbium:YAG and carbon dioxide lasers in resurfacing of facial rhytides. *Arch Dermatol* 1999; 135(4):391.
4. Walsh JT Jr, Flotte TJ, Anderson RR, Deutsch TF. Pulsed CO_2 laser tissue ablation: Effect of tissue type and pulse duration on thermal damage. *Lasers Surg Med* 1988; 8(2):108–118.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

5. Alster TS, Nanni CA, Williams CM. Comparison of four carbon dioxide resurfacing lasers. *Dermatol Surg* 1999; 25(3):153–159.
6. Kaufmann R, Hibst R. Pulsed 2-94-µm erbium–YAG laser skin ablation—Experimental results and first clinical application. *Clin Exp Dermatol* 2006; 15(5):389–393.
7. Alster TS. Clinical and histologic evaluation of six erbium:YAG lasers for cutaneous resurfacing. *Lasers Surg Med* 1999; 24(2):87–92.
8. Alster TS, Kauvar AN, Geronemus RG. Histology of high-energy pulsed CO_2 laser resurfacing. *Semin Cutan Med Surg* 1996; 15(3):189–193.
9. Alster TS, Garg S. Treatment of facial rhytides with a high-energy pulsed carbon dioxide laser. *Plast Reconstr Surg* 1996; 98(5):791–794.
10. Waldorf HA, Kauvar A, Geronemus RG. Skin resurfacing of fine to deep rhytides using a char-free carbon dioxide laser in 47 patients. *Dermatol Surg* 1995; 21(11):940.
11. Fitzpatrick RE, Goldman MP, Satur NM, Tope WD. Pulsed carbon dioxide laser resurfacing of photo-aged facial skin. *Arch Dermatol* 1996; 132(4):395.
12. Perez MI, Bank DE, Silvers D. Skin resurfacing of the face with the erbium:YAG laser. *Dermatol Surg* 1998; 24(6):653–660.
13. Teikemeier G, Goldberg DJ. Skin resurfacing with the erbium:YAG laser. *Dermatol Surg* 1997; 23(8):685.
14. Ziering C. Cutaneous laser resurfacing with the erbium YAG laser and the char-free carbon dioxide laser: A clinical comparison of 100 patients. *Int J Aesthetic Restor Surg* 1997; 5:29–37.
15. Polnikorn N, Goldberg DJ, Suwanchinda A, Ng SW. Erbium:YAG laser resurfacing in Asians. *Dermatol Surg* 1998; 24(12):1303.
16. Goldman MP, Fitzpatrick RE, Manuskiatti W. Laser resurfacing of the neck with the erbium:YAG laser. *Dermatol Surg* 1999; 25(3):164–168.
17. Goldman MP, Manuskiatti W. Combined laser resurfacing with the 950-µsec pulsed CO_2 + Er:YAG lasers. *Dermatol Surg* 1999; 25(3):160–163.
18. Goldman MP, Marchell N, Fitzpatrick RE. Laser skin resurfacing of the face with a combined CO_2/Er:YAG laser. *Dermatol Surg* 2000; 26(2):102–104.
19. Collawn SS. Combination therapy: Utilization of CO_2 and erbium:YAG lasers for skin resurfacing. *Ann Plast Surg* 1999; 42(1):21.
20. Alster TS. Cutaneous resurfacing with Er:YAG lasers. *Dermatol Surg* 2000; 26(1):73–75.
21. Walia S, Alster TS. Prolonged clinical and histologic effects from CO_2 laser resurfacing of atrophic acne scars. *Dermatol Surg* 2001; 25(12):926–930.
22. Jacob CI, Dover JS, Kaminer MS. Acne scarring: A classification system and review of treatment options. *J Am Acad Dermatol* 2001; 45(1):109–117.
23. Tanzi EL, Alster TS. Treatment of atrophic facial acne scars with a dual-mode Er:YAG laser. *Dermatol Surg* 2002; 28(7):551–555.
24. Jeong J, Kye Y. Resurfacing of pitted facial acne scars with a long-pulsed Er:YAG laser. *Dermatol Surg* 2001; 27(2):107–110.
25. Jeong J, Park J, Kye Y. Resurfacing of pitted facial acne scars using Er:YAG laser with ablation and coagulation mode. *Aesthetic Plast Surg* 2003; 27(2):130–134.
26. Cho SI, Kim YC. Treatment of atrophic facial scars with combined use of high-energy pulsed CO_2 laser and Er:YAG laser: A practical guide of the laser techniques for the Er:YAG laser. *Dermatol Surg* 2001; 25(12):959–964.
27. Bernstein LJ, Kauvar A, Grossman MC, Geronemus RG. Scar resurfacing with high-energy, short-pulsed and flashscanning carbon dioxide lasers. *Dermatol Surg* 1998; 24(1):101.
28. Vrijman C, van Drooge A, Limpens J et al. Laser and intense pulsed light therapy for the treatment of hypertrophic scars: A systematic review. *Br J Dermatol* 2011; 165(5):934–942.
29. Angsuwarangsee S, Polnikorn N. Combined ultrapulse CO_2 laser and Q-Switched alexandrite laser compared with Q-Switched alexandrite laser alone for refractory melasma: Split-Face design. *Dermatol Surg* 2003; 29(1):59–64.
30. Nouri K, Bowes L, Chartier T, Romagosa R, Spencer J. Combination treatment of melasma with pulsed CO_2 laser followed by Q-switched alexandrite laser: A pilot study. *Dermatol Surg* 2001; 25(6):494–497.
31. Manaloto RMP, Alster T. Erbium:YAG laser resurfacing for refractory melasma. *Dermatol Surg* 2001; 25(2):121–123.
32. Wanitphakdeedecha R, Manuskiatti W, Siriphukpong S, Chen TM. Treatment of melasma using variable square pulse Er:YAG laser resurfacing. *Dermatol Surg* 2009; 35(3):475–482.
33. Dover JS, Smoller BR, Stern RS, Rosen S, Arndt KA. Low-fluence carbon dioxide laser irradiation of lentigines. *Arch Dermatol* 1988; 124(8):1219.
34. Fitzpatrick RE, Goldman MP, Ruiz-Esparza J. Clinical advantage of the CO_2 laser superpulsed mode: Treatment of verruca vulgaris, seborrheic keratoses, lentigines, and actinic cheilitis. *J Dermatol Surg Oncol* 1994; 20(7):449.
35. Alora MB, Arndt KA. Treatment of a cafe-au-lait macule with the erbium:YAG laser. *J Am Acad Dermatol* 2001; 45(4):566–568.
36. Trelles M, Allones I, Moreno-Arias G, Vélez M. Becker's naevus: A comparative study between erbium:YAG and Q-switched neodymium:YAG; clinical and histopathological findings. *Br J Dermatol* 2005; 152(2):308–313.
37. Horner BM, El-Muttardi NS, Mayou BJ. Treatment of congenital melanocytic naevi with CO_2 laser. *Ann Plast Surg* 2005; 55(3):276–280.
38. Jean Chong S, Jeong E, Jeong Park H, Young J, Cho BK. Treatment of congenital nevomelanocytic nevi with the CO_2 and Q-Switched alexandrite lasers. *Dermatol Surg* 2005; 31(5):518–521.
39. Ostertag J, Quaedvlieg P, Kerckhoffs F et al. Congenital naevi treated with erbium:YAG laser (Derma K) resurfacing in neonates: Clinical results and review of the literature. *Br J Dermatol* 2006; 154(5):889–895.
40. Robinson JK. Actinic cheilitis: A prospective study comparing four treatment methods. *Arch Otolaryngol Head Neck* 1989; 115(7):848.
41. Laws RA, Wilde JL, Grabski WJ. Comparison of electrodessication with CO_2 laser for the treatment of actinic cheilitis. *Dermatol Surg* 2001; 26(4):349–353.
42. Whitaker DC. Microscopically proven cure of actinic cheilitis by CO_2 laser. *Lasers Surg Med* 2005; 7(6):520–523.
43. Trimas SJ, Ellis D, Metz RD. The carbon dioxide laser. An alternative for the treatment of actinically damaged skin. *Dermatol Surg* 1997; 23(10):885.
44. Fulton JE, Rahimi AD, Helton P, Dahlberg K, Kelly AG. Disappointing results following resurfacing of facial skin with CO_2 lasers for prophylaxis of keratoses and cancers. *Dermatol Surg* 2001; 25(9):729–732.
45. Nouri K, Chang A, Trent JT, Jiménez GP. Ultrapulse CO_2 used for the successful treatment of basal cell carcinomas found in patients with basal cell nevus syndrome. *Dermatol Surg* 2008; 28(3):287–290.
46. Humphreys TR, Malhotra R, Scharf MJ, Marcus SM, Starkus L, Calegari K. Treatment of superficial basal cell carcinoma and squamous cell carcinoma in situ with a high-energy pulsed carbon dioxide laser. *Arch Dermatol* 1998; 134(10):1247.
47. Armenores P, James CL, Walker PC, Huilgol SC. Treatment of actinic cheilitis with the Er:YAG laser. *J Am Acad Dermatol* 2010; 63(4):642–646.
48. Jiang SB, Levine VJ, Nehal KS, Baldassano M, Kamino H, Ashinoff RA. Er:YAG laser for the treatment of actinic keratoses. *Dermatol Surg* 2001; 26(5):437–440.
49. Wollina U, Konrad H, Karamfilov T. Treatment of common warts and actinic keratoses by Er:YAG laser. *J Cutan Laser Ther* 2001; 3(2):63–66.
50. Šmucler R, Vlk M. Combination of Er:YAG laser and photodynamic therapy in the treatment of nodular basal cell carcinoma. *Lasers Surg Med* 2008; 40(2):153–158.
51. Madan V, Ferguson J, August P. Carbon dioxide laser treatment of rhinophyma: A review of 124 patients. *Br J Dermatol* 2009; 161(4):814–818.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

52. Simo R, Sharma V. Treatment of rhinophyma with carbon dioxide laser. *J Laryngol Otol* 1996; 110:841–846.
53. Bohigian RK, Shapshay SM, Hybels RL. Management of rhinophyma with carbon dioxide laser: Lahey clinic experience. *Lasers Surg Med* 2005; 8(4):397–401.
54. Orenstein A, Haik J, Tamir J et al. Treatment of rhinophyma with Er:YAG laser. *Lasers Surg Med* 2001; 29(3):230–235.
55. Fincher EF, Gladstone HB. Use of a dual-mode erbium:YAG laser for the surgical correction of rhinophyma. *Arch Facial Plast Surg* 2004; 6(4):267–271.
56. Moreira A, Leite I, Guedes R, Baptista A, Mota G. Surgical treatment of rhinophyma using carbon dioxide (CO_2) laser and pulsed dye laser (PDL). *J Cosmet Laser Ther* 2010; 12(2):73–76.
57. Goon PK, Dalal M, Peart FC. The gold standard for decortication of rhinophyma: Combined erbium-YAG/CO_2 laser. *Aesthetic Plast Surg* 2004; 28(6):456–460.
58. Läuchli S, Kempf W, Dragieva G, Burg G, Hafner J. CO_2 laser treatment of warts in immunosuppressed patients. *Dermatology* 2003; 206(2):148–152.
59. Geronemus RG, Kauvar AN, McDaniel DH. Treatment of recalcitrant verrucae with both the ultrapulse CO_2 and PLDL pulsed dye lasers. *Plast Reconstr Surg* 1998; 101(7):2010.
60. Landsman M, Mancuso J, Abramow S. Carbon dioxide laser treatment of pedal verrucae. *Clin Podiatr Med Surg* 1992; 9(3):659.
61. Lim J, Goh C. Carbon dioxide laser treatment of periungual and subungual viral warts. *Australas J Dermatol* 2007; 33(2):87–91.
62. Phahonthep R, Sindhuphak W, Sriprajittichai P. Lidocaine iontophoresis versus EMLA cream for CO_2 laser treatment in seborrheic keratosis. *J Med Assoc Thai* 2004; 87:S15.
63. Raulin C, Schoenermark MP, Werner S, Greve B. Xanthelasma palpebrarum: Treatment with the ultrapulsed CO_2 laser. *Lasers Surg Med* 1999; 24(2):122–127.
64. Alster TS, West TB. Ultrapulse CO_2 laser ablation of xanthelasma. *J Am Acad Dermatol* 1996; 34(5 Pt 1):848–849.
65. Ullmann Y, Har-Shai Y, Peled IJ. The use of CO_2 laser for the treatment of xanthelasma palpebrarum. *Ann Plast Surg* 1993; 31(6):504.
66. Wang JI, Roenigk HH. Treatment of multiple facial syringomas with the carbon dioxide (CO_2) laser. *Dermatol Surg* 2001; 25(2):136–139.
67. Wheeland RG, Bailin PL, Kronberg E. Carbon dioxide (CO_2) laser vaporization for the treatment of multiple trichoepithelioma. *J Dermatol Surg Oncol* 1984; 10(6):470–475.
68. Kang WH, Kim NS, Kim YB, Shim WC. A new treatment for syringoma. Combination of carbon dioxide laser and trichloroacetic acid. *Dermatol Surg* 1998; 24(12):1370.
69. Rallan D, Harland C. Brooke–Spiegler syndrome: Treatment with laser ablation. *Clin Exp Dermatol* 2005; 30(4):355–357.
70. Sajben FP, Ross EV. The use of the 1.0 mm handpiece in high energy, pulsed CO_2 laser destruction of facial adnexal tumors. *Dermatol Surg* 2001; 25(1):41–44.
71. Sawchuk WS, Heald PW. CO_2 laser treatment of trichoepithelioma with focused and defocused beam. *J Dermatol Surg Oncol* 1984; 10(11):905–907.
72. Belmar P, Boixeda P, Baniandres O, Fernandez-Lorente M, Arrazola JM. Long-term follow up of angiofibromas treated with CO_2 laser in 23 patients with tuberous sclerosis. *Actas Dermosifiliogr* 2005; 96(8):498–503.
73. Papadavid E, Markey A, Bellaney G, Walker N. Carbon dioxide and pulsed dye laser treatment of angiofibromas in 29 patients with tuberous sclerosis. *Br J Dermatol* 2002; 147(2):337–342.
74. Verma KK, Ovung E, Sirka C. Extensive facial angiofibromas in tuberous sclerosis treated with carbon dioxide laserbrasion. *Indian J Dermatol Venereol Leprol* 2001; 67(6):326.
75. Lapid-Gortzak R, Lapid O, Monos T, Lifshitz T. CO_2-laser in the removal of a plexiform neurofibroma from the eyelid. *Ophthalmic Surg Lasers* 2000; 31(5):432.
76. Becker DW Jr. Use of the carbon dioxide laser in treating multiple cutaneous neurofibromas. *Ann Plast Surg* 1991; 26(6):582.
77. Roenigk R, Ratz J. CO_2 laser treatment of cutaneous neurofibromas. *J Dermatol Surg Oncol* 1987; 13(2):187.
78. Dmovsek-Olup B, Vedlin B. Use of Er:YAG laser for benign skin disorders. *Lasers Surg Med* 1998; 21(1):13–19.
79. Manstein D, Herron GS, Sink RK, Tanner H, Anderson R. Fractional photothermolysis: A new concept for cutaneous remodeling using microscopic patterns of thermal injury. *Lasers Surg Med* 2004; 34(5):426–438.
80. Hantash BM, Bedi VP, Sudireddy V, Struck SK, Herron GS, Chan KF. Laser-induced transepidermal elimination of dermal content by fractional photothermolysis. *J Biomed Opt* 2006; 11(4):041115-041115-9.
81. Hantash BM, Bedi VP, Kapadia B et al. In vivo histological evaluation of a novel ablative fractional resurfacing device. *Lasers Surg Med* 2007; 39(2):96–107.
82. Hantash BM, Bedi VP, Chan KF, Zachary CB. Ex vivo histological characterization of a novel ablative fractional resurfacing device. *Lasers Surg Med* 2007; 39(2):87–95.
83. Jih MH, Kimyai-Asadi A. Fractional photothermolysis: A review and update. *Semin Cutan Med Surg* 2008; 27(1):63–71.
84. Helbig D, Bodendorf MO, Grunewald S, Kendler M, Simon JC, Paasch U. Immunohistochemical investigation of wound healing in response to fractional photothermolysis. *J Biomed Opt* 2009; 14(6):064044–064044-8.
85. Xu XG, Luo YJ, Wu Y, Chen JZ et al. Immunohistological evaluation of skin responses after treatment using a fractional ultrapulse carbon dioxide laser on back skin. *Dermatol Surg* 2011; 37(8):1141–1149.
86. Weiss RA, Gold M, Bene N et al. Prospective clinical evaluation of 1440-nm laser delivered by microarray for treatment of photoaging and scars. *J Drugs Dermatol* 2006; 5(8):740–744.
87. Brightman LA, Brauer JA, Anolik R et al. Ablative and fractional ablative lasers. *Dermatol Clin* 2009; 27(4):479–489.
88. Hruza G, Taub AF, Collier SL et al. Skin rejuvenation and wrinkle reduction using a fractional radiofrequency system. *J Drugs Dermatol* 2009; 8(3):259–265.
89. Geronemus RG. Fractional photothermolysis: Current and future applications. *Lasers Surg Med* 2006; 38(3):169–176.
90. Jih MH, Goldberg LH, Kimyai-Asadi A. Fractional photothermolysis for photoaging of hands. *Dermatol Surg* 2008; 34(1):73–78.
91. Wanner M, Tanzi EL, Alster TS. Fractional photothermolysis: Treatment of facial and nonfacial cutaneous photodamage with a 1,550-nm Erbium-Doped fiber laser. *Dermatol Surg* 2007; 33(1):23–28.
92. Rahman Z, Alam M, Dover J. Fractional laser treatment for pigmentation and texture improvement. *Skin Ther Lett* 2006; 11(9):7–11.
93. Mezzana P, Scarinci F, Costantino A, Marabottini N, Valeriani M. Lower eyelid ablative fractional resurfacing: A new technique to treat skin laxity and photoaging. *Acta Chir Plast* 2010; 52(2–4):35–38.
94. Kearney C, Brew D. Single-session combination treatment with intense pulsed light and nonablative fractional photothermolysis: A Split-Face study. *Dermatol Surg* 2012.
95. Behroozan DS, Goldberg LH, Glaich AS et al. Fractional photothermolysis for treatment of poikiloderma of civatte. *Dermatol Surg* 2006; 32(2):298–301.
96. Tierney EP, Eisen RF, Hanke CW. Fractionated CO_2 laser skin rejuvenation. *Dermatol Ther* 2011; 24(1):41–53.
97. Alster TS, Lupton JR. Erbium:YAG cutaneous laser resurfacing. *Dermatol Clin* 2001; 19(3):453–466.
98. Taub AF. Fractionated delivery systems for difficult to treat clinical applications: Acne scarring, melasma, atrophic scarring, striae distensae, and deep rhytides. *J Drugs Dermatol* 2007; 6(11):1120.
99. Chrastil B, Glaich AS, Goldberg LH, Friedman PM. Second-generation 1,550-nm fractional photothermolysis for the treatment of acne scars. *Dermatol Surg* 2008; 34(10):1327–1332.
100. Hu S, Chen MC, Lee MC et al. Fractional resurfacing for the treatment of atrophic facial acne scars in Asian skin. *Dermatol Surg* 2009; 35(5):826–832.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

101. Cho SB, Lee JH, Choi MJ et al. Efficacy of the fractional photothermolysis system with dynamic operating mode on acne scars and enlarged facial pores. *Dermatol Surg* 2008; 35(1):108–114.
102. Cho S, Lee S, Cho S et al. Non-ablative 1550-nm erbium-glass and ablative 10 600-nm carbon dioxide fractional lasers for acne scars: A randomized split-face study with blinded response evaluation. *J Eur Acad Dermatol Venereol* 2010; 24(8):921–925.
103. Manuskiatti W, Iamphonrat T, Wanitphakdeedecha R, Eimpunth S. Comparison of fractional erbium-doped yttrium aluminum garnet and carbon dioxide lasers in resurfacing of atrophic acne scars in Asians. *Dermatol Surg* 2012.
104. Jung JY, Lee JH, Ryu DJ et al. Lower-fluence, higher-density versus higher-fluence, lower-density treatment with a 10,600-nm carbon dioxide fractional laser system: A split-face, evaluator-blinded study. *Dermatol Surg* 2010; 36(12):2022–2029.
105. Seung Lee H, Hee Lee J, Young Ahn G et al. Fractional photothermolysis for the treatment of acne scars: A report of 27 Korean patients. *J Dermatol Treat* 2008; 19(1):45–49.
106. Chan NPY, Ho SGY, Yeung CK, Shek SYN, Chan HH. The use of non-ablative fractional resurfacing in Asian acne scar patients. *Lasers Surg Med* 2010; 42(10):710–715.
107. Tenna S, Cogliandro A, Piombino L, Filoni A, Persichetti P. Combined use of fractional CO_2 laser and radiofrequency waves to treat acne scars: A pilot study on 15 patients. *J Cosmet Laser Ther* 2012; 14(4):166–171.
108. Glaich AS, Goldber LH, Friedman RH, Friedman PM. Fractional photothermolysis for the treatment of postinflammatory erythema resulting from acne vulgaris. *Dermatol Surg* 2007; 33(7):842–846.
109. Tierney E, Mahmoud BH, Srivastava D, Ozog D, Kouba DJ. Treatment of surgical scars with nonablative fractional laser versus pulsed dye laser: A randomized controlled trial. *Dermatol Surg* 2009; 35(8):1172–1180.
110. Tierney EP, Hanke CW. Treatment of CO_2 laser induced hypopigmentation with ablative fractionated laser resurfacing: Case report and review of the literature. *J Drugs Dermatol* 2010; 9(11):1420–1426.
111. Waibel J, Beer K. Fractional laser resurfacing for thermal burns. *J Drugs Dermatol* 2008; 7(1):59.
112. Waibel J, Beer K. Ablative fractional laser resurfacing for the treatment of a third-degree burn. *J Drugs Dermatol* 2009; 8(3):294–297.
113. Waibel J, Wulkan AJ, Lupo M, Beer K, Anderson R. Treatment of burn scars with the 1,550 nm nonablative fractional erbium laser. *Lasers Surg Med* 2012.
114. Kim BJ, Lee DH, Kim MN et al. Fractional photothermolysis for the treatment of striae distensae in Asian skin. *Am J Clin Dermatol* 2008; 9(1):33–37.
115. Lee SE, Kim JH, Lee SJ et al. Treatment of striae distensae using an ablative 10,600-nm carbon dioxide fractional laser: A retrospective review of 27 participants. *Dermatol Surg* 2010; 36(11):1683–1690.
116. de Angelis F, Kolesnikova L, Renato F, Liguori G. Fractional nonablative 1540-nm laser treatment of striae distensae in Fitzpatrick skin types II to IV clinical and histological results. *Aesthetic Surg J* 2011; 31(4):411–419.
117. Yang YJ, Lee GY. Treatment of striae distensae with nonablative fractional laser versus ablative CO_2 fractional laser: A randomized controlled trial. *Ann Dermatol* 2011; 23(4):481–489.
118. Lin JY, Warger II WC, Izikson L, Anderson R, Tannous Z. A prospective, randomized controlled trial on the efficacy of fractional photothermolysis on scar remodeling. *Lasers Surg Med* 2011; 43(4):265–272.
119. Rokhsar CK, Fitzpatrick RE. The treatment of melasma with fractional photothermolysis: A pilot study. *Dermatol Surg* 2005; 31(12):1645–1650.
120. Naito SK. Fractional photothermolysis treatment for resistant melasma in Chinese females. *J Cosmet Laser Ther* 2007; 9(3):161–163.
121. Trelles MA, Velez M, Gold MH. The treatment of melasma with topical creams alone, CO_2 fractional ablative resurfacing alone, or a combination of the two: A comparative study. *J Drugs Dermatol* 2010; 9(4):315–322.
122. Izikson L, Anderson R. Resolution of blue minocycline pigmentation of the face after fractional photothermolysis. *Lasers Surg Med* 2008; 40(6):399–401.
123. Kouba DJ, Fincher EF, Moy RL. Nevus of Ota successfully treated by fractional photothermolysis using a fractionated 1440-nm Nd:YAG laser. *Arch Dermatol* 2008; 144(2):156.
124. Shin J, Kim M, Park S, Oh S. The effect of fractional carbon dioxide lasers on idiopathic guttate hypomelanosis: A preliminary study. *J Eur Acad Dermatol Venereol* 2012.
125. Blankenship CM, Alster TS. Fractional photothermolysis of residual hemangioma. *Dermatol Surg* 2008; 34(8):1112–1114.
126. Brightman LA, Brauer JA, Terushkin V et al. Ablative fractional resurfacing for involuted hemangioma residuum. *Arch Dermatol* 2012 148(11):1294–1298.
127. Laubach HJ, Anderson RR, Luger T, Manstein D. Fractional photothermolysis for involuted infantile hemangioma. *Arch Dermatol* 2009; 145(7):748.
128. Katz TM, Goldberg LH, Marquez D et al. Nonablative fractional photothermolysis for facial actinic keratoses: 6-month follow-up with histologic evaluation. *J Am Acad Dermatol* 2011; 65(2):349–356.
129. Togsverd-Bo K, Haak C, Thaysen-Petersen D, Wulf H, Anderson R, Hædesdal M. Intensified photodynamic therapy of actinic keratoses with fractional CO_2 laser: A randomized clinical trial. *Br J Dermatol* 2012; 166(6):1262–1269.
130. Karsai S, Hammes S, Rütten A, Raulin C. Fractional photothermolysis for the treatment of granuloma annulare: A case report. *Lasers Surg Med* 2008; 40(5):319–322.
131. Chrastil B, Glaich AS, Goldberg LH, Friedman PM. Fractional photothermolysis: A novel treatment for disseminated superficial actinic porokeratosis. *Arch Dermatol* 2007; 143(11):1450.
132. Marra DE, Pourrabbani S, Fincher EF, Moy RL. Fractional photothermolysis for the treatment of adult colloid milium. *Arch Dermatol* 2007; 143(5):572.
133. Kineston D, Kwan JM, Uebelhoer NS, Shumaker PR. Use of a fractional ablative 10.6-μm carbon dioxide laser in the treatment of a morphea-related contracture. *Arch Dermatol* 2011; 147(10):1148.
134. Fife DJ, Fitzpatrick RE, Zachary CB. Complications of fractional CO_2 laser resurfacing: Four cases. *Lasers Surg Med* 2009; 41(3):179–184.
135. Setyadi HG, Jacobs AA, Markus RF. Infectious complications after nonablative fractional resurfacing treatment. *Dermatol Surg* 2008; 34(11):1595–1598.
136. Graber EM, Tanzi EL, Alster TS. Side effects and complications of fractional laser photothermolysis: Experience with 961 treatments. *Dermatol Surg* 2008; 34(3):301–307.
137. Nanni CA, Alster TS. Complications of carbon dioxide laser resurfacing. An evaluation of 500 patients. *Dermatol Surg* 1998; 24(3):315.
138. Firoz BG, Katz TM, Goldberg LH et al. Herpes zoster in the distribution of the trigeminal nerve after nonablative fractional photothermolysis of the face: Report of 3 cases. *Dermatol Surg* 2011; 37(2):249–252.
139. Palm MD, Butterwick KJ, Goldman MP. Mycobacterium chelonae infection after fractionated carbon dioxide facial resurfacing (presenting as an atypical acneiform eruption): Case report and literature review. *Dermatol Surg* 2010; 36(9):1473–1481.
140. Alster TS, Tanzi EL, Lazarus M. The use of fractional laser photothermolysis for the treatment of atrophic scars. *Dermatol Surg* 2007; 33(3):295–299.
141. Metelitsa AL, Alster TS. Fractionated laser skin resurfacing treatment complications: A review. *Dermatol Surg* 2010; 36(3):299–306.
142. Tanzi EL, Alster TS. Single-pass carbon dioxide versus multiple-pass Er:YAG laser skin resurfacing: A comparison of postoperative wound healing and side-effect rates. *Dermatol Surg* 2003; 29(1):80–84.
143. Rahman Z, MacFalls H, Jiang K et al. Fractional deep dermal ablation induces tissue tightening. *Lasers Surg Med* 2009; 41(2):78–86.
144. Alster TS, Wanitphakdeedecha R. Improvement of postfractional laser erythema with light-emitting diode photomodulation. *Dermatol Surg* 2009; 35(5):813–815.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

145. Alster TS, West TB. Effect of topical vitamin C on postoperative carbon dioxide laser resurfacing erythema. *Dermatol Surg* 1998; 24(3):331.
146. Chan HHL, Manstein D, Yu C, Shek S, Kono T, Wei W. The prevalence and risk factors of post-inflammatory hyperpigmentation after fractional resurfacing in Asians. *Lasers Surg Med* 2007; 39(5):381–385.
147. Kono T, Chan HH, Groff WF et al. Prospective direct comparison study of fractional resurfacing using different fluences and densities for skin rejuvenation in Asians. *Lasers Surg Med* 2007; 39(4):311–314.
148. Avram MM, Tope WD, Yu T, Szachowicz E, Nelson JS. Hypertrophic scarring of the neck following ablative fractional carbon dioxide laser resurfacing. *Lasers Surg Med* 2009; 41(3):185–188.
149. Tan KL, Kurniawati C, Gold MH. Low risk of postinflammatory hyperpigmentation in skin types 4 and 5 after treatment with fractional CO_2 laser device. *J Drugs Dermatol* 2008; 7(8):774–777.
150. Alster T, Zaulyanov L. Laser scar revision: A review. *Dermatol Surg* 2007; 33(2):131–140.
151. Neaman KC, Baca ME, Piazza III RC, VanderWoude DL, Renucci JD. Outcomes of fractional CO_2 laser application in aesthetic surgery: A retrospective review. *Aesthetic Surg J* 2010; 30(6):845–852.
152. Mamelak AJ, Goldberg LH, Marquez D et al. Eruptive keratoacanthomas on the legs after fractional photothermolysis: Report of two cases. *Dermatol Surg* 2009; 35(3):513–518.
153. Foster KW, Fincher EF, Moy RL. Heat-induced 'recall' of treatment zone erythema following fractional resurfacing with a combination laser (1320 nm/1440 nm). *Arch Dermatol* 2008; 144(10):1398.
154. Fife DJ, Zachary CB. Delayed pinpoint purpura after fractionated carbon dioxide treatment in a patient taking ibuprofen in the postoperative period. *Dermatol Surg* 2009; 35(3):553.
155. Marra DE, Yip D, Fincher EF, Moy RL. Systemic toxicity from topically applied lidocaine in conjunction with fractional photothermolysis. *Arch Dermatol* 2006; 142(8):1024.
156. Haedersdal M, Katsnelson J, Sakamoto F et al. Enhanced uptake and photoactivation of topical methyl aminolevulinate after fractional CO_2 laser pretreatment. *Lasers Surg Med* 2011; 43(8):804–813.
157. Lee W, Shen S, Al-Suwayeh SA, Yang H, Yuan C, Fang J. Laser-assisted topical drug delivery by using a low-fluence fractional laser: Imiquimod and macromolecules. *J Control Release* 2011; 153(3):240–248.
158. Weiss ET, Geronemus RG. Combining fractional resurfacing and Q-switched ruby laser for tattoo removal. *Dermatol Surg* 2011; 37(1):97–99.
159. Ibrahimi OA, Syed Z, Sakamoto FH, Avram MM, Anderson R. Treatment of tattoo allergy with ablative fractional resurfacing: A novel paradigm for tattoo removal. *J Am Acad Dermatol* 2011; 64(6):1111–1114.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Nonablative lasers

Jean-Michel Mazer

EVOLUTION OF THE CONCEPT OF NONABLATIVE LASERS

For more than 20 years, laser resurfacing has been used for the treatment of facial photodamage, with some use on non-facial skin also. The treatment was based on a type of resurfacing dermabrasion, eliminating the entire epidermis and the outermost part of the dermis—the capillary dermis—to a depth of between 200 and 300 µm. The lasers used were either CO_2 or erbium lasers with a pulsed mode. To judge by efficacy alone, the results were very satisfactory, but dermabrasion has significant drawbacks. The aftereffects of treatment are more prolonged and important and lead to social withdrawal for a period of about 10 days, followed by an extended period of erythema, lasting from 1 to 3 months. Not all patients could accept these consequences, particularly as they first, few days, saw very noticeable swelling and the formation of skin crusts. Furthermore, the appearance of skin hyperpigmentation and, sometimes, a herpes zoster infection were not unusual. Finally, above all, patients could develop lasting hypopigmentation.

The incidence of these side effects has limited demand for the treatment, and from the early 2000s, even before the recognition of a high number of hypopigmentations, they have been much less generally on offer to our patients. Additionally, these treatments were reserved for the facial region because the risks were even greater if the body were treated, particularly areas of very fragile skin, such as the neck and decolletage. Finally, it was difficult to treat dark skin, so the treatment was largely reserved for light skin, before the significant risks of long-lasting hyperpigmentation were recognized.

Thus, it was necessary to seek alternative methods of treatment that can induce synthesis of new collagen fibers without presenting significant risks and lasting side effects.

At first, remodeling lasers seemed to be the answer. These lasers are designed to stimulate the synthesis of collagen by the dermis, either through the vascular action on the blood platelets or the stimulation of dermal fibroblasts. Although studies of high methodological quality have confirmed that they induce new collagen synthesis, and although these devices did not have the same problematic aftereffects (particularly hypopigmentation), their efficiency proved to be moderate and often insufficient to satisfy patient expectations. In any case, their efficiency was much lower than that of laser resurfacing.

A new technology was introduced in the early 2000s—fractional lasers. They were the result of investigations by scientists, like Rox Anderson, who considered that the main problem with laser resurfacing was associated with the destruction of the epidermis, which constitutes both the skin barrier and the area where melanocytic cells are located. Thus, if they could create more important effects than the simple fibroblast stimulation of remodeling lasers, while preserving most of the epidermis and dermis, they could hope for greater efficiency. The concept of the fractional laser is that it creates small lesions in the form of columns of coagulation necrosis—called "microthermal zones" or MTZs—small, spaced from each other, and leaving healthy skin areas in between. The epidermis is not removed, and the majority of melanocytic cells are preserved. Thus, at each session, a fraction of the epidermis and the dermis will be the subject of a powerful thermal effect causing tissue coagulation. It is therefore a case, as with laser remodeling, of fibroblast stimulation but of the induction of lesions such as coagulation necrosis that will cause a healing process that will be the source of new collagen formation. The results, in terms of induction of collagen synthesis, are more important, especially as these lasers can reach greater depths, provided they leave a proportion of skin untouched, sufficient to avoid any problems. In terms of classification, the first fractionated lasers do not cause genuine ablation in the epidermis and dermis but coagulation necrosis, so they are termed nonablative fractional lasers.

In a second wave, other fractionated lasers were marketed using CO_2 lasers and erbium lasers. In these cases, however, they do not create columns of coagulation necrosis so much as ablative shafts, small in size, but deep. These therefore have an ablative character, so are not the subject of this chapter.

There has thus been considerable evolution in the concept of remodeling. Based initially on the induction of significant tissue repair following dermabrasion, they have evolved to a stimulation of fibroblasts that synthesize collagen and then to nonablative fractionated lasers that have an efficiency clearly superior to laser remodeling. Certainly, their efficacy is lower than that of ablative lasers and ablative fractional lasers. However, they can be used on all facial and body regions and on all skin types and can be associated with other lasers especially ablative lasers, and the number of sessions can be increased in order to increase efficiency.

CLASSIFICATION OF NONABLATIVE LASERS

There are two major classes of lasers:

1. Remodeling lasers: these induce a stimulation of synthesis of collagen and elastic fibers by dermal fibroblasts.
2. Fractional nonablative lasers: these create columns of coagulation necrosis in the dermis, followed by tissue repair with new synthesis.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

LASER REMODELING

The principle of remodeling is to use lasers that will induce stimulation of collagen synthesis by dermal fibroblasts, while respecting the other skin tissues. This stimulation of dermal fibroblasts can be obtained in different ways. With laser resurfacing, whether CO_2 or erbium, fibroblast stimulation was very important because it was accompanied by secondary tissue repair, with significant inflammation and destruction of the epidermis and of the superficial papillary dermis. With laser remodeling, there are mainly two different mechanisms [1–5]. One type of these are lasers that, because of their wavelength, will be strongly absorbed by water, the predominant constituent of the dermis. This causes heat transfer as the temperature rises in the dermis, which will induce collagen neosynthesis; this is usually the case with infrared lasers. In order to be well tolerated, such lasers should not interact with the melanin pigment or the epidermis, which is the case of lasers with wavelengths located in the infrared range. The second mechanism is to target vessels with vascular lasers. The thermal diffusion from these vessels will induce a stimulation of platelets. In this case, it is the activation of platelet factors that will cause a degree of collagen neosynthesis.

Dermal Remodeling

A laser whose wavelength is in the infrared range is weakly absorbed by melanin. It is important to create a reaction mainly between 150 and 400 µm deep into the dermis. Based on the studies of Troy [1], which show correlations between wavelength and depth of action, it appears that the wavelengths located between 1400 and 1600 nm can be the most appropriate; for a wavelength of 1400 nm, the absorption coefficient is 16 µm per cm^2 to penetrate the dermis to 270 µm. With a wavelength of 1540 nm, the absorption coefficient is 10 µm per cm^2, for a penetration of 400 µm. Finally, using a laser with a wavelength of 1320 nm, the absorption coefficient for penetration is 1–1490 µm. These wavelengths are poorly absorbed by the melanin, so it is possible to consider the treatment of darker skin types. However, the skin must be protected to avoid destruction of melanocytic cells [6,7]. This may be achieved by the use of an epidermal cooling device. Cooling the skin can also be achieved by different mechanisms, whether dynamic cooling using cryogenic gas, or a chilled sapphire window, or pulsed air cooling.

Remodeling by Direct Action on the Blood Vessels

In this case, the thermal effect induced by the laser is located at the level of the superficial dermis. Vascular lasers (those with a wavelength between 500 and 600 nm), such as Nd:YAG lasers doubled by a KTP crystal (532 nm) or pulsed dye lasers (585 or 595 nm), cause a thermal effect on the vascular wall. The remodeling may be the result of thermal diffusion past the vessel adjoining the fibroblasts, but it is also, most probably for these vascular lasers, caused by the involvement of platelet factors [2]. The activation of platelets, followed by degranulation, will cause the release of platelet-derived growth factors (PDGFs). These growth factors can cause a second stimulation of dermal fibroblasts, resulting in collagen neosynthesis [2]. The current use of injections of platelet factors is intended to mimic this mechanism of action.

Histological Studies

Many studies have been performed for laser remodeling; they are often of good quality and based on biopsies and the identification of different stimulating factors [3,5,7]. These studies show a significant increase in collagen synthesis with the formation of new collagen fibers. A "flattening" of these fibers, together with an increase of the elastic fibers, is also observed.

However, it is worth pointing out that most of these published studies are based on histological or ultrasonographic criteria and that clinical studies demonstrating a clear visual improvement are rarer and less emphatic [8–14]. This is a key point because the main criticism that is made of laser remodeling is precisely the weakness of any clinically visible improvement, whereas obviously the whole point of treatment should reside not in histological improvement but in clinical improvements that patients can see for themselves.

The clearest results concern the eyelids and crow's feet and cervical region [9,12,14,15]. The fact that there are only moderate visible clinical outcomes, when compared to other lasers, explains the current indications for laser remodeling.

Indications for Laser Remodeling

The main indication for laser remodeling is the treatment of wrinkles of the face, and possibly of the neck [15], which are shallow, in a patient who does not want any downtime. Laser remodeling cannot be regarded today as the most effective treatment for reducing the depth of wrinkles. These lasers are effective, they are safe, and, compared with ablative lasers, their aftereffects are extremely simple. However, nonablative fractional lasers also exhibit these characteristics while providing greater efficiency in evidence on a clinical level.

This is why laser remodeling should for the most part be used for the purpose of prevention or the maintenance of results obtained with a more effective treatment—for example, by ablative fractional lasers or nonablative deep lasers. The simplicity of the sessions allows them to be repeated, and since it is clear that ablative lasers, because of their aftereffects (with crusting), cannot be repeated regularly, there is a role for laser remodeling in the maintenance of the results obtained with the other techniques that are much more aggressive in terms of their side effects and downtime.

Aftereffects of Laser Remodeling

The aftereffects are straightforward, usually marked by erythema irregularly scattered as points on the face. There is usually no crusting or vesicular reaction [8,9,13]. The duration of the erythema is usually from 1 to 2 days and is easily covered up by light makeup. Dark skin patients should take care to avoid sun exposure in the month after treatment to avoid the risk of postinflammatory hyperpigmentation; that aftereffect is rare after remodeling but has been observed in a number of cases, especially in skin types III–VI. There are no other side effects to worry about with this technique. It has never been reported to have severe side effects or scarring.

Conclusions

Laser remodeling has been proposed as an alternative to ablative laser resurfacing because while that was certainly very effective, it had a prolonged downtime and had important risks of hypopigmentation. The first technological attempt to induce significant collagen synthesis used these remodeling

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

lasers, designed to stimulate collagen production by fibroblasts. However, as there is only simple stimulation, the importance of collagen synthesis remains moderate. So, the clinical results were also moderate. Having only minor side effects and a lack of real risk, they are especially indicated for the treatment of recent wrinkles in patients who wish to take care of their skin from early on. Another indication is treatment to maintain for longer the results of techniques that are less aggressive but more effective.

NONABLATIVE FRACTIONAL LASERS

The efficacy of laser remodeling has often been considered too moderate and so led to other technical possibilities being proposed. In the early 2000s, Rox Anderson and his team proposed a new technology—fractionated lasers [16]. The first laser of this type was called Fraxel 750, from the company Reliant. It created laser spots of very small diameter, in the order of 100–200 µm as a maximum, regularly and uniformly arranged in a geometric fashion, leaving between them areas of skin untouched. This is made possible through the use of a scanner interpreting the speed of movement of the laser on the skin. Thus, in each pass of the laser, a certain percentage of the skin is treated; a percentage of skin is untouched, in particular in the epidermis where there are melanocytes. Ablative laser resurfacing, through the removal of the epidermis, causes the total elimination of melanocytes, and this explains the risk of hypopigmentation; it can only be avoided through recolonization of the epidermis from follicular reserve cells, depending on how well those are supplied.

When using a fractional laser, only a percentage (of the order of 15%–30%) of melanocytes was affected by laser impacts in each session. So, at most, only a proportion of melanocytes and epidermis have been affected by the treatment. This persistence of melanocytes between laser impacts will avoid the risk of hypopigmentation and thus open up more treatments for all skin types, even in the body regions that are less rich in follicular units, and therefore melanocytes, than in the facial region.

It is not possible to be more efficacious; but this can be offset by two characteristics, when compared with laser resurfacing. One aspect is that sessions can be easily repeated because of the straightforward nature of the aftereffects. The other aspect is that the risk of hypopigmentation is actually eliminated because the aftereffects are much more straightforward, when compared with conventional ablative lasers.

However, for the same reasons, the principle of fractional lasers obliges the physician to undertake multiple sessions, in order to obtain a satisfactory result. Thus, treatment protocols generally combine several sessions spaced from 1 to 3 months, depending on their aggressiveness. For the nonablative fractional laser, the gap between sessions is usually a month, but can be reduced to 2–3 weeks.

Effects on Tissue of Nonablative Fractional Lasers

There are two types of fractionated lasers—ablative and nonablative.

Ablative fractional lasers cause the production of small "holes" in the skin, with a caliber of about 100–200 µm, and a variable depth depending on the type of laser and its parameters. These epidermal and dermal microlesions will cause a repair process, the source of important synthesis of collagen fibers and other fibers.

With nonablative fractional lasers, there is no rupture of the epidermal wall or removal of the epidermis [16–21]. There are vertical columns, conical in shape, of necrosis coagulation at variable depth in the dermis. There are no ablative lesions or tissue vaporization, but nevertheless this necrosis coagulation will be subject to inflammation and a phase of collagen repair and new synthesis. In the epidermis, the lasers show histological coagulation of the skin that will gradually be renewed, but there is no rupture of the epidermal barrier and therefore no risk of infection or bleeding [16,20–22]. Depending on the repetition of sessions, almost all the epidermis and dermis will have been impacted by the laser, implying a progressive program of epidermal renewal and repair with the support of new dermal collagen synthesis.

Different Types of Nonablative Fractional Lasers

There are many nonablative fractional lasers, differing in their power, the size of the laser impacts, and their wavelength. All have a wavelength located in the infrared range around 1500 nm: some are near 1550 nm (Fraxel's Restore, Palomar's Icon, and ProFractional), while others are closer to 1440–1450 nm (Cynosure's Affirm and Lutronic's Mosaic). At this level, the absorption by water—the main coloration agent of infrared lasers—is greater. This higher absorption will result in shallower penetration into the dermis for these lasers, whose wavelength is closer to 1450 nm. We will see that the depth of impact also varies with the irradiance of the laser; however, in general, the techniques using wavelengths of 1550 nm act at greater depths than lasers emitting around 1450 nm (about 0.6 mm for the latter, against 1.4 mm for those lasers emitting around 1550 nm).

Treatment Parameters for Nonablative Fractional Lasers

Although there are some differences between the different nonablative fractional lasers, they have common points: the parameters of treatment depend on irradiance, which is responsible for the depth of action, and on the density (the percentage of skin actually treated).

Density

The density is the percentage of skin actually treated in each session, compared to the percentage of skin that is not. This may be adjusted with different methods, either by direct adjustment of the density figure to be achieved in a single pass or by multiplying the number of passes with lower densities in each passage. For example, if a laser delivering impacts precisely placed is used, but with a low density of around 3% per pass, it will require eight passes for a total density of 24% (3% × 8). If a density of 30% is desired, it is necessary to complete ten passes. Other lasers offer a high density of the order of 20% per pass. While these may seem simple to use, it will be more difficult to modulate the parameters, because if one pass delivers 20%, two passes will deliver 40%, which may be too high. This will cause problems, especially if there is overlapping between passages; some areas may receive two passes instead of one, which could be dangerous. Indeed, the important measure of aggressiveness for fractionated lasers is not the depth but the density. Lasers based on the principle of a multiplication of passes prove longer to use, because of the higher number of passes to be completed, but on the other hand they are safer, which becomes important if one wishes to use lasers with high densities. Indeed, if there is

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

an unintended additional pass, it will only result in an increase in density of the order of 3%. This will be too low, as an error, to pose a real danger.

Density determines the aggressiveness of the treatment [23]: the higher it is, the more the aftereffects will be marked with an exaggeration of erythema (not often problematic), more swelling, and at most the formation of thick little scabs, reflecting the effect of superficial peeling. On the other hand, the higher the density, the lower the number of sessions that is required. Currently, lasers usually offer usable densities from 20 to 35%, which indicates three to five sessions for optimal results [17,18,20,21].

Density clearly is a factor for postinflammatory hyperpigmentation [24]. One of the main benefits of the nonablative fractional laser is that it is able to treat all skin, without major risks, especially that of hypopigmentation. The main side effect is postinflammatory hyperpigmentation, which is especially common with all lasers used on Asian skin. Several studies have shown that this risk was correlated not with power but with the density [24–33]. In darker skin types, therefore, the physician should endeavor to mitigate this risk by reducing the density a little (no more than 25%), even if there may need to be an additional session to compensate, and two other precautions may be taken: avoid treatments during sunny periods and prescribe in advance, for the 3 weeks prior to the session, the application of a nonirritating "depigmentation" cream.

Irradiance

The second parameter is the fundamental irradiance—that is to say, the energy delivered by the laser impact. This parameter determines the depth of the column of tissue coagulation; it scarcely affects the aftermath of treatment and the side effects. There is a relatively linear relationship between irradiance and penetration depth. The apparatus delivering the highest energy absorption with lower absorption (due to a wavelength close to 1500 nm, such as Fraxel's Restore 1550 nm and Palomar's Icon 1540 nm) allows depths of action of the order of 1.3 mm, which reaches the reticular dermis, using irradiance above 60–70 mJ.

Selection of Processing Parameters Depending on the Indication

These lasers thus give us three parameters: irradiance, density (also related to the number of passes), and wavelength (which is in principle defined by the laser). Each parameter interacts to a greater or less extent with the others.

The choice of irradiance may seem simple, because the higher it is, the more there are deep necrosis coagulation lesions; the volume of new synthesis of collagen is the most important, while the risks and consequences of treatment are not changed, regardless of the skin type. It is therefore not very appealing to lower irradiance.

In contrast, the density determines the aftereffects of treatment, the risk of hyperpigmentation, and the number of sessions required. A decrease in density will make the treatment simplest in terms of number of aftereffects and will reduce the risk of postinflammatory hyperpigmentation, but will mean a greater number of sessions to achieve the same efficiency. This should be preferred for the darker skin types [29,30].

If the indication for treatment is based on the requirement for maximum new collagen synthesis, it is better to choose maximum irradiance. If this is less important—for example, if the patient has many discolorations and diffuse but shallow wrinkles—it is better to focus on maximum density, taking into account the skin type, and even to reduce the irradiance slightly.

Indications for Nonablative Fractional Lasers

Fractional nonablative lasers induce less new collagen synthesis tensor and have less tightening effect than fractionated ablative lasers, which, themselves, are less effective than unfractionated ablative laser resurfacing. But the consequences are not the same, while the fractional method has solved the problem of hypopigmentation. In addition, nonablative fractional lasers allow the treatment of all skin on the face, the neck, and nonfacial regions with a remarkable safety profile. Sessions can be repeated easily, and it is easy to perform processing of the whole face, given the simplicity of the aftereffects. Fractional nonablative lasers are most effective on shallow, diffuse wrinkles, especially in the eyelid region. In contrast, they are much less effective on muscle wrinkles (especially those from frowning—the main indication for botulinum toxin treatment), deep wrinkles (especially those around the upper lip, where the result is often incomplete), and on nasolabial folds. They do not improve facial volume.

The best indications are therefore the following, emphasizing the fact that these lasers can be integrated as part of a treatment plan with injections (of dermal fillers or botulinum toxin), each having their interest and limitations:

- Full-face treatment in patients with wrinkles that are shallow, less marked, and with little relaxation of the skin. Efficacy is better for wrinkles of the eyelids. Fractional nonablative lasers have little tightening effect, especially when compared to ablative lasers. In case of skin laxity and deep wrinkles, ablative lasers, whether fractionated or unfractionated, will have more effect.
- Fractional nonablative lasers are often offered in relatively young patients (in their fifties) and not in patients with signs of very marked photodamage. However, the simplicity of implementing treatment for the entire face makes these lasers particularly interesting if one has the ability to combine sessions from fractionated ablative lasers and from fractionated nonablative lasers. Indeed, it is perfectly possible, either during the same session or in several sessions, to achieve nonablative treatment for the entire face and reserve more aggressive treatment on regions more difficult to treat for ablative lasers. The labial region area is clearly the prerogative of ablative lasers. In case of skin laxity, ablative lasers will be particularly useful.

TREATMENT STRATEGIES

If there are two types of fractionated lasers at a physician's disposal—an ablative one (CO_2 or erbium) and a nonablative—it is perfectly possible to consider combining them. The nonablative lasers will be used for the face as a whole, because of their ease of use for the patient and the doctor. Areas more marked by sun damage—especially the upper lip or cheek when there is loose skin or deep wrinkles—will be eligible for a complementary session using ablative lasers. It is perfectly possible to establish some sort of treatment plan tailored for a particular patient involving a number of sessions with a nonablative

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

fractional laser, with others using an ablative laser. Some lasers allow the physician to use a nonablative fractional laser in the same session to allow deep coagulation necrosis, followed by very superficial resurfacing, to maximize results. In the same session, some areas can be treated only with nonablative lasers and others with a combination of ablative and nonablative lasers. Depending on the requirements of each patient (whether he or she can accept downtime or not), on skin type, on the depth of the treated areas and the wrinkles in them, and on their difficulty, one can use one or the other type of lasers, ablative or nonablative.

In conclusion, the nonablative fractional lasers are of special interest because of the simplicity of their side effects and the absence of some risk, provided the skin type to be treated obeys certain very simple rules. The lasers' lack of effectiveness on deep wrinkles, on wrinkles of the upper lip, and on skin laxity must be known. The best solution may be to combine the two types of fractional laser, ablative and nonablative, to enjoy the advantages and disadvantages of each of these two techniques.

SIDE EFFECTS OF UNFRACTIONATED ABLATIVE LASERS

In general, fractional nonablative lasers do not present risks and tolerance is particularly good. There are no publications to date reporting severe complications or sequelae. The main side effect is the occurrence of transient postinflammatory hyperpigmentation [31–34]. It is much more common in darker skin types and in patients subject to intense sun exposure. Darker skin types may be treated by ensuring certain precautions: decreased laser density, avoiding the sun for 2 months, and prior preparation of the skin with use of melanin pigmentation–blocking cream, applied once a day in the 3–4 weeks prior to the sessions.

Typical aftereffects are characterized by diffuse erythema and possible swelling of the eyelids, depending on the region being treated. There is usually no seeping of fluid, scab formation, bleeding, or purpura. If the erythema is isolated but associated with significant xerosis of the skin, the physician should not prescribe dressings but advise the patient to apply soothing and restructuring creams (Cicalfate, Cicaplast B5 balm LCE). Once these creams have been absorbed, it is even possible to apply makeup to the rash.

CHANGE TREATMENT SETTINGS ACCORDING TO THE INDICATION

If lesions of pigmentation are important, it is best to choose a maximum increase of the density [32,33,35]. It will necessarily be very limited if there are darker skin types, but will still be possible on a light skin type where densities of the order of 40% may be considered. Possibly, the wavelength of 1907 nm (in a thulium laser) is particularly useful because it does not cause significant thermal effects, and very high-density lasers can then be used; whatever the laser power used with this length wavelength of 1907 nm, due to an extremely high water absorption, penetration is very low, not exceeding 300 µm. Thus, it is possible to consider combining in the same session the use of a laser with deep impacts with a wavelength of 1550 nm, followed by the application of larger impacts to obtain a much higher density with the thulium laser [35].

CONCLUSIONS

Nonablative fractional lasers have an efficacy intermediate between that of remodeling lasers and that of fractional ablative lasers. The aftereffects are straightforward, and the entire face can be treated on all skin types. As it is less effective on deep wrinkles and lacks the tightening effect, it may conveniently be reserved for the treatment of diffuse and shallow wrinkles in patients wishing to avoid downtime.

They may possibly be combined in the most difficult areas to treat or more marked with treatment with an ablative laser, which will thus be more localized and therefore more easily accepted by the patient.

REFERENCES

1. Troy TL, Thennadil SN. Optical properties of human skin in the near infrared wavelength range of 1000 to 2200 nm. *J Biomed Opt* 2001; 6(2):167–176.
2. Mordon S. Les lasers de remodelage: Principe et caractéristiques techniques. *Inform Dermatol Cosmetol* 2001; 52:11–16.
3. Mordon S, Capon A, Creusy C, Fleurisse L, Buys B, Faucheux M, Servell P. In vivo experimental evaluation of skin remodeling by using an Er:Glass laser with contact cooling. *Lasers Surg Med* 2000; 27(1):1–9.
4. Fournier N, Dahan S, Barneon G, Diridollou S, Lagarde JM, Gall Y, Mordon S. Nonablative remodeling: Clinical, histologic, ultrasound imaging, and profilometric evaluation of a 1540 nm Er:glass laser. *Dermatol Surg* 2001 September; 27(9):799–806.
5. Nouri K, Zhang YP, Singer L, Zhu L, Huo R, Ricotti C, Prodanovich S, Li J. Effect of the 1,450 nm diode non-ablative laser on collagen expression in an artificial skin model. *Lasers Surg Med* 2005 July; 37(1):97–102.
6. Ross EV, Sajben FP, Hsia J, Barnette D, Miller CH, McKinlay JR. Nonablative skin remodeling: Selective dermal heating with a mid infrared laser and contact cooling combination. *Lasers Surg Med* 2000; 26:186–195.
7. Fournier N, Dahan S, Barneon G, Rouvrais C, Diridollou S, Lagarde JM, Mordon S. Nonablative remodeling: A 14-month clinical ultrasound imaging and profilometric evaluation of a 1540 nm Er:Glass laser. *Dermatol Surg* 2002 October; 28(10):926–931.
8. Levy JL, Trelles M, Lagarde JM, Borrel MT, Mordon S. Treatment of wrinkles with the nonablative 1,320-nm Nd:YAG laser. *Ann Plast Surg* 2001 November; 47(5):482–488.
9. Fournier N, Lagarde JM, Turlier V, Courrech L, Mordon S. A 35-month-profilometric and clinical evaluation of non-ablative remodeling using a 1540-nm Er:glass laser. *J Cosmet Laser Ther* 2004 November; 6(3):126–130.
10. Fournier N, Mordon S. Nonablative remodeling with a 1,540 nm erbium:glass laser. *Dermatol Surg* 2005 September; 31(9 Pt 2): 1227–1235; discussion 1236.
11. Tanzi EL, Williams CM, Alster TS. Treatment of facial rhytides with a nonablative 1,450-nm diode laser: A controlled clinical and histologic study. *Dermatol Surg* 2003 February; 29(2):124–128.
12. Paithankar DY, Clifford JM, Saleh BA, Ross EV, Hardaway CA, Barnette D. Subsurface skin renewal by treatment with a 1450-nm laser in combination with dynamic cooling. *J Biomed Opt* 2003 July; 8(3):545–551.
13. Zelickson BD, Kilmer SL, Bernstein E, Chotzen VA, Dock J, Mehregan D, Coles C. Pulsed dye laser therapy for sun damaged skin. *Lasers Surg Med* 1999; 25(3):229–236.
14. Hsu TS, Zelickson B, Dover JS, Kilmer S, Burns J, Hruza G, Brown DB, Bernstein EF. Multicenter study of the safety and efficacy of a 585 nm pulsed-dye laser for the nonablative treatment of facial rhytides. *Dermatol Surg* 2005 January; 31(1):1–9.
15. Dahan S, Lagarde JM, Turlier V, Courrech L, Mordon S. Treatment of neck lines and forehead rhytids with a nonablative 1540-nm Er:glass laser: A controlled clinical study combined with the

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

measurement of the thickness and the mechanical properties of the skin. *Dermatol Surg* 2004 June; 30(6):872–879; discussion 879–880.
16. Manstein D, Herron GS, Sink RK, Tanner H, Anderson RR. Fractional photothermolysis: A new concept for cutaneous remodeling using microscopic patterns of thermal injury. *Lasers Surg Med* 2004; 34(5):426–438.
17. Peukert N, Bayer J, Becke D, Zurakowski D, Luger T, Manstein D, Laubach HJ. Fractional photothermolysis for the treatment of facial wrinkles—Searching for optimal treatment parameters in a randomized study in the split-face design. *J Dtsch Dermatol Ges* 2012 December; 10(12):898–904.
18. Kono T, Chan HH, Groff WF, Manstein D, Sakurai H, Takeuchi M, Yamaki T, Soejima K, Nozaki M. Prospective direct comparison study of fractional resurfacing using different fluences and densities for skin rejuvenation in Asians. *Lasers Surg Med* 2007 April; 39(4):311–314.
19. Laubach HJ, Manstein D. Fractional photothermolysis. *Hautarzt* 2007 March; 58(3):216–218, 220–223.
20. Laubach H, Chan HH, Rius F, Anderson RR, Manstein D. Effects of skin temperature on lesion size in fractional photothermolysis. *Lasers Surg Med* 2007 January; 39(1):14–18.
21. Laubach HJ, Tannous Z, Anderson RR, Manstein D. Skin responses to fractional photothermolysis. *Lasers Surg Med* 2006 February; 38(2):142–149.
22. Oh BH, Hwang YJ, Lee YW, Choe YB, Ahn KJ. Skin characteristics after fractional photothermolysis. *Ann Dermatol* 2011 November; 23(4):448–454.
23. Wanner M, Tanzi EL, Alster TS. Fractional photothermolysis: Treatment of facial and nonfacial cutaneous photodamage with a 1,550-nm erbium-doped fiber laser. *Dermatol Surg* 2007 January; 33(1):23–28.
24. Chan HH, Manstein D, Yu CS, Shek S, Kono T, Wei WI. The prevalence and risk factors of post-inflammatory hyperpigmentation after fractional resurfacing in Asians. *Lasers Surg Med* 2007 June; 39(5):381–385.
25. Lee SM, Kim MS, Kim YJ, Won CH, Lee MW, Choi JH, Moon KC, Chang SE. Adverse events of non-ablative fractional laser photothermolysis: A retrospective study of 856 treatments in 362 patients. *J Dermatolog Treat* 2014 August; 25(4):304–307.
26. Graber EM, Tanzi EL, Alster TS. Side effects and complications of fractional laser photothermolysis: Experience with 961 treatments. *Dermatol Surg* 2008 March; 34(3):301–305; discussion 305–307.
27. Metelitsa AI, Alster TS. Fractionated laser skin resurfacing treatment complications: A review. *Dermatol Surg* 2010 March; 36(3):299–306.
28. Kim S, Cho KH. Clinical trial of dual treatment with an ablative fractional laser and a nonablative laser for the treatment of acne scars in Asian patients. *Dermatol Surg* 2009 July; 35(7):1089–1098.
29. Rerknimitr P, Pongprutthipan M, Sindhuphak W. Fractional photothermolysis for the treatment of facial wrinkle in Asians. *J Med Assoc Thai* 2010 December; 93(Suppl. 7):S35–S40.
30. Sachdeva S. Carolena S. Nonablative fractional laser resurfacing in Asian skin: A review. *J Cosmet Dermatol* 2010 December; 9(4):307–312
31. Clark CM, Silverberg JI, Alexis AF. A retrospective chart review to assess the safety of nonablative fractional laser resurfacing in Fitzpatrick skin types IV to VI. *J Drugs Dermatol* 2013 April; 12(4):428–431.
32. Fisher GH, Geronemus RG. Short-term side effects of fractional photothermolysis. *Dermatol Surg* 2005 September; 31(9 Pt 2): 1245–1249; discussion 1249.
33. Vaiyavatjamai P, Wattanakrai P. Side effects and complications of fractional 1550-nm erbium fiber laser treatment among Asians. *J Cosmet Dermatol* 2011 December; 10(4):313–316.
34. Tanzi EL, Wanitphakdeedecha R, Alster TS. Fraxel laser indications and long-term follow-up. *Aesthet Surg J* 2008 November–December; 28(6):675–678; discussion 679–680.
35. Geronemus RG. Fractional photothermolysis: Current and future applications. *Lasers Surg Med* 2006 March; 38(3):169–176.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Intense pulsed light

Hugues Cartier, A. Le Pillouer-Prost, and Saib Norlazizi

TECHNICAL ASPECTS

Principle of Operation: Light, Laser, and Intense Pulsed Light

Electrical Energy and Optical Spectrum

The main difference between a laser and an intense pulsed light (IPL) is physics: the first one emits a coherent, monochromatic light (one wavelength measured in nanometers [nm]), whereas the second emits a polychromatic, noncoherent light (a spectral band, e.g., from 550 to 950 nm). The wavelength of a laser can be drawn as one color, whereas the spectral band of IPL is composed of all the colors of the rainbow (Figure 37.1).

Flashlamps or IPLs are discharge lamps of high intensity filled with a noble gas, mostly xenon, most rarely krypton. These light sources produce an optical radiation when an electric current is passed through the ionized xenon gas at high pressure. IPLs are very efficient and convert over 70% of electrical energy into light, compared to the best laser efficiency of 17% produced by CO_2 lasers.

The intense radiation of these lamps has been utilized in various medical and nonmedical applications: optical pumping of laser systems (Nd:YAG, dye lasers, Q-switched lasers, frequency-doubled lasers 532 nm, etc.), simulation of solar radiation, absorption measurement or fluorescence, photocopy units, stroboscopes, and IPLs themselves.

The glass or quartz of the flashlamp is made up of cerium or titanium dioxide. The two triggering electrodes are embedded in the flashlamp structure and polarized (anode +, cathode –). Optoelectronic detection systems are used to determine the emission spectrum in a qualitative and quantitative manner.

Apart from the use of optical filters, spectral emission varies according to the electrical energy inducing the intense light emission. Low electrical energies generate a high predominance of infrared (IR) light peaks within the spectral emission. Higher electrical energies induce a progressive shift towards light peaks located within the shorter wavelengths of the spectral emission. All flashlamps modify their light emission according to their progressive decay; therefore,regular device service maintenance is recommended. IPL systems need to limit their emissions to interact with selective skin targets. Specific cutoff optical filters can be used to reduce spectral bands suitable for selective indications (Figure 37.2). The short-wavelength filters are generally used for vascular targets (Figure 37.3) such as thin and light-colored hairs, light-pigmented lesions, etc. Higher-wavelength filters are used for epilation particularly in darker skin types.

For practical purposes, we can use a color coding system to identify optical filters to be used for specific indications (Figure 37.4):

- Blue—acne
- Green—vascular and pigmented (short-wavelength filter will be more selective on lighter and superficial targets such as sunspots or very thin veins, but this filter has the highest risk for burning and is therefore harder to handle)
- Yellow—vascular and pigmented (may be a little less efficient but safer, especially for beginners)
- Orange—vascular or pigmented (photorejuvenation and epilation of light skin types and scars)
- Orange red—epilation and scars

Laser beams are collimated and can concentrate a high intensity of specific photons in relatively small areas. The same light–tissue interaction can be applied to larger areas when scanners are used. IPL systems are able to irradiate relatively large anatomical areas (up to 5 cm^2) with a noncollimated multiwavelength spectral band able to interfere with multiple targets at the same time. The light source needs to be positioned as close as possible to the skin surface to optimize clinical effects. Clinical effects depend on modulation of IPL emission. Proper pulse durations, pulse repetitions, and interpulse delays need to be selected to generate specific photothermal effects.

IPL timings range from 0.5 to 100 ms, and the tissue effects are only of two orders: photothermal or photochemical with low irradiance. The tissue interactions are based on the principle of selective photothermolysis, which does not require a monochromatic irradiation but only an incident beam that can be selectively absorbed by the target chromophore. To juggle effectively with the pulse durations, the pulse train, and the pulse delays, we must have some basis and understand well the notion of thermal relaxation time (TRT) of biological targets and surrounding tissue to use the principle of photothermolysis. As a refresher, TRT corresponds to the time required for heat to conduct away from a directly heated tissue region. It represents the time taken for heated tissue to lose 50% of its maximum heat through diffusion. The parameter settings are therefore the same as for lasers: the adaptation of the pulse widths and pulse delays to the respective TRT of the target chromophores and surrounding tissue for a selective action and safeguard of surrounding tissue. The aim of the pulse train is to improve the selectivity; therefore, instead of emitting a single wide flash of light, we progressively increase, in steps, the temperature of the target tissue and at the same time protect the adjacent tissue that has a different TRT and cools faster between pulses. This is even more important for darker skin type (Figure 37.5).

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

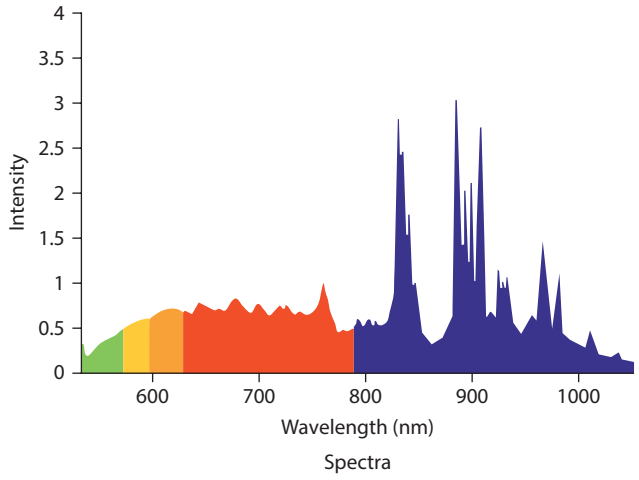


Figure 37.1 IPL spectrum is a polychromatic irradiation and not monochromatic like laser.

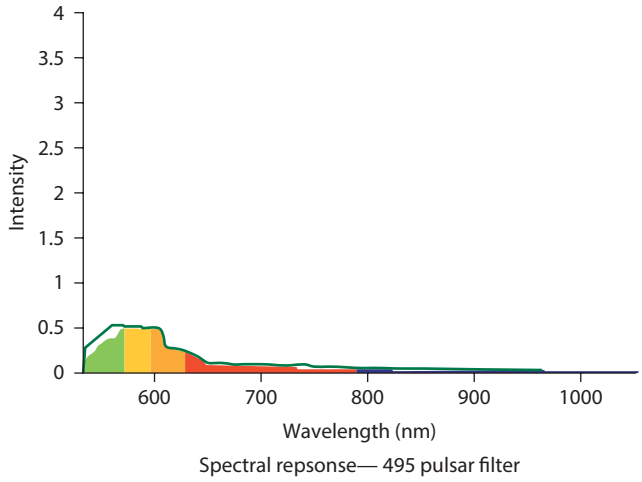


Figure 37.3 Typical spectral response of light emission by a green filter 495–950 nm.

Figure 37.2 IPL handpieces (size 5–22 cm^2) and six different filters.

Even if the mode of operation of IPL technology is univocal, the systems commercialized for medical applications are very diverse, with multiple, more or less, differences making them totally incomparable. The most common technical variations can be found in the lamp arc length, gas pressure, electrode quality and shape, glass material (Figure 37.6), thickness of the quartz, power, sealed or nonsealed joints, filters, and cooling system (water or air cooled), water cooling does indicate that far-IR wavelengths are blocked at the lamp end and the tissue effect could be totally different between the two systems of this category.

New Technologies

Technical innovations are always developed and implemented in IPL technologies. The most recent focused on the following:

- Stabilization of electrical pulsing, obtainable when partial discharge of the capacitors is activated. This important technical achievement can be generated only when high voltages and high electric bank capacitors are used. The end result will consist in a more stable spectral band emission during each IPL pulse. Some manufacturers prefer keeping these specifications and not stabilize the electrical pulsing.
- Optical filters. The quality of filters is important; dichroic filters tend to deteriorate with use and are prone to develop hot spots (where the optical coating comes off), thus exposing partial segments of the exposed isolated spots irregularly distributed on the target area to the full spectrum of light of the lamp and therefore to superficial burns (Figure 37.7). Plain glass filters can break or become cloudy, thus the need to check the filter visually or test it using photosensitive paper (Figure 37.8). The spectral band used for each treatment is chosen spanning from UV to IR, which is lamp emission, except "fluorescent" filters. The use of fluorescent polymer filters helps convert short and more deleterious wavelengths into more useful light. We can therefore reduce the voltage applied to the lamp while keeping an intense emission in the desired area of the spectrum and prolonging the lamp life and efficiency (30%–50% of the unusable shorter wavelengths can be "reconverted" by the use of these filters).
- Calibration. Most of the new IPLs are equipped with a system of calibration (Figure 37.9). This is particularly important as we have, for a long time, blamed these lamps for their lack of reproducibility in time, but some end users (practitioners) prefer investing in a calibration system outside the IPL, which is more reliable and covers the totality of the crystal.
- The handpieces. From large to small.
- Pulse delivery: single pulse, pulse train, pulse delays.
- Cooling systems. Before the advent of efficient cooling systems, it was practical to use thick layers of cold gel. The thickness of the layer of gel and the force applied by the user with the applicator on the treatment area could result in significant variations in the light energy transmitted to the area treated. The emergence of sapphire-based cooling system or special quartz (BK7) (Figure 37.7), via cryospray or pulsed cold air, is one of the major improvements to

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

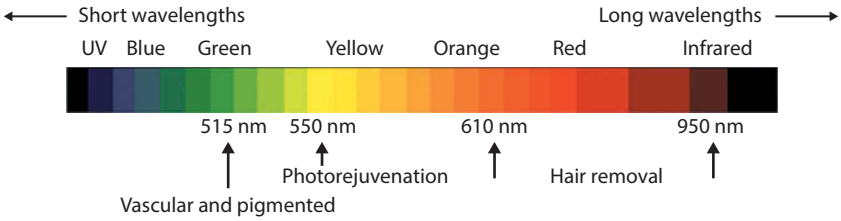


Figure 37.4 Spectrum of flashlamp emission.

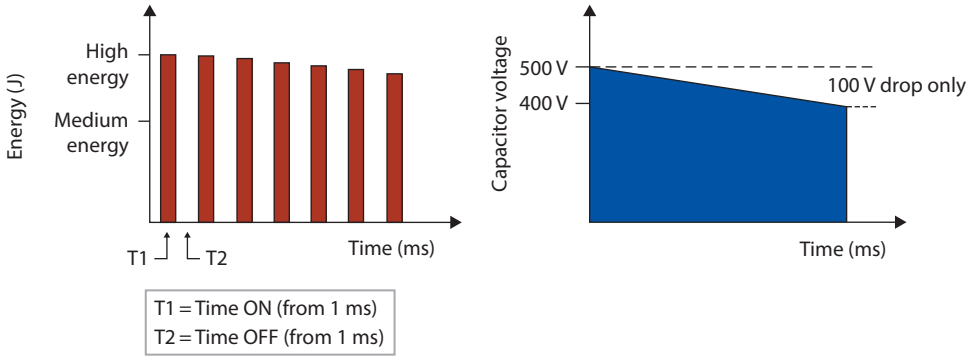


Figure 37.5 Multipulse radiation for an optical light emission and the drop of voltage and energy delivery by a capacitor.

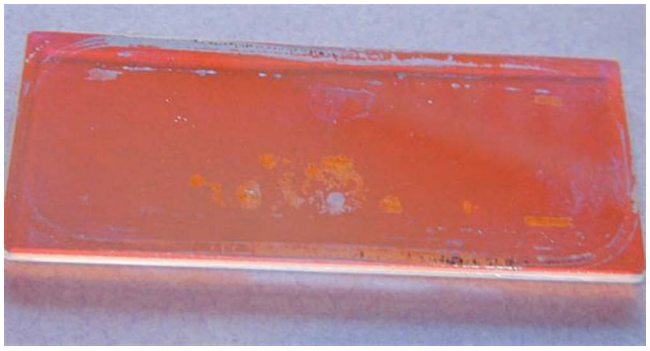


Figure 37.6 Deteriorate dichroic filter.

IPLs (+++ improvement ratio: efficiency/safety). Of course, the filter quality, the spectral range, the energy conversion and the pulse duration, and pulse train/delay are to be considered all around. Some machines privilege the diversity of filters for best absorption to the target area, while others concentrate on the setting of pulse number and duration. Some IPLs do both, but this means the end user has to be specially trained on the particular machine they are going to use, to ensure the total understanding of the IPL and ensure the repeatability of the treatments from one patient to another. Some machines use a skin analyzer to set the treatment parameters automatically for the application.

CLINICAL ASPECTS

It is difficult to give "overall" results because we have widely detailed earlier that IPLs are very different in their specifications (make) and their results are not comparable.

Depilation Field

Recognized and authorized by the FDA since 1997, epilation by IPL has largely proved itself clinically. For the parameters, after analyzing the hair type (thickness, color), skin type, and area of treatment, we use different energy densities, ranging from 6 to 20 J/cm^2 for some IPLs, 30 to 45 J/cm^2 for others, 15 to 40 ms for pulse durations depending on the thickness of the hair to a single pulse or by a train of pulses (3–7 pulses with delays of 1.5–50 ms), etc. All these possible settings permit a high precision and adaptation possibilities for each patient and for the repeat treatments for the patient to the miniaturization and lightening of the hair. The first filter of choice depends on the skin type and color of the hair; we select shorter-wavelength filters for light hair on light skin (between 500 and 550 nm) and higher-wavelength filters (550–755 nm) and/or fractional pulses for darker skin types. In fact, lighter hair contains essentially *pheomelanin*, which has an absorption curve shifted toward the shorter wavelengths compared to *eumelanin* in darker hair/skin type. When using shorter-wavelength filters on lighter skin–type patients, of course, we can expect some very good results from blondes and mousy blondes or those who were blonde/mousy blonde when they were children. In general, we do not treat skin types higher than IV, but some clinical publications have shown the possibility to treat higher skin types V and dark Asians by using filters above 645 nm and to fractionize the pulses with long pulse delays. Finally, while

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

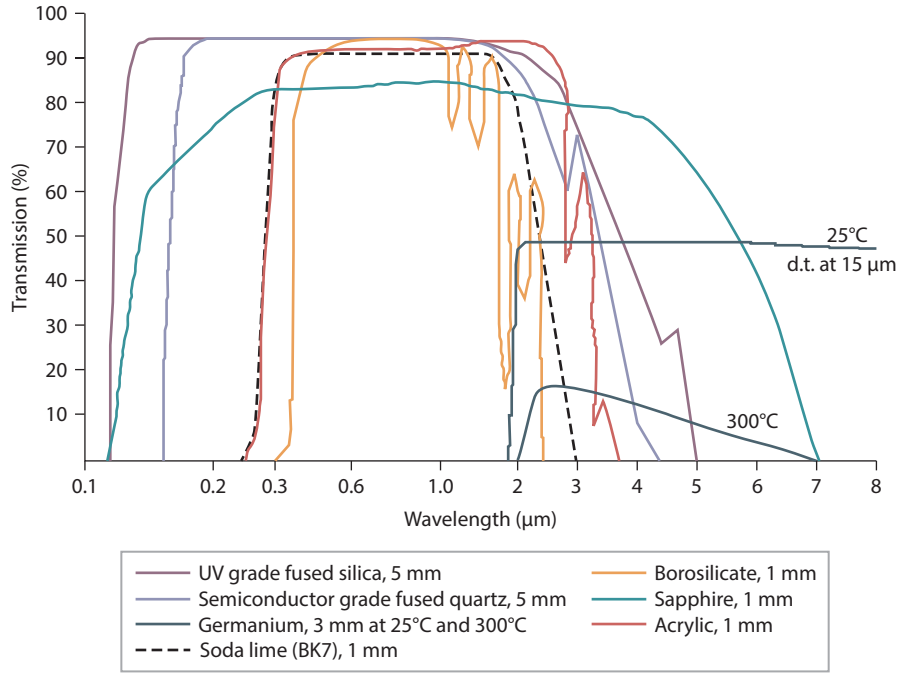


Figure 37.7 Different types of quartz to filter light emission.

Figure 37.8 Plain glass filter.

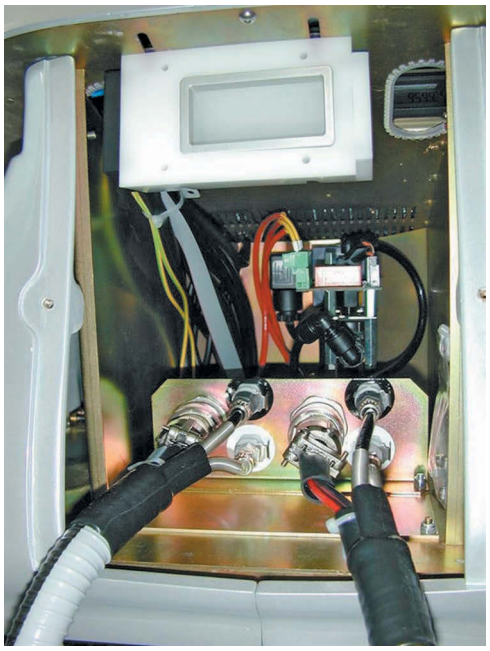


Figure 37.9 Calibration system on the back of an IPL device.

the actual mode of operation was leaning toward high-energy densities to stop the regrowth of simply miniaturized hair, recent publications question again the possibility of using energy densities [1]. To optimize the results on lighter hairs, we can use IPLs that are combined with radio frequency (RF); the publication results are optimistic at the moment but rare and with very low levels of proofs. The French Laser Group User's opinion seems quite homogenous: interest for light, thin hairs, and small areas as the handpieces are small but no results on thick white hairs. It appears to be a good tool in complement to a laser or a depilation IPL of reference.

For the results, the average session for long-lasting (durable) depilation varies between 3 and 6 depending on the skin type, hair color, treatment area, age, sex, and, of course, hormonal status. Maximum efficiency is achieved mainly in the first three treatments (Figure 37.11). After one treatment, all hair types and skin types all mixed, literature numbers indicate an average reduction of hair of 52% at 12 weeks for IPLs, maintained around 40%–75% at 8 or 12 months depending on the equipment. The clinical cases or short tests reported after multiple sessions of photoepilation by IPL give a very interesting and lasting result of 75%–80% efficiency, after five sessions on average. We will not detail all these series, but we will specify two female patients who suffer from hirsutism and have shown recently the efficiency of IPLs [2,3], and two other comparisons with laser (with correct scale) have not displayed significant difference between the

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

machines [4,5]. The comparative study of Mc Gill in 2007 was, by contrast, much in favor of alexandrite laser compared to IPL used [6]. It is therefore difficult to conclude scientifically.

A Part: IPL and Medical Indications of Depilatory Lasers

Approved trials, supporting small sets, have also been made available for applications that are more medical: pseudofolliculitis of the beard, hidradenitis suppurativa, prevention of recurring cyst of the pilonidal sinus, depilation of grafted or torn areas, or depilation après surgical removal of melanocytaire naevus.

As with other depilation lasers, the emphasis is at the end of the literature, for an overall takeover of medical patient's care, with a better understanding of hyperandrogenism. The consensus concerning the assessments to be achieved and the therapeutic management of hirsutism must be known by the medical staff practicing laser depilation. The concomitant prescription of metformin, strongly recommended in the prevention of metabolic problems associated with polymicrocystic ovary syndrome, seems to increase the success of depilation as this has been reported for the first time by an Iranian team using IPL [7]. Among the patients with polymicrocystic ovary syndrome, obesity is correlated with the severity of hirsutism, and these obese patients had needed more depilation treatments with IPL than the nonobese ones; from a recent second lot of patients [8], this can help us in a better way of informing our patients. In practice, the treatment area has to be shaved, and a clear ultrasound gel is applied to the area to help with the light transmission. A small pressure is applied to the skin with the crystal, and the handpiece is moved with an overlap to the adjacent area for the next treatment and again till all the area has been treated. The immediate effect that we are looking for is an expulsion of the hair or at least a modification of the hair (dilation of the stem) and, in a few minutes, the appearance of follicular papules. The pulling of the hair with a pair of tweezers without any skin resistance is enough to prove the inefficiency of the light pulse. The patients feel a brief heat sensation or burning sensation that diminishes in the following few minutes (otherwise we need to reduce the energy). The eventual immediate effects of harmful burn for the tests are delayed; we therefore need to wait several minutes (watch in hand 7–10 minutes) to judge the validity of the parameters used. Contraindications are basically suntanning and spray tanning and dark skin types that increase the risk of burns and their resulting scarring (scars, dyschromia). Photosensitizing medication is contraindicated if there is a dermal accumulation with a peak absorption corresponding to the spectral range used. In other words, there is no contraindication for photoepilation on a patient taking cyclin, for example, as his/her peak absorption will be in the UV and not in the visible light spectrum emitted by IPLs. Treatment of pregnant women is regularly discussed in our French congresses, and there is no more risk of paradoxical regrowth or risk of light diffusion for the baby in utero with regard to the penetration of the photons that are absorbed by the skin and cannot go beyond the hypoderm and even less in the uterine muscle or amniotic fluid.

There are two types of specific secondary effects in depilatory condition:

1. *Leukotrichia*. The study of Radmanesh [9] on 821 patients treated for unwanted hairs by intense flashlamp finds only 29 cases of leukotrichia, 0.04%, which is very low compared to lasers.
2. *Paradoxical stimulation*. But very little studies or reports are certainly possible, as with lasers, in the literature. Always inquire about hormonal anomalies beforehand and spot patients at risk (hirsutism, polymicrocystic ovary syndrome, hyperandrogenism in general, back of young men, period of hormonal instability of women, and, therefore, surely not during pregnancy because the production of oestroprogestatifs protects them against this situation). A recent article reported a paradoxical stimulation rate of 5% on 991 patients, of overall high skin type as these were Iranian women with hirsutism; this looks quite low taking into context the hormonal side [9].

In conclusion, the great adaptability to different skin types, hair color, and hair thickness is one of the major key features of IPL compared to lasers in the field of depilation. For the same patient, we can start with a medium filter and long pulses and then change during the next sessions to a shorter-wavelength filter and smaller pulses to adjust to the progressive miniaturization of the hair. By using highly adapted filters and fractionizing the pulses, we can treat skin types I–V, instead of having to use several lasers. In one of its latest publications *Laser versus IPL: Competing Technologies in Dermatology*, Ross, in 2006, identified the advantages and disadvantages of each of the two technologies, laser and IPL, and the chosen example in the discussion to show that they can be interchanged with lasers in certain fields is epilation" [10]. This is what we have focused on in France for many years. It is later recognized by North American experts, and IPLs have started to outmatch poor man's lasers (Figures 37.10 and 37.11).

Vascular Field

For the theory, with a filter called "vascular" that is determined by a spectral range from 500 to 1000 nm, there are more than 500 monochromatic light lasers that are used. Unfortunately, physics is not the medical clinic, and it happens to be difficult to obtain reproducible results with IPLs than with vascular lasers. A mathematical model study by Wolfgang and colleagues in 2007 is, however, very contributory [11], with a filtered band of

Figure 37.10 Neck depilation with IPL 610–950 nm triple pulse 20 J/cm^2.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 37.11 Neck depilation after three sessions of IPL.

500–1000 nm, 15–30 J/cm², and veins of 60–500 μm diameter, situated at a depth of 1.2 mm:

- It is difficult to go over the 70°C necessary for the veins inferior to 60 μm. It is therefore easier to treat with an IPL the telangiectatic vessels that are diffused by erythrosis.
- For the vessel smaller than 150 μm, we need pulse durations inferior to 10 ms and energy densities of at least 15 J/cm². The thinner the vein, the smaller the pulse and the higher the fluence. For larger veins over 500 μm, we need a longer pulse of 10–30 ms and a fluence of at least adapted fluency.
- It is better to use at first short-wavelength filters around 500 nm for thin veins and filters a little longer (more than 550 nm, even near IR) for larger vessels.
- Integrated cooling systems protect the skin from burns but reduce the efficiency of the treatments by IPL the more the vessel is thin. The IPL indications in this field are those of vascular lasers in general; a large number of publications dating back over a decade talk of good to very good results on all type of couperosis, ruby spots, stellar angiomas, and planar angiomas particularly thicker and older. For poikiloderma of Civatte or erythrosis colli, IPLs are equally referred to in many publications.
- With a new pulse delay less than 1.5 ms or new double broadband of wavelengths, it is now possible to approach the result of the vascular gold standard represented by pulsed dye laser (PDL).

Faurschou et al. have published a comparative study of PDL versus IPL on planar angiomas. They concluded that the lightening with PDL is superior to 65% against 30% with IPL but mentioned, however, that IPL is perhaps more interesting on thicker angiomas or nodular forms. Thanks to its wide spectral band and long wavelengths, IPL permits a stronger penetration and a stronger thermocoagulation effect on deeper vessels [12]. In a 2009 study comparing many machines (alexandrite, Nd:YAG LP 1064, IPL) for the treatment of resistant planar angiomas, IPLs were in a very good position, taking into consideration the ratio efficacy/safety obtained [13]. Nuehaus and colleagues compared PDL with IPL for erythrocouperosis rosaceiform on 22 patients, 3 sessions monthly spaced, and the results using spectrophotometric measurements of the erythema did not show statistically significant difference between the 2 types of machines; besides the decrease in erythema, they report an improvement in skin texture, itchiness, and flushes. The patients indicated a preference to the PDL in the majority of cases relating to the treatment of pain as new PDLs are equipped with cooling tips, but the preference does not relate to posttreatment or results [14]. For us, these series stay isolated, and it is admitted by a large majority of practitioners that vascular lasers are king in their field and that it is much more difficult to obtain reproducible results by laser with IPLs, especially in the hands of a new user. It takes the use of a "powerful" machine, with many filters, and a lot of experience with the machine to set the optimal parameters. A test patch allows a quick estimation for the achievable result of the indicated condition. But be careful; this is only true for light skin type, and it is virtually impossible to treat vascular disorders on skin types above III with IPL without the risk of skin blistering.

We notice as well an improvement in skin said to be reactive, often affected with seborrheic dermatitis and rosacea, probably by various mechanisms (reduction of the lymphocytic infiltrate, reshuffle of procollagen III, reduction of vascular network, or the destruction of *Demodex*). In phlebology, the results are unpredictable. Some studies show certain interest for IPLs, but the majority of the authors agree to writing of sclerosis, and the Nd:YAG stays the valued one. IPLs can sometimes finish off the treatments for the following:

- Thin red vessels or violet ones with no evident connections with nearby reticular veins
- The "red socket" syndrome (Figure 37.12)

It is necessary to be careful when working with the inside of the thigh and on the knees as the skin is very thin, and it is very difficult not to cause a mechanical vasoconstriction during treatment. In practice, avoid pressing the crystal onto the skin when in vascular treatments (in epilation, we actually press down onto the skin) and just touch the skin, thus avoiding the mechanical vasoconstriction. This is harder to achieve with heavy handpieces. You just have to juxtapose the area of flash and be flat on the skin. Ideally, even slightly lift the skin, which is stuck via the gel to the crystal (this is called floating). Some systems supply handpieces with smaller crystals (pointy) for an easy access to the curve areas of the face and reduce the pain (Figure 37.13). It is important as well to avoid

Figure 37.12 Specific triangular IPL handpiece for ruby spot.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 37.13 IPL 495–950 15 cm² 20 ms spot 10 mm² for a treatment of leg red sock.

Figure 37.14 Major face couperosis before treatment with green filter 495–950 nm 11 J/cm² 10 ms monopulse.

vasoconstriction of the topical anesthesia and ice packs; these reduce as much "red target"; some use local anesthesia, a cooled handpiece, or a cold spray. For example, look at the reduction in one session by IPL of a major telangiectasia couperose (Figures 37.14 and 37.15) or improvement of a more classic facial telangiectasia (Figures 37.16 and 37.17). And you can expect an improvement on a papule rosacea after few sessions with IPL, and IPL is also well known to be the gold standard for erythrosis colli (Figures 37.18 through 37.25).

Pigmented Field

Before the advent of lasers, pigmented lesions were treated by cryotherapy, medium peels, or aggressive mechanical/chemical dermabrasion. It has turned out that IPLs are a credible alternative to Q-switched or frequency-doubled (Nd:YAG), alexandrite, or ruby lasers. We must pay attention when using IPL on certain skin types, particularly Asians, and be prepared for noticeable/expected secondary effects due to postinflammatory hyperpigmentation but also severe complications of achromatic type of scars, and we advise variable spectral ranges (450–950/1200 nm) with 2–3 pulses and variable pulse

Figure 37.15 Dramatic improvement of couperosis 4 weeks after one session of IPL.

Figure 37.16 Couperosis before treatment with green filter 495–950 nm 11 J/cm² 1 monopulse 10 ms.

durations depending on the machine (5–10 ms, sometimes fractioned into 2 pulses) much longer than the TRT of the melanosomes and nearer the TRT of the epidermis (10 ms). If in theory IPLs are much less adapted than Q-switched lasers because their pulse duration varies from 5 to 10 ms, while the TRT of melanosomes is 50–280 ms [15]), in clinical practice, we manage to go round the physics principle with fractioned pulses, efficient cooling systems of the epidermis, and the choice of a good spectral band (Figures 37.26 through 37.31). A fundamental controlled study was conducted in 2006 with sophisticated

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 37.17 Dramatic improvement 6 weeks after one session for a couperosis on phototype I.

Figure 37.18 Classic erythrosis and rosacea before IPL.

Figure 37.19 The result 10 weeks after one session of IPL 495–950 nm 18 J 15 ms on facial diffuse erythrosis.

Figure 37.20 The result 1 year after one session of IPL on facial erythrosis.

Figure 37.21 Rosacea before IPL 515–950 nm 15 J 15 ms.

Figure 37.22 Rosacea before second session with IPL 495–950 nm 15 J 15 ms.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 37.23 The result 5 weeks after the second session of IPL on a papulorosacea.

Figure 37.24 Erythrosis colli before IPL treatment.

noninvasive methods (optical confocal microscopy and optical coherent tomography) to understand the action of dynamic mechanisms of intense pulsed lights on pigmented lesions. The images obtained show that the melanosomes of the basal areas of the epidermis migrate rapidly to the surface of the epidermis to be suppressed. On the other hand, melanocytes of the lesions are intact and their hyperactivity starts again after the treatment. The authors therefore concluded that IPLs are efficient for the treatment of lesions, presenting an increase in the melanosome density in the basal layers of the epidermis, but that, when there exists melanocyte hyperactivity, we need to combine topical treatments such as hydroquinone or Q-switched lasers [16]. And these works are fully coherent with the results of our clinical trials that we bring: around 75% of the improvement of lentigines from our trials published in 2000 and the comparative study of Wang [17] on 32 Asian patients of skin type III or IV (15 with ephelides, 17 with lentigines), one cheek treated by Q-switched alexandrite laser (QSAL), the other cheek treated

Figure 37.25 The result after one session of IPL 515–950 nm 18 J/cm^2 on erythrosis colli.

Figure 37.26 Solar lentigo before treatment of yellow filter 515–950 nm double pulse 15 J/cm^2.

with IPL, followed up for 2, 4, 8, and 12 weeks (6 months, if secondary pigmented problems). All patients improved significantly by the treatments. For the lentigines, the efficacy was similar after one session of QSAL and IPL. For the ephelides, the QSAL gave a superior significant improvement of scores compared to the IPL, one or two sessions. A postinflammatory hyperpigmentation reaction was noted in 9 cases (28%) treated by QSAL (more on patients having lentigines than settling ephelides in 3–6 months) and nothing in cases treated by IPL [18]. A few sessions of IPL are managed equally to lighten the

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 37.27 Dramatic improvement 10 weeks after one session for solar lentigo on the cheek.

Figure 37.28 Treatment of solar lentigo with IPL 550–950 double pulse 18 J/cm^2 on the dorsum of the hand.

Figure 37.29 The perfect result 2 months after one session of IPL.

Figure 37.30 Destruction of solar lentigo on the dorsum of the hand with IPL 515–950 nm.

Figure 37.31 The result 3 months after one session of IPL for solar lentigo on the dorsum of the right hand.

pigmented scars. For melasma, the results are very inconsistent for IPLs to be a valuable proposition, and there is a necessity of the use of aftercare depigmenting products.

Hints and Tips

To optimize the result on epidermal spots that are too light to be sufficiently photoabsorbed or small, thin seborrheic keratosis, it is viable to paint them with a permanent brown or black pen (marker) and fire a single low fluence flash with any filter. This gives us an instant photoablation (this technique is called AbraLight®) similar to erbium:YAG technique. Otherwise, in our experience, the sign of a good light absorption ("end point" as the English speakers would call it) is achieved when the pigmented lesion darkens ("graying" or an increase of pigmentation by at least one tone of the treated lesions) on top of moderate erythema, showing a reddish halo around the lesions. Lightening, by fragmentation of the crust formed, will take 8–10 days with the application of a scar repair cream or soothing cream. An interval of 4–8 weeks is required between sessions and obviously sun block that has a sun protection factor of 30 or higher is used.

The photos enclosed personal cases illustrating efficacy of treatments in one session, which is sometimes sufficient for aged patients, they do not desire important demarcation compared to the untreated areas. We sometimes need two or three iterative sessions to get the desired results or the application beforehand of 5-metyl aminolevulinate for 1–2 hours on the

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 37.32 Abralight technique on solar lentigo.

Figure 37.33 Abralight after black painting.

Figure 37.34 Abralight like an ablative erbium:YAG effect.

Figure 37.35 Abralight technique on arm seborrheic keratosis.

Figure 37.36 Appearance immediately following Abralight technique.

Figure 37.37 The result 10 weeks with Abralight technique on a seborrheic keratosis.

lesions to optimize the results when the lesions are not dark (Figures 37.32 through 37.37).

Rejuvenation and Collagen "Remodeling"

Flashlamps have an undeniable efficacy on the two major components of aging skin: telangiectasia and lentigines. Moreover, a number of experienced practitioners report net improvements of skin complexion, pore closure, better texture, even signs of indirect collagenous stimulation with a better skin tone, and a moderate erasure of light lines. In fact, theoretically, flashlamps can act on both stimulation mechanisms of the fibroblast syntheses mentioned in "remodeling" by nonablative lasers: first, a "vascular" action with the shorter wavelengths of the emitted spectrum, by a quick release of

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

vasoactive mediators in the endothelial cells (activation of the packs, freeing of PDGF that is one of the strongest stimulator of fibroblast, triggering of the mechanisms of "scar repair") and second, nonvascular, "thermal" action via the higher wavelengths of their spectral emission, with the action on the system equilibrium of heat-shock proteins (HSPs) and of the transforming growth factor-beta (TGF-β), which are themselves very strong modulators of fibroblast proliferation and collagen synthesis. HSPs are a group of complex molecules, anti- and proapoptotic, whose balance will determine the future and cell functions via the intermediary relation with the system of Fas ligands and other transmembrane receptors acting later on the intracellular transduction system. The TGF-β is itself a "complex" cytokine with paradoxical effects depending on its environment, possessing many β-subunits 1, 2, and 3 and many isoforms of these transmembrane receptors, coreceptors, and soluble receptors, which are in dormant and active forms. The understanding of its regulation, its effects, and its possible role in photorejuvenation is far from being clarified. What we know is that high and prolonged heat allows the transformation of the dormant form into the active form and the stimulation of fibroblasts. For the moment, the study has neither established nor clarified the complex mode of action of nonablative lasers. However, if physiopathogenic hypotheses are persuasive, important progress is needed to improve the objective performances of machines in terms of wrinkle reduction. Zelickson has shown in 2001 that the Photoderm® leads, like the PDL, to an increase of the collagen production of type I. The short tests and studies with histology followed are sometimes contradictory. The problem in interpreting and comparing these studies is, for us, the standardization of these machines, which varies among themselves and depends on the end use. A practitioner could have no results with one machine, but has he used it correctly, with optimum parameters? What can the patient hope for in the end? A brightening of the solar lentigines, an improvement of the complexion, a good skin texture, and a reduction in skin inflammation certainly do not promise results on cutaneous relaxation or deep wrinkles. There are undeniably patients who respond much better than others, but this is not predictable.

The treatment protocols consist generally in a series of 4–5 sessions, every 2–6 weeks, and regular top-up sessions are proposed every 6 months or yearly. Experienced practitioners can obtain a sufficient efficacy in terms of age spot removal and vascular components in one or two sessions; this is acceptable for a large number of patients noticeably in the treatment of hands. The parameters and the filters are chosen depending on the machines, the predominance of vascular or pigmented lesions, and the skin type of the patient. The fluence is increased progressively with the sessions and depending on the tolerance of the patient and efficacy of the treatment. We look to obtain a light erythema and a graying of the pigmented lesions. In the following days, we can see, at most, a darker aspect and even a crusting of the lesions. The patient can get back to work and put makeup on in an hour, if possible. On average, after 8 days, no trace of treatment exists. When a pigmented treatment component exists, it needs to be treated first, and then wait 3 or 4 weeks later for the skin to clear, and therefore, it will not be susceptible to blistering or crusting during sessions with higher vascular settings. In the same manner, it is advisable to use preoperatively topical depigmenting products to improve the benefit-to-risk ratio (Figures 37.38 through 37.42).

Figure 37.38 Before decollete rejuvenation by the IPL system.

Figure 37.39 The result after one session of IPL550–950 rejuvenation on decollete.

Figure 37.40 Face and neck rejuvenation with BoNTB and full pass with IPL 550–950.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

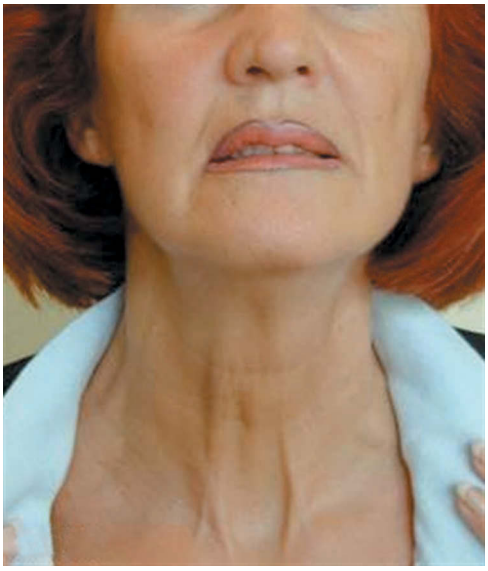


Figure 37.41 Face and neck rejuvenation 1 month after two sessions of IPL.

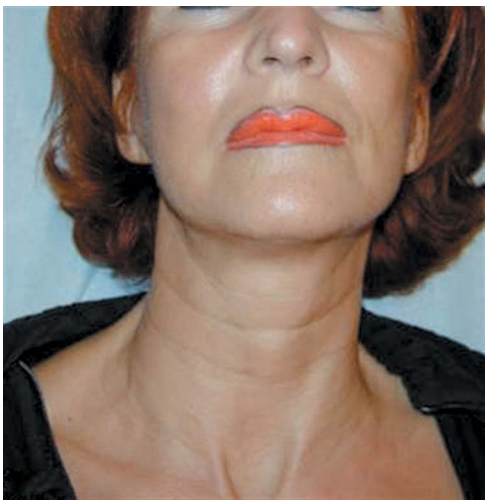


Figure 37.42 Face and neck rejuvenation after one session of BoNTB and 4 sessions of IPL 550–950 nm.

Acne

The latest general scientific reviews in this field agree to a presumption of efficacy of blue light and photodynamic therapy (PDT) for inflammatory acne and for acne vulgaris, but with IPLs alone, a few reported tests have provided very little proof of efficacy although the results are interesting overall, but to date, there are no recommendations in this field. IPLs used could bring a certain degree of "anti-inflammatory" effect by a direct action on the *Propionibacterium acnes*, but for lasting results, we need to combine IPLs with anticomedogenic treatments; otherwise, the lesions will quickly spread (as per treatment with antibiotics). In PDT–IPL treatments, lasting results can be hoped for with a direct action on the sebaceous glands but to the cost of transitory aggravation and noticeable secondary effects. The annex contains the main test results with IPLs or PDT (Table 37.1).

Photodynamic Therapy and IPL

The first scientific study, for the KA, dates back to 2007. It was a randomized intrapatient study, hemiface against hemiface on 25 patients, which compared the painful sensation and the results in 3 months, of one session of MAL(3h)-IPL610-950 versus one session of MAL(3h)-PDT red [19]. The setting was well documented: IPL 610–950 nm at 80 J/cm^2 2 pulses of 5 ms each with subpulses and red LED, 630 nm, 8 minutes, 37 J/cm^2. The results in terms of efficacy were consistent with the documented data and have shown, after only one session, 3 months later, an average healing of 50% of the KAs and an excellent cosmetic result for both types of light sources. Pain levels were less with the IPL (EVA around 4.3) compared to the red LED even though it is cooled by pulsed cold air (EVA around 6.5). Most recently, published papers reported excellent results in the combination IPL and MAL for actinic keratosis, Bowen's disease, and superficial CBC with the following modalities: MAL 3 h under occlusion, IPL 3 pulses of 20 ms on, and a delay of 30 ms; for the KAs, x shots for a total of 39 J/cm^2; and for the Bowen and superficial CBC, x shots for a total of 78 J/cm^2 (Table 37.2). The authors report the quasi-constant efficacy of the treatments by "MAL-square pulse IPL" against the constant stability of the optical spectrum emitted by the machines and the possible oxygenation between pulses (1 ms delay for their equipment, which seemed less appropriate but certainly sufficient enough for the practitioner), thus respecting the use of low repeated fluence [20].

More Aesthetic Field

Ruiz-Rodriguez, in 2002, published his results prior to applying topical 5-ALA to his sessions of IPL, and he used the term "photodynamic photorejuvenation" for this technique. In parallel from 2001 to 2002, medical users of this technique reported noticeable textural improvement, after treatment across actinic keratosis, large Bowen's disease, or superficial CBC using photodynamic photorejuvenation. Other authors have later used varied light sources (PDL, continuous blue or red lamps, LEDs, IPL, etc.) for this "PR–PDT." We will talk now of IPLs, ALA–IPL or MAL–IPL, according to the photosensibilizer used. For ALA–IPL, the application time of the photosensibilizer under opaque occlusion for the condition was at first basically short, ½–1 hour, but they have extended, and actually more and more practitioners are using application times of 2–3 hours. If we refer to publications available to us, the cosmetic results are judged very well by the patients and the observers, in terms of "photorejuvenation," and one session of "ALA–IPL" is equivalent to three sessions of IPL alone. There are little secondary effects (identical to IPL but slightly increased), which, on the other hand, is an interesting efficacy not just for superficial heliodermic marks, pigmented spots, skin texture, and overall aging but also on actinic keratosis (Table 37.3). In fact, these publications present many inadequacies: insufficiency in the methodology and immediate painful secondary effects during treatment, which include palpebral erythema noticeable for 2–3 days and erythema and crusting for 8–10 days, seldom reported and followed most usually only 3–6 months, making it completely insufficient (5 years is the minimum

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Table 37.1 Results of a Series of Treatments with IPL Alone and/or Combined with an Application of a Photosensitizing Product for Acne

Author (year)	PDT	Studies	Results	Monthly follow-up
Gold MH (2004)	Yes ALA		Improvement 54.5% inflammatory lesion 37.5% noninflammatory	NP
Santos G (2005)	Yes ALA 20%, 3 hours	13 patients Hemiface v IPL alone Quantum 560 nm 26 J/cm² 2 sessions	Improvement after 4 weeks, better for the side with ALA Possible transitory aggravation	1 and 2
Rojanamatin J (2006)	Yes ALA 20%, ½ hour	14 patients Hemiface v IPL alone Quantum 560/590 nm 25–30 J/cm², 20–40 ms 3 sessions monthly spaced	Improvement from the first week Placebo-IPL: 66.8% of which 50% showed very good responses at 4 months ALA–IPL: 87.7% of which 80% showed responses after 4 months	1 and 3
Taub A (2007)	Oui ALA	22 patients Hemiface v IPL alone IPL 600–850 nm IPL + RF bipolar Blue light 3 sessions, every 2 weeks	IPL better than other technologies	1 and 3
Yeung CK (2007)	Oui MAL, ½ hours	23 patients Hemiface v IPL alone IPL 530–750 nm 4 séances esp de 3 sem	Improvement of the inflammatory lesions • IPL alone: 22% at 1 month, 23% at 3 months • MAL–IPL: 53% at 1 month, 65% at 3 months Improvement of lesion noninflammatory: • IPL alone: 15% at 1 month, 44% at 3 months • MAL–IPL: 52% at 1 month, 38% at 3 months 25% of studies in the DPT/pain	1 and 3
Chang SE (2007)	NON	30 patients 3 sessions	No improvement for inflammatory acne, (improvement red soars, pigmented irregularities and complexion)	
Wanitphakdeedecha R (2009)	NON	20 patients 4 sessions spaced by 2 weeks	Modest improvement, more importantly/ frequent transitory acne aggravation	

Table 37.2 Results of Down's Studies 2009

	EVA (0–10)	Total efficacy (%) at 4 months
KA	1	10/10 (100%)
KA (scalp)	2	10/11 (91%)
Bowen	3	9/9 (100%)
CBC superficial	3	10/10 (100%)

delay generally acceptable in the studies of skin oncology). It is interesting also to note that the results are based mostly, same for the IPLs alone, on superficial heliodermic stigmata. Wrinkles and laxity are not improved unless we have an important clinical alteration. This is corroborated by the complex immunohistochemical studies recently published by Orringer and colleagues, and they show that after a session of ALA–PDT with a PDL, all the proliferation markers and epidermal–dermal repairers studied increased significantly, and especially there is a correlation between the base rate of p53 and the increase of some markers (CK-16 to J7, peak of collagen I to M1, and then peaks of collagen I and III to M3); significant increases were observed by authors using PDL alone (about twice as much). The base rate of p53, witness as the degree of cellular alteration is induced by UV, which is directly correlated to the increase of CK-16, could become predictive of the individual response to PR-PDT, hence, a clinical indication for the selection of patients. In practice, in terms of PR-PDT, there are no good results with this technique, as we have already known for lasers in general, unless there is sufficient target, meaning UV-induced alterations. In this study, returning to their base state M6, it is necessary to provide top-up treatments or maintenance using other therapeutic methods to maintain the effects. Even if the exact mechanism of the improvement of UV-induced lesions is not yet clarified and even if this study is only on the activation of photosensibilizers by a type of pulsed light source, the PDL, the methodology is very interesting because of the quantity of dermal regeneration and repair produced by the technique, which are good indicators in the induced clinical response [21]. Last, in a general scientific review of Morton and colleagues on PDT in 2008 [22], the authors concluded the photorejuvenation efficacy, with grade B recommendations (scientific presumption) on the basis of studies to a level of proof 2/3. But if we respect, AMM of Metvixia®, the only referenced product in France, it is necessary to treat

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Table 37.3 Resume of the Published Series for Photodynamic Photorejuvenation with IPLs

Author (year)	Number of patients	Photosensitizer	Light	Results	Follow-up
Ruiz-Rodriguez R (2002)	17 Heliodermic 38 KA	ALA	IPL 2 sessions	KA: 33/38 RC "Excellent"/cosmetic	3 months
Gold MH (2003)	10	ALA	IPL (VascuLight)	KA: >85%	None
		½–1 hour	3 sessions	Pigmentation: 90% Couperosis: 50% Texture: >75%	
Avram DK (2004)	17	ALA	IPL 1 session	KA: 68% RC Telangiectasias: 55% Pigment: 48% Texture: 25%	None
Alster T (2005)	10 v IPL alone	ALA	IPL 2 sessions	ALA–IPL > IPL alone	6 months
Marmur ES (2005)	7 v IPL alone	ALA	IPL	Histology, collagen I dosage ALA–IPL > IPL alone	
Kim HS (2005)	12 (Asian) IPL 1 session	ALA 4 hours	IPL 555–950 (12–16 J/cm^2)	50% (42% histologically)	3 months
Dover JS (2005)	20 v IPL alone randomized	ALA	IPL 4 sessions	ALA–IPL > IPL alone IPL + ALA: (16) 80% Photoage, (19) 95% Pigment, (12) 60% Wrinkles IPL: (9) 45% Photoage, (12) 60% Pigment, (5) 25% Wrinkles p: 0.08 Photoage, 0.08 Pigment, 0.08 Wrinkles	1 month
Gold MH (2006)	13 V IPL alone	ALA 30–60 mn	IPL 3 sessions	ALA–IPL > IPL alone (60%–80% > 30%–54%)	1 and 3 months
Babilas P (2007)	25 (KA, pain) Hemiface: IPL v LED	MAL 3 hours 1 session	IPL: 610–950/ pulse train Red LED	Efficacy (around 50%) and cosmetic: idem Pain (EVA medium): 4 in IPL/6 in LED + cold	3 months

dyskeratosis (actinic keratosis and basocellular carcinomas) with red LEDs and not with IPL. Despite everything, this technique has little future in France because the only photosensibilizer that has gained an AMM is Metvixia commercialized by Galderma International, and it can be used in relative safety in France (outside AMM, therefore, under the sole responsibility of the medical practitioner and no reimbursement), and it is very expensive (205 euros for a tube of 2 g in pharmacies with a prescription). We use the Metvixia outside AMM only in rare cases of starting actinic keratosis or severe acne with patients refusing antibiotic, antiandrogenic treatments, or isotretinoin. As soon as the carcinologic lesions are real, we used a red light source according to the standardized protocols of treatment. For acne, the results are reported in the table and are discussed in the specified paragraph.

Pathological Scars and Scar Prevention

It is equally possible to improve scars by releasing a process of scar repair badly started (bridle scars, hypertrophic scars, thin scars). In these indications, collagen remodeling needs as much time as the old scarring process (up to 1 year with 1–6 sessions per month), but the results are good. If the scars are still inflammatory, red and green filters are preferred, followed by yellow or orange filters, and for old scars, lighter or thick filters over 600 nm are recommended. A recently, published study by a team of plastic surgeons on 109 patients suffering from hypertrophic scars obtained very good results but with a high number of treatments (8 on average, spaced 2–4 weeks): 92.5% of patients showed improvement, of whom 65% with good or very good results in relation to scar thickness, scar redness, and scar age [23] (Figures 37.43 and 37.44).

For Stretch Marks

The results are as deceiving as those of other techniques. At the most, we can obtain interesting results for young stretch marks, pink nondehiscent, and "nonanetodermic." For purple stretch marks, IPLs could stabilize them and lighten them faster over time.

Tattoos

Not many studies are published for tattoos, and technically as no flashlamp can deliver the usable energies at pulse times of less than nanosecond or picosecond, it is impossible to achieve the fragmenting of the molecules of pigment (ink). We destroy the color but with a less selective photothermolysis effect. Even though we may get certain effects on superficial tattoos, the use of IPLs in tattoo removal is not fully recommended, as we could provoke skin necrosis or hypertrophic scarring as described in "accidental" tattoo removal (Figure 37.45).

EXPECTED AND UNEXPECTED SECONDARY EFFECTS

Pain: It varies from patient to patient (skin type +++, number, and size of target blemishes) based on the, area treated and the filter used. Patients describe the sensation as an elastic band hitting them or needle pricking and short-lived with the flash. The shorter the wavelengths (near the green/yellow), the less the

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 37.43 Sternal scar before 5 sessions of IPL treatment.

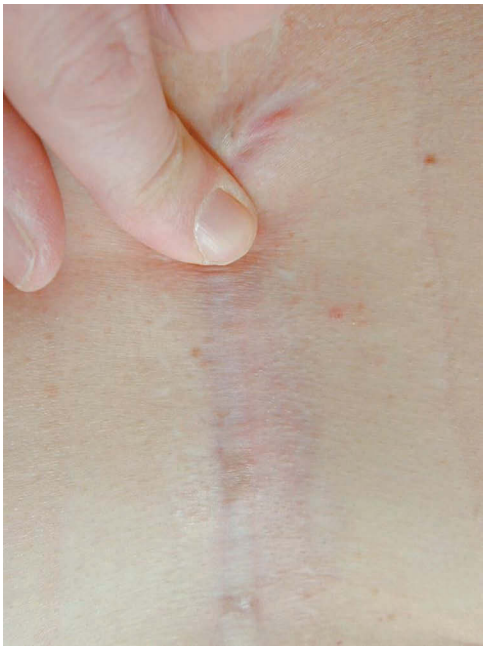


Figure 37.44 Dramatic improvement on this thick hypertrophic-keloid sternal scar with IPL and the using of 4 silicone pad.

light penetration and the more the absorption of high energy on the surface, giving a sharp burning sensation. The therapist has to be very alert to the patient's complaint that is often the alarm signal for the appearance of complications, such as superficial burns. Cold gel and integrated cooling handpieces help comfort the patient and do limit the risk of burns. It is rare to use a surface anesthetic in sensitive areas, except for the first sessions.

Figure 37.45 Partial destruction of a tattoo with dermal burn by an erroneous shot of IPL for depilation.

Burns and scars: In principle, these flashlamps are contraindicated on higher skin types. From skin type IV upward, the fluence must be lowered, filters selected, and/or the pulse durations increased or fractioned. Tans or tanning (arrears that do not lose their tan from one summer to another) is even more at risk and should not be treated by IPL (always try to compare the skin color of the treatment area with an area that is covered before starting the treatment); otherwise, the risk of superficial burns increases. These burn imprints of the crystal left in a regular shape on the treated areas are rare if we take the contraindications seriously and if we have a good understanding of IPL. Lasting scars can be seen, as with lasers, if inappropriate settings are used on darker skin type, but in general with IPLs, if burns are reported, they are usually quite superficial.

Prolonged hyper- or hypopigmentations: These can be seen as consequences of superficial burns described previously (heliodermic skin, tanned dyschromia, pigmented lesions, tanned areas, inadequate parameters compared to the skin type), as with all light sources used in dermatology if we do not pay attention to the counterindications. The loss of pigment in the skin is temporary, and repigmentation occurs in the next summer during the first exposures to sun rays. If summer is far away, then some sessions of UVA or UVB-TL01 could be beneficial. Hyperpigmentation can be long-lasting but is equally transitory, corresponding to postinflammatory hyperpigmentation (sometimes 18 months).

Innocuousness in terms of carcinogens: The majority of IPLs are certified for the emission of visible light only. There is, therefore, no risk of photocarcinogen as per Hedelund et al. [23]: no potential carcinogen directly from IPLs and no influence on UV-induced carcinogenesis. According to Sorg et al. [24], IPLs can generate an oxidative cellular stress but do not induce the formation of thymine dimers. Nonetheless, according to the article of Town et al. [25], there are a certain number of IPLs with CE medical marking (or not) that emit light in the region of the the UV. (very low proportion $\leq 0.1\%$) inclusive of red filters, which are supposed to be far from the UV. It is therefore necessary to be alert and clearly specify the quality of the filtering of the optical radiation, serve the machines, calibrate tests, and keep an eye on the filters. For vascular disorders, if you avoid purpura, it is frequent to induce an edema and blister

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 37.46 Facial edema after IPL session for rosacea.

during few days even for thin and irritative skin like rosacea (Figure 37.46).

Ocular risks: Patients and practitioners must be protected with utmost care from the spectral bands of the flashlamps, which will affect the noble structure of the eye. At most, the patient should wear eye shields and the practitioner protective goggles for protection from the whole spectrum, which is usually very dark green, and it is advised to close the eyes during the flash or use autoshutting goggles similar to welder's protective glasses.

A reminder of the classifications for light machines

Class I—no risk for powers in the range of μW
Class II—low power inferior 1 mW, low risk (certain LED)
Class III A—medium power less than 0.5 mW, low risk
Class III B—medium power less than 0.5 W, medium risk (IPL)
Class IV—high power more than 0.5 W, high risk (laser)

No actual classification takes into consideration the IPLs that we link to Class III B even though they present, in reality, the similar ocular risks to Class IV.

CONCLUSION

IPL systems have been used in dermatology in 1994 and it experienced an exceptional growth that has never been contradicted since, despite the "sad" minds. A multitude of indications have been validated in different fields of dermatology, aesthetics, as in epilation or photorejuvenation, or pathological, as for vascular, pigmented, taking care of scars, as well other indications currently being assessed such as stretch marks or acne. We need, however, to bear in mind that the "multifunction machine," even though good to start with, does not present the best benefit-to-risk ratio in these multiple fields, and if, at first, it appears simple to operate, there is still the need of experience (practice) to apply it to different settings. Therefore, do not consider IPLs, as it has been regarded for a long time, as just a poor man's lasers, but instead consider them as formidable tools, "multipotent" and very subtle to use, and so do not forget a little less the "philosophy" of *laser* in "a good hand and a good clinical eye."

REFERENCES

1. Roosen GF, Westgate GE, Philpott M, Berretty PJ Nuijs T, Bjerring P. Temporary hair removal by low fluence photoepilation: Histological study on biopsies and cultured human hair follicles. *Lasers Surg Med* 2008; 40:520–528.
2. Schroeter CA. Hair removal in 40 hirsute women with an intense laser-like light source. *Eur J Dermatol* 1999 July–August; 9(5):374–379.
3. Nahavandi H, Neumann R, Holzer G, Knobler R, Evaluation of safety and efficacy of variable pulsed light in the treatment of unwanted hair in 77 volunteers. *J Eur Acad Deramtol Venereol* 2008 March; 22(3):311–315.
4. Marayiannis KB, Vlachos SP, Savva MP, Kontoes PP. Efficacy of long- and short pulse alexandrite lasers compared with an intense pulsed light source for epilation: A study on 532 sites in 389 patients. *J Cosmet Laser Ther* 2003 December; 5(3–4):140–145.
5. Toosi P, Sadighha A, Sharifian A et al. A comparison study of the efficacy and side effects of different light sources in hair removal. *Lasers Med Sci* 2006 April 1; 21(1):1–4.
6. McGill DJ, Hutchison C, Mckenzie E, McSherry E, Mackay IR. A randomized, split-face comparison of facial hair removal with the alexandrite laser and intense pulsed light system. *Lasers Surg Med* 2007 December; 39(10):767–772.
7. Rezvanian H, Adibi N, Siavash M, Kachuei A, Shojaee-Moradie F, Asilian A. Increased insulin sensitivity by metformin enhances intense-pulsed-light-assisted hair removal in patients with polycystic ovary syndrome. *Dermatology* 2009; 218(3):231–236.
8. Grippaudo FR, Angelini M, Chiossi MR, Toscano V. Intense pulsed light photoepilation in hirsute women: The role of obesity. *Lasers Med Sci* 2009 May; 24(3):415–418.
9. Radmanesh M. Paradoxical hypertrichosis and terminal hair change after IPL hair removal therapy. *J Dermatol Treat* 2009; 20(1):52–54.
10. Ross EV. Laser versus intense pulsed light: Competing technologies in dermatology. *Lasers Surg Med* 2006; 38:261–272.
11. Baumler W, Vural E, Landthaler M, Muzzi E, Shafirstein G. The effects of IPL on blood vessels investigated by mathematical modelling. *Lasers Surg Med* 2007 February; 39(2):132–139.
12. Faurschou A, Togsverd-Bo K, Zachariae C, Haedersdal M. Pulsed dye laser vs. intense pulsed light for port-wine stains: A randomized side-by-side trial with blinded response evaluation. *Br J Dermatol* 2009 February; 160(2):359–364.
13. McGill DJ, MacLaren W, Mackay IR. A direct comparison of pulsed dye, alexandrite, KTP and Nd:YAG lasers and IPL in patients with previously treated capillary malformations. *Lasers Surg Med* 2008 August; 40(6):390–398.
14. Neuhaus IM, Zane LT, Tope WD. Comparative efficacy of nonpurpuragenic pulsed dye laser and intense pulsed light for erythematotelangiectatic rosacea. *Dermatol Surg* 2009 June; 35(6):920–928.
15. Watanabe S. Basic of laser application to dermatology. *Arch Dermatol Res* 2008 April; 300(Suppl. 1):S21–S30.
16. Yamashita T, Negishi K, Hariya T et al. IPL therapy for superficial pigmented lesions evaluated by reflectance-mode confocal microscopy and optical coherence tomography. *J Invest Dermatol* 2006 October; 126(10):2281–2286.
17. Wang CC, Sue YM, Yang CH et al. A comparison of Q-switched alexandrite laser and IPL for the treatment of freckles and lentigines in Asian persons. *J Am Acad Dermatol* 2006 May; 54(5):804–810.
18. Babilas P, Knobler R, Hummel S, Gottschaller C, Maisch T, Koller M, Landthaler M, Szeimies RM. Variable pulsed light is less painful than light-emitting diodes for topical photodynamic therapy of actinic keratosis: A prospective randomized controlled trial. *Br J Dermatol* 2007 July; 157(1):111–117.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

19. Downs AMR, Bower CB, Oliver DA, Stone CA. Methyl aminolaevulinate-photodynamic therapy for actinic keratoses, squamous cell carcinoma in situ and superficial basal cell carcinoma employing a square wave intense pulsed light device for photoactivation. *Br J Dermatol* 2009 July; 161(1):189–190.
20. Orringer JS, Hammerberg C, Hamilton T, Johnson TM, Kang S, Sachs DL, Fisher G, Voorhees J-J. Molecular effects of photodynamic therapy for photoaging. *Arch Dermatol* 2008 October; 144(10):1296–1302.
21. Morton CA, McKenna KE, Rhodes LE; British Association of Dermatologists Therapy Guidelines and Audit Subcommittee and the British Photodermatology Group. Guidelines for topical photodynamic therapy: Update. *Br J Dermatol* 2008 December; 159(6):1245–1266.
22. Erol OO, Gurlek A, Agaoglu G, Topcuoglu E, Oz H. Treatment of hypertrophic scars and keloids using IPL *Aesthetic Plast Surg* 2008 November; 32(6):902–909.
23. Hedelund L, Lerche C, Wulf HC. Carcinogenesis related to IPL and UV exposure: An experimental animal study. *Lasers Med Sci* 2006 December; 21(4):198–201.
24. Sorg O, Janer V, Antille C et al. Effect of IPL exposure on lipid peroxides and thymine dimers in human skin in vivo. *Arch Dermatol* 2007 March; 143(3):363–366.
25. Ash C, Town G, Bjerring P. Relevance of the structure of time-resolved spectral output to light-tissue interaction using intense pulsed light (IPL) *Lasers Surg Med* 2008 February; 40(2):83–92.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Photobiomodulation and light-emitting diodes

Michele Pelletier-Aouizérate

I am made of light, I am made up of stars.

Don Miguel Ruiz, *The Four Agreements*

INTRODUCTION

Photobiomodulation (PBM) has benefited from the contribution of nanotechnology in the use of semiconductors. The observation of photonic energy induces a major interaction of the energy with biological living matter—*the photoelectric effect*. Since the late nineteenth century, light has been used for medical advances. Niels Ryberg Finsen (Nobel Prize winner in Medicine and Physiology) cured lupus vulgaris with UV radiation, and, in 1896, he founded the first institute for phototherapy, the Finsen Institute, for the study of the biological effects of light and its various applications [1–3]. In 1967, Endre Mester, a Hungarian physician, introduced the term "biostimulation" [4] for hair growth phenomenon after low-energy laser irradiation (as a chance experience) [66]. In 1975, Fritz A. Popp [5,6] took forward the discoveries of A. Gurvitch. He proved that all living plant cells absorb and emit light continuously. This is also observed in animal and human cells.

Light is a system of communication between cells in biophoton form [7,8]. The beginning of the twenty-first century inaugurated several NASA 2000 SBIRS [9] Space Programs studying the growth of cultivated plants: *in vitro* and *in vivo* cell cultures of various tissues (including animal and human ones). The effect of biological stimulation is accelerated, and the quality of healing is improved. These laid the foundation for many research studies on PBM with the use of light-emitting diodes (LEDs) for the management of acute and chronic wounds (e.g., the prevention of radiomucositis). [10–12] A modern concept arises:

The return to "pre-injury/illness level of activity" (*Effect of NASA LED Irradiation on Wound Healing*) [9,13–15].

The status of all clinical lesions becomes dynamic and obeys a nonlinear equilibrium [13].

The emergence of nanotechnologies together with semiconductors and LEDs is translated into an unprecedented development of phototherapy [16].

A diode is a semiconductor that emits a specific wave light when crossed by a low-intensity current. Now, thanks to the availability of new materials, it became possible for the light wave to be declined in several colors and have wavelengths varying from 247 nm (UV) to 1300 nm (near-infrared). Its composition comprises rare-earth minerals.

The semiconductors of the electroluminescent diode are characterized by the PN junction (Figures 38.1 and 38.2).

The energy of the photon in volts is the basis of biological effects: it is actually a photoelectric effect [17]—*an energy quantum* (Figure 38.3).

Absorption, transmission, diffusion, and remission are phenomena of similar expressions. The results depend on the gravity of the electron in its orbit at a time the wave is in a normal or modified position, the latter of which is represented by a dotted line in Figure 38.4). This effect is due to the regulation of the energy levels. After having absorbed or received and reemitted the photon, the electron reverts to its original stable state (when a high-energy photon is absorbed by the electron from its atom, the electron becomes an ion).

All the observed effects are time-related; the reactions take place one after another, which are induced by the photoelectric effect. The clinical effects can be immediate or delayed (primary or delayed reactions) based on the probabilities of collision between photons and electrons that have speeds similar to the speed of light. This is why *power density (photon number, s/cm^2)* received by the cell is fundamental for the threshold that is initially very low but will increase with the energy (Figure 38.4).

When photons are in the violet region, one can observe that the penetration (no electrons hit) is very low and that absorption is maximal, as well as the distribution and retransmission. This effect explains depolarization step by step in the cascade of reemissions that go to the other atoms in all directions. *Fluency (dose in J/cm^2)*, in turn, will allow the arrival at a state of equilibrium in time, but the level of this state depends on the *power density* depending on the doses of energy actually received by the cell [18,19]. The light scattered from the tissue with an incident light beam creates intensity gradient laser fields. They induce modulation of different cells [20]. Spatial coherency should be considered [21].

SEMICONDUCTIVITY IN THE BODY [7]

The principle of semiconductivity exists in our body. It can be classified as inorganic (as we have seen) and organic. The doping of an organic semiconductor [16] is performed by means of the redox system, that is, chemical oxidation or reduction, by electrochemical electric potential difference (acid–base equilibrium). Numerous molecules consist of the following: polypeptides, amino acids, deoxyribonucleic acid, pigments (melanin, carotene/carotenoids, rhodopsin, hemoglobin, bilirubin, chlorophyll, and porphyrins), and neurotransmitters and hormones (dopamine, serotonin, glutamate, and aspartate). Certain components of the extracellular matrix include collagen, proteoglycans, and glycosaminoglycans; the latter are strongly linked to water and are vectors of a greater electronic and ionic charge [22].

They require less current and power than the inorganic C. The doping can be done using *tiny impurities*: an increase in temperature or light irradiation.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

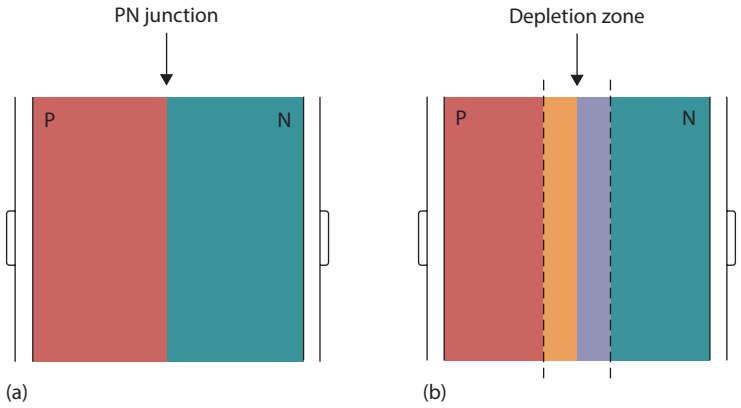


Figure 38.1 (a) A PN Junction is a diode that allows current to flow in only one direction. (b) The holes are positive charges, and the flow of electons will reach the holes, eventually creating a depletion zone that behaves as an insulator preventing subsequent recombination; this creates an electrical imbalance in the crystal, but one insufficient to generate power.

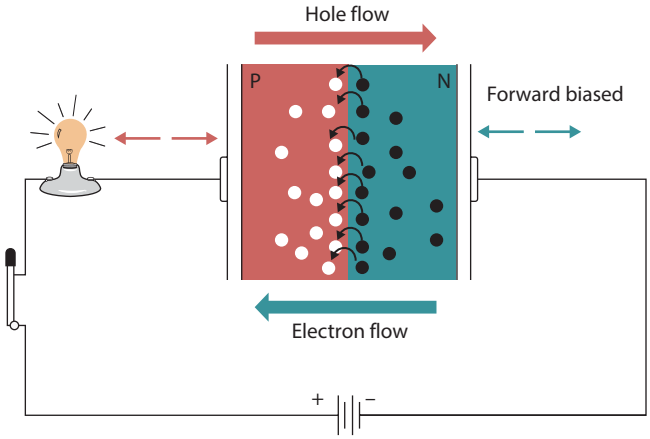


Figure 38.2 "Forward biased" or forward direction. We branch a battery (about 0.7 V) and a lamp across the semiconductor. Shown in the figure are the negative pole to the n-type and the positive pole to the p-type. Thus, charges of the same type repel. The electrons as well as the positive charges or holes are pushed to the depletion zone. They can, with sufficient current, combine at the junction and go through the diode: the lamp lights indicate the passage of current.

Current has a nonlinear relationship with voltage. This state can influence all or just parts of the molecule and can vary at each moment. It constantly varies depending on the physiological state of our body. The difficulty in evaluating the response to PBM of a living tissue at a time is understandable.

Many studies on wound healing using helium–neon lasers have opened, in 30 years, the way for numerous prescriptions: redness, heat, and pain change our approach on inflammation [23]. New molecular-level investigations would precise our PBM targets [24].

The three basic phases of healing are inflammation (3–4 days), proliferation (19–23 days), and remodeling (6 months–1 year). They set in motion various cell types such as mast cells (degranulation), macrophages, and neutrophils, which release proinflammatory factors (cytokines, chemokines) and other anti-inflammatory chemotactic agents [25].

Cicatrization is the result of a *dermoepidermal cross-talk*, as suggested by Prof. Grimaud [26], between the dermoepidermal cells and the extracellular matrix (Figure 38.5).

This dialogue is modulated by the low-energy light that has an informational vocation. *In vitro* studies using PBM-LED reveal (at different wavelengths ranging from 630 to 830 nm) that an inflammatory phase (essential to proliferation) is more rapidly induced and precedes a longer and more precocious proliferative phase. The new term "bio-inflammation" is more appropriate and should be preferred in describing the anti-inflammatory action, which consists of a modulation orchestrated by an improved dialogue (*cellular cross-talk*) of the process leading to reparation. It is what R. Glen Calderhead called "the paradox of LED phototherapy" [23,27].

Our approach on communication allows us to see cicatrization from a different angle: for example, the *Keloid* (Figure 38.6) [28].

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 38.3 (a) Female, 49 years old, treated with photobiomodulation (PBM) to repair burn induced by photodynamic therapy (PDT). (b) After the protocol of 4 sessions of PBM (2 or 3 days apart). Parameters for red- and yellow-pulsed emission mode in photobiomodulation: 12 J during 6 minutes, dark period 30 mW/cm^2. The healing (repairing inflammation) process is the ultimate result of photon energy interacting with living matter.

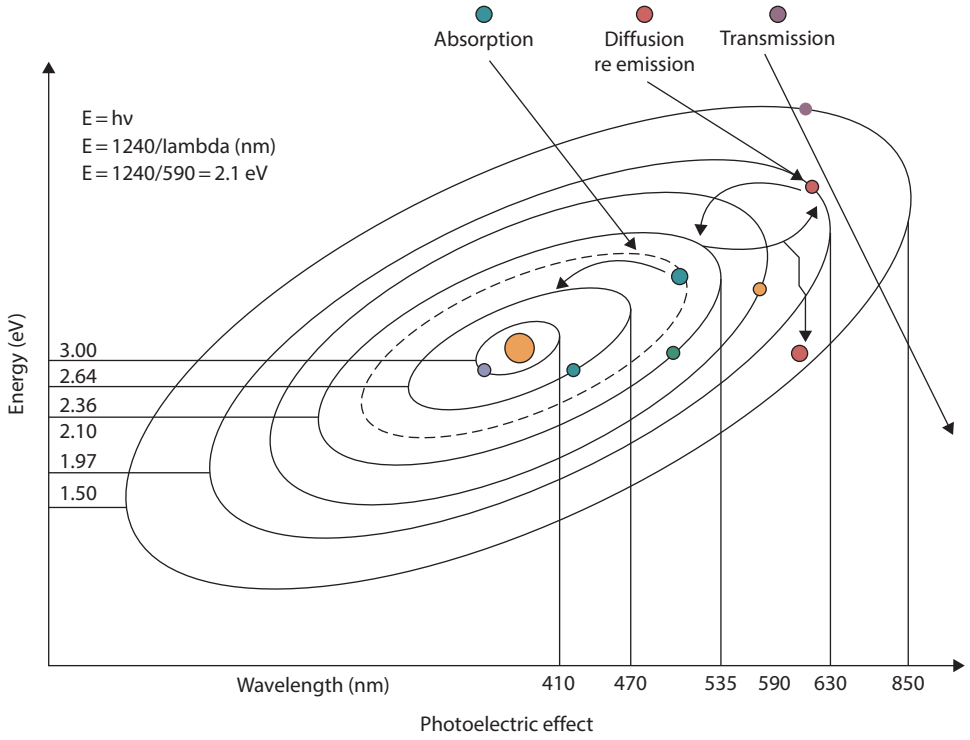


Figure 38.4 Only some of the absorbed light/energy induces biological effects. (Courtesy of Charles Breda.)

PBM not only treats inflammation but contributes to the well-being of the patient by diminishing pain and speeding up the healing process.

PBM is frequently used in clinical physical therapy practice for pain relief and tissue regeneration. It modulates inflammatory processes in a dose-dependent manner and can be titrated to significantly reduce acute inflammatory pain in clinical settings [29]. There are several reports on the effectiveness of PBM on physiological factors, and it has been shown to be an effective treatment fro pain relief form carpal tunnel syndrome [30–34], temporomandibular disorders [35–37], musculoskeletal pain [38], chronic myofascial pain in the neck [39], acute pain from soft-tissue injury [40], and septic arthritis [41]. It was more effective than diclofenac in patients with

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

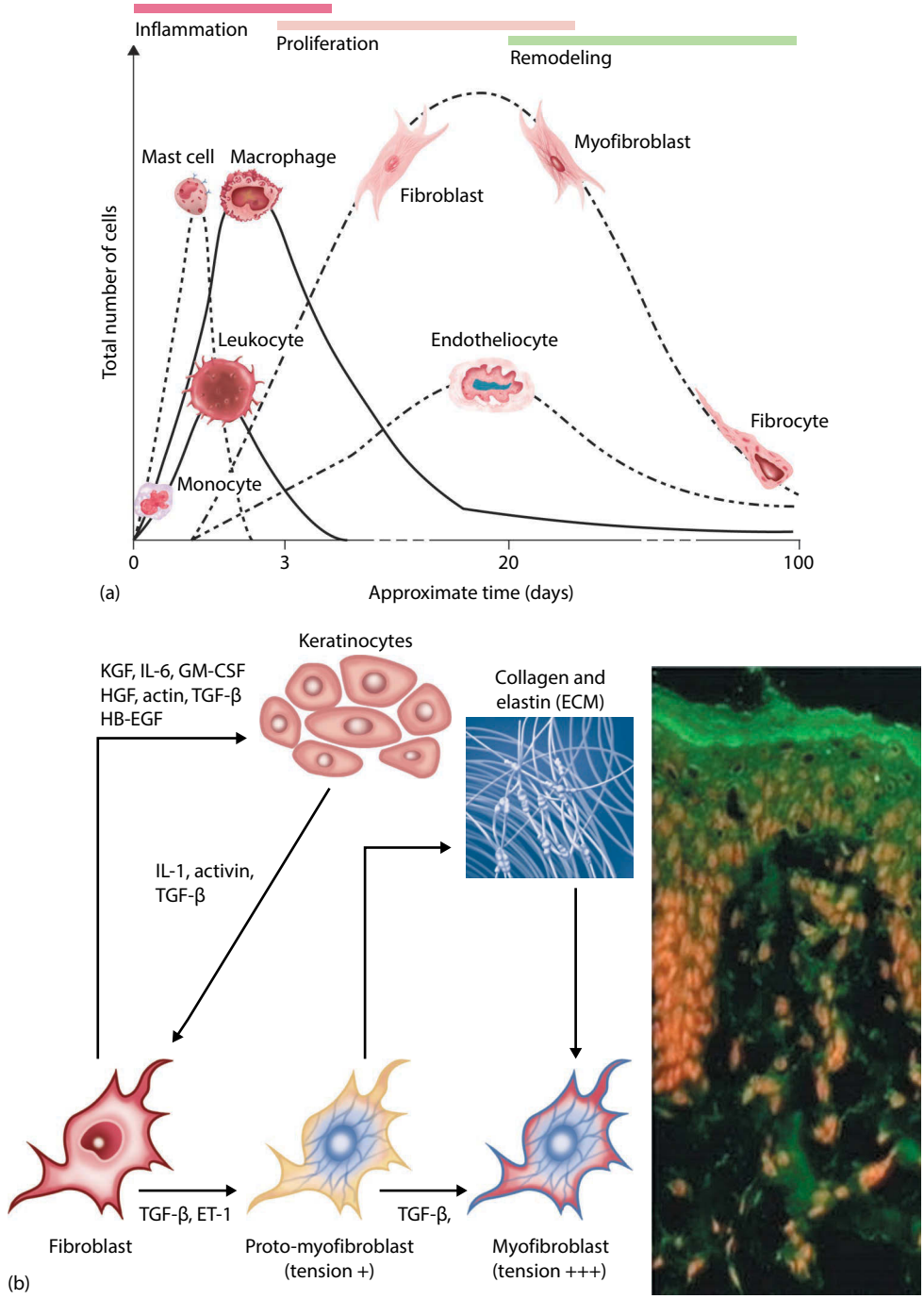


Figure 38.5 (a) The stages of regular healing are the expression of (b) good communication/homeostatic cross-talk between dermal/epidermal cells. (a: Courtesy of Glen Calderhead; b: Courtesy of J.A. Grimaud.)

chronic pyrophosphate arthropathy and patients with chronic apatite deposition disease [42]. We can thus affirm with total confidence that PBM is a complete approach that participates in a global manner in healing and allowing an improvement in the overall state of the patient by also dealing with the pain control [43,44].

PBM is the process by which specific wavelengths are absorbed by cellular photoacceptors, triggering major signaling pathways that determine biological changes involved in the proliferation, reparation and regeneration functions. (Actually in all medical fields) [45,46].

The "photoacceptor" is the last part of the mitochondrial respiratory chain: it includes not only the enzyme cytochrome c oxidase (COX) but also the cell membrane. PBM alters the *redox system* (part of the cell respiration) together with numerous intracellular signaling pathways and their transcriptions in several possible directions: cell adhesion, migration, and proliferation and prevention of apoptosis. Its sensitivity to

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

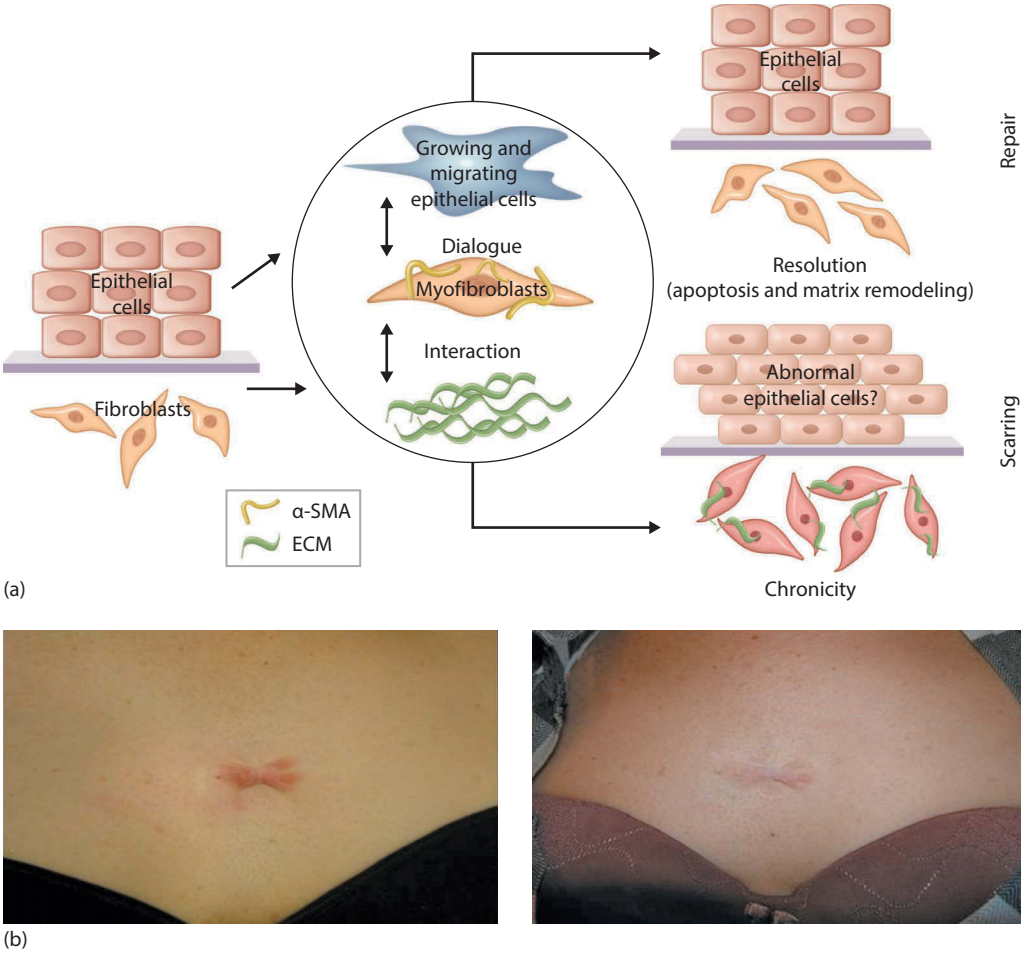


Figure 38.6 (a) If the cross-talk between cells (fibroblasts and keratinocytes) fails, then (b) a Keloid scar can appear. This can be interpreted as the result of a bad-quality cross-talk between fibroblasts and keratinocytes. (a: Courtesy of J.A. Grimaud.)

the range between red and near-infrared involves a particular quality of the mitochondrial signal called "retrograde." Everything happens as if mitochondria (MTC) by variations (cell and MTC differential membrane potential, rate of reactive oxygen species [ROS; free radicals], rate of intracellular and MTC CA++, photodissociation of nitric oxide, pH, fission fusion/homeostasis) informs the nucleus about the environmental conditions [47–49].

What do we mean by environment? It is anything that alters cellular physiology at the following three closely linked stages: molecular, cellular, and tissue representing the three facets of the same phenomenon. These *differential* parameters are all signals that warn the nucleus of the external situation at a moment, allowing it to transcribe new syntheses based on the reading of the signal. The regulation of the expression of nuclear genes could be involved in this notion of an epigenesist. The external environment affects our genetic heritage. PBM (by the photoacceptor function of MTC) integrates these new data [31,48,50,51].

The hypothesis that the mechanism of light therapy at the cellular level was based on the absorption of monochromatic visible and NIR radiation by components of the cellular respiratory chain was advanced for the first time by T. Karu in 1989 [49,52]. The respiratory chain is the main pathway for the transfer of electrons or protons from metabolites to oxygen, and this crossing has *three steps*: (1) glycolysis, (2) citric acid cycle (or Krebs cycle), and (3) the electron transport chain (ETC), with the latter two located in the mitochondria.

The majority of ATP is created within the ETC, while glycolysis and the citric acid cycle provide the necessary precursors. The ETC is located within the inner mitochondrial membrane and is made of five complexes of integral membrane proteins: NADH dehydrogenase (Complex I), succinate dehydrogenase (Complex II), cytochrome c reductase (Complex III), COX (Complex IV), ATP synthase (Complex V), and two freely diffusible molecules ubiquinone and cytochrome c that shuttle electrons from one complex to the next [53] (Figure 38.7).

The first evidence that most of the light absorbed by cells is absorbed by mitochondrial COX was provided by Beauvoit et al. in 1994, and COX has been increasingly shown to be the photoacceptor and photo-signal transducer in the red-to-NIR region of light ever since [54–56]. COX is the terminal enzyme of the ETC in eukaryotic cells and mediates the transfer of electrons from cytochrome c to molecular oxygen (O_2). It is a

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

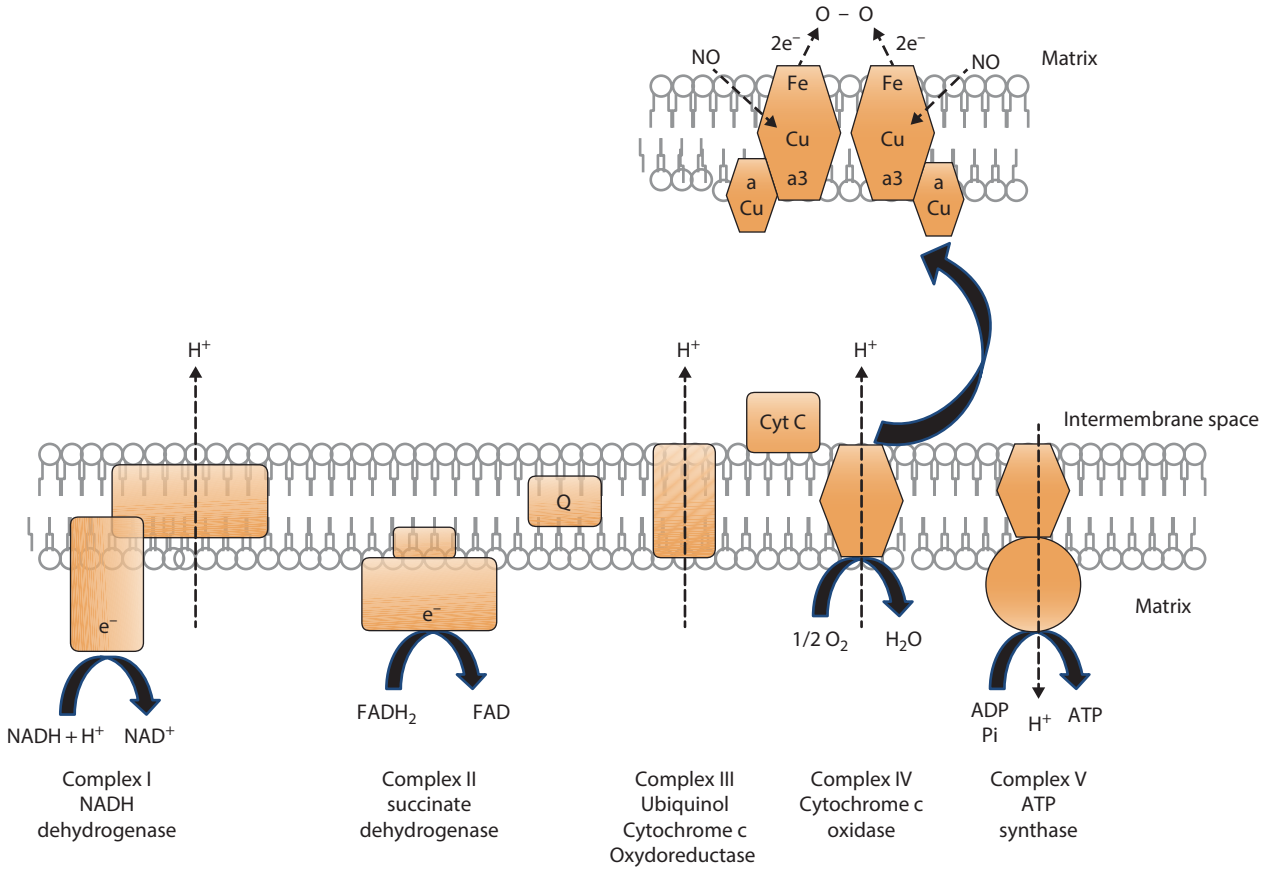


Figure 38.7 Electron transport chain, with reduced binuclear center a3-CuB (top of the figure).

multicomponent protein that contains a binuclear copper center (CuA) along with a heme binuclear center (a3-CuB). The main function of the center copper oxygen (Cco)/H_2O is the reduction of oxygen to water [57]. During the Cco/H_2O reaction, oxygen is reduced by a series of one-electron transfers to ROS.

The absorption of photons by COX leads to electronically excited states and consequently can lead to quickening of electron transfer reactions. More electron transport necessarily causes increased production of ATP.

Another molecule that was found responsive to PBM is nitric oxide (NO) [58–61]. NO is mainly produced by a group of enzymes called "nitric oxide syntheses" (NOSs). It is involved in the modulation of cell respiration by reversibly inhibiting COX [62]. All known facts of the inhibition of COX by NO can be simplified as a direct competition between NO and O^2 for the reduced binuclear center, a3-CuB [63]. For *in vitro* experiments, NIR light shows that NO is liberated from nitrosyl hemoglobin (HbNO) and nitrosyl myoglobin (MbNO) in a wavelength and dose-dependent manner [64]. The reduction of nitrite to nitric oxide can also be performed by COX and not just by NOS, the function being referred to as Cco/NO [57]. Cco/NO activity is inhibited by high oxygen input, the functions being primarily under hypoxic conditions [19], and can be modulated by a wide range of oxygen concentrations [63]. The rate of the Cco/NO reaction increases with increase in nitrite concentration and with decreasing pH. Low-intensity light enhances NOS by COX without altering its ability to reduce oxygen [63].

We can infer that COX by its two main functions, Cco/H_2O and Cco/NO, could act as a "molecular switch" in response to oxygen [63], and it is likely that the signals that initiate signaling pathways in response to light are also oxygen dependent. NO-induced inhibition of COX may regulate the formation of hydrogen peroxide from the respiratory chain for the purpose of signal transduction and controls O_2 (oxygen) gradients in complex organs such as the liver or heart [57,65]. PBM may produce a shift in overall *cell redox potential* (oxydoreduction related to cellular breathing) in the direction of greater oxidation [66]. Several important regulation pathways are mediated through the cellular redox state changes that induce the activation of numerous intracellular signaling pathways, regulate nucleic acid synthesis, and promote protein synthesis, enzyme activation, and cell cycle progression. Redox signaling occurs when a biological system alters in response to a change in the level of a particular ROS or the shift in the redox state of a responsive group. Mitochondria seem to be an important redox signaling node [50] partly because of the flux of the ROS superoxide (O_2^-) [67]. Burnstock in 2009 [68] demonstrated the role of ATP as a signaling molecule allowing cellular cross-talk. Mitochondrial ATP synthesis was enhanced after NIR irradiation of mitochondria [59]. ATP activates the P2 receptors (subtypes P2X and P2Y). When bound by ATP, P2X receptors form a channel that allows sodium and calcium ions to enter the cells releasing the intracellular calcium reserves [66]. Transient oscillations in calcium concentration

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

are important in transmitting intra- and intercellular signals [69]. Mitochondria can propagate calcium-driven signals in two ways: acting as a calcium sink in order to prevent feedback inhibition or acting as a calcium reservoir releasing more calcium to the cytosol to amplify signals [61]. Mitochondria are able to encode and decode Ca^{2+} signals because the respiratory chain generates an electrochemical gradient for protons across the inner mitochondrial membrane. By taking up and subsequently releasing Ca^{2+} ions, mitochondria can alter both the spatial extent and the duration of cytosolic calcium signals [70]. Cytosolic Ca^{2+} elevations have a direct effect on mitochondrial pH, by decreasing it. Changes in cytosolic pH are paralleled by changes in mitochondrial pH [71].

The pH gradient could be compared to Indian smoke messages, as it controls the Ca release and uptake from/by mitochondria. In conclusion, it appears that PBM increases the NO concentration in the mitochondria both by its release from hemoglobins and by being synthesized via an enzymatic reaction catalyzed by COX. This NO accumulation has two proven immediate effects: the reversible inhibition of COX and the lowering of the pH, simultaneously, accessing two different signaling pathways: ROS and calcium mediated. Calcium signals are also controlled by the ATP rise [72].

TOOLS IN CLINICAL PRACTICE

We must distinguish the device parameters (its characteristics) and the illumination parameters (wavelength, energy density, power density or irradiance, illumination times, pulse or continuous mode, and contact or not with the lesion) from the treatment parameters that involve the characteristics of the lesion, and the patient's condition at a time [73–75].

Far from describing a complete list of settings, we will focus on some key points.

Device

1. *The cooling* of the *energy degraded* in the *form of heat* (by *LEDs*) is an essential *element of good parametric efficiency* [20,76,77].

   Three variables are essential for all LED systems:

   - The *electric power* absorbed by the LED
   - The *emitted light* power
   - The stabilized corresponding operating *temperature*

   The electroluminescent diode has a luminous efficiency of about 12%–20% depending on the colors (this is improving with time). The remaining energy is degraded in the form of heat. The machine's cooling system is therefore *essential*.

   a. *Warm-up during a session*: The heat emitted by the LED cannot be efficiently dissipated toward the back of the LED. The heat is therefore dissipated in the form of radiation toward the front of the LED, at the same side as the light emission, and the skin receives a dose of heat, prejudicial to the treatment that should remain *athermal*. A state of equilibrium is established between the thermal power, the emitted optical power, and the reached temperature.

      The more efficient the cooling, the more elevated and stable throughout the session is the light power, ensuring that the programmed parameters are actually received by the cell.

   b. *Displacement effects toward longer wavelengths and degradation of the optical power*: The rise of the temperature of the LED will decrease its performance by half, and the amount of light produced will drop during the session [76].

      There is a spectral shift toward the infrared from 0.2 nm/°C because the emitting crystal improperly cooled malfunctions, creating a shift to the IR of 10 nm for a 50°C temperature increase.

   c. *Near-infrared and the areas to treat*: There is therefore a far-infrared unwanted emission, visible with a thermographic camera, and a near-infrared emission due to the red shift. The emitted light shifts its spectrum to the infrared, and the new colors no longer have the same properties on fabrics. In this case, the material is worn out and the LED is degraded (i.e., converted to thermal energy). No heating of the illuminated tissue should occur, but rather, the interaction of energy/living matter should be the coldest possible to remain within PBM.

   d. *Quick calculation of the overall efficiency of a LED system*: All device manufacturers with medical Conformité Européenne (CE; European Conformity) marking are required to include in their documents the following information as recommended by the doctors:

      The electric power absorbed by the apparatus
      The power density or irradiance in mW/cm^2
      The fluency in $J/cm^2 = mW/cm^2 \times$ time (in seconds)
      or (irradiance × time in seconds)
      The emitted wavelengths
      The surface of the LED panels

   The insufficiency of these data makes it impossible to verify the coherence of the information.

2. *Obtaining a medical CE (FDA approved)*: This process is long, difficult, and expensive; however for medical indications, if we consider only wound healing, dynamic phototherapy requires a device with medical CE: CE. xxxx. In the eventuality of a medical problem, the guaranty of this standard will weight in the legal balance.

   a. *Protect our eyes?*: The protection of the retina is essential because the LED emits a high-brightness wavelength [16]. More specifically, the power density of light on the small retinal surface increases the harmful effects of the wavelength since the same amount of light is shone on a smaller surface. Additionally, near infrared light is invisible to the human eye, and thus, seems innocuous. However, recent data suggested that some wavelengths of near-infrared light could be detected by the human eye.

      The user manual and documentation must be placed on the identification label. The user *must inform himself* before buying the equipment. One should note that the RC Insurance does not cover damage resulting from a problem that was generated by onmarked CE medical equipment. A LED device is classified 2 A under the Medical Devices Directive 93/42CEE.

3. *Knitting, or stamping of LEDs*, tight or not, with an opening angle of 20°–120° roughly determines the distance source target. The wider the opening angle, the closest one must get to the target, and vice versa.

   One can see the relationship between the distance and the emission angle at the same irradiance. There must be a compromise so that the skin is uniformly illuminated by the different colors used at the same time (Figure 38.8).

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

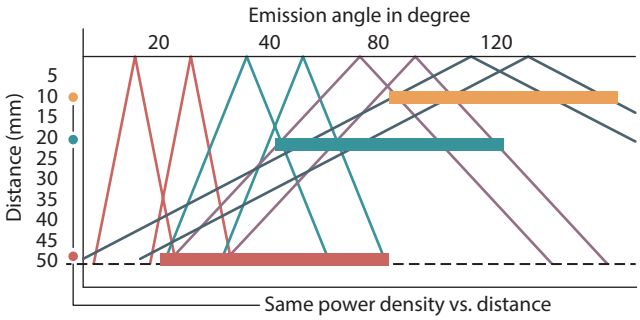


Figure 38.8 The wider the angle of the LED, the less powerful the emitted light. (Courtesy of Charles Breda.)

Electronic Charge of the Used Wavelength Is Responsible for the Biological Effects [14]

The wavelength conventionally defines the tissue penetration from 300 to 600 nm for superficial lesions and from 600 to 1000 nm for deeper lesions. The dose absorbed by the skin depends on the reflection of the wavelengths used as treatment. It is on average equal to 50% for phototype 3 and 40% for phototype 5 in the visible spectra (400–800 nm) [73].

Inside the tissues, part of the light is scattered, retroreflected, or transmitted. The part absorbed by the tissue is the one that has an interest for the treatment [78].

The emission mode can be continuous or pulsed. *In vitro* studies of the pulsed mode yielded discordant results [73,79,80]. Pain reduction, essential for a successful cicatrization, is the main advantage of the pulsed mode, bringing it into the spotlight [34,81] (Figure 38.9).

It is important to focus on the interpulse period or "dark period" (DP). This time zone is perhaps richer in learning than the pulsed time. The same is valid for the intersession period that varies from 48 to 72 hours ("the cell's relaxation time") [73]. The concept of DP can cover beyond the interpulse period: a few weeks or months. We should talk rather about sequential treatment mode than about pulsed mode. Clinical practice should take into account the delayed effect so important for the adherence to the protocol by the patient that needs explanations about it from the clinician. It corresponds to the secondary mechanisms described by T. Karu [49,82]. This would partly explain the biological effects observed in the clinic that *always appear after the illumination time* (primary mechanisms) [82].

Another phenomenon is the *bystander cell theory* [83–85]. Unirradiated cells, neighboring those that have been targeted, seem to respond to very low energy light. This is analogous to the soft x-ray experiment [84]. It could partly explain some systemic PBM effects [75,85–87].

Can we talk about photobioflexible field? [88]

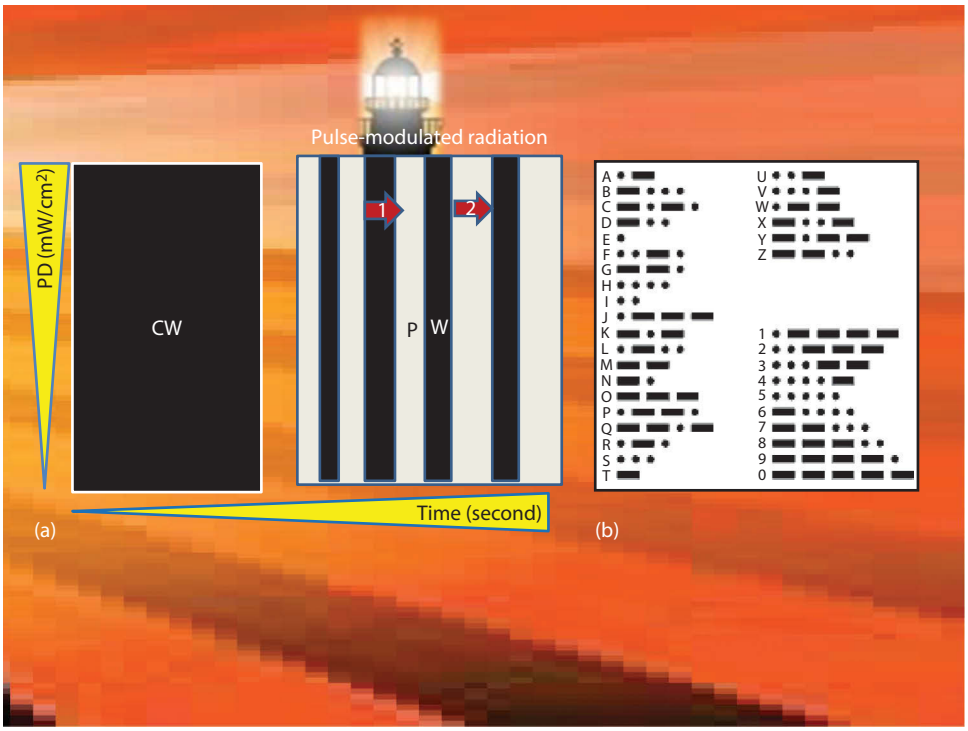


Figure 38.9 The "speaking light" hypothesis, comparing pulse mode patterns to Morse code. (a) The parameters for pulse mode patterns are pulse width (PW), pulse duration, pulse repetition rate, and frequency (hertz = number of pulses/second). 1, pulse duration; 2, dark period; CW, continuous pulse; PD, power density or irradiance; mW/cm², milliwatt per cm square. Computing and *in vivo*/*in vitro* culture cell studies will help us establish different models adapted to choose therapies in the future. (b) In international Morse code, 1 dash = 3 points; interval between 2 elements from the same letter = 1 point; interval between 2 letters = 3 points; interval between 2 words = 7 points.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

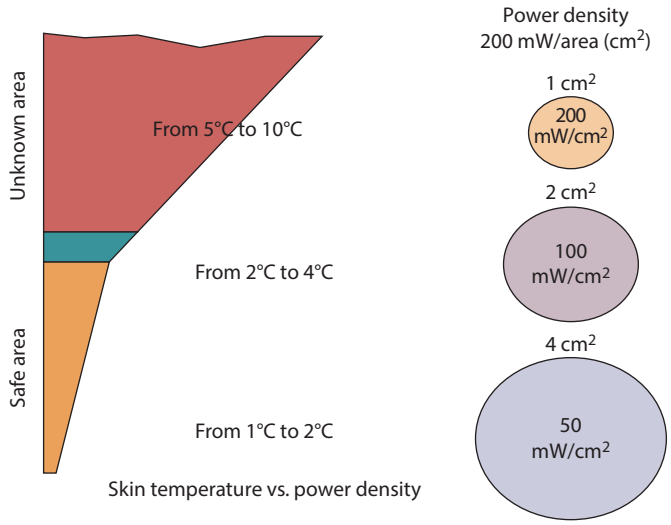


Figure 38.10 The dose and the power density (irradiance) have different biological effects. The same energy dose induces more efficient power density on a smaller surface. (Courtesy of Charles Breda.)

Joules and Power Density: A Dose and a Dosage? [13,74,89,90]

What is the equivalent of a drug prescription? [91]. Let's keep in mind this formula:

$$W = P \times TW\ (\mathrm{J/cm^2}) = P\ (\text{power})\ \mathrm{W/cm^2}\ \text{or}\ \mathrm{J/s/cm^2} \times T\ (\text{time})\ \text{second}$$

See Figure 38.10.

1. *Biphasic dose response* [13,74]: It appears that the release of the PBM process obeys its threshold dose/intensity. There is a *threshold value in deca and beyond it there is no response*. Worse, if the dose is too high, the effect will be negative. The calibration of the *optimum threshold parameter* for each indication is probably the research target for the next years (Figures 38.11 and 38.12).
2. The challenge is to bring together both *in vitro* and clinical studies [73–84].

WHAT ARE THE INDICATIONS?

Inflammation

Inflammation being the base of numerous pathologies is also present in dermatology. Treatment of radiation-induced mucositis of the aerodigestive tract [10–12,92–94] and leg ulcers (heavy economic burden worldwide [95–97], burns [98], and scars [95,99] (Figures 38.13 and 38.14).

Cicatrization Process Marks the Beginning of Modern Rejuvenation

Cicatrization process marks the beginning of modern rejuvenation (it is multifaceted): Chronic inflammation could be the common denominator. It has several levels and is undoubtedly very complex (Figure 38.15).

"Native" PBM uses the alternate set of deep red and near infrared [100–103].

In particular, the irradiation of human fibroblast *in vitro* culture by PBM-LED at 630 nm and 8 J/cm², 8 mW/cm², in some well-defined pulse parameters, optimized the production of type 1 procollagen. The time response (in hours) varies depending on the cell components; it could determine the distance between sessions [104–105].

In vivo, Daniel Barolet showed the importance of a certain pulsed mode of transmission in PBM. LED at 660 nm was used

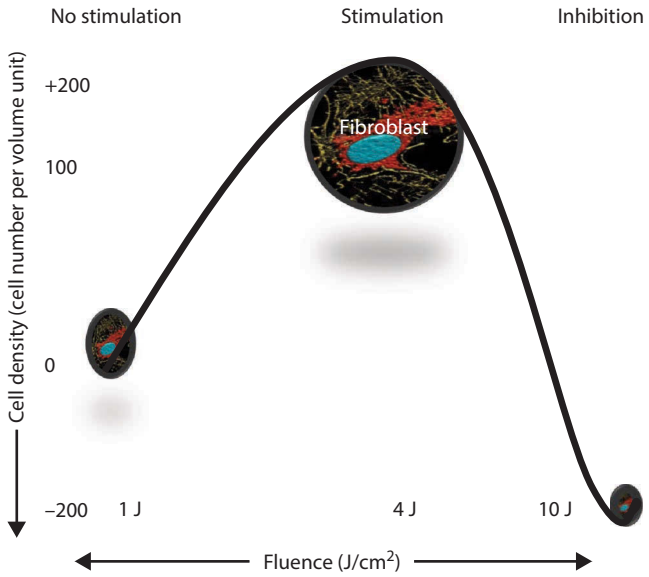


Figure 38.11 The Arndt–Shultz curve. It seems that the triggering of photobiomodulation process obeys dose/intensity thresholds. There is a threshold value deca and beyond which there will be no response. Worse, if dose is too high, the effect will be negative. The parameter-threshold setting optimum for each indication is undoubtedly a challenge for the future.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

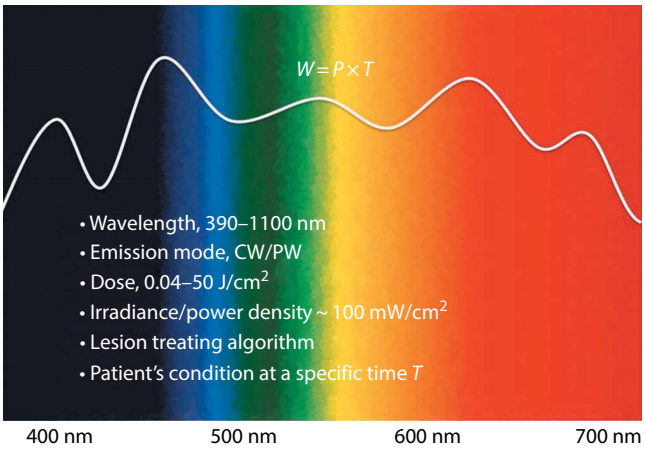


Figure 38.12 Estimated treatment parameters, allowing time *T*. The white line indicates the estimated power density/wavelength (WL) in a visible solar spectrum.

to increase the production of procollagen. It highlights the need for rest cycles in order to get proper cellular response [94].

The *cocicatrizing* PBM effect on CO_2 lasers and fractional ablative radio-frequency procedures is with a recovery time reduced by 50% [103,106,107] and with the reparation of the scarring of numerous dermatoses with a "rejuvenated" effect, for instance, acne, whose incidence is increasing, or burn healing (Figures 38.16 and 38.17).

Stretch Marks

The improvement of the quality of stretch marks despite the scarce information available today offers a promising field of work. The clinical analysis allows evaluating the color, depth, texture, length, and age:

- *Recent*: They have the appearance of fresh scars and are improved by protocols using parameters close to those used to treat inflammatory scars.
- *Old*: They make the object of several protocols used to date, most often combined together.
- It appears that creating a prior hyperemia and an inflammatory phase facilitates the impact of PBM [23].

An unpublished preliminary study (2011, S. Boisnic, M. Pelletier) was dedicated to the action of several wavelengths on the aspect of white stretch marks. Six fragments of abdominoplasty carrying stretch marks (kept alive) were submitted to eight PBM sessions of 84 J/cm² continuously at 415, 470, 590, and 633 nm.

The study revealed clinical repigmentation with an augmentation of melanin content and of the melanocyte numbers and the restructuring of the dermal–epidermal junction. The results obtained in the human clinic (on a small number of patients) seem to confirm these results (Figures 38.18 through 38.20).

Considering the presented clinical cases, we are confident that PBM certainly brings hope.

Persistent Psoriasis [77] (Figure 38.21)

Persistent psoriasis is considered as chronic inflammatory disease where skin is one of the major targets.

Visualizing an *immunological synapse* (the interaction between dendritic cells and T lymphocytes) allows understanding the possibility of a photon impact on the multiple signaling pathways of this vicious circle [108].

A preliminary study on 9 patients [90] reported the following effects of PBM 830 nm: 60 J/cm², 633 nm, 126 J/cm², 5 weeks, 10 sessions of 20 minutes each, and irradiance 105 mW/cm². It offered a solution for controlling inflammation with complete resorption of the plates before the end of the protocol.

"Coaching" Acne under a New Angle (Figure 38.22)

Acne is chronic inflammation of the pilosebaceous follicle involving innate immunity to propionibacterium acnes (PAs)—responsible for inflammatory lesions of sebum and blackheads. The hope brought by PBM comes from the understanding of its physiopathology [109].

PA maintains a vicious circle between the hyperseborrhea, sebum, and sebaceous glands. The alteration of the

(a) (b)

Figure 38.13 (a) Radio epithelitis. (b) Improved with four helium–neon photobiomodulation sessions. (Courtesy of J.R. Bensadoun—Gaston Ciais.)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 38.14 Healing of a varicose ulcer. (a) Female, 67 years old. After failure of other treatments, it was treated by phototherapy. (b) It was treated for 6 sessions, 15 days apart. The following are the involved parameters: continuous red light, 20 J during 10 minutes (from the first to fourth session). (c) Subsequently red and yellow pulsed, 20 J during 6 minutes, and, in addition, red continuous light, 20 J during 10 minutes (from the fifth to sixth session).

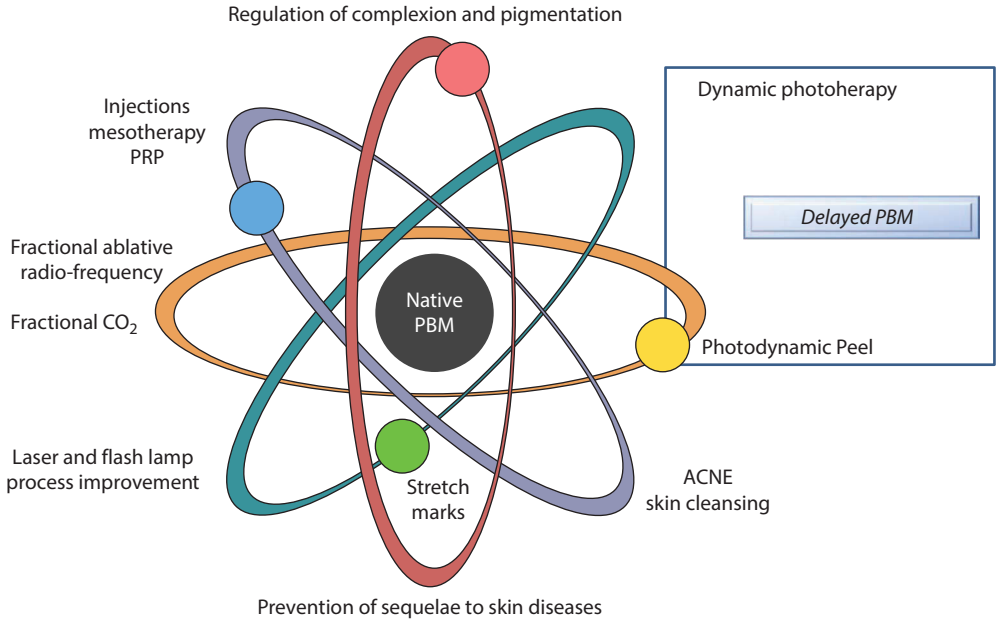


Figure 38.15 Kaleidoscopic rejuvenation. Photobiomodulation rejuvenation process can result from the following: (1) Native PBM (used alone). (2) Combined (different laser or radio-frequency techniques) with improvement of further session. (3) Enhancing injection procedures. (4) Aesthetic effect as a delayed effect of skin disease treatment (e.g., acne) or scar prevention. (5) Finally (in case of dynamic phototherapy or photodynamic peels), one can take advantage of clinical rejuvenation delayed effect.

sebum composition itself (modification of the report between squalene/linoleic acid/waxes, wax esters, and triglycerides) promotes its proliferation. It induces alteration in the keratinocyte maintaining and perpetuating the lesions. The sebaceous gland is an independent peripheral endocrine system equipped with receptors: it has decisive proinflammatory action.

"Propionibacterium Acne"

- Activates the production of proinflammatory cytokines such as IL1-alpha, IL8, IL2, GMCSF, and TNF-alpha by its action on the toll-like receptors, which are protectors of the physiological barriers but also independently by oxidative stress (apoptosis, necrosis of keratinocytes, and production of superoxide anions)
- Encourages the expression of antimicrobial peptides—players of the innate immunity
- Induces the secretion of metalloproteinase—endopeptidases responsible for the spread of inflammation

The *biofilm* [110], a factor of high resistance to the treatment, is a mixture of macrocolonies of PA surrounded by extracellular polysaccharides that adhere (organic adhesive) to the

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

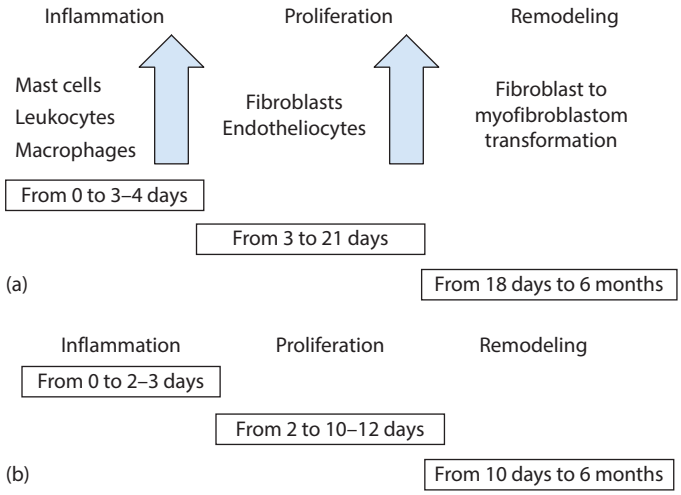


Figure 38.16 (a) The posttrauma wound healing process (b) is shortened with photobiomodulation. (Courtesy of Glen Calderhead.)

Figure 38.17 Antiaging effect (biological time): (a) Burn. (b) After 2 sessions, 1 week apart, red + yellow, 40 J, 10 minutes, 30 mW/cm^2.

keratinocytes and promote the formation of blackheads. Being able to penetrate more or less deeply into the skin (inner sheath follicle, hair shaft, and stratum corneum), it represents another barrier to wound healing. It is capable of expressing a virulence factor: cohemolysin CAMP factor (of different types), a factor of high resistance to treatments [111,112].

These physiopathological hypotheses allow us to point out the contribution of PBM: stimulation of innate immunity [98] by BPM.

One of the treatment targets is blocking the inflammation [113–117].

There are three welcomed actions: limit the PA production, lower the interleukin 8 production, and lower the postinflammatory pigmentation [118].

We can also identify some photobiomodulable clinical forms: inflammatory and moderate forms (papulopustular lesions) [113–116], but there is no effect on whiteheads and blackheads. The combined techniques including skin cleaning are very effective, as well as scar prevention, sun protection with rebounds, amelioration of already existing scars, and the acceleration of the treatments that target their reduction (fractional ablative laser and radio frequency).

PBM declines in both blue (bactericidal) [114,119,120] and in red/blue (anti-inflammatory and bactericidal) at 633 and 415 nm in alternating sessions twice a week for 1 month (the reduction of inflammation and antibacterial effect persist 2 months after the end of the treatment) [115]. The prescription of a home device [121] is recommended for maintaining the good results. It is a method of choice in the follow-up treatment of teenagers and is a part of combined therapy (ATB, retinoid). Its widespread effect on the skin is specific to this PBM treatment since it does not only exhibit a site-specific response; PBM involves the whole skin texture [109,116] and hydration, seborrhea, and melanin+++, which is visible 10 minutes after the end of the treatment.

Hair Growth

Hair growth takes advantage of the new available data for both the LBP mechanism [29,63] and hair growth cycles [29].

With the discovery of stem cell niches of the hair follicle and the impact of the photon on this surface at the molecular, cellular, and tissue levels.

Classically, a typical sequence of cyclic hair renewal has the following three unequal phases: *anagen* 3 years, *catagen* 3 weeks, and *telogen* 3 months, ignoring the processes that control

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

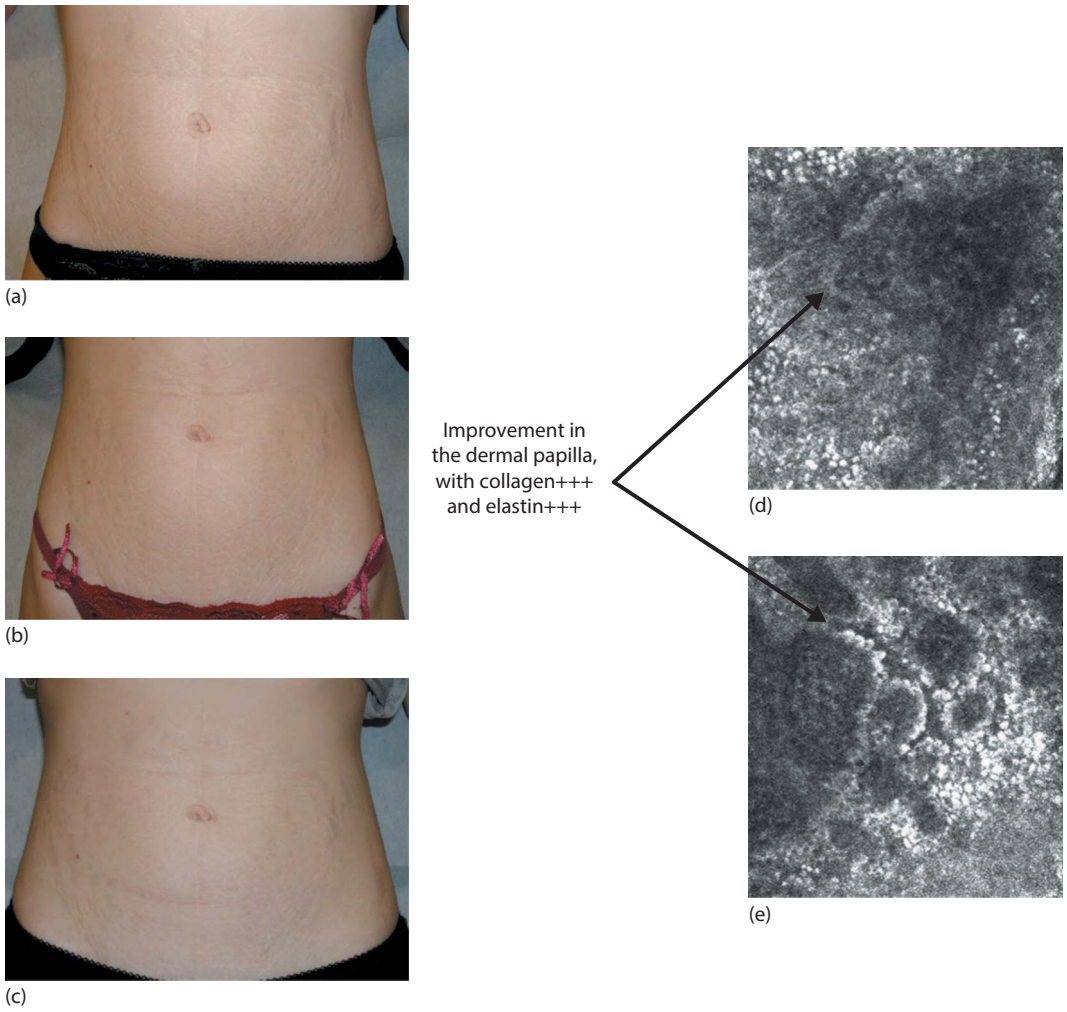


Figure 38.18 (a) Treatment for repulping of stretch marks (b, after four sessions; c, after 7 sessions). (d, e) Dermal rejuvenation process is also involved in stretch mark improvement (VivaScope images by courtesy of Dr. Linda Fouque, Vincience, and Gredeco Boisnic; Photos by Dr. Pelletier). Parameters: A total of 10 sessions, 2 sessions per week; red continues light, 80 J, 20 minutes, 100 mW/cm^2.

the intervention of oxygenation of the papilla of the bubbly capillary irrigation.

A novel vision seems necessary in order to take into account the asynchronous, independent, and somewhat random behavior of this structure especially during the catagen phase, where the hair follicle oscillates between two forms of *stability*. The stable anagen phase remains active, while the stable telogen phase stays *dormant*. The hair in the stable *dormant* metabolic phase remains the same after 3 months. It is at this stage of the cycle that the bulb activates. Between these two states, the catagen phase covers the involution at the end of which the bulbs are empty (kenogene phase) followed by the neogene phase preceding the next telogenesis where the hair is recovering and so on.

The hypoxic reserve will play an important role in the control of stem cell functions: At the bulb level, the niche of epithelial stem cells has two well-individualized compartments easily differentiated by the expression of certain markers (chemokines): hypoxic in the deep portion of the follicle and normoxic in the upper part under the sebaceous gland (bulge). The sites of stem cells and dermal papilla are interactive and act as *signaling tags*. During the telogen phase, the two reserves will merge responding to the activator signals emitted by the dermal papilla and initiate the neogene phase. The base of the bulb will activate under the influence of dermal mediators, which at their turn will activate the stem cells at the base of the bulb in hypoxia bringing them together with the overlying normoxic cells. This oxygenation will be determinant and the bulb will start a 3-year neogenesis phase with a stable active stage. At the end of neogenesis phase, the involution will restart, probably with hypoxia, in order to return to the telogenesis phase where the bulbs will be empty for three months and the cycle will begin again (Figure 38.23).

Androgenic alopecia, considered as an inflammatory disease of the hair follicle, is characterized by an increase in the duration of kenogene phase with an alteration of the deep reservoir of hypoxic environment. We can hypothesize about the impact of excessive inhibition of COX in the MTC (NO) respiratory chain in the genesis of chronic inflammation [122]. The role of the impact of the near-infrared illumination on the release of NO by the copper centers of COX is well known. The discovery of two different

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 38.19 Repigmentation essay for old white stretch marks in a 37-year-old female patient by pricking + phototherapy (4 colors, 32 J; then red + yellow 12 J during 6 minutes). (a) White stretch marks before treatment, (b) white stretch marks after microneedling, (c) white stretch marks after microneedling and one (four colors) PBM session, (d) skin smoothens after (four colors) four sessions PBM 3 weeks later, (e) visible smoothening of the skin 3 weeks later.

compartments of stem cells [29] in hair follicles can be a large avenue for hair growth treatment by varying their oxygen concentrations by the nitric oxide mechanism in COX [63,122,123].

PBM-LED offers several possibilities of treatment in the approach of the type of alopecia [124].

The most commonly used wavelengths are 633 nm [125] and the combination of wavelengths 633 and 850 nm, especially in the inflammatory diseases, where autoimmune pathologies are included (Figure 38.24).

PBM and Pigmentation

The pigmentary function supported by the melanocyte leads us to a necessary approach of the neural crest and its place of origin just before its embryonic migration in the epidermis and hair follicle.

Review of the Elements of Compared Physiology between the Skin and the Eye

1. *The visual function [126–128]* establishes the foundation for new data provided by the comparative analysis of dedicated photoreceptors [129]. We should remember that retinal photoreceptors (rods and cones) transform the light energy into electrical energy, a process known as visual transduction.

   The reactions break down into photochemical followed by electrophysiological reactions.

   Due to retinal (vitamin A aldehyde), photoreceptors (cones) convert the light into photoelectric signals. Retinal combines with a family of proteins named opsins, thus creating 4 types of pigments capable of absorbing different wavelengths of the visible light (400–700 nm). The illumination of this photoreceptor triggers the photo transduction: "Retinal 11 cis" links to *opsin*, it detaches itself and changes to a trans conformation when it absorbs a photon. Rhodopsin is also expressed in the rods. It is the hyperpolarization of the photoreceptor ending in the second stage by closing the sodium channels and inhibiting the neurotransmitters.

   Color vision incorporates an additive synthesis. A wavelength corresponds to a color, but not the reverse. The eye and the skin are sensors adapted to their function. (The skin does not perform additive synthesis.)
2. *Biological clock and the retinohypothalamic–sympathetic pathway*

A fourth type of retinal cone is a melanopsin photoreceptor [129]. It transmits light information from the retina to the central nervous system inducing circadian rhythms.

It regulates the rhythmic secretion (night) of melatonin by the pineal gland [22].

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

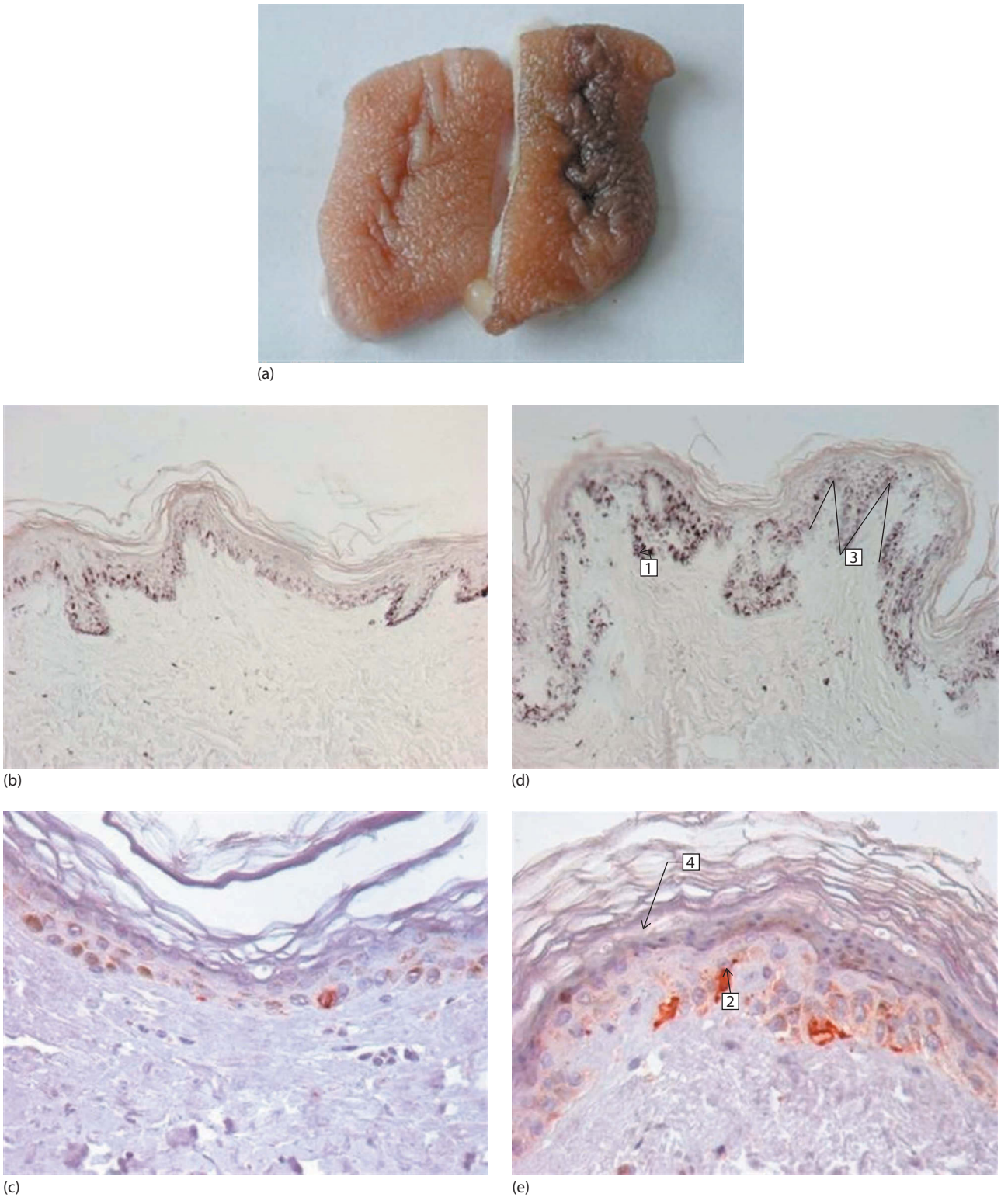
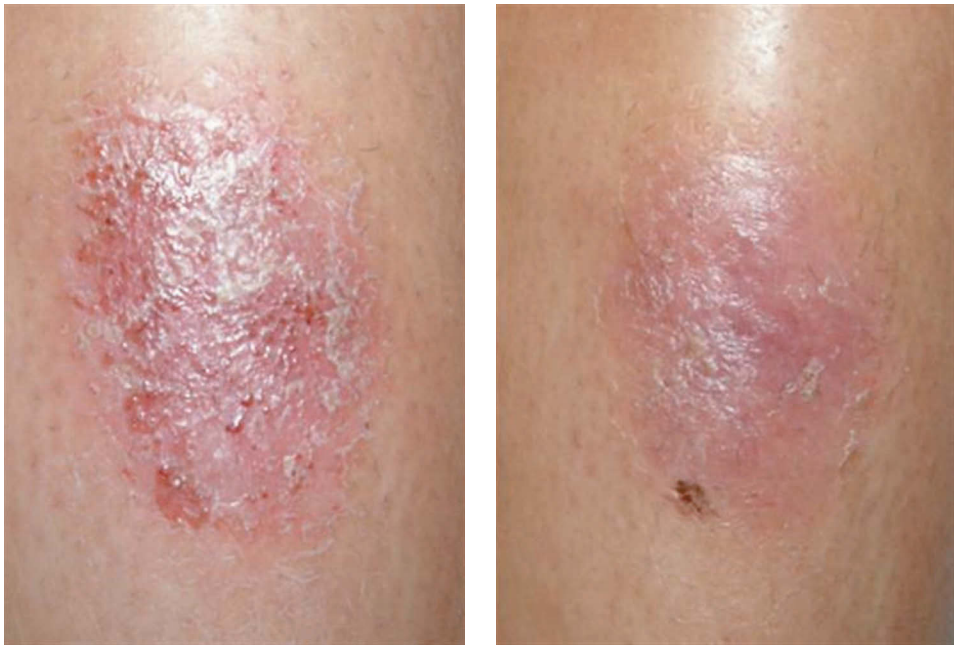


Figure 38.20 (a) Results of ex vivo and clinical study to repigment stretch marks with LED. Skin from abdominoplasty with two stretch marks. (b) After violet, blue, yellow, and red (84 J/cm^2, continuous 14 minute treatment period 100 mW/cm^2). (c–e) After PBM: rejuvenation repigmentation: (1) Increased melanin. (2) Numerous melanocytes. (3) Wavy dermoepidermal junction. (4) Thickened epidermidis. (Courtesy of Dr. Sylvie Boisnic and Dr. Michele Pelletier.)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b)

Figure 38.21 (a) Psoriasis in a 36-year-old patient. (b) After treatment, consisting of 4 colors, CW, 30 J, p3; then red + yellow pulsed, 12 J, 100 mW/cm^2.

(a) (b)

Figure 38.22 LED treatment can help where there has been (a) failure of other acne treatments. (b) Result after treatment with red + yellow, 24 J CW, 70 mW/cm^2 photobiomodulation, combined sessions with flash lamp (500–1100 nm).

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

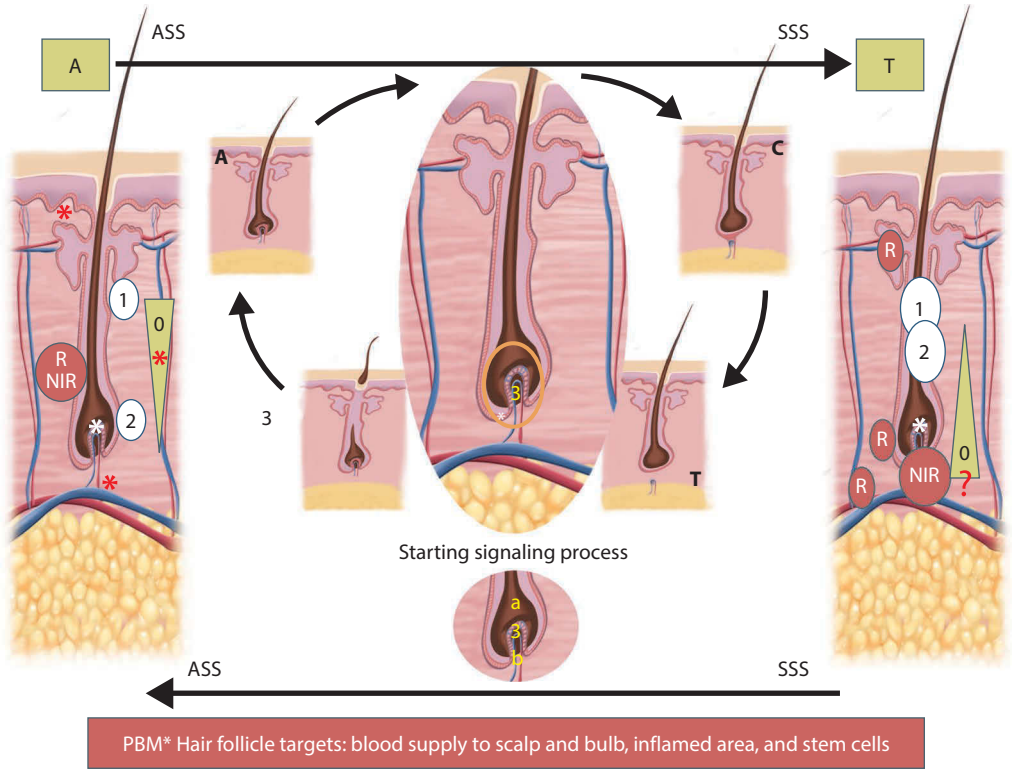


Figure 38.23 Photobiomodulation and the hair growth cycle (HGC): a new vision. HGC can be checked with molecular angle vision as "oxygen movements." The classic and formal description of three phases (A, C, T) is modulated. HC obeys a pendulum motion oscillating between two stable states (active and sleeping ones: ASS and SSS). Two different tanks (specific markers) of epithelial stem cells, immersed in an environment with low oxygen content for deeper and higher for the superficial one are involved in a cross-talk with the dermal papilla. The signal of the active phase (A) is triggered (oxygen pressure change). Change in the oxygen content by NIR-PBM (NO, COX) could represent a novel and innovative track for some alopecia treatment. On the other hand, the inflammation that underlies many diseases (AAG, telogen effluvium) benefits also red-PBM: initiating a phase (studies in progress). A, T, C, anagen, telogen, catagen phases; ASS, active steady state; SSS, sleeping steady state; R, red wavelength around 630 nm; NIR, near infrared around 830/650 nm; 1 SCN, pluripotent stem cell normoxic compartment; 2 SCH, pluripotent stem cell hypoxic compartment; 3, area of activity and start of signaling process; [02], oxygen pressure; a, conjunctive sheath; b, dermal papillae.

Toward Skin Retina? [130,131]

PBM needs photoacceptors.

Several authors reported the presence of nonvisual receptors in the human body [130]. The skin is sensitive to visible light: it responds to red (550–670 nm) for repairing an altered epidermal barrier; the reparation is delayed by blue (430–510 nm). The precise topography of "rhodopsin-like proteins" in the upper layer of the epidermis and the "S-opsin-like proteins" in the lower layer suggests their respective sensitivity for shorter or longer wavelengths. With a preferential localization on the keratinocytes of the exposed areas [131], the quality of the *cross-talk* between the keratinocytes and dermal fibroblasts determines their expression. The immediate pigmentation after sun exposure (UVA 320–400 nm) could be due to an increased and precocious (a few hours) synthesis of a retinal-dependent melanin, with the mobilization of intracellular Ca^{++} and the expression of a "G-protein-coupled receptor rhodopsin" inside the melanocyte. It could be nonvisual phototransduction.

Melanocyte photosensory system in the human skin [132].

A study conducted on the melanophores of the photosensitive *Xenopus laevis* frog led to the identification of the melanocyte photosensory system (MPS) concept: a cutaneous organized system of photoreception complete with pigment synthesis, biogenic amines, and hormones after UV exposure.

Melanocyte network: Keratinocytes, dermal capillaries, and nerve termination are embedded and involved in an interconnected signaling network. It deciphers the diurnal and seasonal cycles by the same principle as the biological clock and the melatonin secretion by the pineal gland. Its distribution (along the dermatomes) testifies about its embryonic origin (the neural crest).

The melanocyte after irradiation (UV irradiation in G2 phase) extends its dendrites toward the keratinocytes via intercellular spaces and desmosomes like an optical fiber [132].

Melanin is a dark pigment found in the human retina and skin.

We can deduce in a predictive manner the absorption coefficients (600–700 nm) and the melanin "scattering" for the transport of light through a pigmented tissue. Calculating the depth of penetration and predicting the necessary irradiance are essential for a clinical effect. Its absorption coefficient depends on its redox state [133].

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 38.24 Clinical results in hair treatment. (a) Before treatment: female patient, 40 years old, with androgenic alopecia. (b) After treatment with red CW 70 J/cm² 10 mW/cm², 12 sessions, 20 minutes each (twice a week).

Table 38.1 LED Parameters for Various Applications Used in our Practice

Applications	WL (nm)	X treatments	Irradiance (mW/cm²)	Fluence (J/cm²)	Time treatment (min/s)	Interval TT time (hours)	Mode (PW/CW)
Sunburn prevention	660–970	ad 7	50	4	2:40–15	24–48	Sequential PW/CW
PIH Prevention	870–970	ad 8	50–80	45–96	15–20	24–48	Sequential PW/CW
Photo preparation	870–970	3 (before every PDT treatment)	>80	72–100	15	24	CW
Photo regulation	660–850	Long term	8–50	4–7.5	5–16	24–48	Sequential PW

Source: Adapted from Barolet D, *Semin Cutan Med Surg*, 27, 227, 2008.
Notes: Sunburn, PIH methods = photoprophylaxis. Photoprophylaxis is not the equivalent of photoprevention. Photoprevention is a much more general term that encompasses photoprophylaxis. LED treatments should be preferably performed a week before UV insult or skin trauma to better prevent sunburn or PIH, respectively.

PBM and Pigmentation Disorders

1. *Postinflammatory pigmentation*: It is a common disabling squeal of some inflammatory processes such as sunburn, infections, phototoxic eruptions, allergic reactions, trauma, acne, lupus, and lichen [134] often related to basal cell damage and disruption of the dermal–epidermal junction. It greatly benefits from the PBM [23,118,135] at different wavelengths. Two-wavelength combinations in particular have an effect on cell viability at two levels: epidermic at 590/633 with a better quality of dermoepidermal junction (reformed dermal papillae), with a configuration similar to the honeycombs observed by confocal microscopy 3 months after simultaneous irradiation in red and yellow [135], and dermic at 650/850 nm boosting the first cicatrization phase [23]. Daniel Barolet outlines a photo prevention (photoprophylaxis) strategy [136,137]. More global photo prevention with LLLT can be the next challenge for preventive medicine [138] (Table 38.1).

   This action may pass through a signaling channel of the tumor suppressor protein P53 that could trigger DNA repair, apoptosis, or cell cycle arrest [139]. It enhances the UV-induced pigmentation and acts on the cytokines of the keratinocyte and melanocyte melanogenesis. This translates into pigmented spots. The near-infrared in PBM could modulate this signaling pathway [136].
2. *Pigmentation and visible light [140]*: The impact on the prevention of photo-induced pigmentation [73,79].
   Typically [139], solar pigmentation is induced by UVB [141]. The use of blue-violet light at 415 nm triggers rapid hyperpigmentation (2 hours), more sustained and durable up to 3 months and less deleterious (less keratinocyte necrosis and P53 expression).
3. *Melasmas and postinflammatory pigmentations*: These may benefit from a screen able to target these short wavelengths daily [139]. The same wavelength (470 nm) with different parameters can induce a unified complexion and sometimes the lightening of the illuminated area [46,118].
4. *PBM and vitiligo*: This achromia is written in the autoimmune profile [142]. Keratinocyte-derived cytokines could make a target for preventing apoptosis in depigmented area in PBM [143]. It undoubtedly involves other ways of

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 38.25 R+IR 102 mJ/s/cm² for 10′35″/Y 60 mJ/s/cm² for 5′35″. (a) Before and (b) after 6 sessions, 1 week apart. (Courtesy of Dr. Suzanne Hausdorfer.)

regimentation than the cited wavelengths. Encouraging results have been obtained with red irradiation at 633 nm [144] and 850 nm and partial regimentation. Various studies are in process [145] (Figure 38.25).

CONCLUSION

Mitochondria through the electron transfer chain are one of the PBM targets but the cell still encloses countless enigmas. The impact of PBM on signaling opens new directions of research orientated toward the cellular dialogue: "cross-talk." Like the letters of a universal alphabet, it can form specific words once they reach the receiver. DPM opens a new approach on skin very different from that of the twentieth century. It sends us back to the embryonic origin by its peculiar photo receptivity, giving a new and different meaning to our body wrap: *an ultrasensitive vibrating plate*.

Many thanks to Cristina Barsan, Charles Breda, Dr. Freddy Chiche, and Pierre Jacquier for their valuable advice.

REFERENCES

1. Roelandts R. The history of phototherapy: Something new under the sun? *Am Acad Dermatol* 2002; 926–930.
2. Grzybowski A, Pietrzak K. From patient to discoverer—Niels Ryberg Finsen (1860–1904)—The founder of phototherapy in dermatology. *Clin Dermatol* 2012; 30:451–455.
3. Finsen NR. La Photothérapie. Publication du Finsen' medicinske Lisinstitut de Copenhague. San Francisco, CA: Lne Medical Library, 1899.
4. Mester EA. The biomedical effect of laser application. *Lasers Surg Med* 1985; 5(1):31–39.
5. Ho MW, Popp FA, Warnke U. *Bioelectrodynamics and Biocommunication*. Singapore: World Scientific Publishing, 1994.
6. Popp FA, Beloussov L. *Integrative Biophysics Biophotonics*. Dordrecht, the Netherlands: Kluwer Academic Publishers, 2010.
7. Bischof M. Semiconductivity in living cells. December 1, 2012, Strasbourg, France.
8. Tafur J, Van Wijk EPA, Van Wijk R et al. Biophoton detection and low-intensity light therapy: A potential clinical partnership. *Photomed Laser Surg* 2010 February; 28(1):23–30.
9. Whelan HT, Smits RL, Buchman EV et al. Effect of NASA light-emitting diode irradiation on wound healing. *J Clin Laser Med Surg* 2001; 19:305–314.
10. Bensadoun RJ. *Les mucites chimio et radio-induites: Du préventif aucuratif*. Saint Rémy de Provence, France, June 3, 2012.
11. Bensadoun RJ. *A Systematic Review of Low Level Laser Therapy (LLLT) in Cancer Therapy-Induced Oral Mucositis*. Saint Rémy de Provence, France, June 3, 2012.
12. Bjordal JM, Bensadoun RJ, Turner J, Frigo L, Gjerde K, Lopes-Martins RA. A systematic review with meta-analysis of the effect of low-level laser therapy (LLLT) in cancer therapy-induced oral mucositis. *Support Care Cancer* 2011 August; 19(8):1069–1077.
13. Sommer AP, Pinheiro A, Mester AR et al. Biostimulatory windows in low-intensity laser activation: Lasers, scanners and NASA's light-emitting diode array system. *J Clin Laser Med Surg* 2001; 19:29–33.
14. Whelan HT, Houle JM, Whelan NT et al. The NASA light-emitting diode medical program—Progress in space flight and terrestrial applications. *Space Technol Appl Int Forum* 2000; 504:37–43.
15. Whelan HT, Buchmann EV, Whelan NT et al. NASA light emitting diode medical applications from deep space to deep sea. *Space Technol Appl Int* 2001; 552:35–45.
16. Valeur B. *Lumière et luminescence*. Paris, France: Editions Belin-Pour la science, 2005.
17. Champion C. Interaction des ondes et des particules avec la matière biologique, pp. 1–31.
18. Jenkins PA, Carrol JD. How to report low-level laser therapy (LLLT)/photomedicine dose and beam parameters in clinical and laboratory studies. *Photomed Laser Surg* 2011; 29:785–787.
19. Castello PR, David PS, McClure T, Crook Z, Poyton RO. Mitochondrial cytochrome oxidase produces nitric oxide under hypoxic conditions: Implications for oxygen sensing and hypoxic signaling in eukaryotes. *Cell Metab* 2006; 3:277–287.
20. Rubinov AN. Physical grounds for biological effect of laser radiation. *J Phys D Appl Phys* 2003; 36:2317–2330.
21. Hode L. Letter to the editor: The importance of the coherency. *Photomed Laser Surg* 2005; 23:431–434.
22. Duforez F. *Modes d'action et Indication de Various WL on Biological Clock*. Paris, France, September 2014.
23. Calderhead G. The conundrum of LED phototherapy. *Inflammation, Healing and Photobiomodulation*, Paris, France, December 7, 2013.
24. Arodz T, Bonchev D, Diegelmann RF. A network approach to wound healing. *Adv Wound Care* 2013; 2:499–509.
25. Calderhead RG. Light emitting diode phototherapy in dermatology practice. In: Nouri K, ed., *Lasers in Dermatology and Medicine*. London, U.K.: Springer, 2011, p. 253.
26. Grimaud JA. Cell biology research on skin ageing: A dermo-epidermal crosstalk? *Inflammation, Healing and Photobiomodulation*, Paris, France, December 7, 2013.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

27. Calderhead RG, Trelles MA. Phototherapy unveiled: A review of the photobiological basics behind athermal photobiomodulation with lasers and other light sources. *Laser Ther* 2005; 14:87–95.
28. Uitto J. IL-6 signaling pathway in keloids: A target for pharmacologic intervention? *J Invest Dermatol* 2007; 127:6–846.
29. Bernard A, Rathman-Jossearand M. La niche du follicule pileux humain, un environnement hypoxique? *Annales de dermatologie et de vénéréologie* 2013; 140:5–8.
30. Piazzini DB, Aprile I, Ferrara PE et al.: A systematic review of conservative treatment of carpal tunnel syndrome. *Padua L Clin Rehabil* 2007; 21:299–314.
31. Joyce KM, Downes CS, Hannigan BM. Radio adaptation in Indian muntjac fibroblast cells induced by low intensity laser irradiation. *Mutat Res* 1999; 435(1):35–42.
32. Frare JC, Nicolau RA. Clinical analysis of the effect of laser PBM (GaAs—904 nm) on temporomandibular joint dysfunction. *Rev Bras Fisioter* 2008; 12(1):37–42.
33. Jiang JA, Chang WD, Wu JH, Lai PT, Ling HY. Low level laser treatment relieves pain and neurological symptoms in patients with carpal tunnel syndrome. *J Phys Ther Sci* 2011; 23:661–665.
34. Naeser MA. PBM of pain in carpal tunnel syndrome: Review of seven laser therapy studies. *Photomed Laser Surg* 2006; 24:101–110.
35. Kulekcioglu S, Sivrioglu K, Ozcan O, Parlak M. Effectiveness of low-level laser therapy in temporomandibular disorder. *Scand J Rheumatol* 2003; 32:114–118.
36. Kato MT, Kogawa EM, Santos CN, Conti PCR. TENS and low-level laser therapy in the management of temporomandibular disorders. *J Appl Oral Sci* 2006; 14(2):130–135.
37. Fikackova H, Dostalova L, Vosicka R, Peterova V, Navratil L, Lesak J. Arthralgia of the temporomandibular joint and low-level laser therapy. *Photomed Laser Surg* 2006; 24(4):522–527.
38. Gam AN, Thorsen H, Lonnberg F. The effect of low-level laser therapy on musculoskeletal pain: A meta-analysis. *Pain* 1993; 52(1):63–66.
39. Gur A, Sarac AJ, Cevik R, Altindag O, Sarac S. Efficacy of 904 nm GaAs low level laser therapy in the management of chronic myofascial pain in the neck: A double-blind and randomize-controlled trial. *J Clin Laser Med Surg* 2004; 35(3):229–235.
40. Bjordal JM, Johnson MI, Iversen V et al. Low-level therapy in acute pain: A systematic review of possible mechanisms of action and clinical effects in randomized placebo-controlled trials. *Photomed Laser Surg* 2006; 24:158–168.
41. Araujo BF, Silva LI, Meireles A et al. Effects of low-level laser therapy, 660 nm, in experimental septic arthritis. *ISRN Rheumatol* 2013; 2013:1–8.
42. Soriano F, Campana V, Moya M, Gavotto A, Simes J, Soriano M, Soriano R, Spitale L, Palma J. Photobiomodulation of pain and inflammation in microcrystalline arthropathies: Experimental and clinical results. *Photomedi Laser Surg* April 2006; 24(2):140–150.
43. Ferreira DM, Zangaro RA, Villaverde AB et al. Analgesic effect of He-Ne (632.8 nm) low-level laser therapy on acute inflammatory pain. *Photomed Laser Surg* 2005; 23:177–181.
44. Enwemka CS. Intricies of dose in laser phototherapy for tissue repair and pain relief. *Photomed Laser Surg* 2009; 27:387–393.
45. Rojas JC, Gonzales-Lima F. Low-level light therapy of the eye and brain. *Eye Brain* 2011; 3:49–67.
46. Avci P, Gupta A, Sadasivam M et al. Low-level laser (Light) therapy (LLLT) in skin: Stimulating, healing, restoring. *Semin Cutan Med Surg* 2013; 32:41–52.
47. Karu TI. Past, present and future of LLLT in medical sciences: Cellular mechanisms behind the clinical findings. Bruxelles, Belgium, March 9, 2013.
48. Karu T. Mitochondrial signaling in mammalian cells activated by red and near-IR radiation. *Photochem Photobiol* 2008; 84:1091–1099.
49. Karu T. *Ten Lectures on Basic Science of Laser Phototherapy*. Grangesberg, Sweden: Prima Books, 2007.
50. Goldenthal MJ, Marín-García J. Mitochondrial signaling pathways: A receiver/integrator organelle. *Mol Cell Biochem* 2004; 262(1–2):1–16.
51. Poyton RO, Ball KA. Therapeutic PBM: Nitric oxide and a novel function of mitochondrial cytochrome c oxidase, discovery medicine. *Discov Med* 2011; 57:154–159.
52. Karu T. Laser biostimulation: A photobiological phenomenon. *J Photochem Photobiol B* 1989; 3:638–640.
53. Hamblin MR, Demidova TN. Mechanisms of low level light therapy. *Proc SPIE* 2006; 6140:614001-1–12.
54. Eells JT, Wong-Riley MTT, VerHoeve J et al. Mitochondrial signal transduction in accelerated wound and retinal healing by near-infrared light therapy. *Mitochondrion* 2004; 4:559–567.
55. Pastore D, Greco M, Passarella S. Specific helium-neon laser sensitivity of the purified cytochrome c oxidase. *Int J Rad Biol* 2000; 76:863–870.
56. Karu TI. Multiple roles of cytochrome c oxidase in mammalian cells under action of red and IR-A radiation. *IUBMB Life* 2010; 62:607–610.
57. Poyton RO, Ball KA, Castello PR. Mitochondrial generation of free radicals and hypoxic signaling. *Trends Endocrinol Metab* 2009; 20:332–340.
58. Moriyama Y, Nguyen J, Akens M, Moriyama EH, Lilge L. In vivo effects of low level laser therapy on inducible nitric oxide synthase. *Lasers Surg Med* 2009; 41:227–231.
59. Zhang R, Mio Y, Pratt PF, Lohr N, Warltier DC, Whelan HT, Zhu D, Jacobs ER, Medhora M, Bienengraeber M. Near infrared light protects cardiomyocytes from hypoxia and reoxygenation injury by a nitric oxide dependent mechanism. *J Mol Cell Cardiol* 2009; 46:4–14.
60. Ball KA, Castello PR, Poyton RO. Low intensity light stimulates nitrite-dependent nitric oxide synthesis but not oxygen consumption by cytochrome c oxidase: Implications for phototherapy. *J Photochem Photobiol B Biol* 2011; 102(3):182–191.
61. Shiva S, Oh JY, Landar AL, Ulasova E, Venkatraman A, Bailey SM, Darley-Usmar VM. Nitroxia: The pathological consequence of dysfunction in the nitric oxide–cytochrome c oxidase signaling pathway. *Free Radic Biol Med* 2005; 38:297–306.
62. Brown GC, Cooper CE. Nanomolar concentrations of nitric oxide reversibly inhibit synaptosomal respiration by competing with oxygen at cytochrome oxidase. *FEBS Lett* 1994; 356:295–298.
63. Antunes F, Boveris A, Cadenas E. On the mechanism and biology of cytochrome oxidase inhibition by nitric oxide. *Proc Natl Acad Sci USA* 2004; 101:16774–16779.
64. Keszler A, Brandal G, Baumgardt S, Ge ZD, Pratt PF, Riess ML, Bienengraeber M. Far-red/near-infrared light-induced protection against cardiac ischemia and reperfusion injury remains intact under diabetic conditions and is independent of nitric oxide synthase. *Front Physiol* 2014; 5:305.
65. Lindgard A, Hulten LM, Svensson L, Soussi B. Irradiation at 634 nm releases nitric oxide from human monocytes. *Lasers Med Sci* 2007; 22:30–36.
66. Nicholls DG. Mitochondria and calcium signaling. *Cell Calcium* 2005; 38(3–4):311–317.
67. Collins Y, Chouchani ET, James AM et al. Mitochondrial redox signalling at a glance. *J Cell Sci* 2012; 125:801–806.
68. Khakh BS, Burnstock G. The double life of ATP. *Sci Am* 2009; 12:84–92.
69. Whelan SP, Zuckerbraun BS. Mitochondrial signaling: Forwards, backwards, and in between. *Oxid Med Cell Longev* 2013; 2013:351613.
70. Poburko D, Demaurex N. Regulation of the mitochondrial proton gradient by cytosolic Ca^{2+} signals. *Eur J Physiol* 2012; 464:19–26.
71. Poburko D, Santo-Domingo J, Demaurex N. Dynamic regulation of the mitochondrial proton gradient during cytosolic calcium elevations. *J Biol Chem* 2011; 286(13):11672–11684.
72. Karu T. Mitochondrial mechanisms of photobiomodulation in context of new data about multiple roles of ATP. *Photomed Laser Surg* 2010; 28:159–160.
73. Barolet D. Light-emitting diodes (LEDs) in dermatology. *Semin Cutan Med Surg* 2008; 27:227–238.
74. Huang YY, Chen CH, Carroll JD, Hamblin MR. Biphasic dose response in low level light therapy. *Dose Response* 2009; 7(4):358–383.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

75. Rochkind S, Rousso M, Nissan M et al. Systemic effects of low-power laser irradiation on the peripheral and central nervous system, cutaneous wounds, and burns. *Laser Surg Med* 1989; 9:174–182.
76. Touseau C. *La Technologie LED Conference*, Strasbourg, France, December 1, 2012.
77. Ablon G. Combination 830-nm and 633-nm light-emitting diode phototherapy shows promise in the treatment of recalcitrant psoriasis: Preliminary findings. *Photomed Laser Surg* 2010; 28(1):141–146.
78. Al-Watban AH, Zhang XY. The acceleration of wound healing is not attributed to laser skin transmission. *Laser Ther* 1999; 11(1):6–10.
79. Farouk A, Al-Watban H, Zahang XY. The comparison of effects between pulsed and CW lasers on wound healing. *J Clin Laser Med Surg* 2004; 22:1–79.
80. Hashmi JT, Huang YY, Sharma SK et al. Effect of pulsing in low-level light therapy. *Laser Surg Med* 2010; 42:450–466.
81. Chow R, Armati P, Laakso EL et al. Inhibitory effects of laser irradiation on peripheral mammalian nerves and relevance to analgesic effects: A systematic review. *Photomed Laser Surg* 2011; 29:365–381.
82. Karu T. Primary and secondary mechanisms of action of visible to near-IR radiation on cells. *J Photochem Photobiol B Biol* 1999; 49:1–17.
83. Calderhead RG. Healite II with photosequencing technology: A novel phototherapeutic approach involving photosequencing with 590 nm and 830 nm LED energy: Preconditioning 590 nm micro-low level light therapy (μ-LLLT) in combination with 830 nm LED phototherapy. Lutronic, Fremont, CA, 2011.
84. Schettino G, Folkard M, Prise KM, Vojnovic B, Held KD, Michael BD. Low-dose studies of bystander cell killing with targeted soft x rays. *Radiat Res* 2003; 160:505–511.
85. Calderhead RG, Omi T. Light-emitting diode phototherapy. In: Nouri K, ed., *Handbook of Lasers in Dermatology*. London, U.K.: Springer, 2014.
86. Schindl A, Heinze G, Schindl M et al. Systemic effects of low-intensity laser irradiation on skin microcirculation in patients with diabetic microangiopathy. *Microvasc Res* 2002; 64:240–246.
87. Rodrigo SM, Cunha A, Pozza DH et al. Analysis of the systemic effect of red and infrared laser therapy on wound repair. *Photomed Laser Surg* 2009; 27:929–935.
88. Michele P. The photobioflexible field. *AMWC*, Monaco, France, April 2014.
89. Smith KC. Laser and led photobiology. *Laser Ther* 2010; 19(2):72–78.
90. Karu T. Is it to consider photobiomodulation as a drug equivalent? *Photomed Laser Surg* 2013; 31:1–3.
91. Hawkins D, Abrahamse H. Effect of multiple exposures of low-level laser therapy on the cellular responses of wounded human skin fibroblasts. *Photomed Laser Surg* 2006; 24:705–714.
92. Bensadoun RJ, Ciais G. Radiation-and chemotherapy-induced mucositis in oncology: Results of multicenter phase III studies. *J Oral Laser Appl* 2002; 2:115–120.
93. Bensadoun RJ, Nair RG. Low level laser therapy in the prevention and management of oral mucositis induced by cancer treatments: Evidence-based data from randomized studies and meta-analyses. *Curr Opin Oncol* 2012 July; 24(4):363–370.
94. Bensadoun RJ, Lepage F, Darcourt V et al. Mucite radio-induite des voies aérodigestives: Prévention et prise en charge: Recommandations du groupe Mucites MASCC/ISOO. *Bull Cancer* 2006; 93:1–11.
95. Fulop AM, Dhimmer S, Deluca JR, Johanson DD, Lenz RV, Patel KB, Douris PC, Enwemeka CS. A meta-analysis of the efficacy of phototherapy in tissue repair. *Photomed Laser Surg* 2009 October; 27(5):695–702.
96. Caetano KS, Frade MAC, Minatel DG et al. Phototherapy improves healing of chronic venous ulcers. *Photomed Laser Surg* 2009; 27:111–118.
97. Fujimura T, Mitani A, Fukuda M et al. Irradiation with a low-level diode laser induces the developmental endothelial locus-1 gene and reduces proinflammatory cytokines in epithelial cells. *Laser Med Sci* 2014 May; 29(3):987–994.
98. Renno ACM, Iwama AM, Shima P et al. Effect of low-level laser therapy (660 nm) on the healing of second-degree skin burns in rats. *J Cosmet Laser Ther* 2011; 13:237–242.
99. Woodruff LD, Bounkeo JM, Brannon WM et al. The efficacy of laser therapy in wound repair: A meta-analysis of the literature. *Photomed Laser Surg* 2004; 22:241–247.
100. Takesaki S, Omi T, Sato S et al. Ultrastructural observations of human skin following irradiation with visible red light-emitting diodes (LEDs): A preliminary in vivo report. *Laser Ther* 2005; 14.4:153–160.
101. Lee SY, Park KH, Choi JW et al. A prospective, randomized, placebo-controlled, double-blinded, and split-face clinical study on LED phototherapy for skin rejuvenation: Clinical, profilometric, histologic, ultrastructural, and biochemical evaluations and comparison of three different treatment settings. *J Photochem Photobiol B Biol* 2007; 88:51–67.
102. Fisher GJ, Kang S, Varani J et al. Mechanisms of photo aging and chronological skin aging. *Arch Dermatol* 2002; 138:1462–1470.
103. Russsel BA, Kellett N, Reilly LR. A study to determine the efficacy of combination LED light therapy (633 nm and 830 nm) in facial skin rejuvenation. *J Cosmet Laser Ther* 2005; 7:196–200.
104. Barolet D, Boucher A, Bjerring P. In vivo human dermal collagen production following LED-based therapy: The importance of treatment parameters. *ASLMS Meeting*, 2005, Orlando, FL.
105. Barolet D, Duplay P, Jacomy H et al. Importance of pulsing illumination parameters in low-level-light therapy. *J Biomed Opt* 2010 July–August; 15(4):048005.
106. Calderhead RG, Kubota J, Trelles MA et al. One mechanism behind LED phototherapy for wound healing and skin rejuvenation: Key role of the mast cell. *Laser Ther* 2008; 17:141–148.
107. Herascu N, Velciu B, Calin M et al. Low-level laser therapy (LLLT) efficacy in post-operative wounds. *Photomed Laser Surg* 2005; 23:70–73.
108. Nosbaum A, Nicolas JF. Physiopathologie du psoriasis. In *Guide*: *European Journal of Dermatology*, Libbey J (ed.), Eurotext, p. 7.
109. Dreno B, Auffret N, Revuz J et al. Quoi de neuf dans l'acné. *Annales de dermatologie et de vénéréologie* 2010; 137:S47–S85.
110. Garcez AS, Nunez SC, Azambuja N et al. Effects of photodynamic therapy on gram-positive and gram-negative bacterial biofilms by bioluminescence imaging and scanning electron microscopic analysis. *Photomed Laser Surg* 2013; 31:519–525.
111. Jones CE, Kennedy JP. Treatment options to manage wound biofilm. *Adv Wound Care* 2012; 1:120–126.
112. Jahns AC, Lundskog B, Ganceviciene R et al. An increased incidence of Propionibacterium acnes biofilms in acne vulgaris: A case-control study. *Br Assoc Dermatol* 2012; 167:50–58.
113. Papageorgiou P, Katsambas A, Chu A. Phototherapy with blue (415 nm) and red (660 nm) light in the treatment of acne vulgaris. *Br J Dermatol* 2000; 142:973–978.
114. Tzung TY, Wu KH, Huang ML. Blue light phototherapy in the treatment of acne. *Photodermatol Photoimmunol Photomed* 2004; 20:266–269.
115. Goldberg DJ, Russell BA. Combination blue (415 nm) and red (633 nm) LED phototherapy in the treatment of mild to severe acne vulgaris. *J Cosmet Laser Ther* 2006; 8:71–75.
116. Lee SY, You CE, Park MY. Blue and red light combination LED phototherapy for acne vulgaris in patients with skin phototype IV. *Lasers Surg Med* 2007; 39:180–188.
117. Gordon YJ, Huang LC, Romanowski EG, Yates KA. Human cathelicidin (LL-37), a multifunctional peptide, is expressed by ocular surface epithelia and has a potent antibacterial and antiviral activity. *Curr Eye Res* 2006 May; 30(5):385–394.
118. Chabert R, Fouque-Parachini L, Pinacolo S et al. How blue LED wavelengths can be effective on acne disorders? *J Invest Dermatol* 2013 April 15; 133:S104–S128.
119. Bumah VV, Masson-Meyers DS, Cashin SE et al. Wavelength and bacterial density influence the bactericidal effect of blue light on methicillin-resistant Staphylococcus aureus (MRSA). *Photomed Laser Surg* 2013; 31:547–553.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

120. Enwemeka CS. Antimicrobial blue light: An emerging alternative to antibiotics. *Photomed Laser Surg* 2013; 31:509–511.
121. Gold MH, Andriessen A, Biron J et al. Clinical efficacy of self-applied blue light therapy for mild-to-moderate facial acne. *Dermatology* 2009; 2:44–50.
122. Zhang R, Mio Y, Pratt PF et al. Near infrared light protects cardiomyocytes from hypoxia and reoxygenation injury by a nitric oxide dependent mechanism. *J Mol Cell Cardiol* 2009; 46:4–14.
123. Tuby H, Maltz L, Oron U. Implantation of low-level laser irradiated mesenchymal stem cells into the infarcted rat heart is associated with reduction in infarct size and enhanced angiogenesis. *Photomed Laser Surg* 2008; 27:227–234.
124. Haushofer S. Photobiostimulation on hair growth with a LED device. *Laser Europe Conference*, May Amsterdam, the Netherlands, 22–23, 2014.
125. Benedicenti A. La biostimulation du cuir chevelu par la lumière Laser—HeNe 632,8. *Communication Congrés*, Syracuse, NY, May 5, 1983.
126. Déribéré M. *La Couleur*. Paris, France: Presse Universitaire de France, 1985.
127. Baumgardt E. *La Vision*. Paris, France: Presse Universitaire de France, 1962.
128. Bouma PJ. *Les Couleurs et leur Perception Visuelle*. Eindhoven, the Netherlands: N.V. Philips Gloeilampenfabrieken, 1949.
129. Traitement rétinien de la vision Photorécepteurs: Photo transduction (documentation internet).
130. Wicks NL, Chan JW, Najera JA et al. UVA phototransduction drives early melanin synthesis in human melanocytes. *Curr Biol* 2011; 21:1906–1911.
131. Tsutsumi M, Ikeyama K, Denda S et al. Expressions of rod and cone photoreceptor-like proteins in human epidermis. *Exp Dermatol* 2009; 18:567–570.
132. Iyengar B. The melanocyte photosensory system in the human skin. *SpringerPlus* 2013; 2:158.
133. Sardar DK, Mayo ML, Glickman RD. Optical characterization of melanin. *J Biomed Opt* 2001; 6:404–411.
134. Ortonne JP, Krieger L, Berneburg M et al. Tour du monde de l'hyperpigmentation. *Annales de dermatologie et de vénéréologie* 2012; 139:S73–S124.
135. Chabert R, Fouque-Parachini L, Oberto G, Restellini L, Pinacolo S, Bressier G. Stimulating mitochondria activity in association with LED exhibits cumulative anti-aging benefits. *J Invest Dermatol* 2012; 132:S50–S65.
136. Barolet D. Photoprevention. *Congres national de medecine esthetique et de chirurgie dermatologique (CNMECD)*, September 2014.
137. Barolet D, Boucher A. LED photoprevention: Reduced MED response following multiple LED exposures. *Lasers Surg Med* 2008; 40:106–112.
138. Michele P. Photoprevention: A new concept for seniors and others. *Congres national de medecine esthetique et de chirurgie dermatologique (CNMECD)*, September 27/28, 2013.
139. Duteil L, Cardot-Leccia N, Queille-Roussel C, Maubert Y, Harmelin Y, Boukari F, Ambrosetti D, Lacour JP, Passeron T. Differences in visible light-induced pigmentation according to wavelengths: A clinical and histological study in comparison with UVB exposure. *Pigment Cell Melanoma Res* 2014 September; 27(5):822–826.
140. Passeron T. Visible light and pigmentation. *AMWC*, May 2011.
141. Krämer M, Sachsenmaier C, Herrlich P et al. UV irradiation-induced interleukin-1 and basic fibroblast growth factor synthesis and release mediate part of the UV response. *J Biol Chem* 1993; 268:6734–6741.
142. Hertl M. Maladies auto-immunes de la peau (chapitres 12, 13, 15 et 18). Pathogénèse, diagnostic et prise en charge, 3éme édition. New York: Springer, 2013.
143. Lee AY. Role of keratinocytes in the development of vitiligo. *Ann Dermatol* 2012; 24:115–125.
144. Lan CCE, Wu CS, Chiou MH et al. Low-energy helium-neon laser induces locomotion of the immature melanoblasts and promotes melanogenesis of the more differentiated melanoblasts: Recapitulation of vitiligo repigmentation in vitro. *J Invest Dermatol* 2006; 126:2119–2126.
145. Hausdorfer S. Photobiomodulation et maladies autoimmunes. AMWC, Monaco, France, April 3–5, 2013.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Radiofrequency

Ines Verner and Boris Vaynberg

INTRODUCTION

Radiofrequency (RF) is a high-frequency alternating electric current with a frequency between 3 kHz and 300 GHz.

The first use of this energy was for radio broadcasting, and the word "radio" is still used for historical reasons. The major use of RF energy nowadays is in TV and radio broadcasting, cellular and computer, and other forms of communication.

The first use of RF current in medicine was in 1928 when Dr. Cushing and Dr. Bovie (a Harvard Physicist) introduced the first electrosurgical unit. They used pulsed RF energy and were able to remove tumors while minimizing hemorrhagic complications.

Nowadays, RF is used in many fields of medicine. It is not only the most commonly used energy source for cutting and hemostasis but also used to treat hepatocellular carcinoma, renal cell carcinoma, osteoid osteomas, and other tumors. In cardiology, it is used to destroy abnormal electrical pathways, thus treating arrhythmias. It is used to treat Barrett's esophagus in gastroenterology, in pain management in neurology, in mole removal in dermatology, and in many other indications.

The first tissue tightening device that used RF energy was a monopolar RF device introduced in 2003 (ThermaCool by Solta Medical). The first bipolar fractional RF device for skin resurfacing was introduced in 2009 (eMatrix by Syneron Medical).

Since then, many other RF devices have been introduced into the market with, nowadays, a plethora of devices for tissue tightening and skin rejuvenation.

PHYSICS OF RF

RF energy may be delivered to the treatment area in two ways:

1. *By conductivity*: A pair of electrical wires is connecting the target tissue with an RF generator.
2. *By radiation*: RF energy is transmitted from the RF generator through an antenna in the form of electromagnetic waves.

In medical devices, the lower part of the RF spectrum (0.3–3 MHz) is mostly delivered by conductivity, whereas the upper part of the spectrum is mostly delivered by radiation.

For a frequency of 1 MHz, for example, we can calculate the wavelength (λ) using the following formulation:

$$\lambda = \frac{c}{f} = \frac{3 \times 10^8}{1 \times 10^3} = 300 \text{ m} \qquad (39.1)$$

where

c is the speed of light in m/s
f is the frequency in Hz

So, at a frequency of 1 MHz, the wavelength will be 300 m.

To be able to radiate this 1 MHz electric field, a simple antenna with the size of ¼ of the wavelength (in this case, 75 m) should be used.

In most medical devices, the electrodes and connective wires are much shorter than 75 m, and therefore, the radiation in this case is negligible.

If we calculate the wavelength in the higher range of the RF spectrum (e.g., above 1 GHz), the RF wavelength will be in the centimeter range. In these cases, the electrodes will operate as antennas and radiate RF energy.

In order to achieve tissue heating and thus hyperthermia by radiation in the high RF spectrum, the antenna will mostly need to be about half the length of the wavelength. This form of RF energy is used extensively to treat nonresectable tumors such as hepatocellular or renal cell carcinoma by hyperthermia.

The "low-frequency" RF energy may be delivered by bipolar, monopolar, or unipolar technology.

In the case of bipolar RF configuration, two electrodes are positioned in close proximity to each other on the tissue. The electrical current in this case will be limited to the area between the electrodes and will thus define the tissue volume to be affected by the RF energy. By having the electrodes separated by only a few millimeters and using low-frequency RF, one can make sure that heating will be confined and limited to the skin between the two electrodes. This bipolar configuration is used in skin tightening procedures.

In monopolar RF, the electrodes are asymmetrical. One electrode, "the active electrode," is usually small and thin and can be used as a knife for tissue cutting. The second or "return" electrode is usually big and is connected to the body at a distance from the procedure spot. Even though the path of the electrical current through the body in this configuration is not well defined, the highest current density will be seen below the "active" electrode. This current density drops sharply away from the "active" electrode, so no heat is produced in the tissue further away. The big contact area of the return electrode is responsible for the low current density where it is in contact with the skin, and so no heating is produced at this level.

The "unipolar" configuration is an intermediate approach between low- and high-frequency RF. When the frequency is low, e.g., few tens of MHz, the RF delivery by both conduction and radiation takes place. Taking as example a 40 MHz device, the RF wavelength will be 7.5 m. The resonant size of the antenna is one-fourth of a wavelength and, in this case, equals to ~1.87 m, which is close to the height of human being. Therefore, a return electrode may not be required. In this case, RF energy delivered to the treatment zone by an "active" electrode and current returns through the radiated electromagnetic field.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

In both bipolar and monopolar RF medical devices, low-frequency RF waves are transmitted through electrodes. These waves cause ionic agitation or friction thus increasing the temperature of the tissue.

Since a sharp boundary may be created between the treated and the surrounding tissue, a high level of precision and control can be achieved.

The lower operating temperatures of RF, as compared to traditional electrosurgical or laser surgery tools, enable surgeons to remove or shrink soft tissue while simultaneously sealing blood vessels.

Unlike other forms of electromagnetic radiation (e.g., lasers), RF energy can be arranged to penetrate the body and be absorbed in the deep tissue layers without any heat sensation, making it virtually painless and potentially speeding patient recovery.

RF AND TISSUE INTERACTION: SCIENTIFIC BASIS

The mechanism by which RF energy can affect our tissue is based on the fact that human tissue is a conductive medium for electrical current.

An RF generator creates an oscillating voltage difference between its electrodes. This voltage difference creates an electric field, which in turn drives the current into the tissue.

Our tissue has a natural resistance to the movement of electrons and thus to the passage of electric current through it. This resistance to the movement of electrons leads to heat production in our tissue following contact with an RF current source. The amount of heat that is produced in our tissue is subject to Joule's first law in which the energy in joules (J) is equal to the square of the current (I) times the impedance or resistance of tissue (R) times the time of exposure (T):

$$J = I^2 \times R \times T$$

The electrical power delivered to a unit of volume of tissue is

$$P\left[\frac{\mathrm{W}}{\mathrm{m}^3}\right] = J \cdot E = \frac{J^2}{\sigma} = \rho J^2 = \sigma E^2 = \frac{E^2}{\rho} \qquad (39.2)$$

where

J is a real current
E is an electric field
ρ and σ are the resistivity and conductivity, respectively, ($\rho = 1/\sigma$)

It should be taken into account that the heat produced in our tissue by RF is distributed both by conduction and convection. Thus, if a highly confined tissue effect is desired, the energy should be delivered with high intensity and a short pulse. For a more widespread effect, longer pulse durations should be used.

To be able to achieve different tissue effects by RF one may vary the power of the generator (pulse amplitude) and the pulse duration (pulse width).

These two main variable parameters, pulse amplitude and pulse duration control the tissue effect of RF energy (volume of heated tissue to desired temperature) and the confinement of the tissue effect (how widespread the effect is).

It is possible to use RF energy on tissue in two different ways: One way is to induce non ablative tissue tightening by "volumetric heating" [1] and another way is to induce fractional ablation of the skin by RF.

It has been suggested first by Zelickson et al. [2] and later by Hantash et al. [3] that a wound healing response is initiated by RF posttreatment.

In a study published in 2004, Zelickson et al. have shown that heating bovine tendons by RF to 55°C–65°C gave immediate scattered shortening and thickening of collagen fibers together with loss of borders due to breakage of the intramolecular hydrogen bonds of the collagen triple helix. They also showed by Northern blot analysis that collagen mRNA I was elevated from day 2 to day 7 after treatment, concluding that RF can induce new collagen production and tissue tightening [2].

Hantash et al. [3] found that after heating skin to 72°C for 4 seconds by a microneedle-based bipolar fractional RF device, thermal zones of denatured collagen can be generated in the treated area. The nontreated dermis and its collagen are spared and serve as healing reservoirs. A vigorous wound healing response with an inflammatory cell infiltrate was generated from day 2 after treatment and lasted for 10 weeks after the procedure. This led to collagen remodeling with complete replacement of old by new collagen at week 10 after treatment. Consistent with this was a progressive increase in HSP47, which is a marker of neocollagenesis. This increase is apparent from days 2 to 28 and is seen diffusely in the dermis throughout 10 weeks after treatment. As the collagen chaperone HSP47 expression levels correlate with the amounts of collagen being synthesized in tissue, these findings mean that new collagen is being formed not only in the treated areas but also in the adjacent nontreated areas. These findings correlate with the gradual and widespread clinical improvement even months after the procedure [3]. Similar HSP47 expression and diffuse distribution were also seen after fractional CO_2 laser resurfacing [4]. Interestingly, also new hyaluronic acid and new elastin (immunohistochemistry and PCR) formation was seen after fractional RF treatment, suggesting renewal of the entire extracellular matrix (ECM) [3]. It should be noted that adnexal structures such as sweat and sebaceous glands, as well as hair follicles, were spared during the treatment due to their much higher resistance to current. Thus, RF current has a predisposition for the ECM and spares the adnexa.

In a prospective, open-label, multicenter clinical trial with randomized and blinded evaluation of 100 subjects with mild to severe facial and neck rhytides and laxity using a bipolar RF device (ePrime Syneron Medical Ltd), it was demonstrated that a single fractional radiofrequency (FRF) treatment results in consistent significant improvements in rhytides and laxity. 100% of the patients had improvement in rhytides, and 95% had improvement in laxity. Resumption of normal activities was possible after 24 hours, and no wound care was needed. Only two cases of punctate atrophy resolved during the follow-up period, and no long-term side effects were seen after the procedure [5].

Interestingly, it was noted here [5] and shown previously in another study [6] that the molecular events after FRF are different from ablative laser resurfacing [7]. After FRF treatment, there is a relatively mild elevation of matrix metalloproteinase (MMP) 1 and 3, which are the catabolic enzymes that break collagen, while at the same time, there is a higher expression of MMP-13 and MMP-9, which are the remodeling or anabolic enzymes. This suggests that after FRF treatment, there is relatively less collagen and elastin breakdown with at the same time relatively high elevation in collagen, elastin, and hyaluronic acid production. These findings correlate with the clinical finding of gradual improvement in wrinkles and skin laxity over 6 months following FRF treatment [8].

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

RF: GENERAL USE AND INDICATIONS

Surgical

In dermatologic surgery, plastic, and oculoplastic surgery, RF energy has been used for many different indications. It enables the surgeon to cut tissue very precisely, to cut and coagulate at the same time preventing bleeding and allowing thus very precise surgery, to coagulate only, or to induce hemostasis depending on the current energy and RF waveform. Clinical benefits as compared to regular surgery include immediate hemostasis, reduced postoperative discomfort, minimal scar formation, enhanced healing, and very good cosmetic results [9]. RF can be used for minimally invasive procedures such as mole or skin lesion removal or during more invasive procedures such as blepharoplasty or face-lift surgery [10].

Tissue Tightening and Rejuvenation

The first technology developed to heat and denature dermal collagen by RF was a monopolar RF device (ThermaCool by Solta Medical). This technology has been used for the treatment of sagging skin of the face and neck, for cellulite, and for striae and let to great excitement due to the possibility to tighten and lift with minimal downtime and without the need for surgery. Unfortunately, skin tightening has been inconsistent with mild to moderate results in a select group of patients. The recommended single treatment pass using relatively high-energy settings led not only to variable results but also to second degree burns and fat atrophy in up to 2.7% of cases [11]. Temporal anesthesia and trigeminal neuralgia were also reported. Subsequent studies using lower-energy levels with multiple passes showed more consistent results and a reduction in side effects [12]. It has been suggested by others that multiple RF treatments may even further improve outcomes and prevent the sagging of tissue with age [13]. In a pilot study on 17 patients with another monopolar RF device, improvement in skin laxity, texture, and wrinkles was seen after six bimonthly treatments. No complications were seen, but only 50% of the improvement was maintained at 6 months post-treatment [14].

With the introduction of fractional photothermolysis with its better safety profile and consistent results, interest in ablative resurfacing has waned mainly due to the high incidence of side effects such as prolonged erythema and the risk for permanent hypopigmentaion and scarring.

In the search for even less-invasive resurfacing procedures with less downtime and an even better safety profile, bipolar FRF resurfacing has been introduced (eMatrix and later the eTwo, by Syneron Medical Ltd.) [15]. In these fractional RF devices, bipolar RF energy is delivered by multiple (44–144) small (250 μm) pins through a tip with large return electrodes. The tissue between the electrodes serves as a healing reservoir. Due to the high impedance of the epidermis to RF current, the current is passing through the upper (high impedance) layer of the skin without divergence resulting in high current density, which leads to a very confined, high-intensity tissue effect (ablation). As was pointed out earlier, the amount of released heat is proportional to the squared current and resistance. Thus, heat production below the electrode is very high. Once current passes to the dermis, which has a lower impedance, it spreads through the dermis with a decreased current density. This results in heating a higher tissue volume of the dermis to lower temperatures (nonablative). This type of impact with minimal epidermal ablation, and, at the same time, a wide dermal heating effect was called "sublative rejuvenation." In this form of resurfacing, the downtime is minimal with only mild redness between 4 and 48 hours and minimal scabs for 3–5 days. There is no need to stay home as all facial changes can be covered by makeup. This, together with the remarkable clinical results after 3–5 consecutive monthly treatments and absolutely minimal risks, makes this form of resurfacing a favorite among the patients [16–28] (Figure 39.1). In an open-label study (eMatrix, Syneron Medical), ten female patients with moderate elastosis (5 as a mean score in the Fitzpatrick classification of wrinkling and elastosis scale) were treated 5 times monthly. All ten had remarkable improvement in tightness, brightness, pores, and luminosity of their facial skin with a mean 1.5 points improvement on the Fitzpatrick elastosis scale. All 10 were very satisfied after the treatment (using the GAIS satisfaction scale) [18] (Figure 39.2).

Another advantage of RF energy is its lack of preference for melanin or other "colored" molecules or structures making it "color blind." Even though any treatment including lasers, chemical peels, or RF can induce skin inflammation and thus postinflammatory hyperpigmentation (PIH), this risk is much lower than any other modalities.

The safe use of fractional RF in darker skin types was demonstrated in a study including 15 patients with skin types V and VI. All patients showed significant improvement in wrinkles, texture, and fine lines without any PIH or other side effects [19]. In our personal experience, fractional RF (especially in the lower energy levels) can safely be used in the darker skin types (IV and V).

In a survey among 645 treated patients in our clinic (skin types I–V) who received 2–5 consecutive fractional RF treatments (eTwo, Syneron Medical), no serious side effects were seen directly after the treatment and none at 1-year follow-up. Five of the 645 patients reacted more vigorously to treatment and had redness and swelling that lasted for 3–5 days. Five patients had acneiform eruptions after the treatment that resolved spontaneously within weeks. No other problems, e.g., infections, PIH, hypopigmentation, or scarring, were seen [20].

Acne Scarring

Acne scarring has been one of the most frustrating indications in aesthetic dermatology. Even though many different treatment modalities have been available such as dermabrasion, deep chemical peels, and ablative laser resurfacing by erbium:yttrium–aluminum–garnet (Er:YAG) or by CO_2, results have been variable and unsatisfactory in many cases. All these modalities are associated with an intensive and long wound healing process and thus a long recovery time with a high risk for complications. Although the nonablative and fractional devices have a better safety profile, results are limited and multiple treatments are required.

Due to all these different limitations, fractional ablative bipolar RF, "sublative," has been introduced. In a prospective study, 10 patients received three monthly treatments with the eMatrix and were followed up for 3 months. All 10 showed significant improvement in acne scarring and had a high to very high patient satisfaction [21].

In another open-label study, 12 patients (4 males + 8 females) with moderate to severe acne scarring aged 20–62 with Fitzpatrick skin types I–III were included. All received 3–5 monthly treatments by eTwo by the "sublative" head. All 12 had some improvement already after the second treatment with

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 39.1 Patient (a) before fractional RF and (b) 15 months after finishing 4 monthly treatments by the eTwo (sublative head) from Syneron Medical. Note the lifting of tissue along the jawline and chin.

(a) (b)

Figure 39.2 Patient (a) before and (b) 1 month after 5 monthly treatments by the sublative head of eTwo (Syneron Candela Medical). Note the improvement in wrinkles, skin tone, and tissue tightening.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 39.3 Patient with severe long-standing acne scarring (a) before and (b) 2 months after 3 monthly treatments by the sublative head of eTwo (Syneron Candela Medical).

very good improvement (at least one scale) after completing the 5 treatments. This improvement in the scars continued in the 3 months following the treatments. Two of the 12 patients are requested to discontinue the treatments due to excellent improvement already after the third treatment. All patients were either satisfied or very satisfied directly after and at 3-month follow-up [22,23] (Figure 39.3).

OTHER INDICATIONS

Striae

Another interesting indication for RF devices is striae distensae or stretch marks. This disorder appears clinically as erythematous (striae rubra) or hypopigmented (striae alba) bands of atrophic skin. Even though multiple treatment modalities have been employed for this indication, most of them (e.g., 585 pulsed dye laser) are effective only during the erythematous, inflammatory stage and not during the hypopigmented later stage of the marks. In addition, the use of lasers in dark-skinned individuals has a high risk for PIH.

In multiple pilot studies, it has been shown that different RF technologies are effective in the treatment of striae alba [24–26]. Even though larger studies are still lacking, the results for this difficult-to-treat indication are impressive.

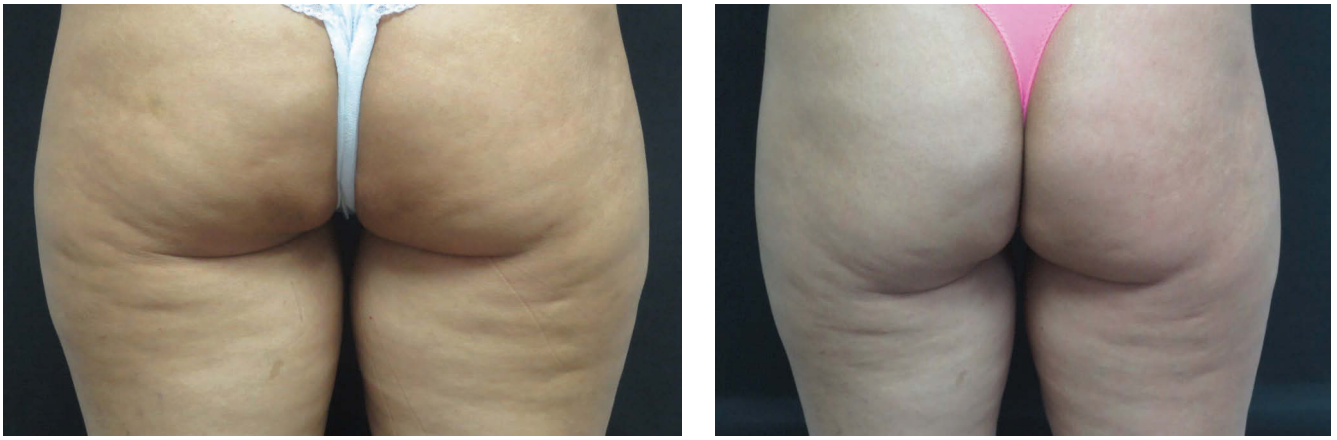
Cellulite

Cellulite is a multifactorial skin condition most commonly found on the posterolateral thighs, buttocks, and abdomen of 80%–90% of postpubertal females and is a major cosmetic concern. Clinically, it is characterized by orange peel appearance and dimpled skin surface. The first description of cellulite dates from 1978 [26], wherein the differences between females and males in the structure of skin and subcutaneous tissue are described. The different septal structure in females (thinner and with a vertical orientation) as opposed to the septal structure in males (thicker and with an angled and parallel orientation) allows for herniation of the subcutaneous fat into the connective tissue, leading to the dimpled clinical appearance [28].

Many different modalities have been used for the treatment of cellulite: topical preparations, mechanical stimulations, acoustic/ultrasound wave therapy, laser and light devices, and RF. By now, all these techniques and technologies offer only limited and variable results [28].

Lately, RF technologies have become very popular for the treatment of cellulite, the reason being the high RF energies (150–200 W) of the new devices leading to better volumetric heating of the subcutaneous fat tissue and thus to better and more consistent clinical results. The rational for the treatment of cellulite by RF stems from the fact that our fat tissue is composed of 1 mm large fat cell microlobules surrounded by septa of connective tissue. Due to the low resistance of the septa to RF energy, they act as conducting wires. Heat is produced within the septa and is conducted further to the fat lobules. Heating the septa induces stimulation of neocollagenesis [3], while heating the adipocytes between 42°C and 45°C for 15 minutes induces fat cell apoptosis [29]. Clinically, it has been shown that high-energy RF in combination with infrared (IR) light and vacuum (VelaShape Syneron Medical) or high-energy RF in combination with magnetic pulses (Legacy Venus Concept) can improve cellulite remarkably and induce abdominal circumference reduction between 2 and 4 cm after 3–6 bimonthly treatments [30] (Figure 39.4).

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b)

Figure 39.4 Patient (a) before and (b) after 6 bimonthly treatments with an RF device.

Hair Growth Stimulation

Recently, it has been noted that RF can induce hair regrowth in female and male pattern hair loss (Innogen Technologies Ltd.). There is a clinical improvement after multiple treatments but data are still preliminary. The mechanism of action is not clear yet. Recently, it has been suggested that in pattern hair loss follicles enter into a period of dormancy between subsequent hair cycles and hair follicles could be reactivated into regrowth [31].

CONCLUSIONS

RF technologies have changed the aesthetic medicine terrain due to their efficacy and their great safety profile. We are now able to offer our patients treatments for tissue tightening and rejuvenation, acne scars, striae, cellulite, body contouring, and circumference reduction with a minimal downtime and a negligible risk for complications. Also, we can treat our darker skin type patients at a lower risk for PIH after the procedure.

With the understanding of RF tissue interactions and the development of new exciting RF technologies, we are now able to treat more effectively a wider range of indications.

Some of the available devices are as follows:

- eTwo (Syneron Medical, Yokneam, Israel): The device has 2 handpieces. One handpiece delivers fractional bipolar RF by different disposables with 40–144 pins, providing up to100 mJ energy per pin. The pulses are tens to hundred milliseconds. The second applicator is a nonablative bipolar RF operating in a pulsed mode combined with IR light for deeper heating.
- Viva (Venus Concept Ltd, Tel Aviv, Israel): The device has 2 handpieces: one with a fractional RF function for skin rejuvenation and tightening and the other with bipolar RF for deeper tissue heating.
- VelaShape (Syneron Medical, Yokneam, Israel) combines bipolar RF with IR light and vacuum for the treatment of cellulite and body contouring.
- Legacy (Venus Concept Ltd, Tel Aviv, Israel) combines bipolar RF with magnetic pulse technology for the treatment of cellulite and body contouring.
- Accent (Alma Lasers, Ltd, Caesarea, Israel) uses combined monopolar and bipolar RF to be delivered simultaneously for deep and superficial volumetric heating of tissue.
- Profound (Syneron Medical, Yokneam, Israel): A bipolar RF device with 4 pairs of electrodes in the form of needles in which each pair is separated at a 1 mm distance. One of the electrodes in each pair has a temperature sensor and each electrode pair operates independently. The needles are inserted into the tissue to a depth of about 1 mm, thus delivering RF energy to the deeper layers.
- EndyMed (3 DEEP, Caesarea, Israel) uses a tip with up to 112 electrodes and 6 RF generators to volumetrically heat the dermis and hypodermis [26].
- Pellevé (Ellman International, Inc, Oceanside, NY): Uses monopolar RF for multiple bimonthly treatments for gradual tissue heating and tightening.
- Thermage (Solta Medical Inc., Hayward, CA): Uses monopolar RF to deliver heat to tissue. The latest CPT technology adds a gentle vibration interspersed by cooling bursts to prevent pain and epidermal side effects.
- Innogen Technologies (Tel Aviv, Israel): A bipolar RF device for hair growth stimulation.

REFERENCES

1. Dierickx CC. The role of deep heating for noninvasive skin rejuvenation. *Lasers Surg Med* 2006; 38:799–807.
2. Zelickson BD, Kist D, Bernstein E et al. Histological and ultrastructural evaluation of the effects of a radio-frequency-based nonablative dermal remodeling device: A pilot study. *Arch Dermatol* 2004; 140:204–209.
3. Hantash BM, Ubeid AA, Chang H, Kafi R, Renton B. Bipolar fractional radio-frequency treatment induces neoelastogenesis and neocollagenesis. *Lasers Surg Med* 2009; 41:1–9.
4. Hantash BM, Bedi VP, Kapadia B, Rahman Z, Jiang K, Tanner H, Chan KF, Zachary CB. In vivo histological evaluation of a novel ablative fractional resurfacing device. *Lasers Surg Med* 2007; 39:96–107.
5. Alexiades-Armenakas M, Newman J, Willey A et al. Prospective multicenter clinical trial of a minimally invasive temperature-controlled bipolar fractional radiofrequency system for rhytid and laxity treatment. *Dermatol Surg* 2013; 39:263–273.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

6. Hantash BM, Renton B, Berkowitz RL et al. Pilot clinical study of a novel minimally invasive bipolar microneedle radiofrequency device. *Lasers Surg Med* 2009; 41:87–95.
7. Orringer JS, Kang S, Johnson TM et al. Connective tissue remodeling induced by carbon dioxide laser resurfacing of photodamaged human skin. *Arch Dermatol* 2004; 140:1326–1332.
8. Willey A, Kilmer S, Newman J et al. Elastometry and clinical results after bipolar radiofrequency treatment of skin. *Dermatol Surg* 2010; 36:877–884.
9. Bosniak S, Cantisano Zilkha M. Radio-surgery: A 25 year history of scarless mole removal. *Oper Techn Oculop Orbital Reconstr Surg* 2001; 4:109–112.
10. Niamtu J. Radiowave surgery versus CO laser for upper blepharoplasty incision: Which modality produces the most aesthetic incision? *Dermatol Surg* 2008; 34(7):912–912.
11. Narins RS, Tope WD, Pope K et al. Overtreatment effects associated with a radiofrequency tissue tightening device: Rare, preventable, and correctable with subcision and autologous fat transfer. *Dermatol Surg* 2006; 32:115–124.
12. Verner I. Clinical evaluation of the efficacy and safety of fractional bipolar radio frequency for the treatment of moderate to severe acne scars. *Dermatol Ther* 2016; 29(1):24–27.
13. Suh DH. Monopolar radiofrequency treatment in Asian skin: Do multiple RF treatments over time have beneficial effects? An observational report with long-term follow-up in eight patients. *Dermatol Surg* 2013; 39:671–672.
14. Taub AF, Tucker RD, Palange A. Facial tightening with an advanced 4-MHz monopolar radiofrequency device. *J Drugs Dermatol* 2012 November; 11(11):1288–1294.
15. Hruza G, TaubAF, Collier S et al. Skin rejuvenation and wrinkle reduction using a fractional radiofrequency system. *J Drugs Dermatol* 2009; 8(3):259–265.
16. Lee HS, Lee DH, Won CH et al. Fractional rejuvenation using a novel bipolar radiofrequency system in Asian skin. *Dermatol Surg* 2011; 37(11):1611–1619.
17. Verner I. Sublative rejuvenation-fractional radiofrequency resurfacing. *IMCAS Congress*, Paris, France, January 8–11, 2010.
18. Verner I. Sublative clinical experience. *Anti-Aging Medicine World Congress* (*AMWC*), Monte Carlo, France, March 2012.
19. Man J, Goldberg DJ. Safety and efficacy of fractional bipolar radiofrequency treatment in Fitzpatrick skin types V-VI. *J Cosmet Laser Ther* 2012; 14(4):179–183.
20. Verner I. Trends and innovations in aesthetic dermatology. *AFID Congress*, Tel Aviv, Israel, May 8–9, 2013.
21. Gold MH, Biron JA. Treatment of acne scars by fractional bipolar radiofrequency energy. *J Cosmet Laser Ther* 2012; 14:172–178.
22. Verner I. Clinical evaluation of the efficacy and safety of fractional bipolar radiofrequency for the treatment of moderate to severe acne scars. *Dermatol Ther* 2015 August 17.
23. Verner I. Tissue tightening by RF. *Anti-Aging Medicine World Congress* (*AMWC*), Monte Carlo, France, April 4–6, 2014.
24. Manuskiatti W, Boonthaweeyuwat E, Varothai S. Treatment of striae distensae with TriPollar radiofrequency device: A pilot study. *J Dermatol Treat* 2009; 20:359–364.
25. Almeida Issa MC, de Britto Pereira Kassuga LE, Chevrand NS et al. Transepidermal retinoic acid delivery using ablative fractional radiofrequency associated with acoustic pressure ultrasound for stretch marks treatment. *Lasers Surg Med* 2013; 45:81–88.
26. Hodgkinson DJ. Clinical applications of radiofrequency: Nonsurgical skin tightening (thermage). *Clin Plast Surg* 2009; 36:261–268.
27. Nurnberger F, Muller G. So-called cellulite: An invented disease. *J Dermatol Surg Oncol* 1978; 4(3):221–229.
28. Luebberding S, Krueger N, Sadick N. Cellulite: An evidence based review. *Am J Clin Dermatol* 2015; 16:243–256.
29. Jimenez Lozano JN, Vacas-Jacques P, Anderson RR, Franco W. Effect of fibrous septae in radiofrequency heating of cutaneous and subcutaneous tissue: Computational study. *Lasers Surg Med* 2013; 45:326–338.
30. Verner I. What's new in body contouring? *Anti-Aging Medicine World Congress* (*AMWC*), Monte Carlo, France, March 25–28, 2015.
31. Rushton DH, Norris MJ, Van Neste D. Hair regrowth in male and female pattern hair loss does not involve the conversion of vellus hair to terminal hair. *Experimental Dermatol*, accepted 2016 January.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Fundamentals of ultrasound sources

Shlomit Halachmi and Moshe Lapidoth

INTRODUCTION TO ULTRASOUND

Aesthetic dermatology and lasers are closely allied in the minds of providers and patients alike. The traditional operating principles of lasers and light-based devices set the stage for the basic understanding of how energy interacts with tissue. Radiofrequency (RF) borrows some of these principles and can perform some of the functions of lasers. Ultrasound, however, requires a conceptual shift. Although therapeutic ultrasound can achieve some of the effects of lasers and RF, the modes of operation, the interaction with tissues, and the basic variables that distinguish one ultrasound source from another are quite different.

Terminology and Principles

All energy waves travel at a speed (c) that is fixed in a given medium. The relationship among speed, wavelength (distance traveled in a single cycle, measured crest to crest or trough to trough, designated as λ), and frequency (cycles per second, designated by f) is described by the following equation:

$$c = f \cdot \lambda$$

In the case of lasers, c is the speed of light, and the wavelength is generally used to identify the spectrum (color range) of light being used, which is measured in nanometers (nm). The human eye can generally perceive light in the range of 390–700 nm, and hence, this spectral range is referred to as "visible light." Objects that reflect light in this range will appear to have a particular color, which is due to the wavelengths they reflect (rather than absorb). Higher wavelengths are infrared and lower wavelengths are ultraviolet.

In distinction to light waves, sound is an oscillating pressure wave. An advancing sound wave induces mechanical changes in the medium in which it travels, as the periodic high and low pressures lead to alternating compression and rarefaction (Figure 40.1).

In describing sound, c is the speed of sound in a particular medium. This speed can vary significantly in air, water, or different solid materials. The speed of sound varies in different tissues as well. In soft tissue, the speed of sound averages 1540 m/s (1.54 mm/μs). The speed is significantly lower in air, and for this reason, the presence of air or air bubbles prevents the application of ultrasound for the diagnostic or therapeutic procedures. The speed of sound is higher in liquids and highest in solids. This variability in speed and attenuation underlies the use of ultrasound for imaging of anatomical structures.

In distinction to light and laser, it is customary to describe acoustic energy by its frequency rather than its wavelength. Acoustic waves with frequencies in the range of 20 hertz (Hz) to 20 kilohertz (kHz) are perceived by the human ear. Frequencies above 20 kHz are in the ultrasound range. Frequencies below 20 Hz constitute infrasound, which is used by geologists to monitor movement and by whales to communicate across long distances.

Since the product of wavelength and frequency is constant, i.e., the speed of the wave in a given medium, as the frequency of a sound wave increases, its wavelength decreases. Higher-frequency sounds, in particular ultrasound, are marked by extremely short wavelengths. Very short wavelengths (i.e., high-frequency ultrasound) can limit the use of the ultrasound in imaging deep structures because of the effect of tissue on the propagation of the sound wave. As waves travel through a medium, there is progressive loss of energy, or attenuation. Higher-frequency ultrasound is more susceptible to attenuation through tissue. This can be explained conceptually by understanding that a wave loses a fixed amount of energy in the span of one wavelength. A sound wave with a longer wavelength will retain its energy for a greater distance than a sound wave with a shorter wavelength. Said differently, over a given distance, a sound source with a shorter wavelength will have completed more "laps" or cycles of its wavelength and will have lost more energy than a sound source with a longer wavelength. Consequently, as with light energy, longer wavelengths (lower frequency) have a greater penetration than shorter wavelengths (high frequency).

Ultrasound has very short wavelengths; therefore, its tissue penetration is limited and is dependent on the wavelength of the ultrasound. Since it is customary to refer to ultrasound by frequency rather than wavelength, it follows that higher-frequency ultrasound has reduced tissue penetration. Therefore, higher frequency, up to 20 mHz, can be used to reach structures that are superficial, while deeper penetration requires ultrasound with lower frequency. The trade-off is resolution: higher-frequency ultrasound provides higher-resolution images and can produce a smaller focus, at the expense of depth of propagation. When deeper penetration of energy is needed, particularly in the case of therapeutic ultrasound, lower-frequency (longer wavelength) ultrasound is applied, usually in the vicinity of 1 MHz but in some devices as low as 200 kHz.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

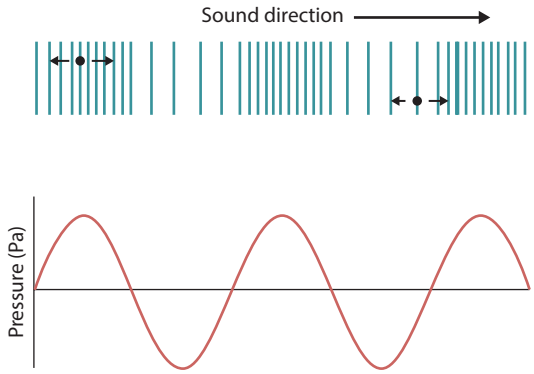


Figure 40.1 Schematic of sound wave propagation through a uniform medium. High pressure corresponds to compression of molecules in the medium, while low pressure corresponds to rarefaction.

Difference in Approach from Laser-/Light-Based Devices

Although both light and sound are energy waves, they can interact with tissues differently. Light energy can be absorbed or reflected, and it exerts its effect on tissue by its specific absorption in that tissue. Acoustic energy can also be absorbed or reflected. Like light, ultrasound can be used to heat tissue. However, since sound is a pressure wave, it can also be conducted. This ability to operate by conducted pressure allows a wide array of physical effects on tissue. The ultrasound may be delivered in a way that induces shear stress on tissue and thereby induces stress fatigue, or that induces vibration, or that delivers ultrashort and extremely powerful bursts of high or low pressures (shock waves and cavitation, respectively), which can cause dramatic tissue damage. Examples of these effects will be presented in the following sections.

Sources of Ultrasound

An ultrasound transducer can generate, deliver, and detect ultrasound energy. Most commonly, ultrasound probes, or transducers, work by the piezoelectric effect (piezo = pressure, from the Greek "push"), which links pressure and electric current. These probes contain crystals that change size or shape in an electric field. When exposed to rapidly alternating electric current, the crystals oscillate rapidly and emit very high-frequency vibration, manifested as acoustic waves. Medical ultrasound devices commonly utilize ceramic crystals, activated by an electronic oscillator, to achieve this. Conversely, when the transducer is exposed to pressure from sound waves, the crystals acquire a charge and emit electricity. Since these crystals link pressure and electric current bidirectionally, they can be used directly for both the production of ultrasound and reception of reflected ultrasound waves.

The size and shape of the transducer modify the effects and uses of ultrasound. Many medical ultrasound single-element probes have a curvature. When the ultrasound is emitted from a convex surface, the waves diverge as they travel away from the probe. This is used, for example, in ultrasound imaging. The convex surface delivers the ultrasound into the tissue and then receives the reflected (echoed) waves along the convex surface (Figure 40.2a). In contrast, therapeutic ultrasound,

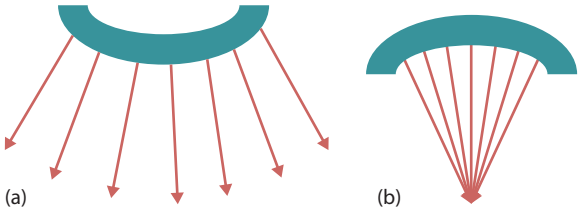


Figure 40.2 (a) Diagnostic imaging ultrasound transducers emit ultrasound from a convex surface. (b) Focused ultrasound waves, delivered from a convex surface, converge at a focal point to deliver high energy density in a small volume of tissue, for therapeutic procedures.

and specifically focused ultrasound, emits ultrasound from a concave surface (Figure 40.2b). This acts as a lens, concentrating the energy within a fixed volume at the geometrically defined focal point where the energy waves converge. In doing so, the transducer accomplishes a unique function: as the ultrasound energy waves converge at a focal point, some distance from the transducer, the small volume of tissue in the focal point is exposed to a very high energy density. The energy converging at the focal point is at a much higher density than at the transducer surface. This allows delivery of energy through the skin, without depositing significant energy at the skin surface. Thereby, focused ultrasound allows high-energy procedures to be performed noninvasively. This has been utilized for treatment of tumors, uterine fibroids, and aesthetic indications that will be described in the following text.

An alternative to curved single-element transducers is the phased array device, which contains many small ultrasonic transducers, each of which can be pulsed and activated independently. By activating the individual elements at different time points, the ultrasound front produced from the transducer as a whole can be steered or focused.

In addition to frequency and to the shape and size of the transducer, the effect of a therapeutic ultrasound device can be modified by changing the output power, the total duration of the pulse, and the duty cycle (percent of time the device is "on"). As with lasers, the use of a low-duty cycle (more "off" time than "on") can allow cooling or relaxation between bursts, whereas a continuous or near-continuous duty cycle would lead to more rapid tissue heating.

CURRENTLY MARKETED DEVICES USED IN DERMATOLOGY OR AESTHETICS

Noninvasive Ultrasound

Ultrasound can be delivered as focused or nonfocused energy. Many nonfocused therapeutic ultrasound devices are available, whereas relatively few focused ultrasound devices have been cleared for marketing for aesthetic indications.

Nonfocused Ultrasound

Nonfocused therapeutic ultrasound is used in aesthetics for its mechanical effects, which induce a massage-like effect, and for its thermal effects. There are several inexpensive tabletops and even home-use devices that claim to work by "cavitation," but there are no clinical studies in support of the ability of these $100–$1000 units to generate cavitation or to provide a therapeutic

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

effect in aesthetics. Some may be able to increase penetration of topically applied agents through the skin based on prior work on sonophoresis. Since the medical literature on consumer ultrasound products is sparse, their role and relative benefit and risk cannot be fairly assessed within the scope of this chapter.

Among professional-use devices marketed for aesthetic use, the early devices were initially developed as diathermy devices for physical therapy and were later remarketed, adapted, or redesigned for aesthetic markets; this history can be seen in the "Indications for Use" for the devices. The most common aesthetic indication for nonfocused ultrasound is "temporary improvement in the appearance of cellulite." Examples of such devices include the previously marketed Dermosonic NonInvasive Subdermal Therapy System (Sybaritic; no longer marketed in the United States), Bella Contour (Real Aesthetics), Med Contour (General Project in Europe, also marketed as VASERshape and now QuantaShape in the United States), and a slate of other devices (Figure 40.3). These devices generally operate in the vicinity of 1 MHz ultrasound and often add additional technologies.

Bella Contour applies three modalities in a format dubbed REAL (Resonant Amplification of Lipid Metabolism) technology, which combines ultrasound at 0.8–3.4 MHz, electrical current delivered by four electrodes, and lymphatic drainage. The device is marketed for body contouring but is cleared for marketing with specific language of "temporary reduction in the appearance of cellulite, relief of muscle spasm, and temporary improvement of local blood circulation." Approximately 10 treatments are performed over the course of 8 weeks; maintenance treatments are recommended.

The Med Contour/QuantaShape line of devices applies "dual low-frequency ultrasound" with vacuum for cellulite and localized adiposities. Other devices in the manufacturer's line in the past have included the Slim Project, MedSculpt, and Med² Contour, which add LED or cavitation for effects. A 5-patient pilot study using MedSculpt, which combines computerized massage, vacuum suction, and 3 Hz continuous sinusoidal ultrasound, showed that after 12 treatments, the mean reduction in thigh circumference was 2.25 cm and the mean reduction in abdominal circumference was 6.5 cm. All subjects also exhibited mild improvement in skin texture and the appearance of cellulite [1].

Figure 40.3 Nonfocused ultrasound: MedContour (EU), also known as VASERshape or QuantaShape (USA), with permission from General Project srl.

These treatments likely exert their effects by a variety of mechanisms: The ultrasound may heat and massage tissue, leading to temporary reduction in edema; RF is thought to stimulate fibroblasts and induce collagen formation, which could reduce fat herniation into the dermis; and LEDs may have a biostimulatory effect, although it is not known whether the light emitted reaches the subcutaneous structures implicated in cellulite. The medical literature in this device space is sparse. One study performed in a swine model demonstrated that nonfocused ultrasound treatments may exert effects on fat through heat [2]. Treatments were performed on one side of each animal, and heating of the tissue was confirmed by thermocouple. Analysis of lymphatic fluid from the treatment area revealed elevated triglycerides relative to fluid from a nontreated area, and vacuoles of fat were seen within lymph nodes draining treated areas. However, electron microscopy revealed free lipids in the extracellular fluid but no tissue necrosis. The authors propose that nonfocused ultrasound devices that induce heating of the fat may trigger temporary changes in permeability of the adipocytes.

The vibrational effects of ultrasound may also induce lymphatic stimulation and/or stimulation of fibroblasts. In some devices, the vibrational massage is combined with a mechanical massage for this purpose. Nonfocused ultrasound can also be used to generate shear stress within tissue. An example of such an effect is the cold mode of Alma Lasers Accent Ultra, which delivers transverse acoustic shear waves, with the aim of causing disruption of adipocyte membranes by repeatedly stretching and relaxing the adipocyte membranes to induce cell death. The manufacturer recommends that the treatment be performed in conjunction with RF.

Focused Ultrasound

As described in the succeeding text, focused ultrasound can provide a noninvasive means to introduce highly concentrated energy into small volumes of tissue and can target structures well below the skin in a noninvasive manner. Focused ultrasound was first described in 1942 and tested for its ability to alter brain tissue noninvasively [3]. The initial studies aimed at nervous system pathology. A natural extension of the work was to target malignancy. Initial targets included brain as well as breast and thyroid tumors. Subsequent work focused on ophthalmologic applications [4,5]. The medical benefits of noninvasive ablative therapies led to the commercialization of high-intensity focused ultrasound (HIFU), initially for benign prostatic hypertrophy, as the Sonablate 200 device [6]. The device was marketed internationally by Focus Surgery and was approved by the FDA after subsequent development. Since then, HIFU devices have been studied for various solid tumors, including malignant lesions and bony metastases, as well as benign proliferations such as uterine fibroids.

In aesthetics, focused ultrasound has been applied to a few indications on both the face and body. Most devices are used for either body contouring or variations of skin tightening.

Body Contouring

Circumference Reduction The first two devices to garner attention in aesthetics in general and in body contouring specifically were known simply by the name of the manufacturers, UltraShape and Liposonix. Both were designed to lyse

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

adipocytes, with the goal of reducing subcutaneous fat volume and thereby to yield circumference reduction. UltraShape was the first on the international market, in 2005, and was cleared by the FDA in 2014 for marketing in the United States with an Intended Use/Indications for Use statement: "The Contour I V3.1 System delivers focused ultrasound energy that can disrupt subcutaneous adipose tissue (SAT) to provide a noninvasive approach to achieve a desired aesthetic effect. It is intended for noninvasive reduction in *abdominal* circumference." Liposonix was cleared by the FDA in 2011 with the Indications for Use "The Liposonix system delivers HIFU energy that can disrupt SAT to provide a noninvasive approach to achieve a desired aesthetic effect. The Liposonix system is specifically indicated for noninvasive *waist* circumference reduction." Despite the difference in Indications for Use (abdominal vs. waist circumference), both devices are often used "off label" for additional body areas.

The devices developed by UltraShape and by Liposonix target similar indications and body areas but operate with different mechanisms of action (Figures 40.4 and 40.5). UltraShape utilizes a single-element ceramic transducer, which operates at a nominal frequency of 200 kHz. The device delivers pulses at a low-duty cycle to induce nonthermal damage to adipocytes. Liposonix applies 2 MHz ultrasound via a steerable multielement phased array to induce thermal necrosis to tissue. Both devices have been well studied and reported in peer-reviewed literature.

Preclinical studies for UltraShape applied ultrasound at a focus 1 cm below the skin and found perforations in fat tissue, with intact vascular and neural structures (Figure 40.4b). The first reported multicenter, controlled clinical trial with the initial UltraShape device, the *Contour I*, was based on a single treatment, which was applied to the abdomen, thighs, or flanks [7]. The study enrolled 164 subjects. Those in the active arm underwent a single treatment at preset parameters. Treatment response (circumference measurements and fat thickness by ultrasound) and safety parameters (serum lipids, liver function, blood counts, and liver ultrasound assessment of hepatosteatosis) were monitored for 12 weeks. Treatments were well tolerated. Effectiveness was reported with a mean circumference reduction of 2 cm and a mean 3 mm reduction in fat thickness by ultrasound, with no weight change. Approximately 50% of the effect was observed at 2 weeks. Response peaked at 4 weeks and was sustained at 12 weeks. No clinically significant changes in the measured safety parameters were recorded. Mild adverse events such as blisters were reported.

Early adopters of the technology developed additional protocols, which included multiple sessions, different tissue positioning approaches, and combinations with other modalities. Moreno-Moraga et al. performed three treatments at a 1-month interval and found a mean circumference reduction of 3.95 ± 1.99 cm [8]. Ascher studied 25 women who underwent three treatments at 2-week intervals and were followed for 84 days after the last treatment [9]. A mean circumference reduction of 2.47 cm was observed on day 14 after the first procedure. At 84 days after the third treatment, the mean circumference reduction was 3.58 cm. Chang et al. treated 32 Asian patients with 3 sessions of focused ultrasound combined with RF to the abdomen at 2-week intervals [10]. The mean circumference reduction was 3.91 ± 1.8 cm. MRI showed an average fat thickness reduction of 25%.

Preclinical studies of Liposonix in swine models demonstrated that application of HIFU at 166–372 J/cm^2 generated tissue temperature approaching 70°C within well-defined

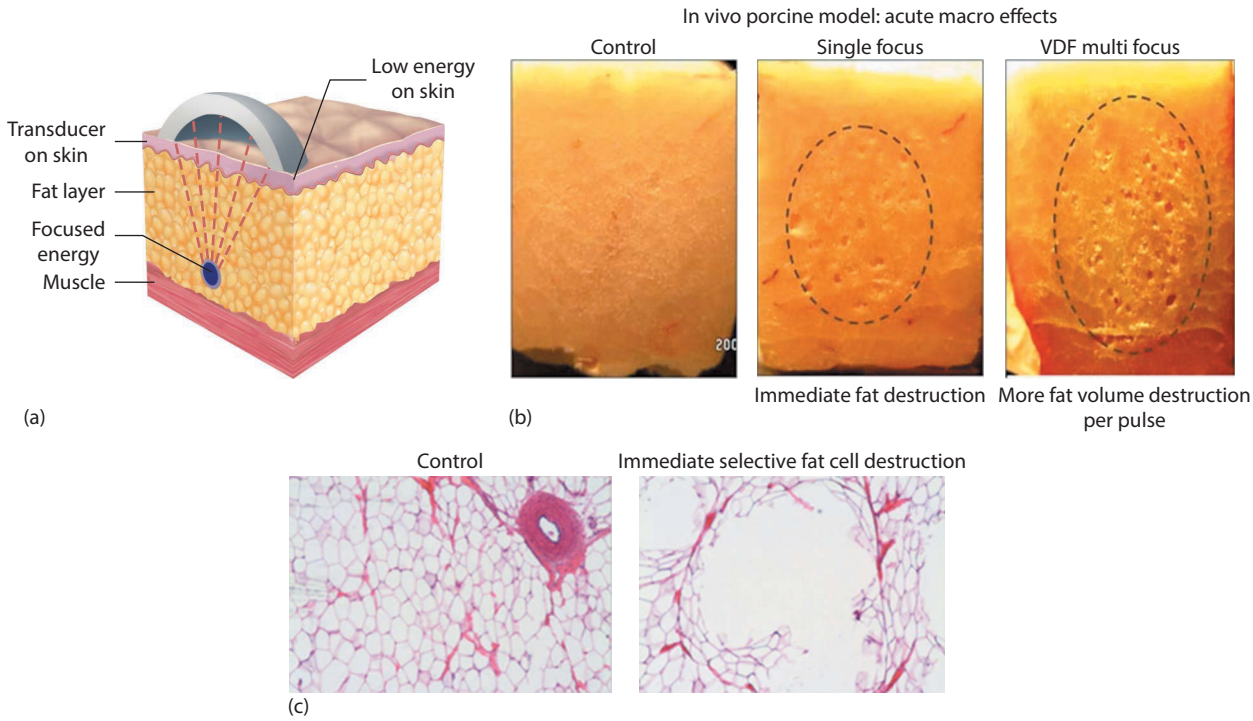


Figure 40.4 UltraShape. (a) Schematic of handpiece in clinical action; (b) tissue effects immediately after treatment (*in vivo* porcine model); (c) histology, showing adipocyte lysis. (Courtesy of Syneron-Candela, Irvine, CA.)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

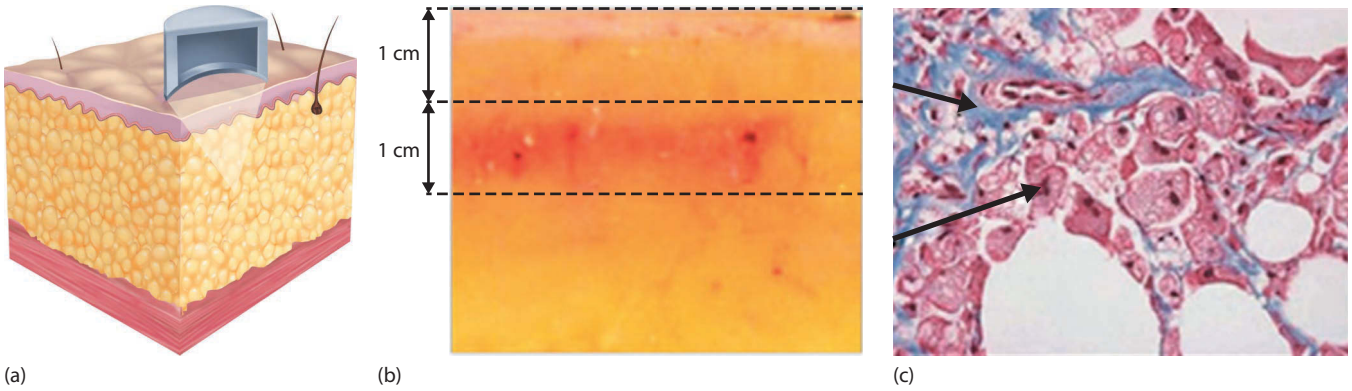


Figure 40.5 Liposonix. (a) Schematic of handpiece in clinical action; (b) tissue effects immediately after treatment (human abdominoplasty tissue); (c) 28-day histology showing fat-laden macrophages. (From Gadsden E, Aguilar MT, Smoller BR, Jewell ML, Evaluation of a novel high-intensity focused ultrasound device for ablating subcutaneous adipose tissue for noninvasive body contouring: Safety studies in human volunteers, *Aesthet Surg J*, 31(4), 410–410, 2011, by permission of Oxford University Press.)

foci [11]. These studies supported safety, with no clinically significant changes in serum lipids or liver function tests. Histology demonstrated well-demarcated zones of disrupted adipocytes within the targeted tissue immediately after treatment, with well-preserved vasculature and intact nerve fibers within the focus. Foamy macrophages, suggestive of phagocytosis of released lipids and cellular debris, were observed after 14–28 days. Necropsy showed no evidence of fat emboli or accumulation in organs.

Liposonix clinical studies in healthy adults followed. Adverse events are consisted primarily of treatment discomfort, erythema, edema, dysesthesia, and bruising [12,13]. Initial clinical studies reported a mean abdomen and waist circumference reduction of 4–5 cm after a single treatment, in which the focus was deposited 1.1–1.8 cm below the skin surface (Figure 40.5b) [13,14]. Subsequent studies, performed in 47 subjects who underwent 3 passes at graduated depths (1.6, 1.3, and 1.1 cm), showed that the average abdominal circumference was reduced by 2.5 cm at 12 weeks [15].

Both devices appear to be effective, with comparable results. The treatment discomfort and adverse events, including bruising and edema, appear to be higher with Liposonix, with reported incidence of 10%–13%, vs. a very low rate of blisters with UltraShape. This has been attributed to the use of thermal energy with Liposonix. Some have countered this by proposing that the use of thermal energy may provide some benefit, such as collagen stimulation or greater reproducibility. No controlled comparative studies are available to shed light on the difference in safety or effectiveness.

An additional device has been reported but is not FDA cleared: the SM-100, a "dual-head HIFU" system being developed by Slender Medical [16]. A 6-patient, 4-week study reports histological damage by the device; clinical efficacy has not yet been reported, nor have operating parameters been disclosed [17].

The limitations of UltraShape and Liposonix, as well as any noninvasive fat-targeting technology, are similar: they are neither intended nor able to treat obesity or to induce weight loss. This limitation is imposed not only on device design or performance but also on physiology: the treatments can lead to disruption of adipocytes, but the released triglycerides (which comprise approximately 90% of the adipocyte) retain their energy (caloric value) and are not removed from the body. Therefore, like any noninvasive approach, these treatments can be effective in the reduction of focal fat deformities but cannot remove fat from the body.

The fate of the triglycerides freed from the targeted adipocytes is not known. It is hypothesized that they are redistributed to other adipocytes. Multiple preclinical and clinical studies for both UltraShape and Liposonix show that these procedures do not lead to elevations of serum triglycerides or cholesterol nor of blood glucose or liver enzymes. Practitioners who perform these treatments often recommend that clients adopt a negative caloric after the treatment, which could potentially lead to consumption of the calories from liberated triglycerides and thereby may reduce redistribution into other adipocytes.

Cellulite Also within the arena of body contouring are focused ultrasound devices whose indication for use is temporary improvement in the appearance of cellulite. These devices deliver acoustic energy in shock waves, much as is used to shatter kidney stones. It is thought that these devices may correct or reduce elastic deficits in cellulite by altering the function of fibroblasts or by directly affecting the septa [18–20]. Animal studies have suggested there may be a direct effect on fat as well [21]. One device, the Cellactor (Storz Medical), is reported to have an additional effect on reduction of "saddle bag" fat deposits on the thighs. Application of the device's planar and radial acoustic wave therapy handpieces in 8 treatment sessions was reported to reduce subcutaneous fat layer thickness and circumference of thighs [22].

This approach, too, has been combined with additional modalities to maximize effectiveness. One device, the Proshock Ice (PromoItalia), incorporates cryolipolysis with shock waves in a single device with two dedicated handpieces and claims to improve cellulite and circumference [23]. The device is reported to operate at a variable acoustic frequency (1–16 Hz) and variable pressure (50–500 bars), with 8 ms pulses, with fat temperatures between –5°C and 5°C, which can, according to the earlier-cited manuscript, "accomplish vascular gymnastics."

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

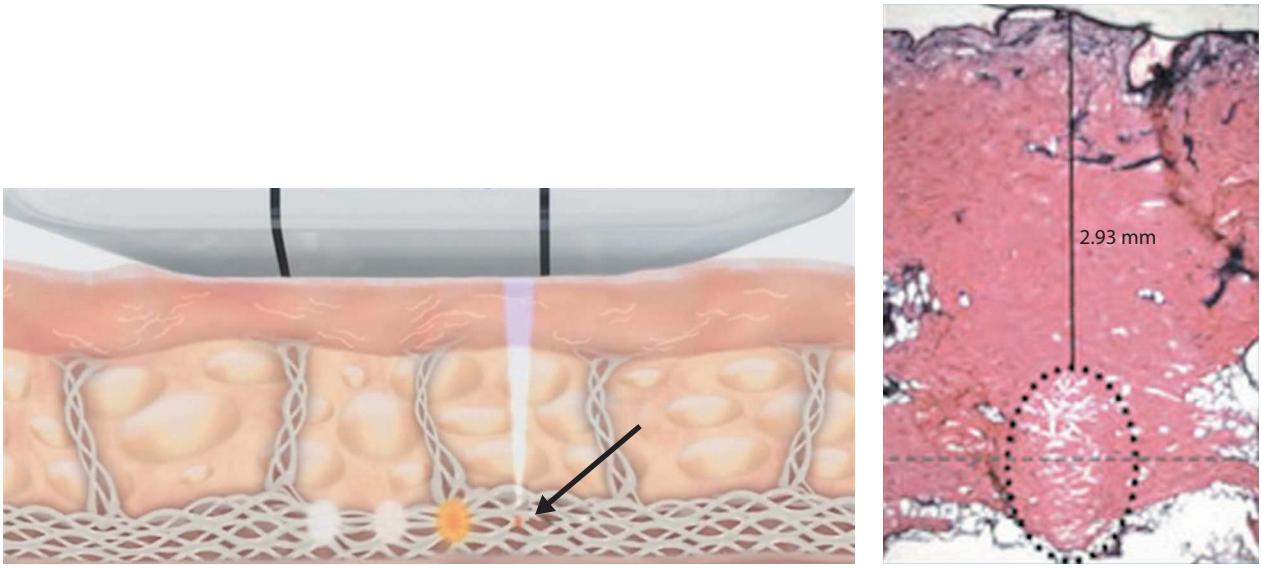


Figure 40.6 Ulthera. (a) Schematic of handpiece in clinical action. (b) Histology showing coagulation necrosis of the deep dermis. ([a] Courtesy of Ulthera, Mesa, AZ; [b] Reproduced from Laubach HJ et al., *Dermatol Surg*, 34(5), 727, 2008. With permission.)

At the time of writing this chapter, this device has not been cleared for marketing by the FDA.

Skin Tightening Focused ultrasound can be applied superficially to heat the dermis or subdermal connective tissues for the purposes of skin tightening. One device is currently marketed for this indication by Ulthera, which was FDA cleared initially to lift the brow and subsequently to lift lax submental and neck tissue (Figure 40.6). The device images the tissues prior to and during placement of the focus. Tissue shrinkage can be adjusted by altering energy and density of the foci.

Initial cadaver studies demonstrated that focused ultrasound could be used to place discrete, reproducible thermal injury zones in the facial superficial musculoaponeurotic system at depths of up to 7.8 mm, without epidermal damage [24,25]. Clinical studies showed that focused intense ultrasound tightening device to the forehead, temples, cheeks, submental region, and side of the neck, applied with specific probes (4 MHz, 4.5 mm focal depth; 7 MHz, 4.5 mm focal depth; and 7 MHz, 3.0 mm focal depth), could produce a mean brow lift of 1.7 mm 90 days after treatment ($P = 0.00001$) [26]. Treatments were performed with topical anesthetic and were well tolerated. Subsequent reports of applying one to three full-face treatments in Asian patients confirmed effectiveness but also reported bruising in 25% of treatment sessions, as well as two cases of postinflammatory hyperpigmentation [27]. Histological evaluation of treated nasolabial skin has shown increase in dermal collagen and thickening of the dermis [28]. Facial and neck laxity also appears to respond, with one study showing 80% improvement by physician assessment, with 90% of subjects reporting subjective improvement [29]. Another group reported improvement in infraorbital laxity in 15 Asian patients who underwent one or two treatments [30]. A split-face study also reported reduction in enlarged facial pores and slight but nonsignificant reduction in sebum production [31]. Treatment of the periorbital area, outside the orbital rim, has also been reported effective in reducing "crepey skin" and crow's feet [32].

Many of the studies have been done in Asian skin, as this skin type is considered to be at higher risk for postinflammatory hyperpigmentation when treated with laser/light or RF for skin tightening. Focused ultrasound provides a specific advantage in higher-risk skin types, since the energy density at the skin surface is relatively low, while higher therapeutic energy densities can be deposited below the epidermis.

The Ulthera device has been assessed for additional indications as well. Alster and Tanzi assessed response on the upper arms, medial thighs, and extensor knees of 18 paired areas. Each side was randomly treated with two different protocols (one- vs. two-pass treatments) [33]. Blinded assessors found significant improvement in all treated areas, with increased effectiveness in areas that underwent double-pass treatments with two transducers. Upper arms and knees showed more skin tightening than thighs. The device has also been reported effective in improving decolletage laxity and wrinkles [34]. The study used a 5-point photonumeric scale, chest wrinkle scale, and measured midclavicular to nipple distance. The score improved by 1–2 points, and midclavicular to nipple distance decreased by 1.5 cm. Sasaki and Tevez also reported skin tightening after treatment of the periumbilical skin, inner thighs, dorsal hands, and buttocks [32].

Other Indications Many other indications have been proposed and are likely in the pipeline. Several patent applications are published, which cover the use of focused ultrasound for hyperhidrosis, acne, and hair removal. The Ulthera device has been reported to be effective in axillary hyperhidrosis, an indication that is not yet approved

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

by the FDA. Two randomized, double-blind, sham-controlled pilot studies showed that a majority of subjects had a reduction of at least 50% in the amount of baseline axillary perspiration, measured gravimetrically, and that the hyperhidrosis disease severity scale scores were significantly improved in most subjects [35]. Results appear to be durable for 12 months.

Invasive Sources

Ultrasound has been used as an adjunct to liposuction in a procedure called ultrasound-assisted lipoplasty (UAL). UAL was first described in 1992 by Zocchi, who developed it to reduce physician fatigue during liposuction [36]. Additional benefits were heat-induced fat disruption skin tightening [37–39]. By disrupting the fat prior to liposuction, smaller cannulae could be used, with subsequent reduction in damage to neurovascular structures. The use of the wet technique of tumescent liposuction increases the effects of ultrasound. Although the first attempts to use ultrasound involved external sources, internal ultrasound probes were found to be more effective [40–42]. The ultimate benefit of ultrasound in improving safety and results is controversial, however, as the tumescent technique alone provides much of the benefit, without the risk of burns, seromas, and other adverse events and without the need for additional instrumentation [43–47].

Vibration amplification of sound energy at resonance (VASER) has been used as an adjunct to liposuction. Marketed initially by Sound Surgical (later acquired by Solta and subsequently by Valeant Pharmaceuticals), VASER applies ultrasound pulses via multiringed after tissue is infiltrated with a fluid that has dissolved gas. In this milieu, low-level ultrasound energy induces acoustic streaming, which is said to separate fat from connective tissue and to emulsify it. VASER has been used to perform what is termed "high-definition liposculpture," in which ultrasound is applied, followed by liposuction with very narrow cannulae (2–4 mm). This technique is used near the muscles of the abdomen, chest, flanks, back, buttocks, and extremities to create a sculpted appearance, accentuating desired prominences and depressions to create the appearance of a desired muscle topology, such as the "six-pack" abdomen [48–50].

Ultrasound-assisted liposuction has also been applied to other indications, notably gynecomastia, accessory breast tissue, breast reduction, lipomas, hyperhidrosis, osmidrosis/bromhidrosis, lipodystrophy, fat necrosis, and more. A partial list is presented in Table 40.1.

Table 40.1 Reported Uses of Ultrasound-Assisted Liposuction beyond Body Contouring

Indication	Reference(s)
Gynecomastia	[51–53]
Accessory breast tissue	[54,55]
Breast reduction	[52,56]
Lipoma	[57]
Hyperhidrosis	[58]
Osmidrosis/bromhidrosis	[58–60]
Lipodystrophy	[61–63]
Fat necrosis	[64,65]
Involuted hemangioma	[66]

REFERENCES

1. Foster KW, Kouba DJ, Hayes J et al. Reductions in thigh and infraumbilical circumference following treatment with a novel device combining ultrasound, suction, and massage. *J Drugs Dermatol* 2008; 7(2):113–115.
2. Garcia O Jr, Schafer M. The effects of nonfocused external ultrasound on tissue temperature and adipocyte morphology. *Aesthet Surg J* 2013; 33(1):117–127.
3. Lynn JG, Zwemer RL, Chick AJ et al. A new method for the generation and use of focused ultrasound in experimental biology. *J Gen Physiol* 1942; 26(2):179–193.
4. Mark DB, Beuerman R. Intracorneal lesions produced with focused ultrasound. *Curr Eye Res* 1982; 2(5):323–326.
5. Coleman DJ, Lizzi FL, Jakobiec FA. Therapeutic ultrasound in the production of ocular lesions. *Am J Ophthalmol* 1978; 86(2):185–192.
6. Sullivan LD, McLoughlin MG, Goldenberg LG et al. Early experience with high-intensity focused ultrasound for the treatment of benign prostatic hypertrophy. *Br J Urol* 1997; 79(2):172–176.
7. Teitelbaum SA, Burns JL, Kubota J et al. Noninvasive body contouring by focused ultrasound: Safety and efficacy of the Contour I device in a multicenter, controlled, clinical study. *Plast Reconstr Surg* 2007; 120(3):779–789; discussion 790.
8. Moreno-Moraga J, Valero-Altés T, Riquelme AM et al. Body contouring by non-invasive transdermal focused ultrasound. *Lasers Surg Med* 2007; 39(4):315–323.
9. Ascher B. Safety and efficacy of UltraShape contour I treatments to improve the appearance of body contours: Multiple treatments in shorter intervals. *Aesthet Surg J* 2010; 30(2):217–224.
10. Chang SL, Huang YL, Lee MC et al. Combination therapy of focused ultrasound and radio-frequency for noninvasive body contouring in Asians with MRI photographic documentation. *Lasers Med Sci* 2014; 29(1):165–172.
11. Jewell ML, Desilets C, Smoller BR. Evaluation of a novel high-intensity focused ultrasound device: Preclinical studies in a porcine model. *Aesthet Surg J* 2011; 31(4):429–434.
12. Gadsden E, Aguilar MT, Smoller BR et al. Evaluation of a novel high-intensity focused ultrasound device for ablating subcutaneous adipose tissue for noninvasive body contouring: Safety studies in human volunteers. *Aesthet Surg J* 2011; 31(4):401–410.
13. Fatemi A. High-intensity focused ultrasound effectively reduces adipose tissue. *Semin Cutan Med Surg* 2009; 28(4):257–262.
14. Fatemi A, Kane MA. High-intensity focused ultrasound effectively reduces waist circumference by ablating adipose tissue from the abdomen and flanks: A retrospective case series. *Aesthetic Plast Surg* 2010; 34(5):577–582.
15. Solish N, Lin X, Axford-Gatley RA et al. A randomized, single-blind, postmarketing study of multiple energy levels of high-intensity focused ultrasound for noninvasive body sculpting. *Dermatol Surg* 2012; 38(1):58–67.
16. Shalom A, Wiser I, Brawer S et al. Safety and tolerability of a focused ultrasound device for treatment of adipose tissue in subjects undergoing abdominoplasty: A placebo-control pilot study. *Dermatol Surg* 2013; 39(5):744–751.
17. Halachmi S, Lapidoth M. Commentary: Safety and tolerability of a focused ultrasound device for treatment of adipose tissue in subjects undergoing abdominoplasty, a placebo control pilot study. *Dermatol Surg* 2013; 39(5):752–754.
18. Angehrn F, Kuhn C, Voss A. Can cellulite be treated with low-energy extracorporeal shock wave therapy? *Clin Interv Aging* 2007; 2(4):623–630.
19. Siems W, Grune T, Voss P et al. Anti-fibrosclerotic effects of shock wave therapy in lipedema and cellulite. *Biofactors* 2005; 24(1–4):275–282.
20. Christ C, Brenke R, Sattler G et al. Improvement in skin elasticity in the treatment of cellulite and connective tissue weakness by means of extracorporeal pulse activation therapy. *Aesthet Surg J* 2008; 28(5):538–544.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

21. Goncalves WL, Graceli JB, Santos RL et al. Ultrasound lipoclasia on subcutaneous adipose tissue to produce acute hyperglycemia and enhance acute inflammatory response in healthy female rats. *Dermatol Surg* 2009; 35(11):1741–1745.
22. Adatto MA, Adatto-Neilson R, Novak P et al. Body shaping with acoustic wave therapy AWT((R))/EPAT((R)): Randomized, controlled study on 14 subjects. *J Cosmet Laser Ther* 2011; 13(6):291–296.
23. Ferraro GA, De Francesco F, Cataldo C et al. Synergistic effects of cryolipolysis and shock waves for noninvasive body contouring. *Aesthetic Plast Surg* 2012; 36(3):666–679.
24. White WM, Makin IR, Barthe PG et al. Selective creation of thermal injury zones in the superficial musculoaponeurotic system using intense ultrasound therapy: A new target for noninvasive facial rejuvenation. *Arch Facial Plast Surg* 2007; 9(1):22–29.
25. Laubach HJ, Makin IR, Barthe PG et al. Intense focused ultrasound: Evaluation of a new treatment modality for precise microcoagulation within the skin. *Dermatol Surg* 2008; 34(5):727–734.
26. Alam M, White LE, Martin N et al. Ultrasound tightening of facial and neck skin: A rater-blinded prospective cohort study. *J Am Acad Dermatol* 2010; 62(2):262–269.
27. Chan NP, Shek SY, Yu CS et al. Safety study of transcutaneous focused ultrasound for non-invasive skin tightening in Asians. *Lasers Surg Med* 2011; 43(5):366–375.
28. Suh DH, Shin MK, Lee SJ et al. Intense focused ultrasound tightening in Asian skin: Clinical and pathologic results. *Dermatol Surg* 2011; 37(11):1595–1602.
29. Lee HS, Jang WS, Cha YJ et al. Multiple pass ultrasound tightening of skin laxity of the lower face and neck. *Dermatol Surg* 2012; 38(1):20–27.
30. Suh DH, Oh YJ, Lee S et al. A intense-focused ultrasound tightening for the treatment of infraorbital laxity. *J Cosmet Laser Ther* 2012; 14(6):290–295.
31. Lee HJ, Lee KR, Park JY et al. The efficacy and safety of intense focused ultrasound in the treatment of enlarged facial pores in Asian skin. *J Dermatolog Treat* 2015 February; 26(1):73–77.
32. Sasaki GH, Tevez A. Clinical efficacy and safety of focused-image ultrasonography: A 2-year experience. *Aesthet Surg J* 2012; 32(5):601–612.
33. Alster TS, Tanzi EL. Noninvasive lifting of arm, thigh, and knee skin with transcutaneous intense focused ultrasound. *Dermatol Surg* 2012; 38(5):754–759.
34. Fabi SG, Massaki A, Eimpunth S et al. Evaluation of microfocused ultrasound with visualization for lifting, tightening, and wrinkle reduction of the decolletage. *J Am Acad Dermatol* 2013; 69(6):965–971.
35. Nestor MS, Park H. Safety and efficacy of micro-focused ultrasound plus visualization for the treatment of axillary hyperhidrosis. *J Clin Aesthet Dermatol* 2014; 7(4):14–21.
36. Zocchi M. Ultrasonic liposculpturing. *Aesthetic Plast Surg* 1992; 16(4):287–298.
37. Zocchi ML. Basic physics for ultrasound-assisted lipoplasty. *Clin Plast Surg* 1999; 26(2):209–220, vii.
38. Kenkel JM, Robinson JB Jr, Beran SJ et al. The tissue effects of ultrasound-assisted lipoplasty. *Plast Reconstr Surg* 1998; 102(1):213–220.
39. Zocchi ML. Ultrasonic assisted lipoplasty: Technical refinements and clinical evaluations. *Clin Plast Surg* 1996; 23(4):575–598.
40. Cook WR Jr. Utilizing external ultrasonic energy to improve the results of tumescent liposculpture. *Dermatol Surg* 1997; 23(12): 1207–1211.
41. Kinney BM. Body contouring with external ultrasound. Plastic Surgery Educational Foundation DATA Committee. Device and Technique Assessment. *Plast Reconstr Surg* 1999; 103(2):728–729.
42. Rosenberg GJ, Cabrera RC. External ultrasonic lipoplasty: An effective method of fat removal and skin shrinkage. *Plast Reconstr Surg* 2000; 105(2):785–791.
43. Igra H, Satur NM. Tumescent liposuction versus internal ultrasonic-assisted tumescent liposuction: A side-to-side comparison. *Dermatol Surg* 1997; 23(12):1213–1218.
44. Troilius C. Ultrasound-assisted lipoplasty: Is It really safe? *Aesthetic Plast Surg* 1999; 23(5):307–311.
45. Fodor PB. Power-assisted lipoplasty versus traditional suction-assisted lipoplasty: Comparative evaluation and analysis of output. *Aesthetic Plast Surg* 2005; 29(2):127.
46. Fredricks S. Analysis and introduction of a technology: Ultrasound-assisted Lipoplasty Task Force. *Clin Plast Surg* 1999; 26(2):187–204, vii.
47. Neuhann-Lorenz C. Ultrasound-assisted lipoplasty: The ad hoc situation. *Aesthetic Plast Surg* 2009; 33(2):219.
48. Garcia O Jr, Nathan N. Comparative analysis of blood loss in suction-assisted lipoplasty and third-generation internal ultrasound-assisted lipoplasty. *Aesthet Surg J* 2008; 28(4):430–435.
49. de Souza Pinto EB, Abdala PC, Maciel CM et al. Liposuction and VASER. *Clin Plast Surg* 2006; 33(1):107–115, vii.
50. Jewell ML, Fodor PB, de Souza Pinto EB et al. Clinical application of VASER—Assisted lipoplasty: A pilot clinical study. *Aesthet Surg J* 2002; 22(2):131–146.
51. Strasser EJ. Ultrasound aspiration for gynecomastia. *Plast Reconstr Surg* 2003; 112(7):1967–1968; author reply 1968–1969.
52. Di Giuseppe A. Breast reduction with ultrasound-assisted lipoplasty. *Plast Reconstr Surg* 2003; 112(1):71–82.
53. Wong KY, Malata CM. Conventional versus ultrasound-assisted liposuction in gynaecomastia surgery: A 13-year review. *J Plast Reconstr Aesthet Surg* 2014 July; 67(7):921–926.
54. Emsen IM. Treatment with ultrasound-assisted liposuction of accessory axillary breast tissues. *Aesthetic Plast Surg* 2006; 30(2):251–252.
55. Walgenbach KJ, Riabikhin AW, Galla TJ et al. Effect of ultrasonic assisted lipectomy (UAL) on breast tissue: Histological findings. *Aesthetic Plast Surg* 2001; 25(2):85–88.
56. Pedron M. Minimal-scar breast reduction and mastopexy. *Aesthetic Plast Surg* 2005; 29(4):261–273.
57. Silistreli OK, Durmuş EU, Ulusal BG et al. What should be the treatment modality in giant cutaneous lipomas? Review of the literature and report of 4 cases. *Br J Plast Surg* 2005; 58(3):394–398.
58. Commons GW, Lim AF. Treatment of axillary hyperhidrosis/bromidrosis using VASER ultrasound. *Aesthetic Plast Surg* 2009; 33(3):312–323.
59. Chung S, Yoo WM, Park YG et al. Ultrasonic surgical aspiration with endoscopic confirmation for osmidrosis. *Br J Plast Surg* 2000; 53(3):212–214.
60. Park S. Very superficial ultrasound-assisted lipoplasty for the treatment of axillary osmidrosis. *Aesthetic Plast Surg* 2000; 24(4):275–279.
61. Baynosa RC, Shah HR, Khiabani KT et al. Ultrasound-assisted liposuction in the treatment of lipodystrophy secondary to cushingoid-type disease of unknown cause. *Plast Reconstr Surg* 2004; 114(2):474–477.
62. del Mar Gutierrez M, Mateo G, Domingo P. Strategies in the treatment of HIV-1-associated adipose redistribution syndromes. *Expert Opin Pharmacother* 2007; 8(12):1871–1884.
63. Hultman CS, McPhail LE, Donaldson JH et al. Surgical management of HIV-associated lipodystrophy: Role of ultrasonic-assisted liposuction and suction-assisted lipectomy in the treatment of lipohypertrophy. *Ann Plast Surg* 2007; 58(3):255–263.
64. Caterson SA, Tobias AM, Slavin SA et al. Ultrasound-assisted liposuction as a treatment of fat necrosis after deep inferior epigastric perforator flap breast reconstruction: A case report. *Ann Plast Surg* 2008; 60(6):614–617.
65. Hassa A, Curtis MS, Colakoglu S et al. Early results using ultrasound-assisted liposuction as a treatment for fat necrosis in breast reconstruction. *Plast Reconstr Surg* 2010; 126(3):762–768.
66. Fisher MD, Bridges M, Lin KY. The use of ultrasound-assisted liposuction in the treatment of an involuted hemangioma. *J Craniofac Surg* 1999; 10(6):500–502.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Lasers for tattoo removal

Isabelle Catoni, Tiago Castro, and Mario A. Trelles

INTRODUCTION

Tattoos are an ancient art form with origins that trace back as far as the Stone Age (12,000 BCE). Tattoos have remained popular throughout time and across many cultures and continents. Although most psychological studies of persons with tattoos have been restricted to psychiatric inpatients, prisoners in correctional institutions, and military personnel (thus reflecting only specific populations), one common conclusion is that, of all the motives for obtaining a tattoo, the quest for personal identity is central.

The skin serves as a useful canvas on which to portray statements of individuality, sexuality, belonging, machismo, frustration, boredom, and anger. However, the quest for identity by teenagers often becomes irrelevant or embarrassing by age 40. While tattoos are acquired for internal expectations of self-identity at an early age, tattoo removal also seems to be internally motivated to dissociate from the past and to improve self-identity [1].

Egyptian mummies from 4000 BCE show evidence of attempts at tattoo removal. However, since most people live in the present moment, rather than in anticipation of future endeavors, tattoos remain popular.

In recent years, the number of tattooed individuals has increased significantly [2,3]. In the United States, up to 24% of the population are tattooed [3], whereas in European countries such as Germany and the United Kingdom, approximately 9% and 12% of the population, respectively, have tattoos [4,5]; some of them are of artistic nature or extremely sophisticated (Figure 41.1).

In general, tattoos are not well received by the public and often create a barrier to employment. Individuals with tattoos are often perceived as antisocial, aggressive, or immature and as being unable to accept controls and authority.

Tattoo removal can be attempted or achieved by a variety of modalities, some of which may be painful, expensive, and not without adverse effects (Figure 41.2).

The commonly used lasers for tattoo removal are the 694 nm Q-switched ruby laser (QSRL), the 755 nm QS alexandrite laser, the 1064 nm Nd:YAG laser, and the 532 nm Nd:YAG laser. Current research focus is on newer picosecond lasers as an alternative for the QS systems.

HISTORY OF TATTOOING

The word "tattoo" is said to have two major derivations—from the Polynesian word *ta*, which means striking something, and the Tahitian word *tatau*, which means "to mark something." The history of tattoo began over 5000 years ago and is as diverse as the people who wear them.

A particularly well-preserved mummy dating back ~4000 years demonstrated intact tattoos [6]. Many artifacts that have been discovered from this era show markings resembling the tattoos on this mummy. Thus, tattooing was probably widespread many thousands of years ago and even earlier.

Tattooing has been a Eurasian practice at least since Neolithic times. The earliest known tattoo representing an image was found portraying the Egyptian god Bes. Tattoos of Bes have been found on female mummies dating from approximately 400 BCE [7,8]. Body decoration has evolved throughout the world at many sites independently of one another and has been used for beautification, religious expression, and healing and as a form of punishment. Mummies discovered in Russia and South America have demonstrated evidence of tattooing and, together with mummies from Egypt that demonstrate tattoos, have shown that independent populations conceived the art of tattooing independently [8,9].

Pre-Christian Germanic, Celtic, and other central and northern European tribes were often heavily tattooed, according to surviving accounts. The Picts were famously tattooed (or scarified) with elaborate, war-inspired black or dark blue woad (or possibly copper for the blue tone) designs. Julius Caesar described these tattoos in Book V of his *Gallic Wars* (54 BCE).

Various other cultures have had their own tattoo traditions, ranging from rubbing cuts and other wounds with ashes to hand pricking the skin to insert dyes.

Tattooing in the Western world today has its origins in Polynesia and in the discovery of tatau by eighteenth-century explorers. The Polynesian practice became popular among European sailors. As sailors traveled abroad and returned home with tattoos inscribed on their bodies, they began to show up in mainstream European, and eventually North American, figurations.

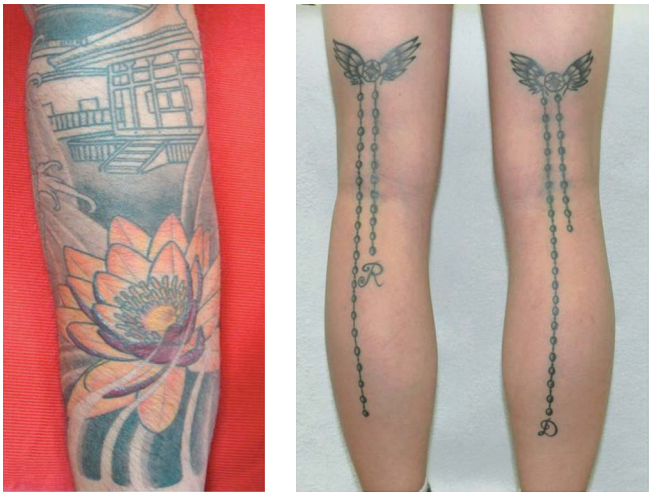
TYPES OF TATTOOS

Tattoos are foreign pigment particles implanted into the dermis and can be easily detected histologically, with hematoxylin/eosin staining (HE/EO). Pigment particles can vary in size, composition, and dermal depth and are in accordance with the expertise of the tattooist when inoculating the pigment, which can be in random or well-structured layers (Figures 41.3 and 41.4).

The majority of tattoo pigments are not FDA approved, and, therefore, it usually is not clear what compounds make up any given tattoo ink. Generally, tattoo pigments comprise inorganic and/or organic compounds, such as chromium, mercury, iron, copper, carbon, and polycyclic compounds.

Tattoos can be divided into five categories: professional, amateur, cosmetic, traumatic, and medical.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b)

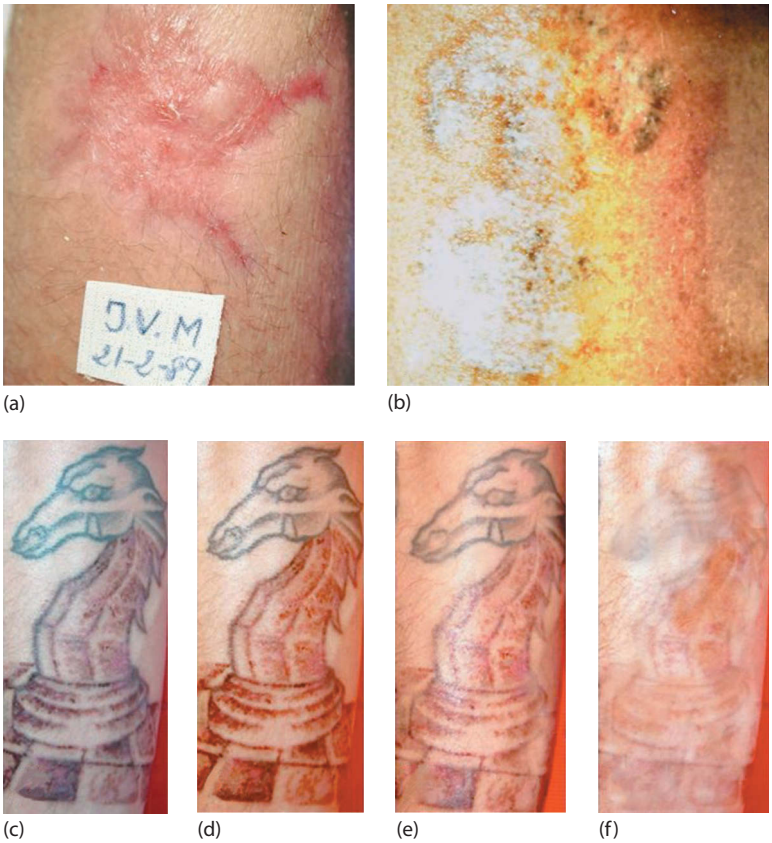
Figure 41.1 (a) Forearm decorative tattoo. The artist used the skin as a canvas using oriental motif designs. (b) This tattoo was probably meant to be funny when it was done, but now, just 30 days after, the patient does not like it, requesting that it be removed.

Professional tattoos, placed by the vibrating needle of a tattoo machine, are the most common. These tattoos are created with pigments in a variety of colors that are known to withstand the test of time.

In comparison, *amateur tattoos* are composed of substances such as charcoal, pen ink, and soot. It is unusual to see colors other than black in amateur tattoos. Since these tattoos are usually light and made of organic ink, they tend to be quite easy to remove. The pigment is administered using homemade "tattoo machines" or simply a handheld needle [10].

Cosmetic tattoos have become increasingly popular in recent years, which are used to enhance physical appearance. When used as a form of cosmetics, tattooing includes permanent makeup to enhance the eyebrows, lips (liner and/or lipstick), and eyes (liner). Although cosmetic tattoos are composed of a mixture of compounds, the pink, red, and flesh-colored tones often contain ferric oxide and titanium dioxide [11] (Figure 41.5).

Traumatic tattoos, also called "natural tattoos," result from injuries, especially asphalt from road injuries or pencil lead. These materials become lodged in the dermis after reepithelialization of the wound and result in blue or black tattoos, depending on their depth [12]. These particles may be deeply embedded, which makes their removal extremely difficult [13,14] (Figure 41.6).



(a) (b)

(c) (d) (e) (f)

Figure 41.2 Complications as a consequence of tattoo elimination. (a) Hypertrophic scarring with evident fibrosis and chronic erythema. (b) Recurrent ulcering of difficult resolution and hypopigmentation. (c–f) Correspond to the various sessions involved in eliminating a black tattoo with color changes due to the type of ink used. There is hemosiderin as a consequence of vessel rupture due to the photoacoustic effect produced by the laser's high energy pulses.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

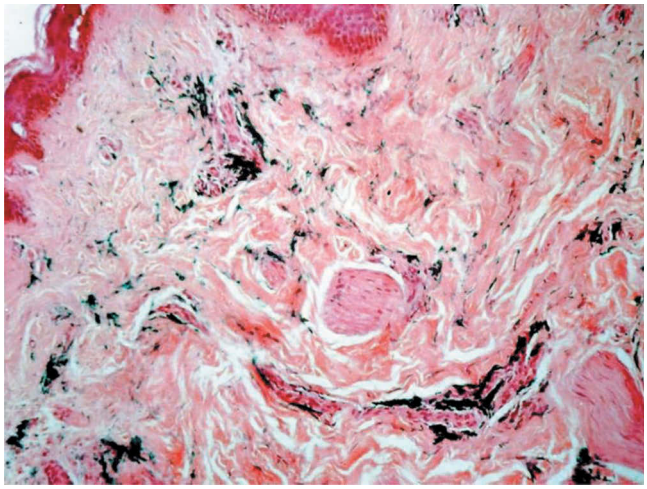


Figure 41.3 Skin ×250 HE/EO. Inhomogeneous pigment deposits in dermis are observed, corresponding to a tattoo done by an amateur.

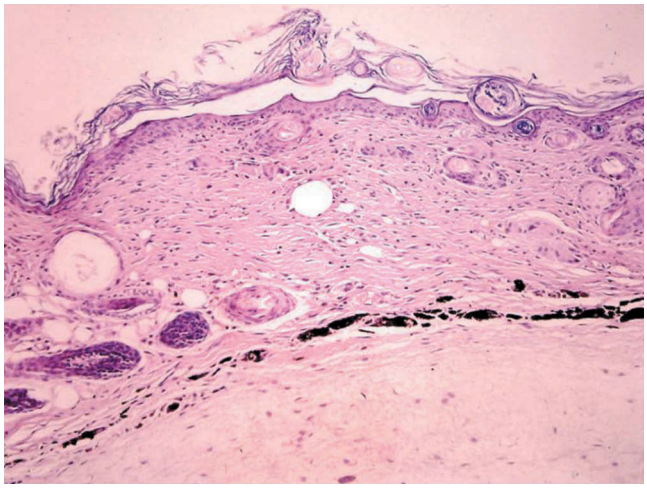


Figure 41.4 Skin ×100 HE/EO. A homogeneous display of the pigment, in well-ordered layer, is observed in a tattoo done by a professional using a tattooing device.

Medical tattoos are used as markers for administering radiation therapy and for the areola in some forms of breast reconstruction. Tattooing has also been used to convey medical information about the wearer (e.g., blood group, medical condition, etc.) and in skin tones to cover vitiligo.

TATTOO REMOVAL TECHNIQUES

Over the centuries, different methods for tattoo removal have been explored. The earliest report of attempted tattoo removal was from Aetius, a Greek physician, who described salabrasion in 543 CE [15].

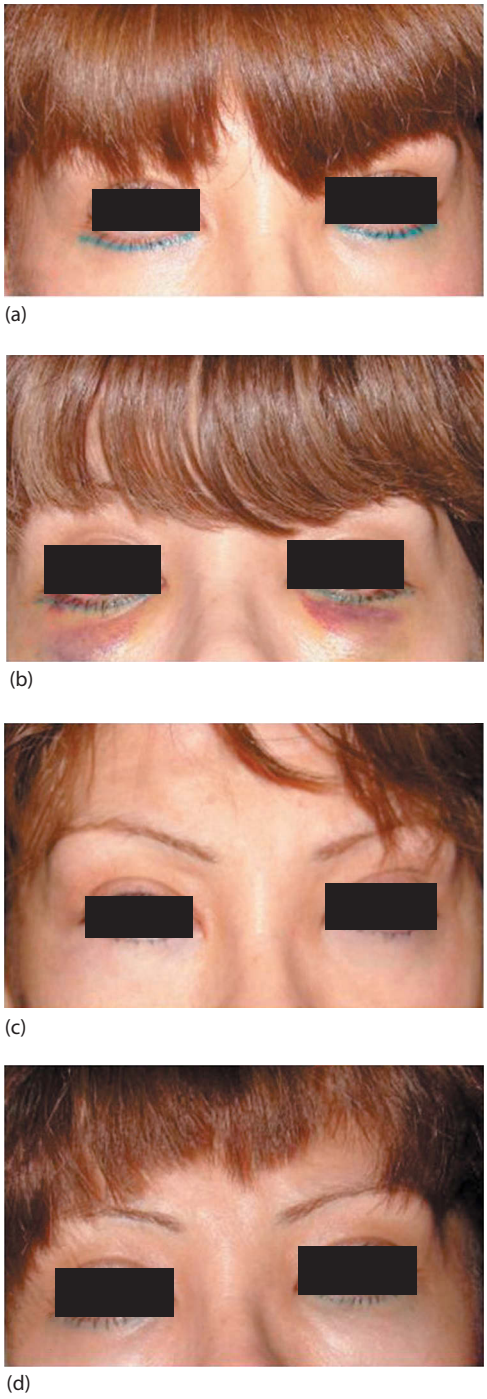
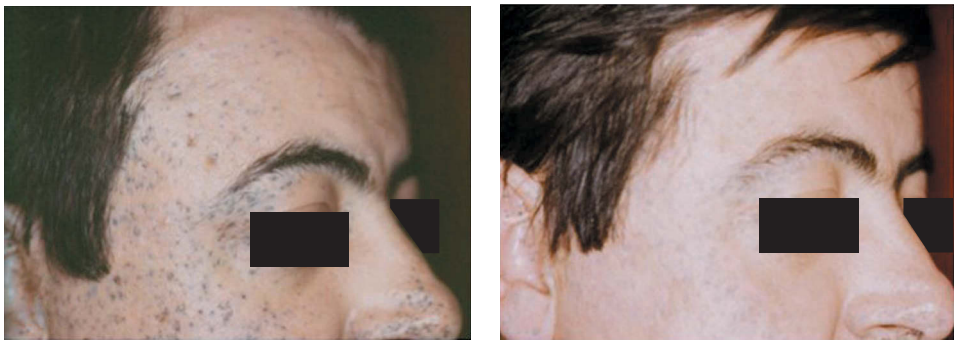


Figure 41.5 Eye lining with a permanent green tattoo, with titanium dioxide, on the bottom eyelashes. (a) Before treatment for elimination. (b) One week after, edema and ecchymosis are observed. (c) Three weeks after. (d) Two months after the second treatment with a CO_2 laser.

Less modern tattoo removal techniques involve the destruction or removal of the outer skin layers by mechanical, chemical, or thermal means, accompanied by inflammation. Transepidermal elimination of pigment occurs through denuded skin and via an exudative phase that allows tattoo pigment to migrate to the wound surface. The inflammatory

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b)

Figure 41.6 Traumatic tattoo due to explosion of gunpowder. (a) Before treatment. (b) Results after 8 treatment sessions with a 1064 nm Q-switched Nd:YAG laser.

response may also promote macrophage activity, with increased phagocytosis, enabling additional pigment loss during the healing phase [16,17].

Mechanical Methods

Salabrasion, the oldest method of physical tissue destruction, involves abrading the superficial dermis with coarse granules of common table salt and a moist gauze pad. Salt is applied to the wound surface and left under a surgical dressing for 24 hours. A variation on this method is the removal of the salt immediately after salabrasion to minimize scarring and hypopigmentation [18]. Salabrasion seems to be most effective for the removal of amateur tattoos [19,20], but given the associated risk of scarring, this technique has decreased in popularity over the last decade and is now rarely used (Figure 41.7).

Dermabrasion involves the use of a diamond fraise wheel or a wire brush that removes the surface of skin that has been frozen to create a rigid surface. In addition to resulting in a high incidence of scarring, this technique also aerosolizes blood and tissue, which can be a hazard to the treating physician and other people in the treatment room. Dermabrasion for the removal of tattoos is usually administered in a single treatment, although sometimes a series of treatments are used in an attempt to decrease the scarring that may occur from a single, more intensive treatment. Utilizing multiple, less deep dermabrasion treatments can reduce scarring; however, there is virtually always some scarring, loss of normal skin pigment, and residual tattoo when using this method of tattoo removal [18,20–24] (Figure 41.8).

Using salt or other rough surfaces such as sandpaper in an attempt to remove tattoo can also remove the surface of the skin. The resulting inflammation that occurs enables removal of some tattoo pigment. After salabrasion, a dressing may be applied that also contains salt. The use of all of these destructive modalities (dermabrasion, salabrasion, or sandpaper) often results in significant scarring of the treated area, loss of pigment, and residual tattoo (Figure 41.9).

These destructive methods are not recommended for modern tattoo removal and carry a significant risk of hypertrophic scarring or keloid formation after the procedure.

Another mechanical method is the surgical excision, which completely removes the tattoo (Figure 41.10).

Surgery can be used for small tattoos located in areas of adequate skin laxity [25].

The techniques vary according to the location and size and the surgeon's experience [25]. However, surgery remains somewhat controversial because it exposes healthy individuals to numerous immediate and late complications of surgical procedures. Scarring is not avoidable, and pigmentary skin changes may occur in some subjects [25].

Koljonen and Kluger [26] observed that patients seeking surgery as a tattoo removal method tend to find their tattoos

(a) (b) (c)

Figure 41.7 Elimination by salt abrasion of a black amateur tattoo on forearm. (a) Before treatment. (b) Results 3 weeks after treatment. Tissue is not yet repaired. (c) Aspect 2 months after treatment. Some residual pigment is observed as well as hypopigmentation and atrophic scarring.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 41.8 Elimination of an amateur monochromatic (black) tattoo on forearm. (a) Before treatment. (b) Two weeks after treatment carried out mechanically with a high rotating diamond drill. These results will most likely lead to a complication with skin healing.

(a) (b)

Figure 41.9 (a) Aspect of an amateur tattoo on the arm, done 25 years ago, which is presently fading. (b) Immediately after one intent at elimination using sand paper. The total epidermis has been eliminated as well as the papillary dermis. There is no bleeding, and the tattoo appears deeply erased although there is still residual pigment.

more disturbing and may have sought medical advice earlier. They speculate that those patients expected faster and more "radical" tattoo removal, despite the risk of scarring. The author (MAT) found that the patients would prefer to accept a quick scar instead of progressive whitening of the tattooed skin, reflecting the deep emotional and personal states associated with the tattoo itself. Therefore, they concluded that the possibility of surgical tattoo removal should be accessible to patients if the tattoo is small and discussion with the patient reveals strong personal motivation (Figure 41.11).

Surgical removal is also preferable in situations where people have allergic reactions to their tattoos. Attempts at laser removal in this situation may lead to anaphylactic reactions and is not advised. This includes treatment with a CO_2 laser.

Chemical Methods

Chemical tissue destruction methods using compounds such as tannic acid and silver nitrate have also been described. The technique known as the French method involves disruption of the skin surface with punctures and incisions, followed by the application of caustic chemicals. An eschar forms in the subsequent 2–3 weeks, leading to the removal of the tattoo [27]. This technique can be used for the removal of amateur tattoos

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 41.10 Professional tattoo on the forearm, partially removed surgically. Observe the line of incision sutured in the center of the tattoo, indicating the need for various future surgical interventions.

of any size. The results and complication risks are comparable to cryotherapy, infrared coagulation, and focal salabrasion [19]. This method is rarely used today (Figure 41.12).

Thermal Methods

Thermal methods of tattoo removal destroy the superficial layers of the skin and result in massive inflammation, with significant scarring. Virtually any source of heat has been used at one point or another to remove tattoos. Patients have used cigarettes and cigars, heated metal objects, fire, and other sources of heat to remove tattoos. Although most commonly resulting in a scar, there seems to be an extremely narrow range where thermal removal of tattoo pigment works with little or no scarring.

There are various thermal methods of tattoo removal: cryotherapy, cauterization, infrared coagulation, and ablation with CO_2 laser. These modalities most often result in incomplete removal of the tattoos or varying degrees of scarring [28].

The CO_2 laser targets water and has the capacity to vaporize superficial skin, making it a potential option for removing skin tattoo. Although its nonselective nature makes it similar

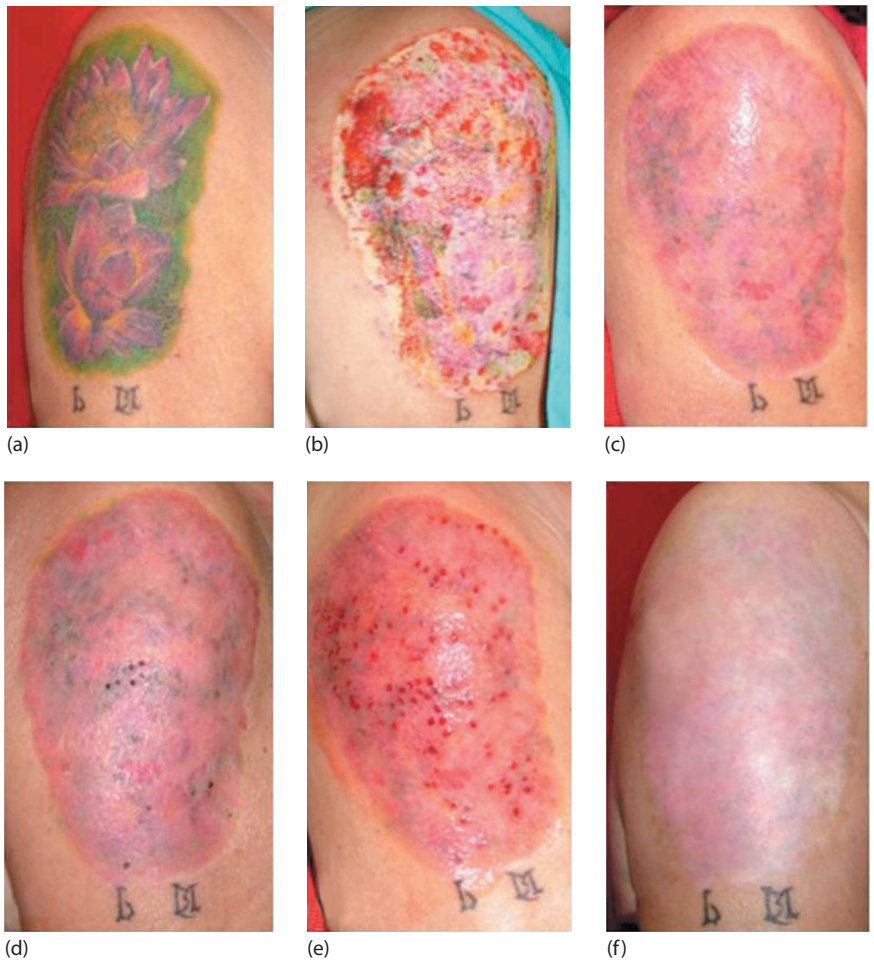
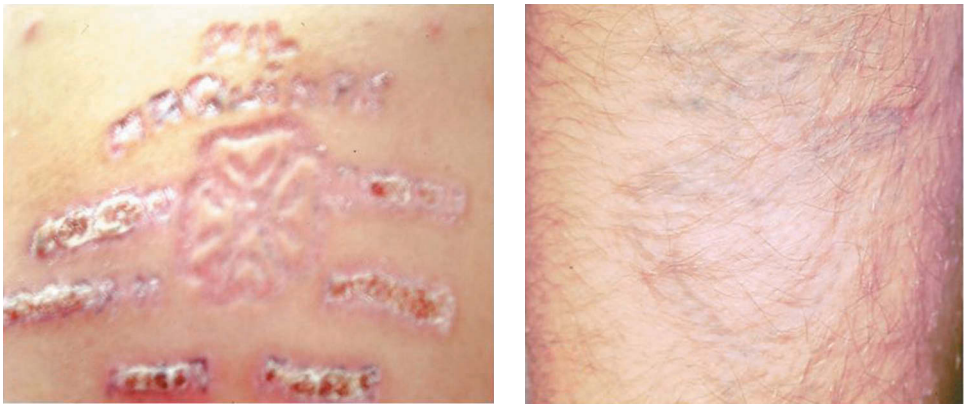


Figure 41.11 Radical one-time removal of a polychromatic tattoo, on the deltoid region. This is a double-layered tattoo, carried out over an older one using pigment with color of difficult elimination. (a) Before treatment. (b) Immediately after Er:YAG laser ablation. Two passes of 22 J/cm^2 were necessary. (c) Aspect 1 month after treatment. Residual pigment is observed. (d) Using the same laser with power density of 44 J/cm^2 in the form of "punch ablations" was carried out. (e) After 15 days, the same "fractionalized" treatment was repeated to eliminate deep residual pigment. (f) Results 6 months after treatment.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b)

Figure 41.12 Chemical elimination of a polychromatic amateur tattoo. (a) Two weeks after treatment with 70% trichloroacetic acid (TCA) applied with a cotton swab. (b) Results 1 year later.

(a) (b)

Figure 41.13 Lip liner tattoo for vermilion border enhancement. (a) Before treatment, patient also presented wrinkles on the upper lip. (b) Two months after treatment with CO_2 laser, pigment has disappeared and the wrinkles have been corrected after resurfacing with the same laser. The whole aspect of the lip is rejuvenated.

to other destructive modalities, the CO_2 laser has the ability to ablate more uniform and superficial layers of skin as compared to other, more primitive methods [29], thereby reducing the risk of hypertrophic scarring. The CO_2 laser can be helpful, especially for the removal of cosmetic tattoos on the face, such as lip or eyeliner tattoo [30] (Figure 41.13); however, it is impractical for areas of the face or for large, extensive tattoos. In these cases, the result once again is an incompletely removed tattoo with scarring [31,32].

Modern Thermal Methods: QS Lasers

Anderson and Parrish's [33] principle of selective photothermolysis revolutionized the treatment of tattoos. They proposed that if a wavelength was well absorbed by the target and the pulse width was equal to or shorter than the target's thermal relaxation time, the heat generated would be confined to the target. To specifically target tattoos, laser wavelength and pulse duration must be chosen appropriately.

First, the pigment molecules must absorb the laser light in order to convert a sufficient amount of light energy to heat inside the pigment particle. The type of pigment in the skin and its absorption spectrum is usually unknown to the patient and the physician. Therefore, the tattoo color and the transient whitening of the skin directly after laser impact can guide the physician. The explosion of pigment particles causes skin whitening, which lasts for about 30 minutes, indicating proper light absorption by the pigments.

Second, the radiant exposure of the applied laser pulses must be high enough to provide a sufficient temperature increase in the pigment particle. Considering the short pulse duration of the laser pulses, their intensity is in the range of 107–108 W/cm^2. Owing to the small size of the particles and the rapid heating process in the particle, the pigment particles reach very high temperatures of several hundred degrees Celsius within nanoseconds (Figure 41.14).

Consequently, the particles explode, which is necessary for pigment transportation via the lymphatic system.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b) (c)

Figure 41.14 (a) Q-switched 532 nm laser effects after elimination of a polychromatic, professional tattoo on the buttock. (b) Presence of typical white elevations that correspond to detachment of the epidermis due to effect of the acoustic wave produced during the interaction of laser energy and pigment. (c) This epidermis can be easily detached to attempt a new laser pass in view of removing the difficult colors of pigments.

These explosions of pigment particles in the skin have been already detected by histology [34].

Third, the duration of the laser pulses must be adapted to the size of the target, which is the pigment particle in the skin. The pulse duration must be in the range of nanoseconds because the size of pigment particles is in the range of a few micrometers. These very short pulse duration and high light intensities are feasible only using a special laser technique called Q-switch. Therefore, only these laser types can be recommended for tattoo removal.

Q-switching is a technique that produces nanosecond laser pulses by suddenly releasing all of the excited state energy from a laser medium.

Using QS lasers, a rapid thermal expansion of the target occurs, which leads to its fragmentation. The high-temperature gradients produced result in the formation of acoustic waves. Propagation of these waves causes mechanical destruction of surrounding structures [35]. Therefore, the underlying mechanism of laser tattoo removal may be explained through these photoacoustic effects, and the effects on tissue can be well followed histologically in order to recognize the various aspects of skin reaction (Figure 41.15).

At present, there are four different types of QS lasers that are employed successfully in tattoo removal: 532 and 1064 nm Nd:YAG, alexandrite, and ruby. With appropriate use, the risk of scarring is less than 4.5% for all treatments [36,37]. During the laser treatment of tattoos, energy impulses should be placed without considerable overlap in order to avoid additional thermal damage (Figure 41.16).

QSRL (694 nm)

In 1965, Goldman documented the earliest report of tattoo pigment interaction with short-pulsed lasers [38]. He compared the reaction of a dark blue tattoo to a QSRL with nanosecond pulses to that of a microsecond-pulsed ruby laser. With microsecond impacts, he demonstrated nonspecific thermal necrosis, while nanosecond impacts only produced transient edema accompanied by a peculiar whitening of the impact area. No thermal necrosis was present with nanosecond pulses, but retention of tattoo pigment was reported, so this attempt of Goldman was deemed to be a failure.

Many years later, other investigators confirmed and expanded these results by using a QSRL (694 nm) to remove blue and black tattoo pigment successfully without tissue damage [39].

The QSRL laser has historically been extremely effective at removing black and blue tattoo pigments. In general, amateur tattoos tend to respond much more rapidly to treatment with the QSRL than professionally placed tattoos do [29,40] (Figure 41.17).

Taylor et al. [40] demonstrated clearing of amateur and professional tattoos using the QSRL. They used a ruby laser with a 40–80 ns pulse duration using fluences that ranged from 1.5 to 8.0 J/cm^2. It was found that higher fluences resulted in better tattoo clearance and 4–8 J/cm^2 was the optimal fluence range. The overall results were excellent in 78% of amateur tattoos but in only 23% of professional tattoos. Despite these discouraging results, the authors were optimistic that the QSRL would become the preferred treatment for tattoos because of the rare result of scarring (only one of 57 tattoos treated).

In another study by Scheibner et al. [41], 101 amateur and 62 professional tattoos were treated with a QSR laser. The laser utilized a 5–8 mm spot size and fluences of 2–4 J/cm^2. An average of three treatments was administered to each tattoo. Amateur tattoos responded well with complete removal in 4 tattoos, nearly complete removal in 84, and significant pigment removal in 11, with minimal tattoo removal in only 2. In the case of professional tattoos, there was complete pigment removal in 2, nearly complete pigment removal in 5, significant pigment removal in 18, minimal pigment removal in 25, and very little pigment removal in 12. Tattoos of the face and the neck responded faster but were more sensitive to tissue damage, necessitating lower fluences. Among the professional tattoos, a better response was noted with older tattoos and blue and black inks in comparison to other colors (red, yellow, and green). No scarring was reported in any of these patients.

Leuenberger et al. treated 47 blue–black tattoos simultaneously with the QS ruby, QS Nd:YAG, and QS alexandrite lasers and demonstrated that the QS ruby produces superior clearing of these pigments [42].

Kilmer and Anderson [43] found the QSRL to be effective not only for black and blue pigments. Using fluences of 6–8 J/cm^2 with a 40–80 ns pulse width, they reported black and green ink to be the most responsive, with other colors requiring significantly more treatments.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

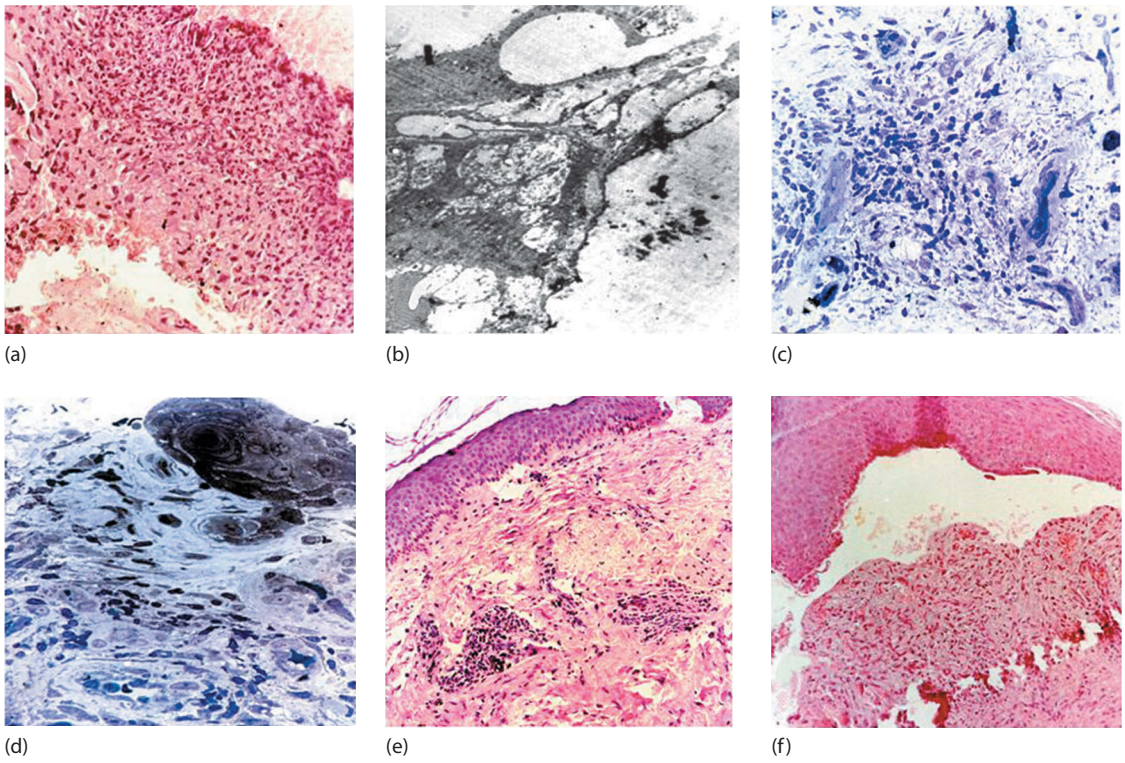


Figure 41.15 (a) Skin × 250 HE/EO. Sample of a tattoo immediately after treatment with a Q-switched laser. Fibronecrotic material including pigment and blood is seen. (b) Electron microscopy sample × 6300 of tattoo immediately after treatment with Q-switched laser. There are extended tissue necrosis and vascularization of the reticular endothelium. Small pigment deposits are noticed in the extracellular spaces. (c) Skin × 250 toluidine blue. A semi-fine cut 4 days after treatment of tattoo with Q-switched laser shows dermal changes with neovascular formation. There are inflammatory components, as well as edema, but no residual. (d) Skin × 250 toluidine blue. Two weeks after treatment of a tattoo with the Q-switched Nd:YAG laser, there is dermal neovascularization. Mature lymphoid elements are noticed but no pigment. (e) Skin × 250 HE/EO. Three weeks after Q-switched laser treatment, the epidermis is well in the process of regeneration. There is a correct cellular maturation, and scattered pigment in both superficial and deep dermis is observed. Collagen fibers appear lax. (f) Skin × 250 HE/EO. Four weeks after treatment for removal of a black tattoo with the Q-switched 1064 nm laser. The epidermis is completely regenerated. Abundant new vascularization is present in the dermis with fibroblasts of prominent nucleus. There is no residual pigment. (Reproduced from Sanchez Pérez J, Análisis Experimental par optimización de los parámetros de eliminación de los tatuajes por acción multifotónica coherente, PhD thesis, University of Valencia School of Medicine, Valencia, Spain, 1989. With permission.)

The QSRL is remarkably effective in removing tattoos with minimal scarring. The wavelength produced by the QSRL (694 nm) is also well absorbed by melanin. Therefore, the QS ruby laser can be associated with posttreatment hypopigmentation and, although usually transient, may be permanent. Transient hyperpigmentation seems to be related more to skin type than to laser treatment [39,42,43].

QS Nd:YAG Laser (1064 nm)

The QS Nd:YAG laser was developed in 1989 with an emission of 1064 nm and pulse duration of 10–20 ns. In this wavelength, it is possible to treat dark pigments. In addition, the red, yellow, and orange pigments can also be removed because the laser has the property to be modified to a green light with an emission of 532 nm by placing a potassium-titanyl-phosphate (KTP) crystal within the laser cavity [44].

The QS Nd:YAG laser was explored in anticipation that its longer wavelength (1064 nm) would increase dermal penetration and decrease melanin absorption, thus improving the response of QSRL-resistant tattoos and avoiding pigmentary changes.

Kilmer et al. treated 39 tattoos using a QS Nd:YAG laser with fluences from 6 to 12 J/cm^2 [45] They achieved greater than 75% ink removal in 77% of black tattoos treated, without secondary hypopigmentation. Treatment with highest fluences (10–12 J/cm^2) was proved to be more effective at removing black tattoo ink, with more than 95% of the black ink cleared in 28% of the tattoos after four treatment sessions. Colors other than black were removed less effectively in the study.

Dark tattoo pigments effectively absorb the relatively long 1064 nm wavelength, which is less well absorbed by epidermal melanin pigment. This property makes this laser well suited for tattoo removal in dark-skinned patients with less risk of affecting epidermal melanin pigment (Figure 41.18). In a case report of 15 tattoos treated with the QS Nd:YAG laser in patients with skin type VI, more than half the tattoos treated were rated as being 75%–95% improved after three to four treatments, and no scarring was reported [46]. Only 2 of the 15 patients had slight lightening of the skin. This offers a potential advantage in darkly pigmented individuals. Other studies have demonstrated similar results in this population [47,48].

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

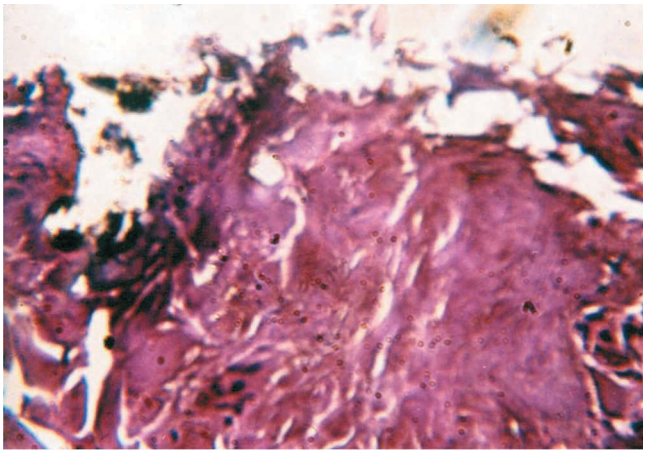
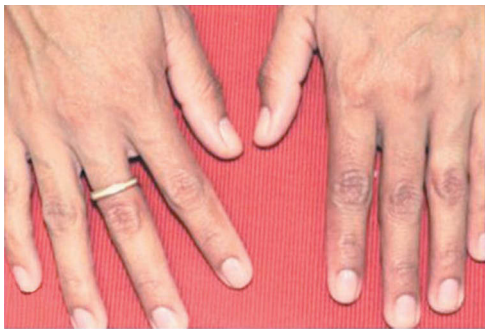


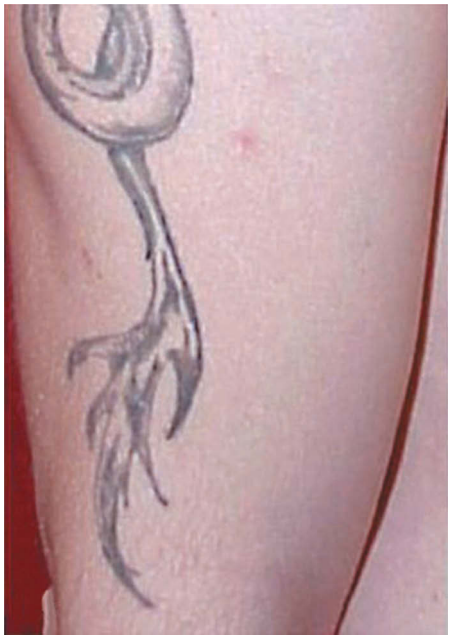
Figure 41.16 Skin × 250 HE/EO. Scattered pigment deposited in the papillary and reticular dermis. The random layout of the pigment in different skin depths is a good indication for the use of a Q-switched laser operating in a train of pulses (Linline®, Belarus). The sequential action of the laser energy paves the way, layer by layer, to reach deep pigment for elimination.

(a)

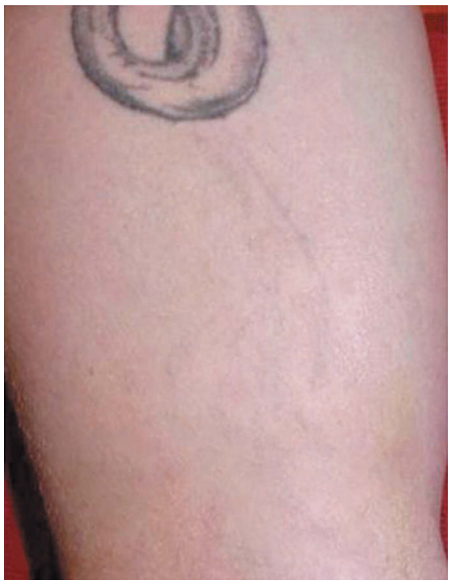


(b)

Figure 41.17 Amateur tattoos on the middle fingers of both hands in a phototype IV patient. These types of tattoos usually represent enrolment to groups or gangs with specific ideals. (a) Before treatment with a 1064 nm Q-switched Nd:YAG laser. (b) Complete removal 2 months after the second treatment session.



(a)



(b)

Figure 41.18 Tattoo on the right deltoid region. Patient wanted only to eliminate the pigment located below the round part of the tattoo design. (a) Before treatment. (b) Results 3 months after 4 sessions with a 1064 nm Q-switched Nd:YAG laser.

Lin et al. compared [49] QSRL and QS Nd:YAG laser in removing black–blue Chinese tattoos. They demonstrated that edema and exudation were more common immediately after ruby laser treatment and QS Nd:YAG laser was more effective at tattoo lightening after a single treatment. There was no significant difference in adverse effects between the two lasers.

In conclusion, the QS Nd:YAG laser is somewhat more effective in removing black ink, creating rare textural changes and almost no hypopigmentation. These improvements are attributable to the longer wavelength, higher fluence, and

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

shorter pulse width. In addition, the Nd:YAG laser offers a very rapid repetition rate (1–10 Hz), which shortens the treatment session.

Currently, larger spot sizes up to 6 mm are available with new, higher-powered Nd:YAG laser systems, which also enable deeper penetration and more effective treatment of deeper, denser tattoos. Better beam profiles minimize epidermal damage and decrease bleeding, tissue splatter, and transient textural changes.

QS Alexandrite Laser (755 nm)

The third QS laser developed for the treatment of tattoos, the QS alexandrite laser, has a wavelength of 755 nm, a pulse width of 50–100 ns, and a repetition rate of 1 Hz. The 3 mm diameter beam is delivered via a fiberoptic system or an articulated arm.

The alexandrite laser has become known as the treatment of choice for removing green-colored tattoos, although like the other types of QS lasers, it is also quite effective at removing black and blue tattoo pigments.

Fitzpatrick and Goldman [50] evaluated 25 patients with amateur and professional tattoos and demonstrated 95% removal of tattoo pigment using an average of 8.9 treatment sessions. These authors concluded that the QS alexandrite laser was safe and effective for removing blue and black tattoo pigments.

In another study, Alster [51] examined 24 professional and 18 amateur tattoos and concluded that the professional tattoos required more treatments for total removal (average of 8.5 sessions) than the amateur tattoos (average of 4.6 sessions).

Zelickson et al. compared the three types of QS lasers and concluded that the QS alexandrite laser was superior to the QSRL and QS Nd:YAG lasers in the removal of blue and green pigments [52], whereas the red, brown, and orange pigments responded best to the Nd:YAG laser. The QSRL was most effective in removing purple and violet pigments, and the 532 nm wavelength of the Nd:YAG laser was considered best to treat red pigment. All lasers were found to be equivalent in removing black tattoos.

The QS alexandrite laser is also effective in the removal of cosmetic and traumatic tattoos (Figure 41.19).

The best response, defined as greater than 95% clearance, has been achieved in blacktop, surgical pen, and gravel tattoos, although an acceptable degree of lightening could be obtained in tattoos due to gunpowder or fireworks [12]. In addition, the 755 nm alexandrite laser is safe and effective in the eradication of amalgam tattoos and cosmetic tattoos (permanent makeup) [53].

Unfortunately, as with the 694 nm wavelength of the QS ruby laser, the 755 nm wavelength of alexandrite is well absorbed by melanin, which may result in transient hypopigmentation following treatment sessions [42].

QS Nd:YAG Laser (532 nm)

The light emitted from the QS Nd:YAG laser may also be frequency-doubled to produce light with a wavelength of 532 nm.

Red-, orange-, and purple-colored tattoos have been shown to respond well to this wavelength [52,54].

Besides that, the QS 532 nm Nd:YAG laser has been found to be a safe and effective method of treatment for red ink tattoo allergic reactions in combination with topical corticosteroid [55] as confirmed by our personal experience (Figure 41.20).

In addition, currently available Nd:YAG laser offers special hand pieces that convert a 532 nm laser light to a 585 or 650 nm light, thus doubling the number of wavelengths available from this single laser and enabling the removal of more varied tattoo colors (green ink, sky blue ink, etc.).

LASER TREATMENT

Patient Evaluation

Managing patient expectations and providing proper treatment are imperative parts of any medical procedure. In the past, these crucial components were, unfortunately, often not given as much emphasis in the world of tattoo removal as they are today. By incorporating widely acknowledged best clinical practice recommendations, physicians can provide patients who desire tattoo removal a more thorough understanding of the process, proper treatment, and, ultimately, a more satisfying experience.

Figure 41.19 Monochromatic (black) tattoo on the ear. (a) Before treatment with Q-switched alexandrite laser. (b) Results 2 months after 2 sessions. (c) Results 6 months after the third session.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 41.20 Tattoo with an allergic reaction to the red pigment used. (a) Before treatment. (b) After corticosteroid injections. (c) Elimination with 532 nm Q-switched Nd:YAG laser to remove the pigment. At 6 months after control, results were good. (d) Elimination of residual pigment by fractional Er:YAG laser at high energy density.

The initial consultation is not only important for the patient who must leave with realistic expectations but also important for the physician to identify those patients who will be noncompliant or have unrealistic expectations (Tables 41.1 and 41.2). A complete medical history (including a medication history, information regarding wound healing and scarring tendencies, and history of infectious diseases) is crucial to achieve a successful treatment.

Table 41.1 Clinical Considerations

The treatment can be uncomfortable but tolerable in most cases.
Multiple treatment sessions are required to remove a tattoo.
Treatment sessions are spread out over 6–8 weeks.
Possible adverse outcomes.
Colored tattoos, tattoos on distal extremities, darker skin types, and "double tattoos" are more likely to be associated with scarring after laser treatment.
The importance of sun avoidance.
Complete clearance cannot be guaranteed.
The importance of patient compliance and aftercare instructions.

Table 41.2 Contraindications to Laser Tattoo Removal

Uncontrolled diabetes mellitus
Recent episode of cellulitis (MRSA)
Significant peripheral vascular disease
Rheumatoid arthritis, collagen vascular diseases
Malignancy, immunosuppression
Medications (isotretinoin in the past 6 months, gold salts, etc.)
Fulminate hepatitis
Renal failure (acute or chronic)
Unrealistic expectations

One of the biggest clinical challenges faced by laser practitioners, and a frequent, significant source of patient frustration, is the estimated number of treatment sessions that are needed to effectively remove a tattoo. In the past, patients were simply informed that they might need between "5 and 15 treatment sessions." In our experience, such a large variability in the estimated number of treatments offered patients little reassurance that their tattoo ink would be resolved over the course of a predictable timeline. However, if tattoo progressively responds to treatment and skin quality is preserved, perseverance of treatment is advisable (Figure 41.21).

In 2009, publication of the Kirby–Desai Scale [56] offered both clinicians and patients a much more precise estimation as to the number of laser tattoo treatments they would need. This scale is now widely accepted, and it is highly recommended that, during the initial visit, this scale be implemented to educate and provide a more reasonable number of treatments necessary.

In the Kirby–Desai scale, numerical values are attributed to six parameters: skin type, location, color, amount of ink, scarring or tissue change, and layering. Parameter scores are then added to form a combined score that will show the estimated number of treatments needed to achieve satisfactory results. Once calculated, this number of predicted treatments should be clearly noted in the patient's medical records in his or her presence. Tattoos scoring greater than 15 points may be difficult to remove with laser methods.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 41.21 Elimination of a professional polychromatic decorative tattoo. (a–f) Different treatment phases with the 1064 and 532 nm Nd:YAG lasers in various sessions, achieving good and progressive results. Some residual pigment is seen with hardly any changes in skin texture.

Treatment and Technical Considerations

Pretreatment

Laser tattoo removal can be uncomfortable but is very tolerable in most cases. Adequate pain control is necessary to deliver a more comfortable treatment experience. The pain is often described to be similar to that of hot oil on the skin or a "slap" from an elastic band.

Depending on the size of the tattoo, its location, and the pain tolerance of the patient, the use of some form of local anesthesia is generally required.

The use of forced cold air applied to the desired area just before and during the procedure makes the experience much more tolerable and should be incorporated into every laser tattoo removal treatment as a standard measure (Figure 41.22).

Topical anesthetic cream under occlusion applied 45–90 minutes prior to laser treatment session is another means by which the pain of the procedure can be attenuated and should be offered to all patients. If complete anesthesia is necessary, it can be administered locally by injections of 1%–2% lidocaine with epinephrine. In rare cases, it is also possible to use regional nerve block, especially to treat very large areas. In these cases, one may consider treating the tattoo in sections or the use of oral or intramuscular sedation.

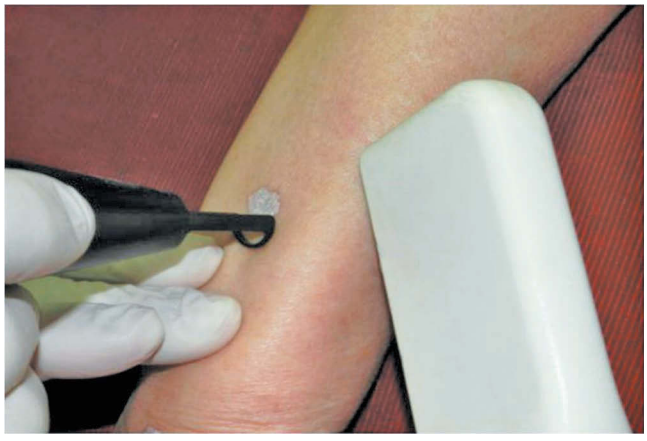


Figure 41.22 During treatment of an amateur monochromatic (black) tattoo, with a 1064 nm Q-switched Nd:YAG laser (Spectra SP, Lutronic Korea). Observe that treatment is done with the aid of cold air to decrease pain experienced during laser pulses.

Anecdotal reports have noted that patients receiving anesthesia by local injection may require additional treatment as the injection causes mechanical edema, a spreading out of the tattoo ink, which in turn makes it more difficult for the laser light to act on specific ink particles. This may also increase the risk of scarring and/or additional treatment [57]. So, if local anesthesia is to be used, it is recommended to inject the minimum amount necessary and perform a massage to ensure that adequate infiltration has taken place. It is also recommended to wait at least 15 minutes between the injection and the treatment.

To ensure the best results with minimal side effects, before the start of the procedure, the physician has to take into account some fundamental aspects, such as tattoo color and patient skin type. As discussed, blue–black tattoos are most suitable for removal with any type of the QS lasers due to the color's broadband absorption, whereas colored tattoos tend to be resistant. Some lasers may treat particular colors more effectively, such as the QS Nd:YAG (532 nm) and QS alexandrite lasers for red and green pigments, respectively, but purple and yellow inks can be therapeutically challenging. Consequently, colored tattoos may require the use of two or more types of QS devices in order to cover the spectrum of colors. In patients with darker skin types (Fitzpatrick IV–VI), the QS 1064 nm Nd:YAG laser should be favored due to deeper penetration and less melanin absorption, which results in a lower probability of hypopigmentation.

Nevertheless, test treatments should always be performed because of the possibility of permanent unwanted pigmentary changes (paradoxical darkening reaction), as well as laser-induced allergic reactions in skin areas with permanent makeup. Usually after the first session of treatment, iron pigment can chemically change color, but changing the wavelength to adapt it to the lighter color requirement will give adequate results (Figure 41.23).

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 41.23 Lip liner tattoo. (a) Note that before treatment pigment is black. (b) Effects after first session, with changes in the pigment color, which turned brown. Oxidation of the iron due to the laser transforms the pigment color. (c) Good results achieved after 2 sessions with a 532 nm Q-switched Nd:YAG laser.

Treatment

In any laser procedure, the physician must select the appropriate parameters that can ensure an effective treatment.

The main parameters include pulse duration, wavelength, fluence, and spot size.

All of the QS lasers are in the nanosecond range. *Wavelength* is chosen based on the best available wavelength for the tattoo ink color. For example, red ink is best treated by a green wavelength (510 or 532 nm), and green ink is best treated by a red wavelength (694 or 755 nm). When melanin is present, the 1064 nm wavelength is the best choice to avoid disruption of the epidermis.

Pulse width or pulse duration is a critical laser parameter. All QS lasers have appropriate pulse durations for tattoo removal. However, lasers with shorter pulses have a safer and more efficient removal method because the peak power of the pulse is greater.

Fluence or energy level is another important consideration. Fluence should be sufficient to produce immediate whitening without immediate bleeding or blistering. When QS laser energy is directed at the tattoo, the desired end point is usually immediate tissue whitening. This effect, which lasts approximately 20–30 minutes, is a result of rapid heating of the chromophore, leading to a reduction in both pigment size and density, as well as triggering molecular structural changes [58]. This rapid localized heating causes gas and plasma formation and subsequent dermal vacuolization, leading to the visible transient whitening of the skin after therapy [40]. So, the optimal fluence is the lowest possible setting that elicits this end point in order to minimize the risk of thermal injury, such as blister formation and scarring (Figure 41.24).

Frequently, the initial treatment session produces a more dramatic response than subsequent sessions. Definite sites of clearing, corresponding to laser impacts, are often seen. Other tattoos are highly unresponsive during early treatment phases, although biopsy samples reveal fragmentation of tattoo granules. The difference in response from one patient to another likely involves the efficiency of mobile macrophages in removing fragmented tattoo pigment debris, as well as the density and amount of tattoo pigment present. The speed of the macrophage response, as well as the maximum amount of pigment removed per session, likely varies from patient to patient and, to some extent, from treatment to treatment according to our experience, and can be detected in histologies (Figure 41.25).

Spot size is another parameter that affects treatment. Larger spot sizes slightly increase the penetration depth of the laser light, thus enabling more effective targeting of deeper tattoo pigments. This maximizes the distribution of laser light to the dermal pigment and minimizes cutaneous injury. Larger spot sizes also help make treatments faster.

Complete laser tattoo removal requires numerous treatment sessions, typically spaced at least 4–6 weeks apart. If the laser treatments are spaced lesser than 4 weeks apart, the risk

Figure 41.24 Polychromatic tattoo. (a) Before treatment. (b) Results 10 days after first session, with formation of blisters due to an excess of laser fluence. (c) After 4 treatment sessions, some residual pigment is observed but no changes in the skin texture.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

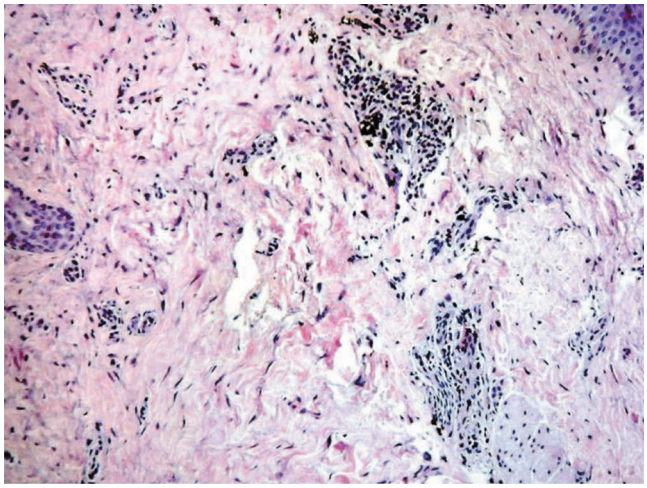


Figure 41.25 Macrophages can be noticed placed close to pigment deposits, representing active ingestion of residual pigment and debris for elimination.

of adverse effects increases and does not necessarily increase the rate of ink absorption. At each session, some but not all of the tattoo pigment particles are effectively fragmented, and the body removes the smallest fragments over the course of several weeks. The result is that the tattoo becomes lighter over time. The remaining large particles of tattoo pigment are then targeted at subsequent treatment sessions, causing further lightening. The number of sessions and spacing between treatments depends on various parameters, including the area of the body treated and skin color. Tattoos located on the extremities, such as the ankle, generally need more treatment sessions. In the same manner, professional tattoos require more treatments than amateur tattoos, which is attributable to the higher density of ink pigments used and deeper skin placement. Removal of black color injected over red ink can be successful; the black pigment disappears with the red color remaining (Figure 41.26).

Posttreatment

As discussed before, immediately after laser treatment, a slightly elevated, white discoloration with or without the presence of punctuate bleeding is often observed. This white

(a) (b)

Figure 41.26 Black tattoo to hide a previous red pigment tattoo. The design covers practically the whole length of the spinal column. Patient only wanted to eliminate the black birds from the sacrococcygeal region. (a) Before treatment. (b) Results after 4 sessions with a 1064 nm Q-switched Nd:YAG laser. Observe the red color that remains unaltered.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 41.27 Occlusive treatment with polyurethane and antibiotic cream, after treatment of tattoo. Bandage is removed after 3 days proceeding with open cures. In fact, the *quasi* cellophane layer of this dressing avoids the gauze to stick, which would delay wound healing, and prevents risk of infection and probable scarring. (From Trelles MA et al., *Arch Dermatol*, 137, 674, 2001. With permission.)

color change is thought to be the result of rapid, heat-formed steam or gas, causing dermal and epidermal vacuolization. Pinpoint bleeding represents vascular injury from photoacoustic waves created by the laser's interaction with tattoo pigment. Minimal edema and erythema of adjacent normal skin usually resolve within 24 hours. Subsequently, a crust appears over the entire tattoo, which sloughs off at approximately 7–14 days posttreatment.

Suitable postoperative care is important to optimize cosmetic outcomes. An easy and economical way of bandaging the area is to use clear plastic wrap, appropriately sterilized beforehand and applied directly to the treated area. The plastic adapts aptly and avoids exposure of the wound preventing it to stick to normal gauze bandaging due to any blood extravagation (Figure 41.27).

Clear hydrogel dressings or clear occlusive dressings can be used immediately following treatment because all QS lasers, particularly the Nd:YAG (1064 nm), are associated with splatter of blood and tissue [29]. Kuperman-Beade et al. recommend an immediate application of topical antibacterial ointment following the laser therapy session as part of routine postoperative care to reduce the risk of infection that can cause scarring [44]. Patients should practice strict sun avoidance for several months before and after treatment. In our experience (MAT), phototherapy light-emitting diode (LED) sessions with 635 nm wavelength proved to be very helpful as preventive treatment against scarring formation (Figure 41.28).

Side Effects and Complications

Although QS lasers have been shown to be highly effective in tattoo removal, some possible adverse effects may occur. The main acute events that may be seen include purpura, crusting, blistering, infection, and oxidative darkening of pigment [59].

About half of the patients treated with QS lasers for tattoo removal will show some transient changes in the normal skin pigmentation. These changes usually resolve in 6–12 months but may rarely be permanent [60].

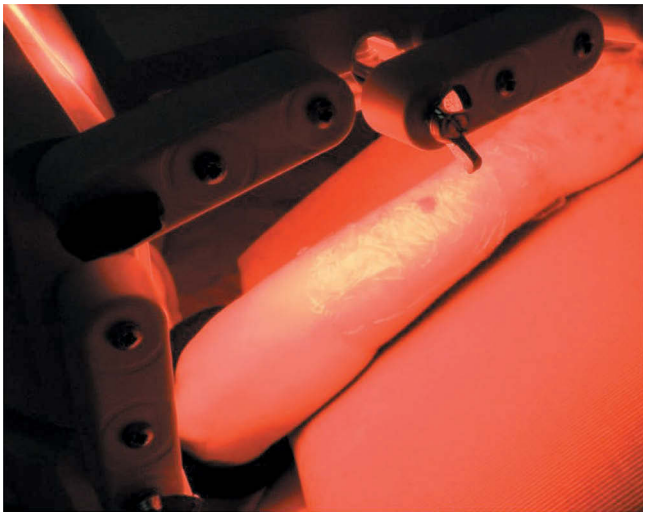


Figure 41.28 Patient after one laser session to eliminate tattoo, receiving phototherapy with a 633 nm LED intense red light (Omnilux™ Medical). This treatment, in the authors' experience, is very beneficial to activate wound repair and prevent scarring. (From Trelles MA et al., *Med Laser Appl*, 21, 165, 2006.)

Dyspigmentation and Textural Changes

The increased melanin absorption seen with shorter wavelengths increases the risk for hypopigmentation, especially in the treatment of dark-skinned patients. With 510 and 532 nm wavelengths, the hypopigmentation may be transient [46]; however, long-term hypopigmentation is possible with the 694 nm QSRL. Comparatively, the Nd:YAG laser has no incidence of hypopigmentation [42]. The exact mechanism for thermally induced destruction of melanocytes is not known; however, there are some possible explanations, including damage from shock waves, the physical effects of thermal expansion, and extreme temperature gradients within the cells [59,61].

Hyperpigmentation can occur as well, especially in dark-skinned and tanned individuals. In these cases, the use of bleaching agents (hydroquinone) before and after laser treatment and broad-spectrum sunscreens usually resolves the hyperpigmentation within a few months, although, in some patients, resolution can be prolonged [60]. Additionally, in patients prone to pigmentary changes, the use of the Nd:YAG laser for tattoo removal, as well as longer treatment intervals, may be helpful to reduce the incidence of hyperpigmentation.

Transient textural changes are often noted but resolve within 1–2 months; however, permanent textural changes and scarring are rare.

Blister formation is due to epidermal thermal damage and can occur after QS laser therapy for tattoo removal. The use of excessive laser fluence or inadvertent absorption of laser energy attributable to the tattoo pigment may be some of the explanations for the development of this side effect. The concomitant use of tissue cooling system, such as cryogen spray, can protect the epidermis from excessive thermal injury during laser irradiation and may reduce epidermal damage [62].

Allergic Reactions

Local allergic responses to many tattoo pigments have been reported, and allergic reactions to tattoo pigment after QS

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

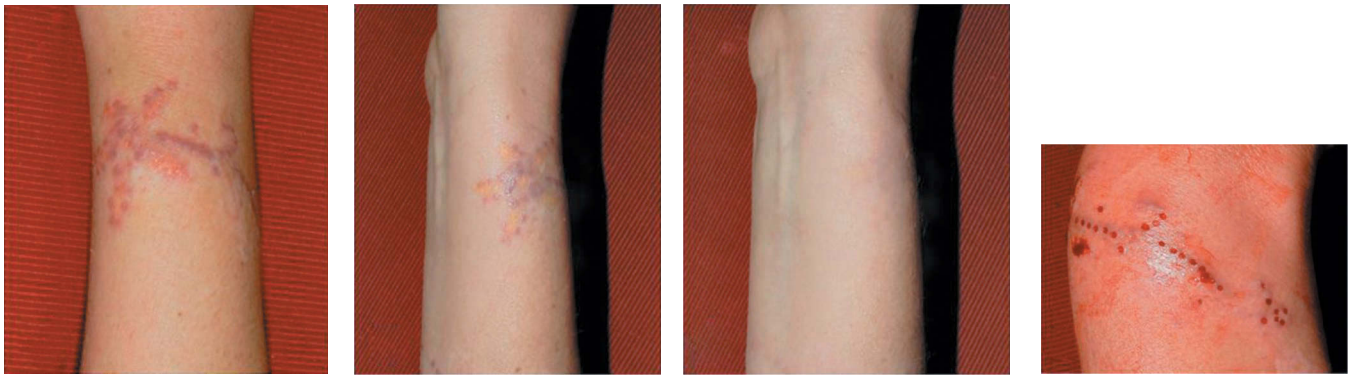


Figure 41.29 Polychromatic tattoo on the wrist, with an allergic reaction to the yellow pigment of cadmium sulfide, which does not benefit from treatment with steroids. (a) Before treatment. (b) Immediately after treatment. Notice the deep ablation achieved with the Er:YAG laser. (c) Due to the difficulty in removing the yellow pigment, pulses of the Er:YAG laser in separate punch fashion generated a form of fractional treatment. "Erasing" of the tattoo occurs with good results.

laser treatment are also possible. The most common color that patients become allergic to is red [63]. Clinically, the allergy may manifest as nodular, scaly, and pruritic change in the red pigment area of the tattoo. Other colors rather than red may also induce an allergic response, such as yellow. Cadmium sulfide is often used to make yellow tattoo pigment and is the most common cause of a photoallergic reaction within a tattoo as we have observed (Figure 41.29).

As the QS laser acts by dispersing the ink, it may generate a systemic allergic response. So, if an allergic reaction to ink is noted, QS laser treatment is not advised.

In two recently reported cases, fractional Er:YAG, with or without adjunctive QS laser therapy, was effective in treating tattoos undergoing allergic reactions [64]. However, some authors report a systemic allergic reaction after these laser treatments (CO_2 laser or erbium laser) [65].

The treatment of tattoos undergoing allergic reactions consists of strict sunlight avoidance, sunscreen, intralesional steroid injections, or, in some cases, surgical removal [55].

Ink Darkening

Paradoxical darkening of pink, red, and white tattoo inks with QSRL, QS Nd:YAG, and QS alexandrite lasers has been reported, but yellow, blue, and green inks could also get altered in a similar way [66,67]. These pigments used in cosmetic tattooing contain iron oxide and titanium dioxide. Iron oxide changes color from brown to black when heated above 1400°C due to oxidation–reduction reaction or the ignition of ferric oxide. The extreme temperatures generated during the short pulse of QS lasers are required to perform these reactions.

After turning black or brown, cosmetic tattoos can be removed by further laser treatment. However, it may be difficult to treat these tattoos as it often requires many more treatment sessions than it does to remove a typical black tattoo [67–69]. Patients should be warned of the potential for cosmetic tattoo darkening, and test spot treatment should be performed initially. When paradoxical darkening occurs, clearing can at times be achieved with additional QS laser treatment [67]. Therefore, if tattoo darkening occurs, it is advisable to re-treat the same area and then wait several weeks to assess the darkened tattoo's response. If it has lightened significantly, treatment can proceed.

Destructive lasers (fractional CO_2 or Er:YAG devices) have been used to remove white, tan, or brown cosmetic tattoo pigments that are refractory to removal with QS lasers [70]. These lasers alone or in combination are more likely to cause scarring and produce less-predictable results than QS lasers, but in the appropriate clinical setting, they can be of use leading to satisfactory results, especially when considering the difficulty involved in eliminating colors such as green, red, or yellow, or in the case of multilayer tattoos (Figure 41.30).

Epidermal Debris

The high-energy short pulses cause a pressure shock wave that ruptures blood vessels and aerosolizes tissue. There may be potentially infectious particles present in this material, and thus, a barrier or a cone device is required to protect the operator from tissue and blood contact.

Lower fluences largely eliminate this problem but result in more treatment sessions. High-energy output and larger spot size are effective in reducing hazards to the operator and adverse effects (less epidermal disruption) for the patient [44].

ADVANCES AND FUTURE PERSPECTIVES

New Techniques

Tattoo removal by QS lasers is generally safe and effective, but many treatment sessions are needed, and residual tattoo ink often remains.

Research is under way to improve both the techniques and devices used for laser tattoo removal. The recently presented "R20" method suggests repeating QS laser treatment four times in a single session spaced 20 minutes apart to allow whitening to fade [71]. The authors demonstrated that, after 3 months, treatment with the "R20" method was much more effective than conventional single-pass laser treatment, with most of the tattoos being removed in a single session. There was no scarring, despite greater epidermal injury with this method. They believe that delayed, multiple-pass

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 41.30 A multilayer polychromatic tattoo in the deltoid region. (a) The design had been embedded in the skin with more intense colors each time, to cover two previous designs that the patient was not happy with. (b) Effect after one session with 1064 and 532 nm Q-switched Nd:YAG lasers. (c) Results after 3 sessions. Observe the persistence of the deep pigment and the design of the previous tattoos. (d) Eight months after treatment, it was agreed to carry out a session with the Er:YAG laser. (e) The area during treatment where some portions that are not treated can be observed. (f) Results 3 months after a single session.

treatment could significantly change the paradigm of the treatment of tattoos.

There is another new technique, known as modulated imaging (MI), that may be useful for clinical characterization of tattoo pigment prior to tattoo removal. MI is a spatially resolved, noncontact imaging modality based on diffuse optical spectroscopy (DOS) principles, which can provide quantitative absorption and scattering contrast of superficial *in vivo* tissue. The authors [72] applied MI to several multicolored tattoos and demonstrated that it is possible to distill macroscopic reflectance images into spatially resolved maps of optical properties. In addition, they were able to render absorption and reduced scattering spectra between 650 and 970 nm, from different regions of these tattoos. They concluded that MI provides spatially resolved quantitative information with a potential for quantitative assessment of response to treatment and may provide guidance for laser tattoo removal in the future.

New-Generation QS Lasers

Laser Devices

As lasers are well established for the removal of pigmentation, the purchase of a laser for this purpose can be costly.

Therefore, the possibility of counting on a multiapplication laser platform, in which different wavelength emissions can be selected, provides the option of a single-unit polyapplication appliance as an alternative to the typical situation of having a separate laser device for each specific application [73,74].

Within the large availability of laser devices on the market (e.g., Linline™), many now offer a sophisticated technology that accommodates a range of lasers adapted to a console with built-in programs for the treatment of cutaneous vascular and pigment disorders [75]. In our experience, in the case of monochromatic (black) tattoos and especially those done by amateurs, only a few sessions are necessary when using these devices (Figure 41.31).

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a)

(b)

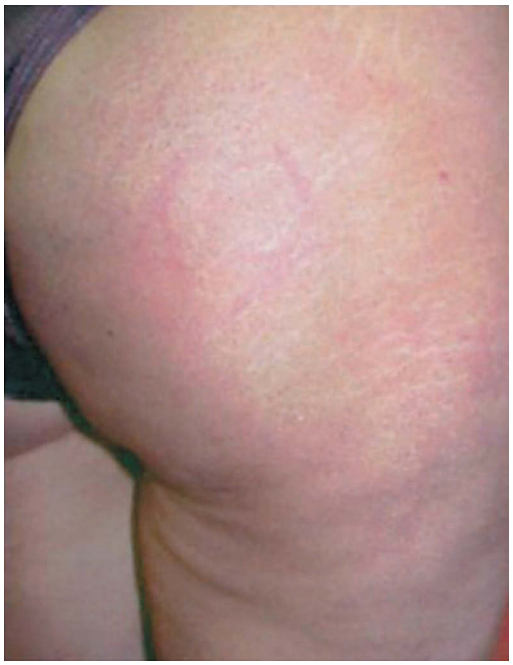

(c)

Figure 41.31 Amateur monochromatic tattoo on the buttock. (a) Before treatment. (b) Four weeks after a single treatment. (c) After 1 year, results were good.

Traditional QS lasers produce single-pulse widths for a duration of 10–12 ns. This energy is absorbed "in one go" by the matching color located at the most external point of the skin. The deeper located pigment remains unaffected, and therefore, multiple sessions are needed to eliminate a tattoo. Tattoos of dark dense color made up of a considerable amount of ink, or multilayer colored pigments, are especially difficult to eliminate and will require a number of treatment sessions [43,76]. With these multiple sessions, the reparative tissue process following laser treatment leads to reactive fibrosis formation, which prevents light from adequately penetrating to eliminate deep pigment in the following session.

Wavelengths

Contrary to this, the pulses of the Linline are packed as a block in a carrier pulse and delivered to the skin as a series of pulses, which interact with a different mechanism for pigment elimination.

The train of pulses, programed for operation in a frequency of 1–4 Hz, obtains sequential movement effects on reaching deep pigment. During interaction, the small-width, nonstop pulses of essentially lower energy are delivered in sequence as a train of pulses. Delay time between the block of repeated pulses is of a few microseconds, and energy is absorbed first by the pigment chromophore located more superficially.

The elimination of this pigment opens access for the following minipulses contained in the "carrier block" to penetrate and interact with deeper located colors of the tattoo.

Selectivity of laser wavelength QS energy interaction with pigment progressively increases in efficacy during treatment, and the train of pulses acts layer after layer fragmenting the tattoo. During "continuous" exposure of tissue to pulse after pulse, minimal acoustic waves are produced, which are not heard during treatment. Although microhemorraging occurs internally, the visual perception is not of bleeding and skin fragmentation, but of a progressive change in the skin color, which becomes grayish, so that cleaning of the pigment is produced with minimal damage to the epidermis. Under these circumstances, treatment with an absence of thermal lesions in neighboring structures occurs, and therefore, the speed of skin recovery is not compromised. Sessions can be carried out within shorter periods of time.

Results

In order to obtain consistent results with a complete removal of the tattoo and keep the skin quality and texture in good condition, laser sessions should be performed with a delay time of 3–6 months, giving the microhematomas a chance to completely resolve.

This technique of treatment, being different from conventional QS lasers, needs a training period, particularly to recognize when to stop pulses on the same spot and how to program pulse repetition rate. The train of pulses penetrates and destroys pigment layers with quasi-nonaudible photoacoustic waves rebounding inside the tissue. This should be recognized in order to stop pulsing the laser, when external changes in the skin appear, and to avoid tissue collateral damage.

On the other hand, advanced technology by the manufacturer should consider producing a larger changeable beam diameter, together with a longer focal distance. The solution to this, in particular, will entail maintaining the effective high fluence necessary for treatment in a larger beam diameter.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Picosecond Lasers

Lasers in the picosecond (10^{-12}) domain are currently under development [77].

Theoretically, delivering a subnanosecond pulse could more effectively confine the energy to the tattoo particle, resulting in increased photoacoustic breakup of the target. This would allow for effective treatment utilizing lower fluences, thereby decreasing thermal energy transfer to surrounding tissues and minimizing the risk of scarring.

In one study, Ross et al. [78] compared two Nd:YAG lasers. They treated designated parts of the same tattoo (black pigment) with 35 ps and 10 ns pulses. In 12 of 16 tattoos, there was significant lightening in the picosecond-treated areas compared with those treated with nanosecond pulses.

Another study compared the efficacy of the picosecond titanium/sapphire (795 nm, 500 psec) laser and the QS alexandrite (752 nm, 50 ns) laser in the treatment of pigs' tattoos. There was greater clearance of tattoo in titanium/sapphire laser–treated areas in 2 of the 4 surviving guinea pigs. In addition, in some areas, total clearing was observed after a single laser treatment. No scarring was present [79]. Recently, in the same way, Izikson et al. examined the effect of a novel 758 nm 500 ps laser on a black tattoo in an animal model. The 758 nm 500 ps laser produced greater tattoo clearance at all tested fluences than the QS alexandrite laser (755 nm) [77].

Fortunately, new technology is emerging, notably microchip QS lasers operating in the picosecond domain and wavelength-tunable ultrafast femtosecond (10^{-15} seconds) lasers. A femtosecond is an almost inconceivably small fraction of a second, about the same as 1 minute compared with the age of our solar system. Femtosecond pulses have not yet been tested for efficacy in tattoo removal.

Fractional Resurfacing

Since the introduction of QS laser treatment, the technique of tattoo removal has changed little. Ablative fractional resurfacing (AFR) and nonablative fractional resurfacing (NAFR) systems are now commonly used for a variety of dermatologic conditions, and these systems have demonstrated an excellent safety profile.

AFR uses laser microbeams to create an array of very small, deep zones of tissue removal with intervening areas of normal-appearing skin [80]. AFR stimulates rapid remodeling of the skin, as the microscopic zones of ablation are replaced with *de novo* skin, and has a very low risk of scarring. First, tattoo ink removal likely occurs because AFR physically removes a portion of the tattoo with each treatment. Second, there is a transepidermal elimination of tattoo ink through the newly created microscopic channels, and, finally, the wound-healing process might permit additional tattoo ink removal. We actually use the Er:YAG laser in manual fractional mode, at high energy densities (over 20 J/cm^2), with good results to ablate small holes in the tattoo to eliminate pigment of difficult colors. Excellent results are achieved after repeated sessions. The fact that the high energies used are practically all converted to ablation effects there are hardly any thermal residual deposits in the skin. This entails excellent tissue repair, and skin restitution is achieved with no significant alteration in texture (Figure 41.32).

Weiss et al. [81] studied the clinical outcomes using a combination of fractional resurfacing and QSRL for tattoo removal. All patients received fractional CO_2 laser treatment (Fraxel Re:pair, Solta Medical, Inc., Hayward, CA) or fractionated 1550 nm laser treatment (Fraxel Re:store, Solta Medical, Inc.) to half of the tattoo in addition to QSRL treatment (Sinon, Wavelight Laser, Technologie AG, Erlanger, Germany) to the entire tattoo.

The authors demonstrated that AFR and NAFR in combination with QSRL enhance tattoo clearance, eliminate blistering, shorten recovery, and diminish treatment-induced hypopigmentation. They also found that fractional CO_2 laser therapy immediately after QS laser treatment enhanced the rate of pigment clearance versus QS laser alone. The theoretical mechanisms described include the fractional CO_2 laser ablation of superficial tattoo pigment and the induction of an immune response that potentiates removal of the treated pigment.

In another recent study, Ibrahimi et al. have studied [64] the application of AFR as a novel method for removal of allergic tattoos. They concluded that AFR might also permit removal of ink colors, such as yellow, orange, brown, and white, that are recalcitrant to QS lasers.

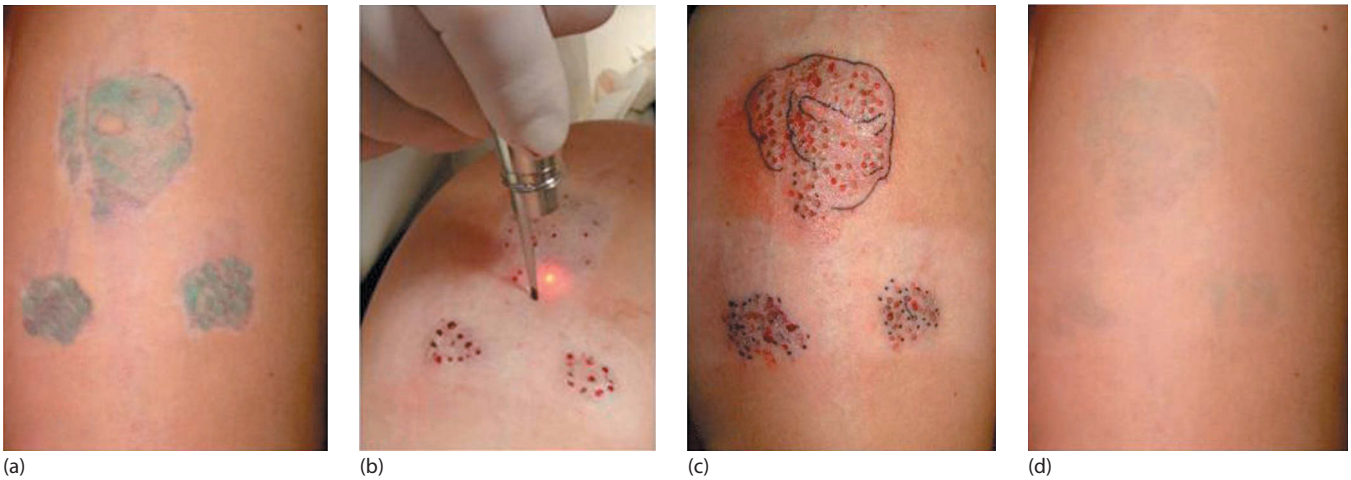


Figure 41.32 Polychromatic tattoo in green and yellow colors. (a) Before treatment. (b, c) Due to the difficulty in eliminating the green and yellow pigment, treatment with the Er:YAG laser at high fluences was decided. Fractional laser impacts were used in the tattooed area. Observe the clear ablation effect. (d) Results 4 months after a single treatment session.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Imiquimod

One of the newest methods for tattoo removal is the use of imiquimod cream. In animal studies, topical application of imiquimod cream fades tattoos. The combination of both imiquimod and laser treatment may result in enhanced tattoo pigment clearance in guinea pigs. In a study [82], the combination of QS alexandrite laser and imiquimod-treated group was clinically and histologically rated as having less pigment than the tattoos that were treated with laser alone, though some authors describe different experiences in their practice [83,84].

Generally, the adjuvant imiquimod treatment had greater inflammation and fibrosis on posttreatment skin biopsies [82].

Laser Tattoo Ink Interaction: Scatter Reduction

Topical- and intradermal-injected solutions (hyperosmotic substances), such as glycerol, dimethylsulfoxide, and glucose, have been shown to significantly reduce dermal scatter in animal models [85].

These agents should enable one to remove a tattoo more effectively; however, intradermal injection may result in tissue necrosis and scarring, making it a poor coadjuvant treatment [86].

New Tattoo Inks

In addition to improving lasers and improving the optical properties of skin, new tattoo inks are being developed that should be easier to remove from skin.

Available in the United States since 2009, there is a new tattoo ink (Infinitink, Freedom Inc., Cherry Hill, NJ). It is constituted by microsphere-encapsulated bioresorbable pigments. The laser treatment during the tattoo removal would cause the capsule to break, exposing the pigment. The body then resorbs the pigment. Tattoos created with this ink can be removed in far fewer laser treatments than those with traditional pigments.

In the future, the adoption of these types of inks by the tattoo industry and consumers will offer safer and more-effective laser tattoo removal. We should continue to work on making tattoos safer and more removable than ever.

PERSONAL EXPERIENCE ON TATTOO REMOVAL WITH A FEEDBACK OF OVER 20 YEARS: CASE EXAMPLES

After 14 years using the QS Nd:YAG laser, C3 (Hoya Conbio), the author (IC) has now been using the QS Nd:YAG Q+ (Quanta System) for 5 years.

This type of laser was our first acquisition in private practice, and today, our technical platform includes 13 lasers, radiofrequency devices, and LED devices. However, QS lasers remain our favorite technology because its effectiveness, which most of the time, is very notable both on natural pigmentation (Ota nevus) and on artificial pigments (tattoos).

Indications and Results

The indications of laser tattoo removal are subjected to many technique-dependent parameters, which are linked to the type of ink, depth, and color and to patient specificity (skin reaction to the laser shock wave). The best results are obtained on black tattoos, amateur or professional, large or small, with superficial pigment location (Figure 41.33). In these cases, tattoos fade in 1–3 sessions (Figure 41.34) without leaving any residual traces. If the tattoo is a monochrome, very deep or highly dense black

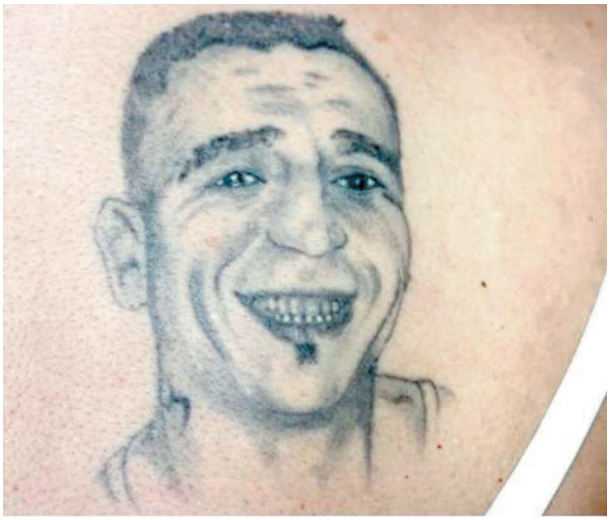
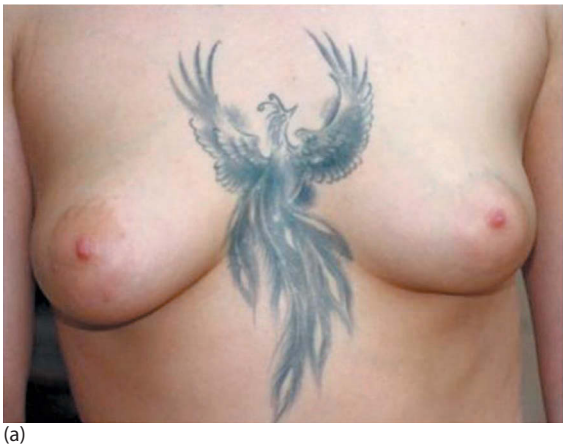


Figure 41.33 Superficial design professional monochromatic, black tattoo. QS laser treatment can be started immediately.



(a)

(b)

Figure 41.34 Superficial pigment professional tattoo. (a) Before treatment. Notice not too marked black color. (b) Result obtained after 2 sessions with the 1064 nm QS Nd:YAG laser. Great improvement with minimal residual pigment.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

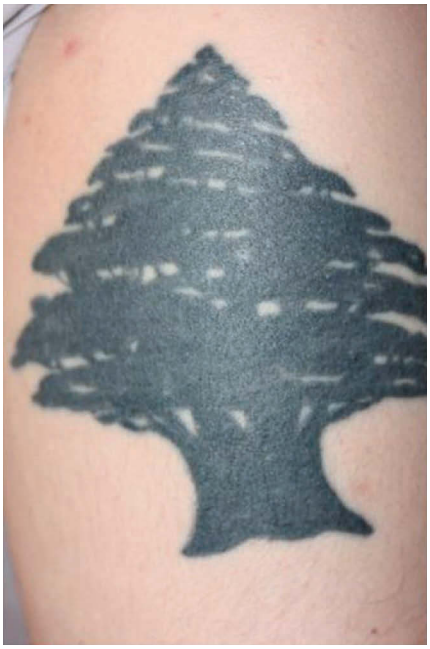


Figure 41.35 Monochromatic black tattoo made with several layers of pigment. The black color is dense and deeply located. This tattoo, in principle, is difficult to treat with success.

Figure 41.37 The same tattoo as in Figure 41.36, showing in detail reactive erythema and edema immediately after treatment.

(Figure 41.35), we do prefer not to treat with laser; such a treatment would require a large number of sessions with an uncertain result (Figures 41.36 through 41.39). In these cases, it would be advisable to combine, as we do, the QS laser and the CO_2 fractional laser (Quanta System Youlaser) (Figure 41.40).

In polychromatic tattoos, certain colors do not fade (turquoise, Figure 41.41, or orange, Figures 41.42 and 41.43).

The Maghreb ritual tattoos disappear usually after 1–3 sessions (Figure 41.44); on the other hand, those of black Africans (Figure 41.45) have to be only treated with the QS 1064 nm laser and require a minimum of 5 sessions. After treatment, a certificate for patient's country border is necessary because without the tattoo the appearance is changed (Figure 41.46).

Edema is prevented with antihistaminic drugs (Figures 41.47 through 41.49), and lower fluences and longer intervals between each session permit to avoid hypochromia.

For cosmetic tattoos, we use the Er:YAG laser alone (Figure 41.50) or combined with a fractional CO_2 laser, usually 5 sessions or more (Figures 41.51 and 41.52). We prefer the Er:YAG laser because the color pigment is frequently modified under the impacts of the QS laser (Figure 41.53).

QS lasers do not eliminate hair, and there is only temporary hair whitening; therefore, it is possible to treat, in principle, any area of the body (Figures 41.54 through 41.58).

If we use the correct parameters and the delay between sessions is at least 2 months, scars or skin textural changes can be avoided (Figure 41.59).

Current Problems to Solve

We still cannot predict the exact number of sessions needed to eliminate tattoos.

Moreover, even after enough sessions, we cannot predict if the result will be total or partial elimination. The inks

(a) (b) (c)

Figure 41.36 (a) Professional extensive tattoo on the back. (b) Moderate results achieved after 3 sessions with the 1064 nm QS Nd:YAG laser. (c) Detail of the result achieved after 6 sessions due to the dense and deeply located pigment.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 41.38 Professional tattoo with deep ink. (a) Before treatment. (b) Changes operated in the skin during treatment. (c) Results achieved after 5 sessions. (d) According to results observed in further controls, one recommends to use the CO_2 fractional laser, combined with QS laser for following treatments.

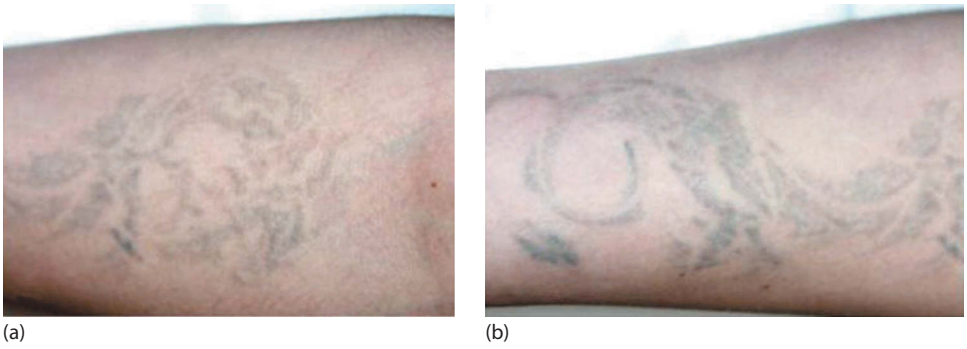


Figure 41.39 The same tattoo as Figure 41.38. (a, b) Different phases of the results, maintaining correct skin texture.

used for tattoos may fade or disappear. In this case, ablative fractional laser, combined in the same session, may treat the remaining pigment (Figure 41.60) (Youlaser Quanta System) and QS laser (Figures 41.61 through 41.63).

Some inks are resistant to QS lasers: the color does not correspond to a specific available length (green or violet colors) (Figure 41.64) or ink quality (Figure 41.65). The same difficulty is encountered with the amount, the density, or the deposition pigment or if the tattoo has sculpture-like appearance (Figure 41.66). In the same way, we cannot predict the postinflammatory hyperpigmentation risk (Figure 41.67) after one or several sessions with the QS lasers (Figure 41.68).

In case of postinflammatory hyperpigmentation, we recommend sun exposure because when suntan disappears, it will lead to hyperpigmentation disappearance (Figure 41.69), and topical hydroquinone preparations at night may help.

During tattooing, we may observe atypical mycobacteria infections (Figure 41.70) and ink allergies (especially red color), seen as eczema or granular lesions (Figure 41.71) related sometimes to sarcoidosis.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b) (c)

Figure 41.40 Professional monochromic tattoo. (a) Before treatment. (b) Immediately after the same session with CO_2 fractional laser and QS laser treatment. (c) Results achieved after one session.

(a) (b)

Figure 41.41 Polychromatic tattoo. (a) Before treatment. (b) Excellent results for black ink removal and no response for turquoise blue pigment, which persists after 2 sessions with 1064 nm QS Nd:YAG laser.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

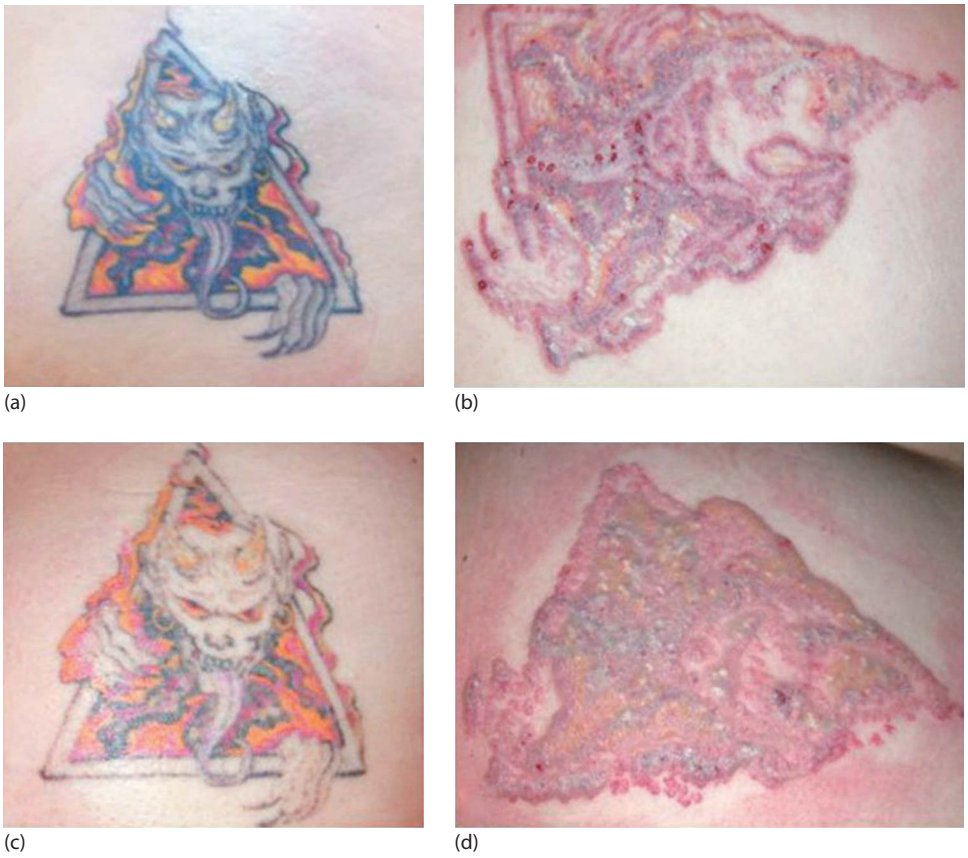


Figure 41.42 (a) Professional polychromatic tattoo on the buttock before treatment. (b) Immediately after QS Nd:YAG laser using 1064 and 532 nm for the red ink. (c) Result after 2 sessions. (d) Skin aspect immediately after the second session.

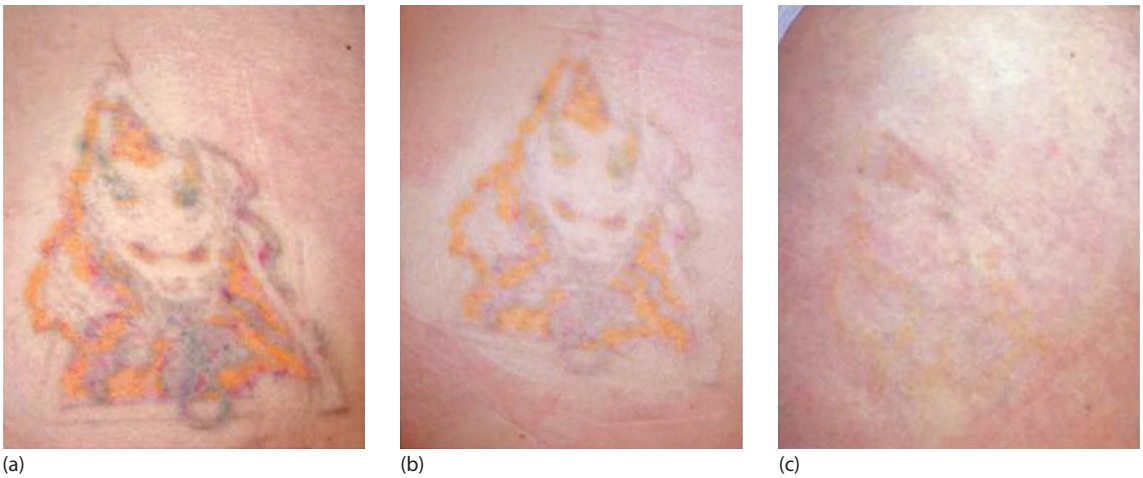
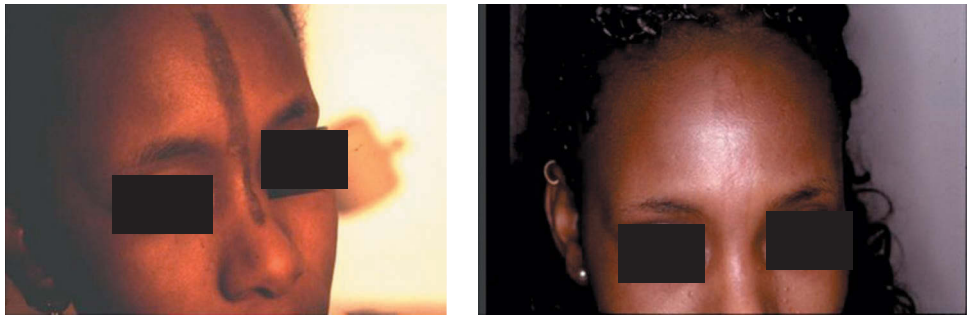


Figure 41.43 The same tattoo as in Figure 41.42. (a, b) Results after 5 sessions. (c) Skin aspect after 11 years. Only yellow pigment remains with minimal textural changes.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 41.44 Maghreb ritual tattoo. (a) Before treatment. (b) Results after 2 sessions with the 1064 nm QS Nd:YAG laser.



(a) (b)

Figure 41.45 Mali ritual tattoo. Pigments made of mixed spices. (a) Before treatment. (b) After 5 sessions with the 1064 nm QS Nd:YAG laser.

Figure 41.46 Final result after 4 sessions with a 1064 nm QS laser on black African ritual tattoo.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 41.47 Senegal ritual tattoo after 2 sessions with a 1064 nm QS Nd:YAG laser immediately after laser treatment edema.

(a) (b) (c) (d)

Figure 41.48 Monochromatic ritual Ethiopian tattoo. (a) Edema developed 5 minutes after treatment with a 1064 nm QS laser. (b) Results after 4 sessions of treatment. (c) Contralateral side of the neck showing tattoo before treatment. (d) Results after 4 sessions.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 41.49 Senegal ritual tattoo. (a) Before treatment. (b) Results after 5 sessions with a 1064 nm QS laser. Some hypopigmented spots and traces of tattoo on the internal side of the lower lip.

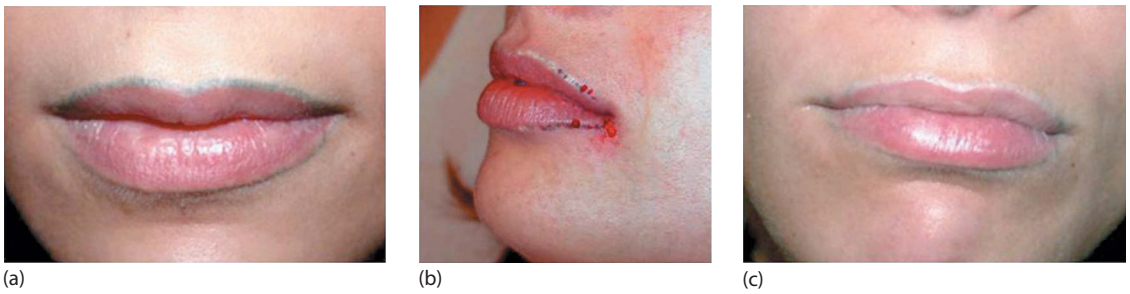
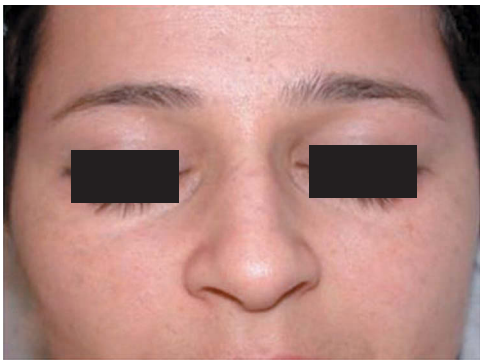


Figure 41.50 (a) Cosmetic tattoo on the lips before treatment. (b) Immediate results after treatment with Er:YAG long-pulsed laser. (c) Results after 3 sessions.

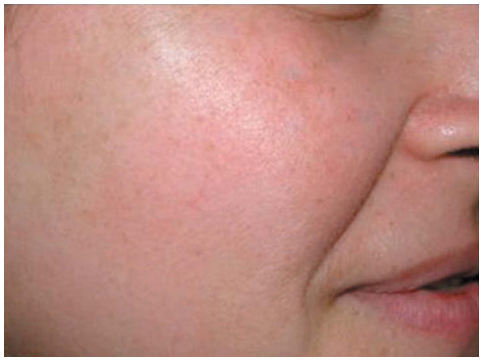
Figure 41.51 (a, b) Cosmetic tattoo with iron pigment, resistant to QS Nd:YAG laser treatment. (c) Results after Er:YAG long-pulsed laser.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

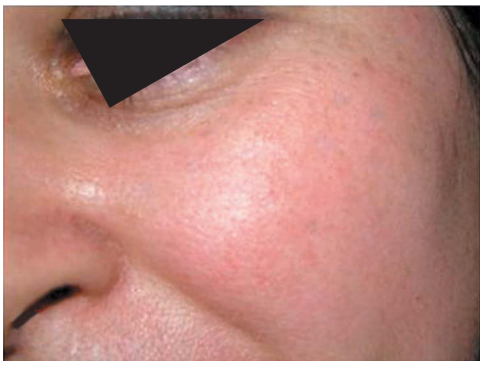
(a)



(b)



(c)



(d)

Figure 41.52 The same patient as in Figure 41.51. (a) Aspect before treatment. (b) Result 10 years after. (c, d) Detail showing the good skin condition and total pigment elimination 10 years after.

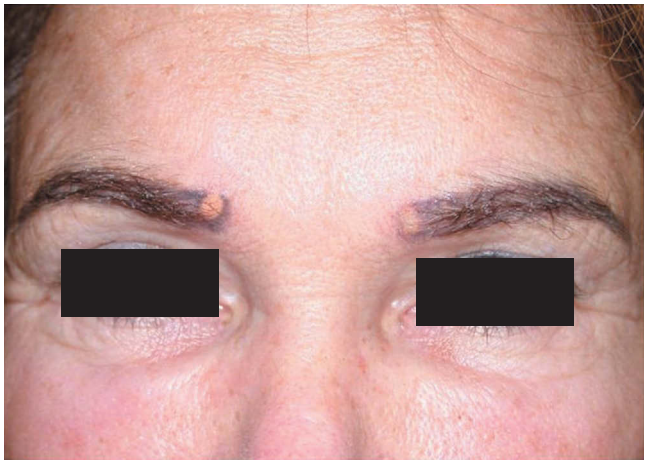


Figure 41.53 Results of test done with a 1064 nm QS Nd:YAG laser on cosmetic tattoo for eyebrow lining. Notice brown pigment changed to lightening ochre.

(a)

(b)

Figure 41.54 (a) Tattoo on nonhairy skull area to hide baldness. (b) Treatment done before hair grafting. There is whitening of the area treated without loss of grafted hair.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 41.55 (a–c) Black tattoo on the whole scalp. (d) During test with a 1064 nm QS Nd:YAG laser.

Figure 41.56 The same patient as Figure 41.55. (a) Results of test are positive. (b, c) Posttreatment immediate aspect of all the whole tattooed area. Patient developed large painful edema. This could be attributed to high melanin pigment coefficient absorption in hair.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

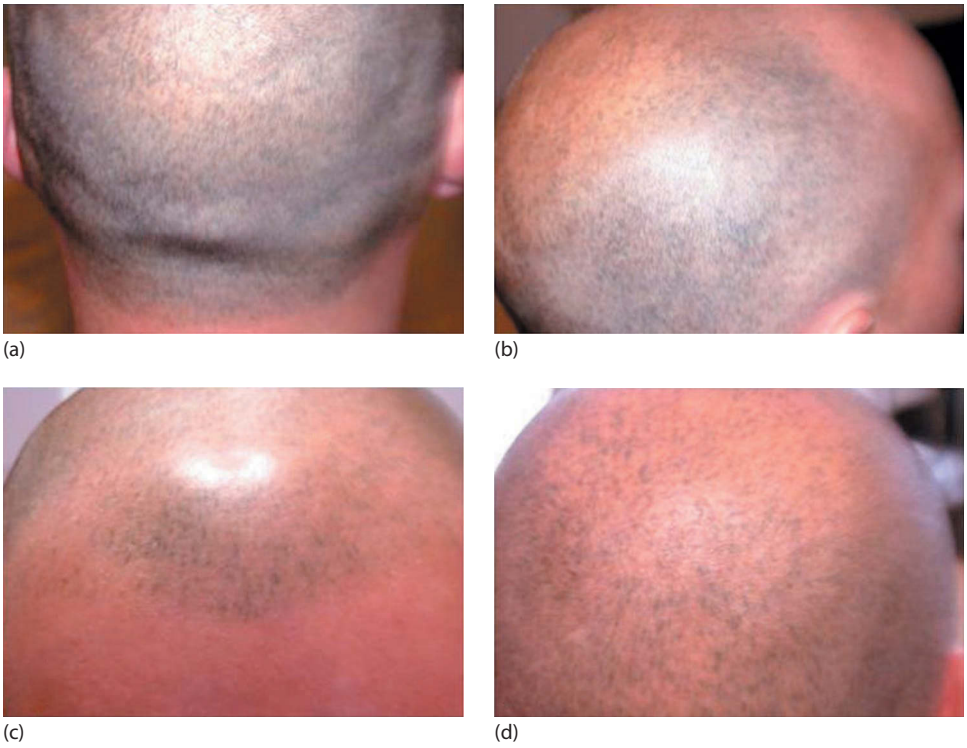


Figure 41.57 The same patient as in Figures 41.55 and 41.56. (a, b) Results after one session. (c, d) After two sessions.

Figure 41.58 The same patient as in Figures 41.55 through 41.57 after two treatment sessions. Only traces of pigment without hair elimination.

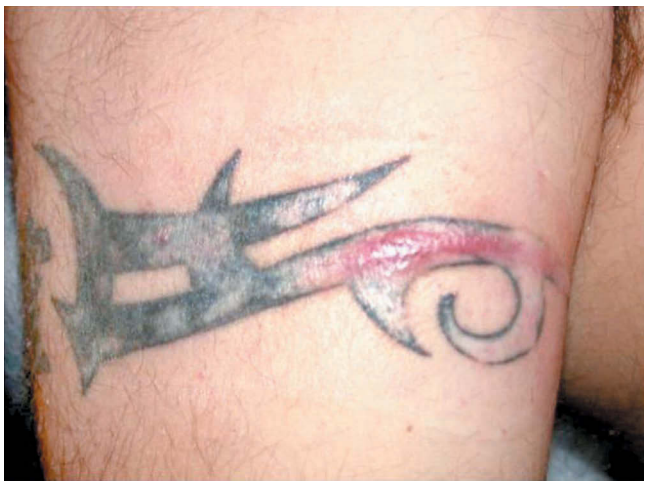
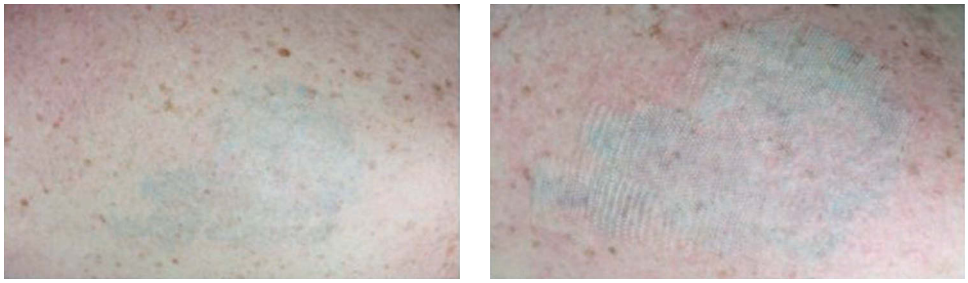


Figure 41.59 Polychromatic tattoo with scarring reaction due to high fluence and/or too short delay between laser sessions.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b)

Figure 41.60 (a, b) Aspect of the skin after fractional CO_2 laser done after QS laser treatment on a polychromatic tattoo.

(a) (b)

Figure 41.61 (a) Monochromatic professional tattoo before treatment. (b) Final result 3 years after five sessions.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 41.62 (a) The same monochromatic professional tattoo as in Figure 41.61, before treatment. (b) Immediately after treatment with a 1064 nm QS laser.

Figure 41.63 The same monochromatic professional tattoo as Figure 41.62. (a–e) Various aspects of treatment evolution with a 1064 nm QS Nd:YAG laser and a CO_2 fractional laser in the same session.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

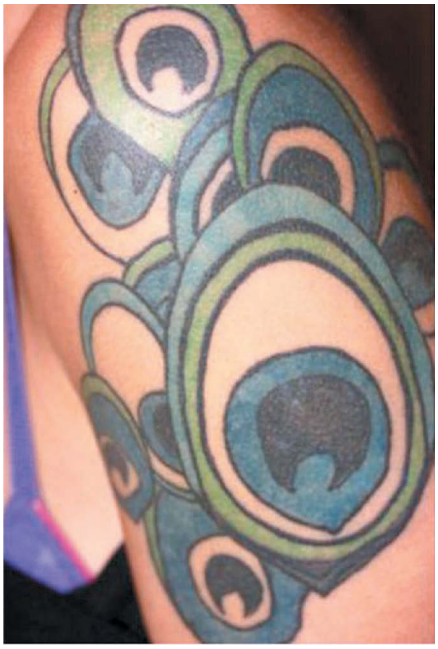


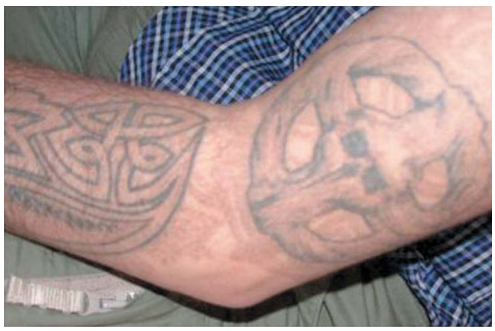
Figure 41.64 This polychromatic tattoo is impossible to treat because of green and violet colors and deep location and black ink density.

(a)

(b)

Figure 41.65 (a) Black tattoo with black ink difficult disappearance. (b) Results after 10 minutes treatment with a 1064 nm QS Nd:YAG laser. Bad prognosis with black ink turning to green; treatment is not recommended in this case.

Figure 41.66 Sculpture-like tattoo. Notice skin elevation pigment difficult to treat successfully.

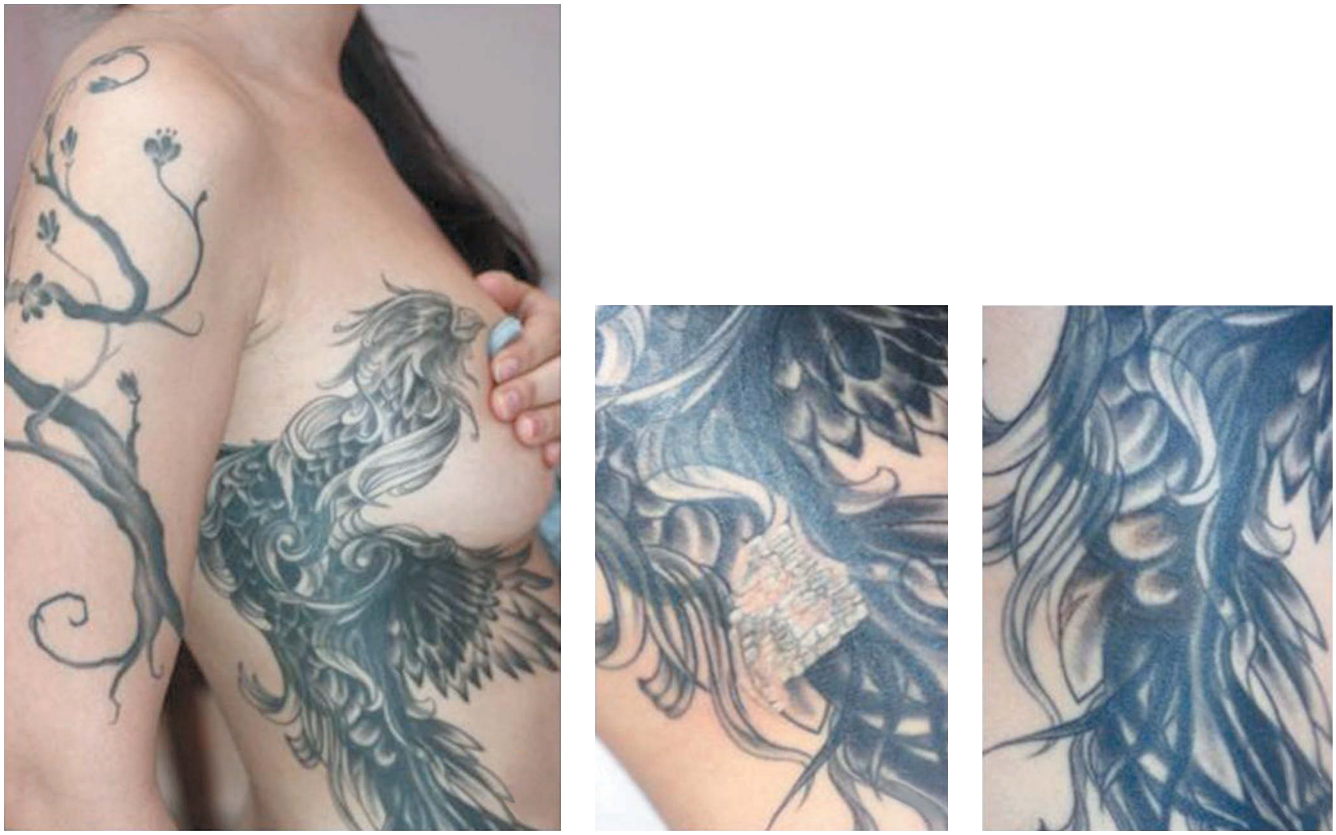


(a)

(b)

Figure 41.67 (a) Postinflammatory hyperpigmentation observed after treatment. (b) Twelve months after hyperpigmentation resisted to all treatments after three sessions.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b) (c)

Figure 41.68 (a) Upper body part professional tattoo on a 19-year-old female. (b) Immediate postoperative results with a 1064 nm QS Nd:YAG laser: postinflammatory hyperpigmentation. Black ink changed into brown. (c) After treatment with hydroquinone and another 755 nm wavelength QS alexandrite laser.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

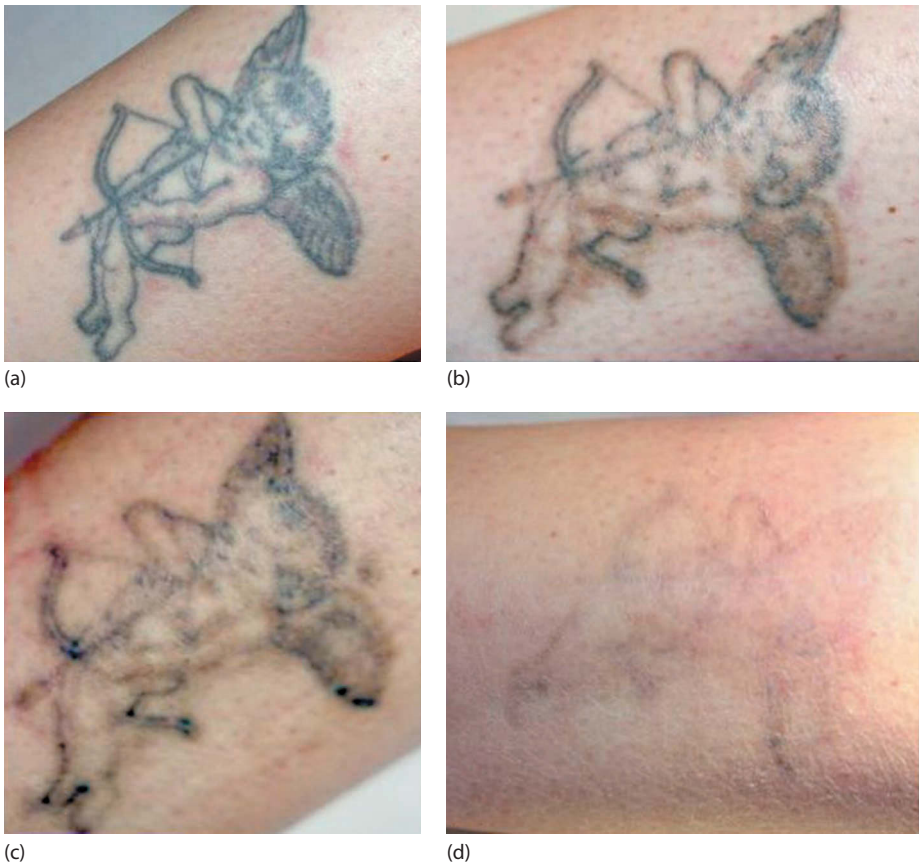


Figure 41.69 (a) Monochromatic tattoo before treatment. (b, c) Postinflammatory hyperpigmentation reaction. Treatment stopped and 6 months discontinuation. Patient was recommended sun tanning of the area. (d) Results achieved 3 years after five sessions.

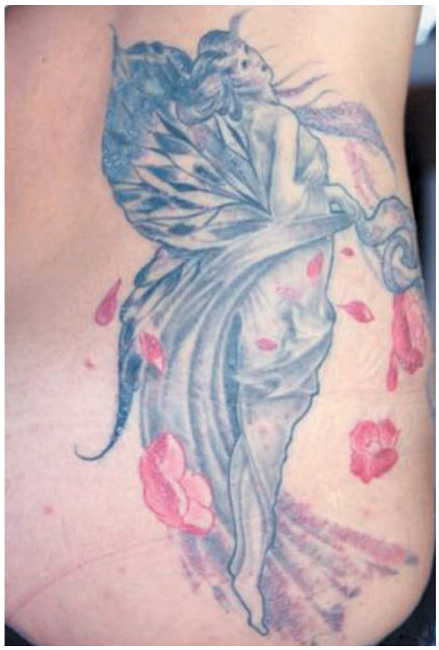


Figure 41.70 Atypical mycobacteria reaction in a tattooed area.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

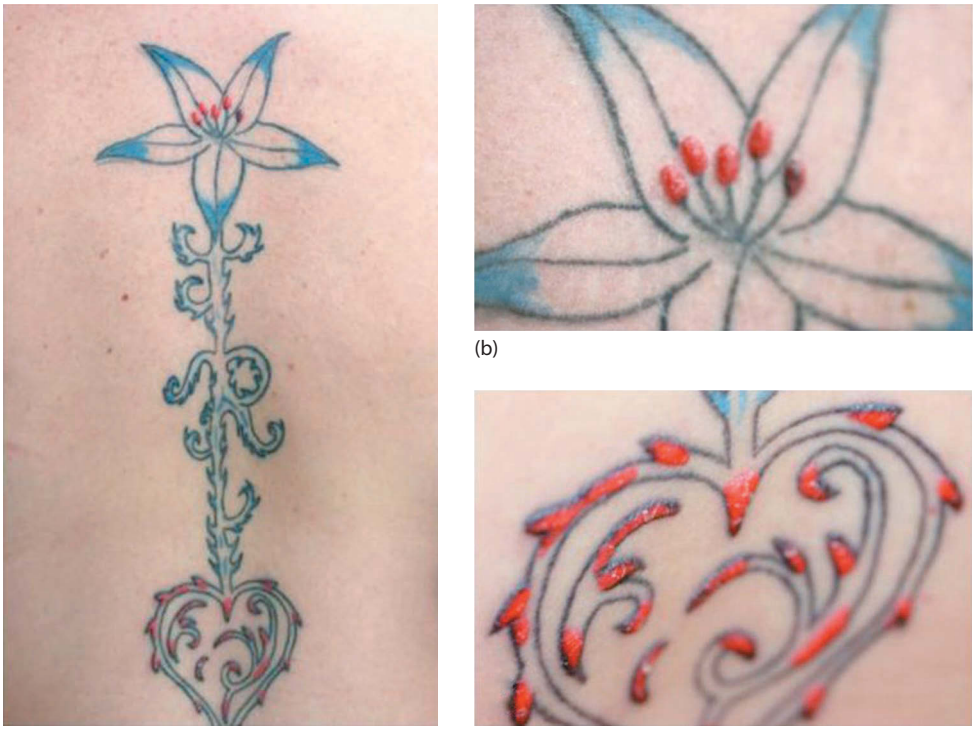


Figure 41.71 (a–c) Various aspects of red ink skin allergy granular lesions.

Guidances

Need to have good relationship with patients and try to indicate different possibilities regarding laser session results.

New tattoo techniques (skin carving, inlay depth) and new inks (colors, plastics, fluorescein, etc.) often make laser techniques more and more ineffective.

Thus, dermatologists' collaboration with tattoo artists is desirable. We observe that more and more tattoo artists are using QS lasers for tattoo removal. The use of these lasers is a medical act, with rules, side effects, and contraindications. QS lasers and any other therapeutic laser should be used only by trained medical doctors.

CONCLUSIONS

QS lasers remain the gold standard for tattoo removal, but employing the appropriate device and technique does not guarantee a successful clinical outcome.

The physician must take a detailed history and determine the correct laser to use as it will vary based on tattoo pigments, skin color, and tattoo etiology. They must educate their patients in detail regarding the process of laser tattoo removal and the realistic posttreatment expectations in order to create a successful therapeutic alliance.

Future innovations in laser technology as well as newer, easier-to-remove tattoo inks should enable more effective tattoo removal in the future, possibly requiring only a single device.

REFERENCES

1. Armstrong ML, Roberts AE, Koch JR et al. Motivation for contemporary tattoo removal. *Arch Dermatol* 2008; 144(7):879–884.
2. Drews DR, Allison CK, Probst JR. Behavioral and self-concept differences in tattooed and nontattooed college students. *Psychol Rep* 2000; 86:475–481.
3. Laumann AE, Derick AJ. Tattoos and body piercings in the United States: A national data set. *J Am Acad Dermatol* 2006; 55:413–421.
4. Long GE, Rickman LS. Infectious complications of tattoos. *Clin Infect Dis* 1994; 18:610–619.
5. Stirn A, Brahler E, Hinz A. Prevalence, sociodemography, mental health and gender differences of tattooing and body piercing (in German). *Psychother Psychosom Med Psychol* 2006; 56:445–449.
6. Scutt RWB, Gotch C. *Art, Sex and Symbol*. London, U.K.: Cornwall Books, 1985.
7. Spindler K. *The Man in the Ice: The Preserved Body of a Neolithic Man Reveals the Secrets of the Stone Age*. London, U.K.: Weidenfeld and Nicolson, 1994, p. 172.
8. Bianchi RS. Tattoo in ancient Egypt. In: Rubin A, ed. *Marks of Civilization*. Los Angeles, CA: Museum of Cultural History, The University of California, 1988, p. 26.
9. Rudenko SI. *Frozen Tombs of Siberia: The Pazyryk Burials of Iron Age Horsemen*. Berkeley, CA: The University of California Press, 1970, pp. 110–114.
10. Choudhary S, Elsaie ML, Leiva A et al. Lasers for tattoo removal: a review. *Lasers Med Sci* 2010; 25(5):619–627.
11. Timko AL, Miller CH, Johnson FB et al. In vitro quantitative chemical analysis of tattoo pigments. *Arch Dermatol* 2001; 137:143–147.
12. Moreno-Arias G, Casals-Andreu M, Camps-Fresneda A. Use of Q-switched alexandrite laser (755 nm, 100 nsec) for removal of traumatic tattoo of different origins. *Lasers Surg Med* 1999; 25(5):445–450.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

13. Achauer BM, Nelson JS, Vander Kam V et al. Treatment of traumatic tattoos by Q-switched ruby laser. *Plast Reconstr Surg* 1994; 93:318–323.
14. Ashinoff R, Geronemus RG. Rapid response of traumatic and medical tattoos to treatment with the Q-switched ruby laser. *Plast Reconstr Surg* 1993; 91:841–845.
15. Armstrong ML, Stuppy DJ, Gabriel DC et al. Motivation for tattoo removal. *Arch Dermatol* 1996; 132:412–416.
16. Kent KM, Graber EM. *Laser Tattoo Removal: A Review. Dermatol Surg* 2012; 38:1–13.
17. Adatto MA, Halachmi S, Lapidoth M. Tattoo removal. *Curr Probl Dermatol* 2011; 42:97–110.
18. Koerber WA Jr, Price NM. Salabrasion of tattoos: A correlation of the clinical and histological results. *Arch Dermatol* 1978; 114:884–888.
19. van der Velden EM, van der Walle HB, Groote AD. Tattoo removal: Tannic acid method of Variot. *Int J Dermatol* 1993; 32:376–380.
20. Johannesson A. A simplified method of focal salabrasion for removal of linear tattoos. *J Dermatol Surg Oncol* 1985; 11:1004–1005.
21. Alster T, Apfelberg D. *Cosmetic Laser Surgery*. New York: Wiley-Liss, 1996.
22. Scutt RW. The chemical removal of tattoos. *Br J Plast Surg* 1972; 25:189–194.
23. Manchester GH. Removal of commercial tattoos by abrasion with table salt. *Plast Reconstr Surg* 1974; 53:517–521.
24. Clabaugh W. Removal of tattoos by superficial dermabrasion. *Arch Dermatol* 1968; 98:515–521.
25. Wollina U, Kostler E. Tattoos: Surgical removal. *Clin Dermatol* 2007; 25:393–397.
26. Koljonen V, Kluger N. Specifically requesting surgical tattoo removal: Are deep personal motivations involved? *J Eur Acad Dermatol Venereol* 2012; 2(6):685–689.
27. Penoff J. The office treatment of tattoos: A simple and effective method. *Plast Reconstr Surg* 1987; 79:186–191.
28. Zinberg M, Heilman E, Glickman F. Cutaneous pseudo-lymphoma from a tattoo. *J Dermatol Surg Oncol* 1992; 8:955–958.
29. Bernstein EF. Laser treatment of tattoos. *Clin Dermatol* 2006; 24(1): 43–55.
30. Mafong EA, Kauvar AN, Geronemus RG. Surgical pearl: Removal of cosmetic lip-liner tattoo with the pulsed carbon dioxide laser. *J Am Acad Dermatol* 2003; 48:271–272.
31. Bailin PL, Ratz JR, Levine HL. Removal of tattoos by CO_2 laser. *J Dermatol Surg Oncol* 1980; 6:997–1001.
32. Reid R, Muller S. Tattoo removal by CO_2 laser dermabrasion. *Plast Reconstr Surg* 1980; 65:717–721.
33. Anderson RR, Parrish JA. Selective photothermolysis: Precise microsurgery by selective absorption of pulsed radiation. *Science* 1983 April 29; 220(4596):524–527.
34. Ferguson JE, Andrew SM, Jones CJ et al. The Q-switched neodymium:YAG laser and tattoos: A microscopic analysis of laser-tattoo interactions. *Br J Dermatol* 1997; 137:405–410.
35. Ara G, Anderson R, Mandel K et al. Irradiation of pigmented melanoma cells with high intensity pulsed radiation generates acoustic waves and kills cells. *Lasers Surg Med* 1990; 10(1):52–59.
36. Kilmer SL. Laser treatment of tattoos. *Dermatol Clin* 1997; 15(3): 409–417.
37. Pfirrmann G, Karsai S, Roos S et al. Tattoo removal—State of the art. *J Dtsch Dermatol Ges* 2007; 5(10):889–897.
38. Goldman L, Wilson RG, Hornby P et al. Radiation from a Q-switched ruby laser: Effect of repeated impacts of power output of 10 megawatts on a tattoo of man. *J Invest Dermatol* 1965; 44:69–71.
39. Levine VJ, Geronemus RG. Tattoo removal with the Q-switched ruby laser and the Q-switched Nd:YAG laser: A comparative study. *Cutis* 1995; 55(5):291–296.
40. Taylor CR, Gange RW, Dover JS. Treatment of tattoos by Q-switched ruby laser: A dose-response study. *Arch Dermatol* 1990; 126:893–899.
41. Scheibner A, Kenny G, White W et al. A superior method of tattoo removal using the Q-switched ruby laser. *J Dermatol Surg Oncol* 1990; 16:1091–1098.
42. Leuenberger M, Mulas M, Hata T et al. Comparison of the Q-switched alexandrite, Nd:YAG, and ruby lasers in treating blue-black tattoos. *Dermatol Surg* 1999; 25(1):10–14.
43. Kilmer SL, Anderson RR. Clinical use of the Q-switched ruby and the Q-switched Nd:YAG (1064 nm and 532 nm) lasers for treatment of tattoos. *J Dermatol Surg Oncol* 1993; 19(4):330–338.
44. Kuperman-Beade M, Levine VJ, Ashinoff R. Laser removal of tattoos. *Am J Clin Dermatol* 2001; 2:21–25.
45. Kilmer SL, Lee MS, Grevelink JM et al. The Q-switched Nd:YAG laser effectively treats tattoos: A controlled, dose-response study. *Arch Dermatol* 1993; 129:971–978.
46. Jones A, Roddey P, Orengo I et al. The Q-switched ND:YAG laser effectively treats tattoos in darkly pigmented skin. *Dermatol Surg* 1996; 22:999–1001.
47. Grevelink J, Duke D, van Leeuwen R et al. Laser treatment of tattoos in darkly pigmented patients: Efficacy and side effects. *J Am Acad Dermatol* 1996; 34(4):653–656.
48. Lapidoth M, Aharonwitz G. Tattoo removal among Ethiopian Jews in Israel: Tradition faces technology. *J Am Acad Dermatol* 2004; 51(6):906–909.
49. Lin T, Jia G, Rong H et al. Comparison of a single treatment with Q-switched ruby laser and Q-switched Nd:YAG laser in removing black-blue Chinese tattoos. *J Cosmet Laser Ther* 2009; 11(4):236–239.
50. Fitzpatrick RE, Goldman MP. Tattoo removal using the alexandrite laser. *Arch Dermatol* 1994; 130:1508–1514.
51. Alster TS. Q-switched alexandrite laser treatment (755 nm) of professional and amateur tattoos. *J Am Acad Dermatol* 1995; 33:69–73.
52. Zelickson B, Mehregan D, Zarrin A et al. Clinical, histologic, and ultrastructural evaluation of tattoos treated with three laser systems. *Lasers Surg Med* 1994; 15(4):364–372.
53. Moreno-Arias GA, Camps-Fresneda A. The use of Q-switched alexandrite laser (755 nm, 100 ns) for eyeliner tattoo removal. *J Cutan Laser Ther* 1999; 1:113–115.
54. Ferguson J, August P. Evaluation of the Nd:YAG laser for treatment of amateur and professional tattoos. *Br J Dermatol* 1996; 135(4):586–591.
55. Antony FC, Harland CC. Red ink tattoo reactions: Successful treatment with the Q-switched 532 nm Nd:YAG laser. *Br J Dermatol* 2003; 149(1):94–98.
56. Kirby W, Desai A, Desai T et al. The Kirby-Desai scale: A proposed scale to assess tattoo-removal treatments. *J Clin Aesthetic Dermatol* 2009; 2(3):32–37.
57. Kirby W, Desai A, Desai T, Kartona F. Tattoo removal techniques: Effective tattoo removal treatments—Part 2. *Skin Aging* 2005 October.
58. Taylor CR, Anderson RR, Gange RW et al. Light and electron microscopic analysis of tattoos treated by Q-switched ruby laser. *J Invest Dermatol* 1991 July; 97(1):131–136.
59. Handley J. Adverse events associated with nonablative cutaneous visible and infrared laser treatment. *J Am Acad Dermatol* 2006; 55:482–489.
60. Kirby W, Koriakos A, Desai A, Desai T. Undesired pigmentary alterations associated with Q-switched laser tattoo removal. *Skin Aging* 2010 August.
61. Lanigan S. Incidence of side effects after laser hair removal. *J Am Acad Dermatol* 2003; 49:882–886.
62. Willey A, Anderson RR, Azpiazu JL et al. Complications of laser dermatologic surgery. *Lasers Surg Med* 2006; 38:1–15.
63. Dave R, Mahaffey PJ. Successful treatment of an allergic reaction in a red tattoo with the Nd-YAG laser. *Br J Plast Surg* 2002; 55:456.
64. Ibrahimi OA, Syed Z, Sakamoto FH et al. Treatment of tattoo allergy with ablative fractional resurfacing: A novel paradigm for tattoo removal. *J Am Acad Dermatol* 2011; 64(6):1111–1114.
65. Jimenez G, Weiss E, Spencer JM. Multiple color changes following laser therapy of cosmetic tattoos. *Dermatol Surg* 2002; 28:177–179.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

66. Goldman MP. *Cutaneous and Cosmetic Laser Surgery*, 1st ed. Philadelphia, PA: Elsevier, 2006, pp. 127–130.
67. Fitzpatrick RE, Lupton JR. Successful treatment of treatment-resistant laser-induced pigment darkening of a cosmetic tattoo. *Lasers Surg Med* 2000; 27:358–361.
68. Herbich GJ. Ultrapulse carbon dioxide laser treatment of an iron oxide flesh-colored tattoo. *Dermatol Surg* 1997; 23:60–61.
69. Baumler W, Eibler ET, Hohenleutner U, Sens B, Sauer J, Landthaler M. Q-switch laser and tattoo pigments: First results of the chemical and photophysical analysis of 41 compounds. *Lasers Surg Med* 2000; 26:13–21.
70. Vasold R, Naarmann N, Ulrich H et al. Tattoo pigments are cleaved by laser light-the chemical analysis in vitro provide evidence for hazardous compounds. *Photochem Photobiol* 2004; 80:185–190.
71. Kossida T, Rigopoulos D, Katsambas A et al. Optimal tattoo removal in a single laser session based on the method of repeated exposures. *J Am Acad Dermatol* 2012; 66(2):271–277.
72. Ayers FR, Cuccia DJ, Kelly KM et al. Wide-field spatial mapping of in vivo tattoo skin optical properties using modulated imaging. *Lasers Surg Med* 2009; 41(6):442–453.
73. Trelles MA. Cosmetic laser surgery: Current procedures and developments to come. In: Taylor S, ed. *Private Hospital Healthcare Europe*. London, U.K.: Campden Publishing Limited, 2003.
74. Vélez M, Serra M, Trelles MA et al. Estado actual del laser quirúrgico en España. *S.E.L.M.Q. Boletin Informativo* 2001; 1:9–15.
75. Multifunctional laser complex Multiline. France: Linline. www.linline.com. Accessed August 4, 2011.
76. Dixon J. Laser treatment of decorative tattoos. In: Arndt KA, Noe JM, Rosen S, eds. *Cutaneous Laser Therapy: Principles and Methods*. New York: John Wiley & Sons, 1983.
77. Izikson L, Farinelli W, Sakamoto F et al. Safety and effectiveness of black tattoo clearance in a pig model after a single treatment with a novel 758 nm 500 picosecond laser: A pilot study. *Lasers Surg Med* 2010; 42(7):640–646.
78. Ross V, Naseef G, Lin G et al. Comparison of responses of tattoos to picosecond and nanosecond Q-switched neodymium: YAG lasers. *Arch Dermatol* 1998; 134:167–171.
79. Herd RM, Alora MB, Smoller B et al. A clinical and histologic prospective controlled comparative study of the picosecond titanium:sapphire (795 nm) laser versus the Q-switched alexandrite (752 nm) laser for removing tattoo pigment. *J Am Acad Dermatol* 1999; 40(4):603–606.
80. Izikson L, Avram M, Anderson RR. Transient immunoreactivity after laser tattoo removal: Report of two cases. *Lasers Surg Med* 2008; 40:231–232.
81. Weiss LT, Geronemus RG. Combining fractional resurfacing and Q-switched ruby laser for tattoo removal. *Dermatol Surg* 2011; 37:97–99.
82. Ramirez M, Magee N, Diven D et al. Topical imiquimod as an adjuvant to laser removal of mature tattoos in an animal model. *Dermatol Surg* 2007; 33:319–325.
83. Ricotti CA, Colaco SM, Shamma HN et al. Laser-assisted tattoo removal with topical 5% imiquimod cream. *Dermatol Surg* 2007; 33(9):1082–1091.
84. Elsaie ML, Nouri K, Vejjabhinanta V et al. Topical imiquimod in conjunction with Nd:YAG laser for tattoo removal. *Lasers Med Sci* 2009; 24(6):871–875.
85. Vargas G, Chan K, Thomsen S et al. Use of osmotically active agents to alter optical properties of tissue: Effects on the detected fluorescence signal measured through skin. *Lasers Surg Med* 2001; 29(3):213–220.
86. McNichols RJ, Fox MA, Gowda A et al. Temporary dermal scatter reduction: Quantitative assessment and implications for improved laser tattoo removal. *Lasers Surg Med* 2005; 36:289–296.
87. Sanchez Pérez J. Análisis experimental par optimización de los parámetros de eliminación de los tatuajes por acción multifotónica coherente. PhD thesis, University of Valencia School of Medicine, Valencia, Spain, 1989.
88. Trelles MA, Velez M, Allones I. Easy dressing: An economical, transparent nonporous film for wound care post laser resurfacing. *Arch Dermatol* 2001; 137:674–675.
89. Trelles MA, Allones I, Mayo E. Combined visible light and infrared light-emitting diode (LED) therapy enhances wound healing after laser ablative resurfacing of photodamaged facial skin. *Med Laser Appl* 2006; 21:165–175.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Laser and pigmented (melanotic) lesions

Thierry Passeron

The color of the skin results from the presence of pigments in the epidermis and in the dermis. The melanins are the most important pigments in human skin. However, other endogenous pigments such as hemoglobin and bilirubin also play a role in the color of the teguments. Dyschromia can result from a darkening, a lightening, and the occurrence of an unusual skin color [1]. Quantitative or qualitative defects in the production or in the deposition of melanin explain most of the pigmentary disorders, but abnormal variations of other endogenous pigments and deposit of exogenous pigments also lead to dyschromic lesions. Lasers have provided significant progresses in the treatment of many of those hyperpigmented lesions. This chapter will focus on hyperpigmentation related to melanotic lesions. However, this is a heterogeneous group with many pathophysiological origins requiring specific treatment approaches. Indeed, when laser treatment can provide significant improvement of some pigmented lesions, it can also worsen others. Thus, a precise diagnosis is mandatory to assess if a laser approach can be useful and to determine the optimal parameters.

HOW LONG HAS IT BEEN ESTABLISHED?

The successful removal of benign cutaneous pigmented lesions, such as lentigines, café-au-lait macules, or Ota nevus, was reported for almost 50 years now. A variety of lasers such as the excimer (351 nm), argon (488,514 nm), ruby (694 nm), Nd:YAG (1,060 nm), and CO_2 (10,600 nm) were used during the first two decades. However, the use of lasers in dermatological indications as we know nowadays is based on the principle of the selective photothermolysis [2]. In 1987, Luigi Polla demonstrated that the Q-switched (QS) 694 nm ruby laser specifically targets melanosomes [3]. Progressively, the treatment with a selective laser approach was assessed for most of the pigmented lesions [4,5].

SCIENTIFIC BASIS

The treatment of pigmentary disorders by lasers is based on the selective photothermolysis [2]. In order to have a selective action, the length of the laser impulsion has to be at least ten times shorter than the relaxation time of the target. This relaxation time is proportional to the size of the target (but also depends on the shape and the thermal diffusivity of the target). For pigmentary troubles due to melanin defects, the target is the melanosome. It is a lysosome-related organelle specific of the melanocytes within the melanin is produced. With their maturation, the melanosomes will be progressively filled with melanin and be transferred to the surrounding keratinocytes [6]. Melanin is the chromophore targeted by the pigmentary lasers. There are two types of melanins: Eumelanins are dark brown to black pigments, while pheomelanins are red brown. Eumelanins are mostly observed in dark skin types and have photoprotective properties, when pheomelanins are the most important type of melanin in fair skin types and might contribute to skin cancers and melanomagenesis [7]. Beyond those crucial photobiological differences, the difference in color of these two types of pigment induces some differences in their absorption curve. When compared to eumelanins, the pheomelanins have better absorption in shorter wavelengths. Thus, pigmented lesions with high proportion of pheomelanins, such as freckles or actinic lentigos in fair skin patients, are better treated with a laser emitting a 532 nm wavelength. Most of the other pigmented lesions usually contain more eumelanin and are better targeted by 694 and 755 nm wavelengths.

The size of a melanosome is about 1 µm. Its relaxation time varies from 1 to 10 µs. Thus, the impulsion time of the laser has to be inferior to 100 ns. The lasers that are used for pigmentary disorders are Q-switched and their impulsion length is from 10 to 100 ns, allowing them to target the melanosomes and most of the exogenous pigments [8].

The location of the pigment in the dermis or the epidermis guides in part the choice of the wavelength. An increased amount of melanin in the skin is called hypermelanosis or melanoderma. A brown hypermelanosis is caused by excessive amounts of melanin within the epidermis, whereas ceruloderma (or blue hypermelanosis) results from large amounts of melanin in the dermis. Mixed hypermelanosis is characterized by an excess of melanins in both epidermis and dermis may also occur. Epidermal hypermelanosis may result from increased melanin production by a quantitatively normal melanocyte density in the epidermis (melanotic hypermelanosis) or by an increased number of epidermal melanocytes (melanocytic hypermelanosis). Dermal hypermelanosis can be due to the production of melanin by ectopic dermal melanocytes (dermal melanocytosis) or to an abnormal transfer of melanin from epidermal cells to the dermis (pigmentary incontinence). In this situation, melanin granules accumulate within melanophages or may be free in the extracellular matrix of the dermis. Thus, dermal pigmentations will be better treated with 1064 nm Nd:YAG lasers, which wavelength could penetrate deeper in the skin tissue. Those lasers are also preferred for dark skin people as they less interact with the melanin of the superficial layers of the skin.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

TREATMENT OF HYPERPIGMENTED LESIONS

Solar Lentigines

Solar lentigines are effectively treated with topical blanching cream, liquid nitrogen, Q-switched lasers, and intense pulsed light (IPL). The treatment with Q-switched laser has been proven to be the most effective approach, especially if the lesions are numerous, but it remains more expensive [9]. One or two laser sessions are sufficient [10] (Figure 42.1). While 694 and 755 nm are usually preferred in most cases, light lentigos are better treated with 532 nm Q-switched lasers. More recently, the thulium laser in fractionated mode was reported to improve solar lentigines [11]. The 1927 nm wavelength of this laser has a strong affinity for water. In contrast to QS lasers that will selectively target the melanin, the thulium laser approach has best to be considered for a more global photoageing care. Patients are advised to use sunscreens to tackle the menace of recurrences. If the lesion is atypical, a skin biopsy has to be performed to detect a lentigo maligna.

Lentigines and Freckles

Q-switched lasers are effective in treating lentigines, including those associated with a genetic disorder such as Peutz–Jeghers–Touraine syndrome [12].

Freckles can also be treated with laser. As they contain mainly pheomelanin, the optimal wavelength is 532 nm. However, the relapses after treatment are constant and strongly limit the use of lasers in this indication [13,14].

Café-au-lait Macules

Café-au-lait macules can be treated with lasers, but the response is variable and recurrences are frequent. No clinical or histological markers have been determined to predict the response to treatment [15]. Thus, the patient should be clearly informed of those risks. For large lesions, we advise to conduct a test session on a small area and to see the patient after one summer to evaluate the response and the stability after treatment before treating the entire lesion.

Nevus Spilus

Q-switched lasers including ruby and alexandrite have demonstrated their efficacy in treating nevus spilus [16,17] (Figure 42.2). As for café-au-lait macules, relapses could be observed. Moreover, the risk of melanoma, even though rare, is real and laser treatment should be proposed with caution, and a biopsy has to be done if the lesion is atypical.

Becker Nevus

The hair component of Becker nevus responds well to laser hair removal. The hyperpigmentation can also be treated with Q-switched lasers, but the response is more inconstant and recurrences are observed. A test session is required before treating large lesions [18]. Most of the authors advise to first treat the hair component, but the sequence of treatment does not change the final result, and the choice mainly depends on the requests of the patient. The use of fractional CO_2 laser was recently proposed in a pilot study [19]. The mild improvement and the side effects observed (including 3 postinflammatory hyperpigmentation [PIH] on 11 treated patients) strongly limit the interest of such an approach for treating Becker nevus.

Ota Nevus, Ito Nevus, and Acquired Dermal Hypermelanocytosis

Ota nevi are dermal hypermelanocytosis of the periorbital region. Such dermal hypermelanocytosis can also affect the shoulder (Ito nevus) or rarely other parts of the body. Acquired dermal hypermelanocytoses are usually not well known. However, they are not so uncommon. They can appear from infancy to adulthood (most cases have an onset in the second or the third decade of age), and they also correspond to the abnormal presence of melanocytes with the dermis [20]. Some forms are bilateral and affect the face. Hori's nevus or acquired bilateral nevus of Ota-like macules is one of the main differential diagnoses of melasma [21].

Although all types of dermal hypermelanocytosis are more frequently observed in Asian people, they have been reported worldwide. Ruby, alexandrite, and Nd:YAG QS lasers have proved their efficacies. The depth of the target pigment leads to the use of longer wavelength. The 1064 nm QS Nd:YAG has shown its superiority compared to the 755 nm alexandrite [22]. Early treatment of the children and brown rather than blue lesions are good predictive factors of response to treatment [23,24]. Relapses can be observed and patients have to be aware of this [25].

Although there is no literature/research on these, Ito nevus and acquired dermal hypermelanocytosis can also be effectively treated with those lasers [26] (Figure 42.3).

(a) (b)

Figure 42.1 (a) Solar lentigines of the cheek. (b) Two months after one session of 532 nm QS laser.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 42.2 (a) Nevus spilus of the face. (b) Three years after three sessions of QS 755 nm QS laser. Note the slight relapse of the lesion.

(a) (b)

Figure 42.3 (a) Acquired hypermelanocytosis of the forehead. (b) Clinical results 6 months after sour sessions of 1064 nm QS laser.

Giant Congenital Nevus

Beyond the increased risk of melanoma, giant congenital nevus also induces a major cosmetic problem with a deep impact on the quality of life in most cases. Several laser approaches have been proposed when a surgical treatment cannot be done. Nonselective destruction with CO_2 or Er:YAG laser dermabrasion, sometimes associated with QS lasers, can lead to a marked reduction of the hyperpigmentation that sometimes last for many years [27]. Unfortunately, the results are inconsistent and the scaring sequelae can be prominent. A selective approach, using ruby, alexandrite, or Nd:YAG QS lasers, can also induce a significant improvement in pigmentation and texture of the congenital nevus [28]. Histological studies have shown the persistence of nevus cells, explaining the partial or complete relapses of the hyperpigmentation that are almost constant. Interesting results have also been reported on a combination of pulsed dye laser (PDL) and ruby QS lasers [29]. A promising approach has been reported using a QS ruby laser from the first month of age. Using increasing doses coupled with sessions every 2 weeks for 2–3 months, 8/9 children showed good to excellent results at 1-year follow-up [30]. The long-term effect of the fibrosis induced by laser treatment on the risk of developing melanoma is still unknown, and careful follow-up of patients is advised in any cases.

Linear and Whorled Nevoid Hypermelanosis

There is almost no data on the treatment of linear and whorled nevoid hypermelanosis (LWNH). We have treated with QS lasers a series of 4 children, 6–18 years old, with LWNH.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

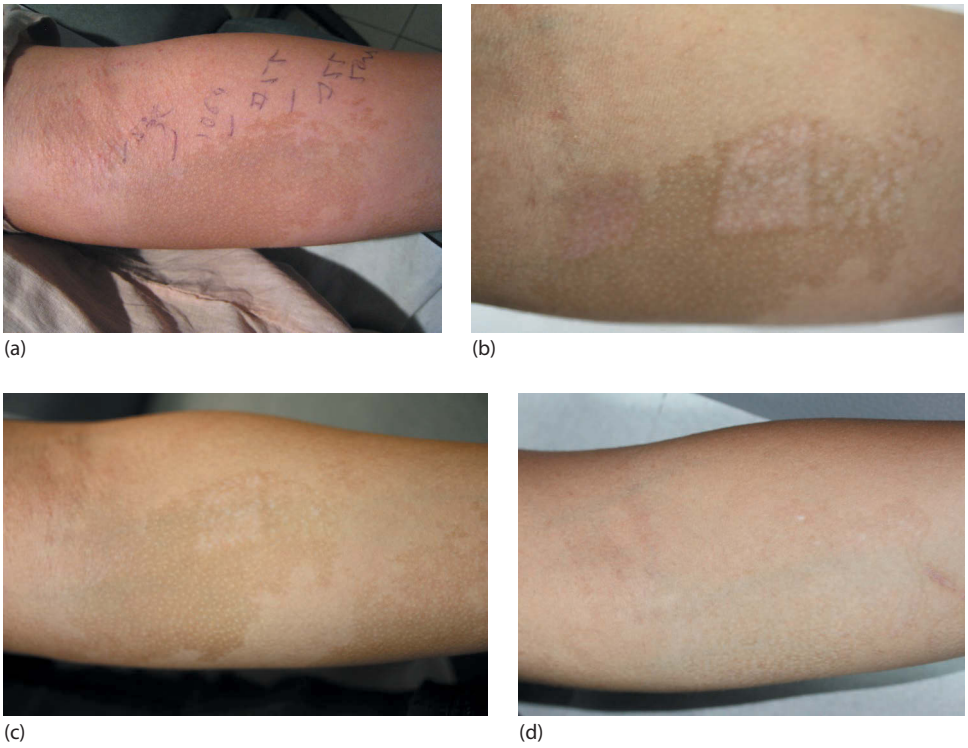


Figure 42.4 (a) LWNH of the arm before the test session with 532, 755, and 1064 nm QS lasers. (b) Clinical results 1 month after the test session. (c) Clinical results after one summer. The 755 nm QS laser was then chosen to treat the entire lesion. (d) Clinical results at a 2-year follow-up after two sessions of 755 nm QS laser.

For each case, a test session with 532, 755, and 1064 nm QSL was first performed. The entire lesion was only treated if at least one of the lasers showed a decrease in pigmentation of more than 50% after the test session and without recurrence after one summer period. The 532 and 755 nm QSL led to a clearing of the hyperpigmented lesions in 1–2 sessions with a good tolerance. With a mean follow-up of 26 months (13–38), only one patient showed partial recurrences that were effectively treated with one maintenance session per year [31] (Figure 42.4). Although patients have to be warned of the possible long-term recurrences after such a treatment, this series suggests that QSL might be an effective approach for treating LWNH.

Dark Rings

The dark rings under the eyes are a heterogeneous group with multifactorial etiologies, which depends mainly on physiological factors such as superficial location of vasculature, periorbital edema, and shadowing due to skin laxity. In some patients, the dark rings are due to hypermelanosis, mainly in the dermis. Topical treatments, including tretinoin cream, peeling, CO_2 laser, and surgical approaches, have been reported [32–35]. However, best results are usually obtained with QS lasers and IPL [36,37].

Poikiloderma of Civatte

Laser and IPL approaches are the best treatments for the poikiloderma of Civatte. Both PDL and IPL have shown their efficacy [38–41]. However, persistent depigmentation has been reported as a late adverse event and high fluencies should be avoided in this fragile location [42]. More recently, some authors suggested the use of fractional photothermolysis with interesting results, but the data remain limited [43,44].

Postinflammatory Hyperpigmentation

PIH is frequent and can be observed after a surgical or cosmetic procedure. Laser treatments are usually not a good option for hyperpigmentation as they can worsen the lesions. Photoprotection and treatment of the underlying dermatosis, if there is one, are mandatory and could be effective by themselves. If needed, class 3 topical steroids alone or combined with 4%–10% hydroquinone can be considered. Combined topical treatment with lasers (QS lasers and PDL) can be discussed as an alternative, but the risk of relapse and worsening of the PIH should be clearly stated to the patient [45].

Melasma

The gold standard treatment for melasma is topical bleaching agents. The Kligman's formula is the most effective treatment especially in its stabilized form [46–48]. Ablative and nonablative fractional lasers have been reported to improve melasma [49,50]. However, such approaches, although interesting, are not superior to conventional therapies [51], and results at 6 months are not significantly different from sun protection alone [52]. Pigmentary lasers, such as QS ruby, alexandrite, or Nd:YAG lasers, induce

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 42.5 (a) Vitiligo universalis with disfiguring remaining areas of normal pigmented skin on the face. (b) Clinical aspect at 1-year follow-up after 1 session of QS 755 nm laser.

almost constant PIH and frequent relapses. Thus, such lasers are usually not recommended for the treatment of melasma [6]. More recently, QS 1064 nm Nd:YAG used with low fluencies has shown preliminary interesting results in treating melasma. Unfortunately, a prospective randomized trial comparing such an approach to 2% hydroquinone revealed that after a nice improvement at the end of the laser sessions, there was a constant relapse of the melasma with PIH in 20% of cases [53]. IPL has shown some efficacy in the treatment of melasma [54–57]. The risk of PIH remains important but appears to be lower than the one observed with Q-switched lasers. Topical bleaching preparations, frequently containing hydroquinone, have been used with IPL in order to prevent PIH [58,59]. Although potentially useful, this combined approach has never been compared to bleaching cream used in monotherapy. More recently, a retrospective analysis of 20 cases of melasma treated with the 1927 nm fractional *thulium laser* showed more than 50% of clearance in 12 of the 20 patients [60]. With a mean follow-up of 12 months, 7 patients of 15 showed relapses and PIH was noted in 10% of the cases. A prospective study comparing this new laser approach to Kligman's trio is clearly needed. Histological and laser confocal microscopy studies showed that in addition to the increase in pigmentation, melasma lesions show more elastosis and vascularization, as compared to the perilesional skin [61,62]. The propigmenting role of the vascularization has been recently demonstrated emphasizing the interest of targeting the vascular component of melasma [63]. The use of a copper bromide laser emitting a dual wavelength at 511 and 578 nm that also targets the vascular component of melasma initially showed promising results [64]. However, this pilot study was not confirmed in a prospective randomized comparative trial [65].

Vitiligo

The aim of vitiligo treatment is usually to repigment the lesional areas. However, in widespread vitiligo resistant to repigmenting therapies, a depigmentation of the remaining pigmented skin in achieving uniform skin tone can be very useful to the patients. Blanching creams, such as monobenzylether of hydroquinone, can be used, but the length of the treatment and the side effects strongly limit their use in practice. QS lasers have been reported to be effective where blanching agents have failed [66]. In a retrospective study with long-term follow-up (mean duration of follow-up of 36 months [19–120]), we have shown that QS lasers used initially can achieve a complete depigmentation in about 2 sessions [67]. Two-third of patients showed minimal relapses, and they were effectively treated with a maintenance session. The tolerance and satisfaction were excellent. QS lasers appear as an efficient and safe modality for depigmenting normal skin in vitiligo (Figure 42.5). Interestingly, better results with laser depigmentation seem to be obtained in active vitiligos [68].

ADVERSE REACTIONS

All lasers can induce side effects and the patients have to be clearly informed about those potential risks. Transient superficial crusts are observed after sessions. Purpura can be observed with 532 nm QS lasers. In both cases, they disappear in the 2 weeks following the laser session. Bullous reaction can be observed with high fluencies or in fragile skin. Scars are rare with QS lasers. In most cases, they are due to excessive fluencies. PIH is the most common side effect. PIH is mostly observed in dark skin types. Photoprotection is required after the laser session to decrease this risk. PIH usually regressed in a couple of weeks or months. Topical steroids eventually combined with hydroquinone can be helpful. Leukodermas are less frequently observed. They are usually transient, but permanent leukodermas have been reported mainly with 694 nm ruby lasers.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

WHAT TO AVOID?

Hyperpigmentation disorders are a heterogeneous group with numerous causes. Although most of the patients will consult for the cosmetic disturbance due to the dyschromia, it is essential to determine the origin of the pigmentary trouble in order to propose the more suitable treatment and if necessary to ask for expert opinions. The main caveat is to rule out a lentigo maligna before treating solar lentigines. In most cases, the diagnosis is obvious, but any abnormality in color or shape should prompt a dermoscopy examination and a skin biopsy if there are any doubts. Patients with numerous lentigines or café-au-lait macules searching for a cosmetic improvement of their conditions have to be first carefully examined to rule out a genodermatosis. Finally, PIH is clearly the most frequent side effect. Prevention of PIH with strict avoidance of sun and sunscreens use, before and after the laser sessions, is required. Topical steroids, eventually combined with topical hydroquinone, can be useful in patients at risk.

Lasers are a very effective approach for treating many hyperpigmented lesions. They are the gold standard treatment for actinic lentigos and dermal hypermelanocytosis, such as Ota nevus. Becker nevus, hyperpigmented mosaicisms, or lentigines can also be successfully treated with lasers, but they could be less effective and relapses can be observed. However, lasers cannot be proposed for all types of hyperpigmentation. Thus, freckles and café-au-lait macules should not be treated as the relapses are almost constant. Due to its complex pathophysiology, melasma has a special place in hyperpigmented dermatoses. The Q-switched lasers (using standard parameters or low fluency) should not be used due to the constant relapses and the high risk of PIH. Targeting the vascular component of melasma lesion with lasers could improve the effect of blanching creams. However, those results are yet to be confirmed. In all cases, a precise diagnosis of the type of hyperpigmentation is mandatory before any laser treatment, and the limits and the potential side effects of the treatment must be clearly explained to the patients.

REFERENCES

1. Nordlund JJ, Boissy RE, Hearing VJ et al. *The Pigmentary System: Physiology and Pathophysiology*. New York: Oxford University Press, 1998, pp. 1–1025.
2. Anderson RR, Parrish JA. Selective photothermolysis: Precise microsurgery by selective absorption of pulsed radiation. *Science* 1983; 220(4596):524–527.
3. Polla LL, Margolis RJ, Dover JS et al. Melanosomes are a primary target of Q-switched ruby laser irradiation in guinea pig skin. *J Invest Dermatol* 1987; 89(3):281–286.
4. Goldberg DJ, Nychay SG. Q-switched ruby laser treatment of nevus of Ota. *J Dermatol Surg Oncol* 1992; 18(9):817–821.
5. Nelson JS, Applebaum J. Treatment of superficial cutaneous pigmented lesions by melanin-specific selective photothermolysis using the Q-switched ruby laser. *Ann Plast Surg* 1992; 29(3):231–237.
6. Ortonne JP, Passeron T. Melanin pigmentary disorders: Treatment update. *Dermatol Clin* 2005; 23(2):209–226.
7. Mitra D, Luo X, Morgan A et al. An ultraviolet-radiation-independent pathway to melanoma carcinogenesis in the red hair/fair skin background. *Nature* 2012; 491(7424):449–453.
8. Fusade HvL, Passeron, T. Traitement des lésions pigmentaires. In: Cartier H, Dahan S, Toubel G, eds. *Les lasers en dermatologie*. Rueil-Malmaison, France: Doin, 2010.
9. Todd MM, Rallis TM, Gerwels JW et al. A comparison of 3 lasers and liquid nitrogen in the treatment of solar lentigines: A randomized, controlled, comparative trial. *Arch Dermatol* 2000; 136(7):841–846.
10. Tanzi EL, Lupton JR, Alster TS. Lasers in dermatology: Four decades of progress. *J Am Acad Dermatol* 2003; 49(1):1–31; quiz 31–34.
11. Polder KD, Harrison A, Eubanks LE et al. 1,927-nm fractional thulium fiber laser for the treatment of nonfacial photodamage: A pilot study. *Dermatol Surg* 2011; 37(3):342–348.
12. Kato S, Takeyama J, Ta Y et al. Ruby laser therapy for labial lentigines in Peutz-Jeghers syndrome. *Eur J Pediatr* 1998; 157(8):622–624.
13. Ye T, Pawlak A, Sarna T et al. Different molecular constituents in pheomelanin are responsible for emission, transient absorption and oxygen photoconsumption. *Photochem Photobiol* 2008; 84(2):437–443.
14. Kollias N, Baqer AH. Absorption mechanisms of human melanin in the visible, 400–720 nm. *J Invest Dermatol* 1987; 89:384–388.
15. Grossman MC, Anderson RR, Farinelli W et al. Treatment of cafe au lait macules with lasers: A clinicopathologic correlation. *Arch Dermatol* 1995; 131(12):1416–1420.
16. Grevelink JM, González S, Bonoan R et al. Treatment of nevus spilus with the Q-switched ruby laser. *Dermatol Surg* 1997; 23(5):365–369; discussion 369–370.
17. Moreno-Arias GA, Bulla F, Vilata-Corell JJ et al. Treatment of widespread segmental nevus spilus by Q-switched alexandrite laser (755 nm, 100 nsec). *Dermatol Surg* 2001; 27(9):841–843.
18. Passeron T. Lasers. *Ann Dermatol Venereol* 2012; 139(Suppl. 4): S159–S165.
19. Meesters AA, Wind BS, Kroon MW et al. Ablative fractional laser therapy as treatment for Becker nevus: A randomized controlled pilot study. *J Am Acad Dermatol* 2011; 65(6):1173–1179.
20. Hori Y, Kubota Y, Takayama O et al. Acquired hypermelanotic disorders: Clinical and pathological features. In: Bagnara JT, ed. *Advances in Pigment Cell Research*. New York: Alan R. Liss, 1988, pp. 237–246.
21. Park JM, Tsao H, Tsao S. Acquired bilateral nevus of Ota-like macules (Hori nevus): Etiologic and therapeutic considerations. *J Am Acad Dermatol* 2009; 61(1):88–93.
22. Chan HH, Ying SY, Ho WS et al. An in vivo trial comparing the clinical efficacy and complications of Q-switched 755 nm alexandrite and Q-switched 1064 nm Nd:YAG lasers in the treatment of nevus of Ota. *Dermatol Surg* 2000; 26(10):919–922.
23. Kono T, Erçöçen AR, Chan HH et al. Use of Q-switched ruby laser in the treatment of nevus of ota in different age groups. *Lasers Surg Med* 2003; 32(5):391–395.
24. Ueda S, Isoda M, Imayama S. Response of naevus of Ota to Q-switched ruby laser treatment according to lesion colour. *Br J Dermatol* 2000; 142(1):77–83.
25. Chan HH, Leung RS, Ying SY et al. Recurrence of nevus of Ota after successful treatment with Q-switched lasers. *Arch Dermatol* 2000; 136(9):1175–1176.
26. Lee WJ, Han SS, Chang SE et al. Q-switched Nd:YAG laser therapy of acquired bilateral nevus of ota-like macules. *Ann Dermatol* 2009; 21(3):255–260.
27. Dave R, Mahaffey PJ. Combined early treatment of congenital melanocytic naevus with carbon dioxide and NdYag lasers. *Br J Plast Surg* 2004; 57(8):720–724.
28. Noordzij MJ, van den Broecke DG, Alting MC et al. Ruby laser treatment of congenital melanocytic nevi: A review of the literature and report of our own experience. *Plast Reconstr Surg* 2004; 114(3):660–667.
29. Funayama E, Sasaki S, Furukawa H et al. Effectiveness of combined pulsed dye and Q-switched ruby laser treatment for large to giant congenital melanocytic naevi. *Br J Dermatol* 2012; 167(5):1085–1091.
30. Kishi K, Okabe K, Ninomiya R et al. Early serial Q-switched ruby laser therapy for medium-sized to giant congenital melanocytic naevi. *Br J Dermatol* 2009; 161(2):345–352.
31. Catherine S, Lacour JP, Passeron T. Treatment of linear and whorled hypermelanosis with Q-switched laser. *Dermatol Surg* 2014; 40(9):1044–1046.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

32. Ditre CM, Griffin TD, Murphy GF et al. Effects of alpha-hydroxy acids on photoaged skin: A pilot clinical, histologic, and ultrastructural study. *J Am Acad Dermatol* 1996; 34(2 Pt 1):187–195.
33. Olsen EA, Katz HI, Levine N et al. Tretinoin emollient cream for photodamaged skin: Results of 48-week, multicenter, double-blind studies. *J Am Acad Dermatol* 1997; 37(2 Pt 1):217–226.
34. West TB, Alster TS. Improvement of infraorbital hyperpigmentation following carbon dioxide laser resurfacing. *Dermatol Surg* 1998; 24(6):615–616.
35. Zarem HA, Resnick JI. Expanded applications for transconjunctival lower lid blepharoplasty. *Plast Reconstr Surg* 1999; 103(3):1041–1043; discussion 1044–1045.
36. Watanabe S, Nakai K, Ohnishi T. Condition known as "dark rings under the eyes" in the Japanese population is a kind of dermal melanocytosis which can be successfully treated by Q-switched ruby laser. *Dermatol Surg* 2006; 32(6):785–789; discussion 789.
37. Cymbalista NC, Prado de Oliveira ZN. Treatment of idiopathic cutaneous hyperchromia of the orbital region (ICHOR) with intense pulsed light. *Dermatol Surg* 2006; 32(6):773–783; discussion 783–784.
38. Batta K, Hindson C, Cotterill JA et al. Treatment of poikiloderma of Civatte with the potassium titanyl phosphate (KTP) laser. *Br J Dermatol* 1999; 140(6):1191–1192.
39. Langeland J. Treatment of poikiloderma of Civatte with the pulsed dye laser: A series of seven cases. *J Cutan Laser Ther* 1999; 1(2):127.
40. Weiss RA, Goldman MP, Weiss MA. Treatment of poikiloderma of Civatte with an intense pulsed light source. *Dermatol Surg* 2000; 26(9):823–827; discussion 828.
41. Rusciani A, Motta A, Fino P et al. Treatment of poikiloderma of Civatte using intense pulsed light source: 7 years of experience. *Dermatol Surg* 2008; 34(3):314–319; discussion 319.
42. Meijs MM, Blok FA, de Rie MA. Treatment of poikiloderma of Civatte with the pulsed dye laser: A series of patients with severe depigmentation. *J Eur Acad Dermatol Venereol* 2006; 20(10):1248–1251.
43. Behroozan DS, Goldberg LH, Glaich AS et al. Fractional photothermolysis for treatment of poikiloderma of civatte. *Dermatol Surg* 2006; 32(2):298–301.
44. Tierney EP, Hanke CW. Treatment of Poikiloderma of Civatte with ablative fractional laser resurfacing: Prospective study and review of the literature. *J Drugs Dermatol* 2009; 8(6):527–534.
45. Ho SG, Yeung CK, Chan NP et al. A retrospective analysis of the management of acne post-inflammatory hyperpigmentation using topical treatment, laser treatment, or combination topical and laser treatments in oriental patients. *Lasers Surg Med* 2011; 43(1):1–7.
46. Chan R, Park KC, Lee MH et al. A randomized controlled trial of the efficacy and safety of a fixed triple combination (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) compared with hydroquinone 4% cream in Asian patients with moderate to severe melasma. *Br J Dermatol* 2008; 159(3):697–703.
47. Ferreira Cestari T, Hassun K, Sittart A et al. A comparison of triple combination cream and hydroquinone 4% cream for the treatment of moderate to severe facial melasma. *J Cosmet Dermatol* 2007; 6(1):36–39.
48. Taylor SC, Torok H, Jones T et al. Efficacy and safety of a new triple-combination agent for the treatment of facial melasma. *Cutis* 2003; 72(1):67–72.
49. Rokhsar CK, Fitzpatrick RE. The treatment of melasma with fractional photothermolysis: A pilot study. *Dermatol Surg* 2005; 31(12):1645–1650.
50. Tannous ZS, Astner S. Utilizing fractional resurfacing in the treatment of therapy-resistant melasma. *J Cosmet Laser Ther* 2005; 7(1):39–43.
51. Lee HS, Won CH, Lee DH et al. Treatment of melasma in Asian skin using a fractional 1,550-nm laser: An open clinical study. *Dermatol Surg* 2009; 35(10):1499–1504.
52. Karsai S, Fischer T, Pohl L et al. Is non-ablative 1550-nm fractional photothermolysis an effective modality to treat melasma? Results from a prospective controlled single-blinded trial in 51 patients. *J Eur Acad Dermatol Venereol* 2012; 26(4):470–476.
53. Wattanakrai P, Mornchan R, Eimpunth S. Low-fluence Q-switched neodymium-doped yttrium aluminum garnet (1,064 nm) laser for the treatment of facial melasma in Asians. *Dermatol Surg* 2010; 36(1):76–87.
54. Li YH, Chen JZ, Wei HC et al. Efficacy and safety of intense pulsed light in treatment of melasma in Chinese patients. *Dermatol Surg* 2008; 34(5):693–700; discussion 700–701.
55. Konishi N, Kawada A, Kawara S et al. Clinical effectiveness of a novel intense pulsed light source on facial pigmentary lesions. *Arch Dermatol Res* 2008; 300(Suppl. 1):S65–S67.
56. Chan HH, Kono T. The use of lasers and intense pulsed light sources for the treatment of pigmentary lesions. *Skin Therapy Lett* 2004; 9(8):5–7.
57. Chan H. The use of lasers and intense pulsed light sources for the treatment of acquired pigmentary lesions in Asians. *J Cosmet Laser Ther* 2003; 5(3–4):198–200.
58. Wang CC, Hui CY, Sue YM et al. Intense pulsed light for the treatment of refractory melasma in Asian persons. *Dermatol Surg* 2004; 30(9):1196–1200.
59. Moreno Arias GA, Ferrando J. Intense pulsed light for melanocytic lesions. *Dermatol Surg* 2001; 27(4):397–400.
60. Niwa Massaki AB, Eimpunth S, Fabi SG et al. Treatment of melasma with the 1,927-nm fractional thulium fiber laser: A retrospective analysis of 20 cases with long-term follow-up. *Lasers Surg Med* 2013; 45(2):95–101.
61. Kang WH, Yoon KH, Lee ES et al. Melasma: Histopathological characteristics in 56 Korean patients. *Br J Dermatol* 2002; 146(2): 228–237.
62. Kang HY, Bahadoran P, Suzuki I et al. In vivo reflectance confocal microscopy detects pigmentary changes in melasma at a cellular level resolution. *Exp Dermatol* 2010; 19(8):e228–e233.
63. Regazzetti C, De Donatis GM, Ghorbel HH, Cardot-Leccia N, Ambrosetti D, Bahadoran P et al. Endothelial cells promote pigmentation through endothelin receptor B activation. *J Invest Dermatol* 2015; 135(12):3096–3104.
64. Lee HI, Lim YY, Kim BJ et al. Clinicopathologic efficacy of copper bromide plus/yellow laser (578 nm with 511 nm) for treatment of melasma in Asian patients. *Dermatol Surg* 2010; 36(6):885–893.
65. Hammami Ghorbel H, Boukari F, Fontas E, Montaudié H, Bahadoran P, Lacour JP, Passeron T. Copper bromide laser vs triple-combination cream for the treatment of melasma: A randomized clinical trial. *JAMA Dermatol* 2015; 151(7):791–792.
66. Njoo MD, Vodegel RM, Westerhof W. Depigmentation therapy in vitiligo universalis with topical 4-methoxyphenol and the Q-switched ruby laser. *J Am Acad Dermatol* 2000; 42(5 Pt 1):760–769.
67. Boukari F, Lacour JP, Ortonne JP et al. Laser-assisted depigmentation for resistant vitiligo: A retrospective case series with long-term follow-up. *J Eur Acad Dermatol Venereol* 2014 March; 28(3):374–377.
68. Komen L, Zwertbroek L, Burger SJ, van der Veen JP, de Rie MA, Wolkerstorfer A. Q-switched laser depigmentation in vitiligo, most effective in active disease. *Br J Dermatol* 2013; 169:1246–1251.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Lasers, intense pulsed light, and skin redness

Agneta Troilius Rubin

For the purposes of clarification, this chapter will cover both laser and intense pulsed light (IPL) treatments of the numerous conditions that result in vascular discoloration of the skin. Vessels are not simply red, but may be pink, purple, or even blue, depending on the size, flow, and depth of the vessels involved. It is the sheer range of vascular anomalies, found in patients of all ages, which makes light-based dermatology a challenge, which requires the use of various light sources, and which makes successful treatments rewarding to both the patient and the dermatologist.

HISTORY

Laser treatment of vascular problems began in the late 1970s with treatment of port wine stain, principally using an argon laser in continuous-wave mode. While this successfully reduced the color of the target lesion, the nature of the pulse resulted in a more general heating of the area with resultant scarring [1]. A major breakthrough occurred in the 1980s following publication of the paper by Anderson and Parrish on selective photothermolysis [2]. This set out the principle used in the subsequent 30 years of research and treatment of vascular conditions: suitably brief pulses of selectively absorbed optical radiation can cause selective damage to pigmented structures, cells and organelles *in vivo*. Radiation is optimized in terms of wavelength, pulse length and energy to a target, based on the presence in the target of a required chromophore (hemoglobins when treating vascular conditions), which converts the selected light to heat. Surrounding tissue that contains less target, or other chromophores with different absorption spectra, should suffer little or no adverse effect. Indeed the last three decades have seen attempted alliances between selective photothermolysis and the applied physics and biology of light-tissue interaction, in order to treat vessels of all types.

BACKGROUND

When light enters the skin, there are four possible results. The light can be *reflected* either from the uneven skin surface or within the stratum corneum. The level of reflection should be reduced wherever possible. This is partly mechanical and partly application oriented. Ensuring the light enters the skin perpendicularly will reduce the reflection. Use of an optical coupling gel reduces the reflection from the epidermis and this can be optimized by moisturizing the skin a day prior to treatment. Non-reflected light will be *transmitted* through the epidermis. Some of the transmitted light may be *scattered* by the target wall, or by collagen fibers, or any structures in the skin. If scattered, the photons leave the main beam of light and unless back-scattered they do not contribute to the treatment. The remaining light is *absorbed*, either by the target or competing chromophores. The basis of a successful treatment is therefore to maximize absorption by the target chromophore, while minimizing reflection, scattering, or absorption by competing chromophores.

APPLIED SELECTIVE PHOTOTHERMOLYSIS

Vascular treatments are based on selective photothermolysis, but the vessel wall is more or less transparent for visible and infrared light and so cannot be used as a target. The direct targets are hemoglobin and oxy-hemoglobin in the blood inside the vessels; these chromophores transform the absorbed light into heat, which is then conducted to the lamina intima of the vessel wall. The lamina intima will be destroyed if it reaches a temperature of 70°C for more than 1 ms.

Four Core Criteria for a Successful Treatment

To ensure a successful vascular treatment there are certain core criteria that must be met.

Wavelength

To maximize treatment efficacy, the wavelength or waveband used must have a penetration depth sufficient to reach the target and must also be more readily absorbed by hemoglobins than by the surrounding tissue. Oxy-hemoglobins have three absoption peaks at 414 nm, 542 nm and 578 nm, and reduced hemoglobin has peaks at 432 nm and 556 nm (Figure 43.1). As the penetration depth for wavelengths shorter than 450 nm is less than 100 µm, use of these wavelengths is not practical for vascular treatments. Additionally, absorption by the competing chromophore melanin is significantly higher than by hemoglobin at wavelengths shorter than 520 nm. However, the waveband between 520 nm–595 nm has a penetration depth up to 500 µm (Figure 43.2) and is highly efficient for treatment of more superficially situated vessels. As penetration depth continues to increase with higher wavelengths until high absorption by water becomes dominant, deeper situated vessels have to be treated with near infrared light, and the Nd:YAG, emitting at 1064 nm, is the most commonly used laser for this purpose.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

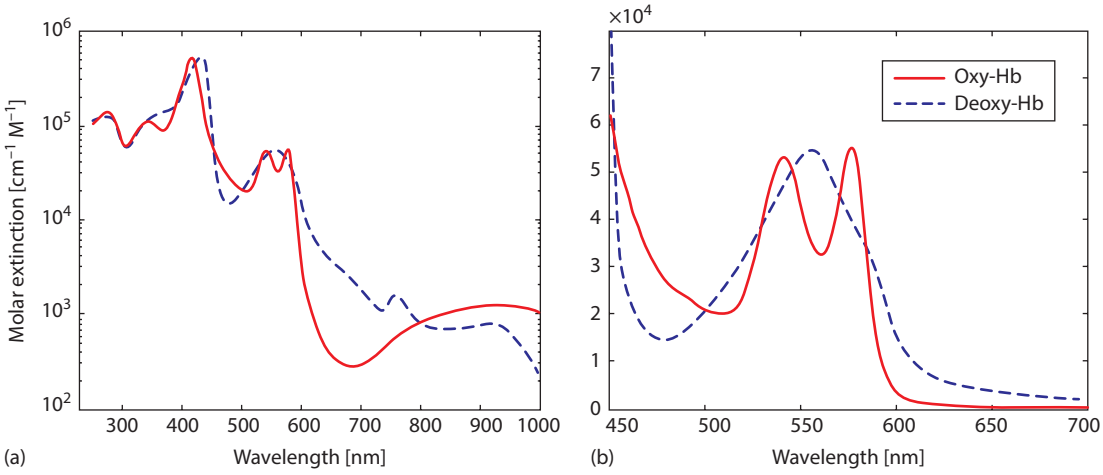


Figure 43.1 Absorption curves of hemoglobin and oxy-hemoglobin [3].

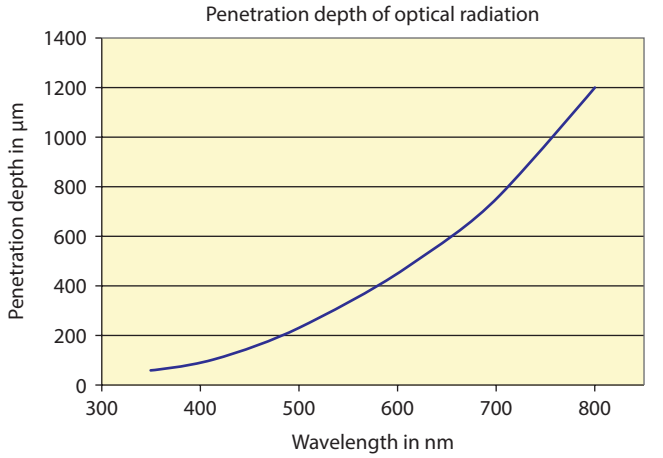


Figure 43.2 Penetration depth of different wavelengths.

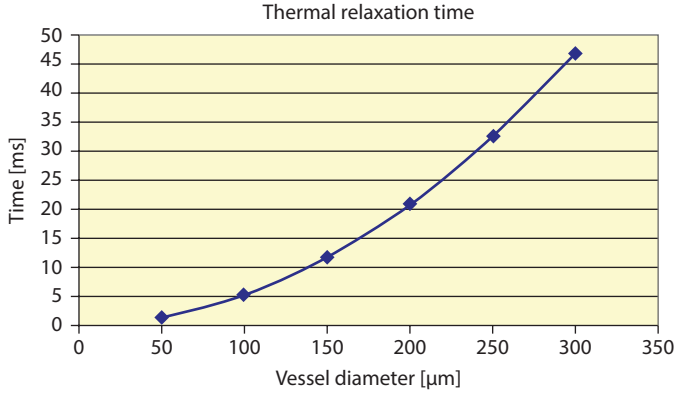


Figure 43.3 Thermal relaxation time depends on surface area to volume ratio.

Thus, the theoretically optimal wavelengths for vascular treatments are dependant on the depth of the vessels and lie between 500 and 1064 nm [5] (Figure 43.1).

This means that no single technology (light source) enables the universal treatment of all vascular problems presented to a dermatologist and has resulted in the evolution of treatment systems that offer multiple technologies (Figure 43.2).

Pulse Time

The duration of the light pulse has to be selected so that the target (the vessel) is lethally damaged with minimal conduction of heat into the surrounding tissue. In accordance with the theory of selective photothermolysis [2] the pulse duration must be equal to or less than the thermal relaxation time (TRT) od the vessels. The TRT for vessels can be calculated by

$$TRT = d^2/16\ K$$

where d is the vessel diameter (measured in millimeters) and K (the tissue diffusivity) = 0.13 mm^2 per second.

A thick vessel, with a large volume, has a longer TRT, and thus requires longer pulse duration to reach the target temperature of 70°C for at least 1 ms, than does a thin vessel with a smaller volume. The pulse duration has to be adjusted according to the target size (Figure 43.3).

If a pulse duration much shorter than the TRT is chosen, there is a risk of rupturing the vessel as the blood it contains may boil, leading to purpura and the possible formation of hemosiderin. Conversely, too long a pulse time will allow energy to escape into the surrounding tissue, causing unspecific "bulk" heating. More energy is then needed to raise the target to a sufficiently high temperature, and patient pain level will increase.

Fluence

The correct energy level (measured in J/cm^2), has to be chosen to create the necessary heat to lethally damage the target within

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

the given pulse duration. Depending on the vessel diameter and flow, photovaporization may be observed as the apparent clearance of the vessel being treated. Another clinical endpoint is a blue response of the vessel due to photo-induced met-hemoglobin formation by oxidation of hemoglobin. This bluing may last for several minutes (e.g., in treatment of capillary malformation) or may be hidden in less than a second by a more general erythema (e.g., in treatment of small telangiectasias).

Spot Size

Scattering will cause loss of photons from the main beam during light penetration of the skin, and thereby light intensity will drop as depth increases, even without absorption by competing chromophores. However, photons will be scattered several times, and some of them will "back-scatter" and re-enter the main beam. Larger spot sizes have relatively less perimeter compared to smaller ones, and less photons will leave the main beam without being back-scattered, resulting in larger spot sizes having a larger penetration depth. The efficient penetration depth for the same fluence for visible light increases from 1 mm to 3 mm to 4.3 mm when the spot size increases from 3 mm to 7 mm to 19 mm. Thicker and deeper situated vessels have therefore to be treated with a bigger spot size and it is recommended to use a spot diameter at least two to three times the diameter of the vessel.

LASERS, AND INTENSE PULSED LIGHT (IPL)

Though patients often refer to any light-based treatment as "laser treatment," there are significant differences between the technologies. Laser provides a source of monochromatic electromagnetic energy (a single wavelength) in a parallel beam of coherent light (the light does not spread out and the waves are always in phase).

The wavelength of the laser depends on the source material used, and within dermatology, the wavelengths chosen are typically between 308 mm (excimer, using xenon chloride, to treat psoriasis) and 10,600 nm (carbon dioxide). In vascular dermatology, the main lasers in current use are the following:

Laser	Wavelength (nm)
Copper vapor/bromide	510/578
KTP (potassium titanyl-phosphate)	532
PDL Pulsed dye laser	570/585/595/600
APTD (argon-pumped tunable dye)	577/585
Diode	800/810/915/940
Nd:YAG	1064/532

Unfiltered intense pulsed light (IPL) produces a broad waveband between 240 nm and 1200 nm. By applying filters, the emitted light can to a greater or lesser extent be optimized in respect of the absorption spectrum of the target chromophore. Ultraviolet wavelengths (<400 nm) are always unwanted for treatment of vascular lesions and cut off filters are used to remove shorter wavelengths. Efficient wavelengths for vascular treatments start at around 520 nm and use of cut-off filters to remove wavelengths below 520–580 nm is common. A higher cut-off enables treatment of darker skin types and pigmented patients. More advanced IPL systems have additional "upper" filters to restrict the wavebands to the ranges 530–750 nm or 555–950 nm (Ellipse A/S, Denmark) or 500–670 nm and 870–1200 nm (Palomar, USA).

State of the art vascular treatments involve use of pulsed dye laser (PDL) and IPL for superficial vessels such as capillary malformations and telangiectasias, and Nd:YAG for deeper situated vessels such as leg veins and reticular veins.

It is unimportant is the light source is coherent or incoherent as a laser beam will become incoherent after penetration of a few tens of micrometers of the skin, due to the high scattering of the wavelengths used for vascular treatments. However, IPL systems emit polychromatic light, which potentially gives them and advantage over monochrome lasers, as the absorption spectra of hemoglobins are very broad.

The main difference between IPL and PDL treatments is the different possibilities to adjust the pulse durations used. In older PDL systems, the pulse duration was fixed, typically at 0.45 ms–1.5 ms. Today the pulse duration of LPDL can be adjusted typically in the range 0.45–10 ms. Until recently, IPL did not have the ability to emit sufficient fluence in a pulse duration shorter than approximately 5 ms.

The vessel size of pink Port Wine Stains (PWS Grade I) as well as that of diffuse redness very thin telangiectasias) is very small (50–80 μm) with a TRT corresponding to 1.2 ms. These require very short pulse durations with a high fluence (6–9 J/cm^2) and is the explanation for IPL systems' traditional lower efficacy than that of PDL in treatment of thinner vessels.

PRACTICAL APPLICATION, SUBSEQUENT DEVELOPMENTS, AND CHALLENGES

The principal concern must be to reduce the risk of unintended treatment of the other major chromophores, melanin, and water, and this has resulted in a move away from KTP laser (542 nm) toward the first purpose-built vascular laser and technology of modern dermatology, the pulse dye laser (585 nm). PDL's relatively lower hemoglobin absorption compared to KTP is more than compensated for by significantly lower melanin absorption and deeper penetration. In both cases, the fluence required is low. For deeper vessels, diode and Nd:YAG lasers used and these require significantly higher fluence due to the relatively low absorption in all chromophores.

The PDL sub-millisecond pulses that were used initially have been replaced by longer 1.5–64 ms pulses, dependent on vessel size, that have been found to produce fewer side-effects, a greater degree of patient comfort, and almost no lack of clinical efficacy.

The use of IPL devices in vascular dermatology began in late 1990s [5], and a tailored waveband aimed to maximize hemoglobin absorption was quickly developed [6]. The larger (rectangular) spot size and an appropriately chosen waveband available on certain systems result in vascular clearance of certain conditions that equal clearance by the laser of choice. A recently-developed new generation of Ellipse Nordlys IPL applicators enable three times higher fluence with pulse duration as low as 0.5 ms, which enables treatments even of thinner vascular lesions, with the same or better efficacy as PDL. The Nordlys system also supports an Nd:YAG laser ans thereby offers a complete vascular treatment system. Various cooling devices have also been developed to reduce bulk heating and the risk of postinflammatory hyperpigmentation and thereby improve safety and comfort.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

New machines, of all types, are presented daily and offered to users of all abilities. The traditional roles of the dermatologist, in correctly assessing the condition being treated and in participating in developmental research to find new treatments and improve existing ones, remain true. But to this must be added two new tasks, correctly educating those patients who have received biased or partial advice from the Internet and exploring the mythical claims of those manufacturers and importers who offer no clinical proof of efficacy.

PRACTICAL APPLICATIONS FOR TREATMENT

Classification

To facilitate uniformity of classification, the International Society for the Study of Vascular Anomalies (ISSVA) introduced a standard classification based on clinical and vascular features, natural behavior, biological differences, and hemodynamic characteristics (Box 43.1).

BOX 43.1 CLASSIFICATION (COURTESY OF INTERNATIONAL SOCIETY OF THE STUDY OF VASCULAR ANOMALIES, ISSVA)

Vascular tumors:

- Infantile hemangiomas (IH)*
- Congenital hemangiomas (RICH and NICH)
- Tufted angioma (with or without Kasabach–Merritt syndrome)
  - Kaposiform hemangioendothelioma (with or without Kasabach–Merritt syndrome)
  - Spindle cell hemangioendothelioma
  - Others, rare hemangioendotheliomas (epithelioid, composite, retiform, polymorphous, Dabska tumor, lymphangioendotheliomatosis, etc.)
  - Pyogenic granuloma*

Slow-flow vascular malformations:

- Capillary malformation (CM)*
- Venous malformation (VM)*
  - Sporadic VM
  - Bean syndrome (multiple VM) also known as blue rubber bleb nevus syndrome
  - Familial cutaneous and mucosal venous malformation (VMCM)
  - Glomuvenous malformation (GVM)
  - Maffucci syndrome
- Lymphatic malformation (LM)

Fast-flow vascular malformations:

- Arterial malformation (AM)
- Arteriovenous fistula (AVF)
- Arteriovenous malformation (AVM)

Complex-combined vascular malformations

*Superficial and small parts are treatable with laser and/or IPL.

Diagnostic tools are especially useful for confirming vascular tumors, which may respond better to drugs (e.g., propranolol for IH), or surgical interventions, and arterial malformations, which should not be treated with laser or IPL.

GENERAL GUIDANCE FOR TREATMENT

Before examining individual conditions, it is important to assess the patient, as well as the lesion, and to ask four groups of questions.

Q1: Skin type/degree of pigmentation?

Caution must be taken when treating patients with a higher degree of pigmentation and higher Fitzpatrick skin types. PDL and IPL both tend to have a limit of treating Fitzpatrick phototype IV/light pigmentation. The darker the skin type, the higher is the risk of an adverse event (hyperpigmentation, hypopigmentation, and burn) and it is generally not enough to reduce the energy. The physician should never hesitate to postpone a treatment if the patient is too tanned, bleaching cream can reduce the background level of melanin, and the patient should be encouraged to use sun protection, not only to reduce melanin but also to reduce the risk of sun-induced erythema prior to treatment. While skin type is less of an obstacle with Nd:YAG, recent suntan should always be avoided.

Q2: Medical history?

It is important to know of any contraindications to treatment, medications, or medical conditions that impact on the treatment itself or on recovery. A tendency to hyperpigment or to produce keloid or hypertrophic scarring should not *per se* rule out all treatments, but the patient must be informed about the risk to reward ratio involved in the treatment outcome. While light-based treatments, according to our knowledge, do not harm the unborn child, pregnant women are never treated for psychosocial reasons.

Q3: Previous treatments carried out?

It is important that an adequate (4–8 week) interval be left between treatments to reduce the risk of treating erythematous skin or of causing postinflammatory hyperpigmentation. Other treatments, such as electrodessication, can result in tissue fibrosis. A patient history will also indicate if any complications are patient, operator, or equipment related.

Q4: Goals and expectations?

It is important that the patient (or in pediatric cases, the parent) has realistic expectations of the treatment. Results can be dramatic, but a realistic scenario in terms of the number of treatments, ability to handle posttreatment care, and likelihood of reoccurrence (and severity of reoccurrence) has to be agreed. It is also prudent to mention the likelihood, duration, and nature of side effects.

PATIENT PREPARATION, BACKED UP BY ORAL AND WRITTEN INFORMATION

Having examined the both the patient and the lesion, it is important that makeup should be removed and that any hairs in the treatment area should be shaved and removed. It is unusual to require local anesthesia or topical anesthesia for laser treatments of adult patients, unless there are overriding

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

factors. Topical anesthesia may cause vasoconstriction, reducing the target, and a certain degree of discomfort is a good indication of correct settings; the absence of discomfort may result in lack of good treatment results, while too much discomfort may indicate a higher risk of side effects. If anesthesia is used, it is important to keep the patient warm, by directing warm air during general anesthetic or by wrapping the patient in a blanket, and it is also useful to position the patient such that the vessels to be treated are full of blood, so treatment sites should be lowered rather than raised, for example, by lowering the head.

Emla®, lidocaine cream plus twice the normal dose of paracetamol, may also help, if given 1 hour prior to treatment.

When treating children, it is important that both the child and accompanying parents should be as relaxed as possible, and *letting* the parent *try* the treatment in the presence of the *child may calm* both.

Different light-based systems require different treatment parameters, so for each case, it is important to have the correct starting fluence, pulse length, and spot size (for lasers); for IPL, it may be advantageous to reduce the effective spot size by using wet gauze to protect areas of skin that do not require treatment. These parameters differ according to patient skin type, degree of suntan, response to the test shot carried out, and body location. (Sensitive areas such as neck or chest require a lower fluence, as does the presence of bone immediately underneath the treatment area.) It is extremely useful to have your own experience and that of your colleagues to fall back on, but similarly, it is useful to compile settings used elsewhere for the laser or IPL system at hand. However, it is even more important to avoid "magic numbers" and concentrate on the clinical effects you encounter in the patient you are currently treating.

Since larger vessels tend to be more deeply situated, a longer wavelength (laser or longer waveband for IPL) is required as is a large spot size. Light penetration into the skin must always be enhanced by a thin layer of optical coupling gel (such as ultrasound gel). Cooling is generally beneficial, but cooling to too low a temperature prior to release of the shot can cause vasoconstriction. Nonsteroidal anti-inflammatory drugs (NSAID) should not be used.

The first shot is always the least comfortable, but patients normally adjust quickly to the sensation of the shot and should be encouraged to give this a place on a 0–10 scale (where 0 is no pain and 10 the worst pain imaginable). Having given a score to a "normal" shot, the patient should be encouraged to advise if the score changes, as this may indicate the need to slow down or a change in the vessel or underlying tissue.

For all of the aforementioned reasons, informed consent by the patient is essential.

INDIVIDUAL TREATMENTS

The following vascular lesions respond well to light-based treatments and will be examined in more detail:

Congenital lesions

- Capillary malformations (CMs)
- Superficial venous malformation
- Blue rubber bleb nevus syndrome (BRBNS)

Acquired vascular alterations

- Campbell de Morgan angiomas (senile angiomas)
- Facial telangiectasias
- Granuloma telangiectaticum(pyogenic granuloma)
- Leg veins and telangiectasias
- Morbus–Osler syndrome (hereditary hemorrhagic telangiectasia)
- Spider angioma (nevus araneus)
- Poikiloderma of civatte
- Rosacea
- Venous lake

Other skin diseases with vascular alterations

- Acne
- Red or hypertrophic scars

Because of the range of spot size, fluence, and pulse length within laser systems, the waveband and intensities available within IPL systems and skin type, degree of suntan, and body site within patients, it is not possible to give settings for each of the conditions listed. What is possible is to give some background information to assist in diagnosis and to suggest the treatment of choice.

Hemangioma

Background Information: Infantile hemangioma (IH) is present in 10% of the population at the age of 1 year, particularly in fair female premature babies with low birth weight [7]. Originally present as flat erythematous well-demarcated red patches, these may rapidly proliferate to three-dimensional structures, usually confined to the original anatomical site by 3 months of age. Superficial hemangiomas appear bright red; a bluish tinge strongly suggests a deeper component. After proliferation, there is a period of quiescence for 9–12 months, followed by a period of involution (natural decrease) over the next 5–9 years (Figure 43.4).

In most cases, watchful waiting is the major attitude toward IH. Treatment of proliferating hemangioma is normally given in 40% of cases where there is a risk of sight, breathing, cardiac failure, or bleeding ulceration or permanent disfigurement. Since 2008, the treatment of choice has been low-dosage use (1–3 mg/kg body weight, up to age 1 year) of the beta-blocker propranolol, which is effective but carries a risk of hypoglycemia and sleeping disturbances.

Alternatives are in rare cases surgery, sometimes followed by PDL/IPL treatment. PDL/IPL treatment will deal only with the more superficial aspects of the hemangioma, and Nd:YAG is the treatment of choice for any deeper component. The clinical endpoint is a bluing of the vessel. Superficial lesions and genital ulcerations are sometimes treated using a combination of topical propranolol and PDL/IPL, and this combination is also offered if there is parental objection to use of systemic medicine. General anesthetic is normally given for severe cases and for large hemangiomas.

Any telangiectasial remnants can be dealt with by PDL/IPL treatment.

Capillary Malformations (CM)

Port-wine stains (PWSs) are a capillary malformation present at birth; vessels are located within the upper dermis and grow commensurate with the child, though vessel diameter will increase, and in adulthood, the appearance will change from red through purple to blue. The surface may become

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 43.4 IH. (a) Before. (b) After: 3 PDL, 7–10 mm, 1.5–10 ms, 7–9 J/cm², 30/20 DCD. (c) Subsequently: after xylocaine spray, 1 Nd:YAG 1064 nm, 1.5 mm, 25 ms, 250 J/cm²; cooling air from handpiece. There seems to be less pain than after IPL.

Figure 43.5 Hypertrophic PWS in Asian skin: PDL/IPL/YAG. (a) Before. (b) After.

raised and nodular with age, and nodules may bleed spontaneously. Soft tissue in the area affected by the PWS may enlarge. PWSs develop in areas where there is a partial of absolute defect of the nerves that control vessel constriction (Figures 43.5 and 43.6).

Diagnosis should enable the current stage of the development of PWS to be established

Grade I: Earliest, smallest vessels, ø50–80 µm. Light and dark pink macules. First choice of treatment short pulsed IPL, PDL and KTP (Figure 43.7).

In Figure 43.7a, a four month old female baby with PWS situated on the right eyelid, forehead and scalp is seen before treatment. Clinical endpoint for treatment of PWS is purpura as shown in Figure 43.7b. Treatment with the new short pulsed IPL (Ellipse Nordlys) was performed at the first session with 1.7 ms pulse duration and a fluence of 7.9 J/cm². In the second session, it was decided to target the deeper and slightly larger vessels and the pulse duration was extended to 2.5 ms with a fluence of 8.0 J/cm². A very nice clearance at the 1-month follow-up after only two treatments was registered (Figure 43.7c).

Grade II: Clearly indistinguishable, more advanced, ø80–120 µm with individual vessels clearly visible to the naked eye. First choice of treatment IPL, PDL (long pulse), KTP.

Grade III: Reddish patches with vessels even more ectatic, ø120–150 µm. First choice of treatment short pulsed IPL, long pulsed PDL.

Grade IV: Thick, purple, palpable, and possibly nodular. Advanced dilated vessels ø150 µm. First choice IPL, diode, and Nd:YAG (avoiding the orbital area)

Pulse length must always be chosen according to the TRT of the vessels.

Generally, treatment should be carried out at an earlier age below 12–18 months, both to take advantage of the thinner vessels present (which may result in complete clearance) and to ensure that the patient has little memory about the grueling treatment. From ages 3 to 8 years, an increased number of treatments may be required compared to ages outside this range because of the growth of the child between these ages.

Some PWS are resistant to IPL as well as PDL, and if no improvement is seen within one to two treatments, the modality used should be changed [8,9]. In older, nodular PWS, a

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

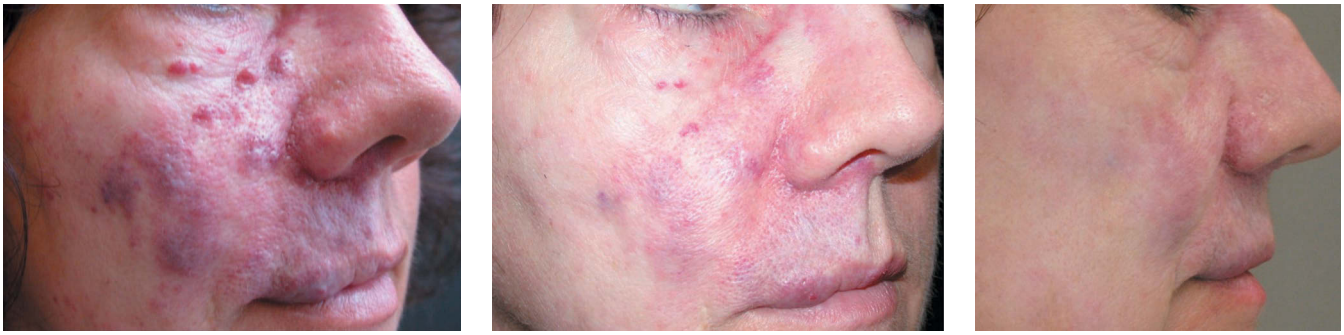


Figure 43.6 Hypertrophic capillary malformation: argon, diode, multiple >21 PDL hypopigmented by phosphor plate radiation during the 1960s. (a) Before. (b, c) After diode 2.5 mm spot, contact cooling, 50 ms, 80 W, 2 Hz PDL 10 mm spot, 0.45–1.5 ms, 8 J, 30/20 DCD (around the eye PDL 7 mm spot, 0.45–1.5 ms, 7 J/cm^2) IPL, PR, 13–15 ms, 11–13, 5 J/cm^2 YAG 3 mm spot, 25 ms, 254 J/cm^2.

Figure 43.7 Capilary malformation in four month old female baby, treated with short pulse IPL (Ellipse Nordlys). (a) Before. (b) Purpura immediately after treatment. (c) Clearance after two IPL treatments (eyelid not treated).

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

change to the longer wavelengths offered by diode or Nd:YAG is often beneficial. While most adult patients tolerate treatment well, in young children, general anesthesia should be considered, but topical anesthesia (EMLA) should be avoided in children under 1 year with large areas to be treated or if ulceration is present, as there is a risk of methemoglobin formation.

Location of the PWS plays an important part in determining the success of the treatment. The order of response is central forehead > periorbital > peripheral facial > neck > centrofacial (V2) > trunk > proximal extremities > distal extremities. A large homogeneous PWS responds less well than a series of physically separate ones.

Improvement following an individual treatment is progressively less between successive treatments, though reducing the pulse length slightly may have a positive impact, and treatment may continue while an improvement is seen, typically resulting in 5–6 treatments, at which point consultation between doctor and patient is necessary to discuss the appropriateness of further treatment.

A 100% blanching is very rare, and vessels will most often reoccur after a few years, requiring maintenance treatments.

See also Video 43.1.

Venous Malformation (VM)

VMs are congenital and require ultrasound examination to determine the depth of the vessels. Nd:YAG laser treatment is often given to the small superficial elements of the VM either alone or after surgery and sclerotherapy. Up to 3 treatments may be required. Clinical endpoint: small lesions will produce a "popping" sound, as well as turning blue (Figure 43.8).

Blue Rubber Bleb Nevus Syndrome

This is a rare hereditary disorder characterized by multiple cutaneous venous malformations in the skin and gastrointestinal tract. It is associated with intestinal hemorrhage, resulting in iron deficiency. Other organs may also be involved. There is potential for serious or fatal bleeding. It is important to treat it early when the lesions are small; larger lesions need to be excised, which can difficult due to the location and the number. Skin lesions respond to the longer wavelength and deeper penetration of diode or Nd:YAG lasers, often giving a "popping" sound when they close. Usually only a single treatment is necessary (Figure 43.9).

Senile Angioma (Campbell de Morgan Angioma, Ruby Dot, Cherry Spot)

A wide variety of popular names illustrate the fact that senile angiomas are very prevalent. Most often occurring in middle age (though in some cases earlier), they increase in frequency with age. Most common on the trunk, they may disappear with extreme age and are mainly an aesthetic problem, though they may bleed profusely if cut. Initially presenting as small red dots, they typically increase in size up to 1–3 mm and sometimes

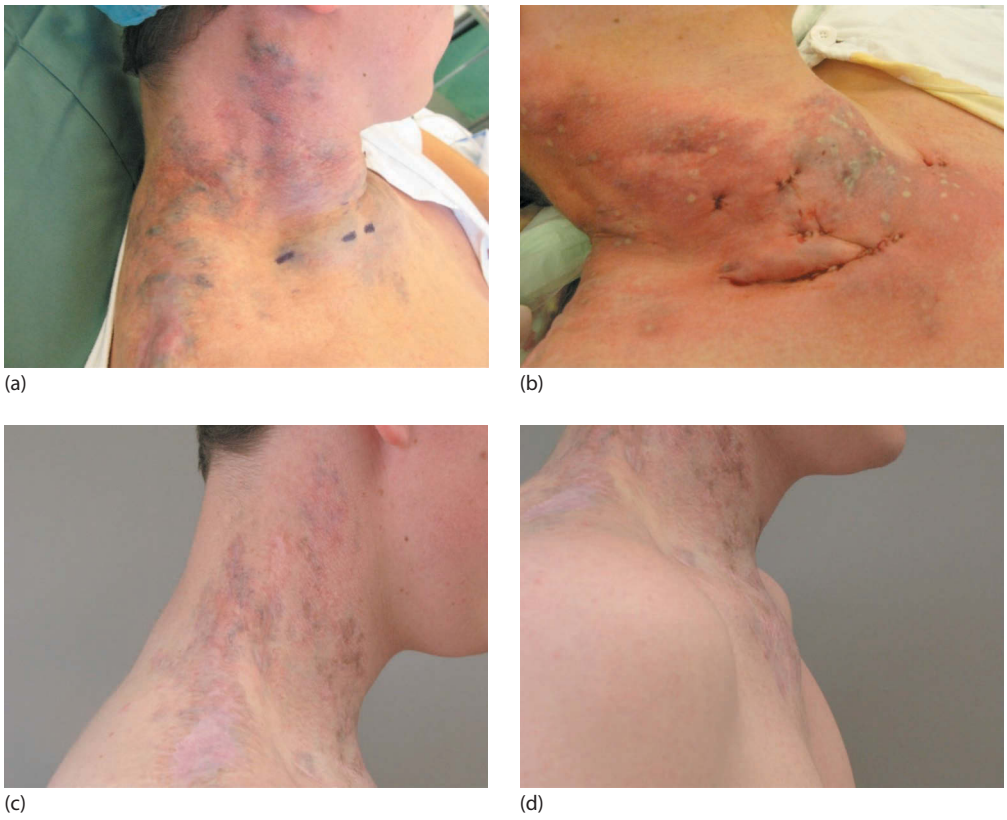
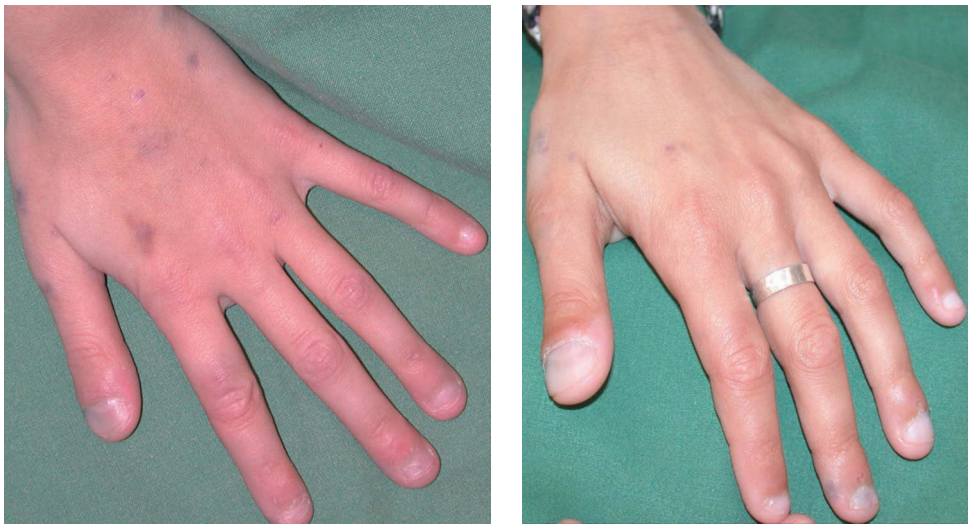


Figure 43.8 Congenital VM: increasing pain and swelling. (a, b) Before. (c, d) After: excision of calcified nodules (after thromboses) and 2 × Nd:YAG laser air cooling, 5 mm, 45 ms, 274–300 J/cm^2.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b)

Figure 43.9 Blue rubber bleb nevus syndrome: Painful! Treat early before they are too large and need excision. (a) Before. (b) After.

(a) (b) (c)

Figure 43.10 Multiple senile angiomas on thorax: Respond perfectly to Nd:YAG handpiece, 1064 nm, 3 mm spot. Cool air, no scarring. (a) Before. (b) Erythema during treatment. (c) Individual angiomas darken with light edema.

larger; the color darkens slightly with size. Campbell de Morgan spots respond well to PDL, IPL, KTP, diode, and Nd:YAG lasers. Most frequently, only a single treatment is required. With IPL, the surrounding skin should be protected with gauze, best results are obtained on smaller examples, and a double pulse is required (Figure 43.10).

Telangiectasias

Telangiectasias are small dilated vessels on the skin or mucous membrane that may be congenital (present in CM or as a result of hereditary hemorrhagic telangiectasia) but are most often induced, as a result of exposure to sun or extremes of temperature. However, there is a genetic disposition to produce induced telangiectasias. Vessels may be individual or presented in conjunction with other conditions (poikiloderma of civatte, advanced rosacea). Telangiectasias can occur anywhere but are most frequently found on face or legs. Typically size may be between 0.1 and 1 mm, though smaller vessels exist as a diffuse redness, typically on the cheeks (Figure 43.11).

Untreated, telangiectasias will increase in size, and color will change from red to blue, and discomfort is normally related to the diameter of the vessels. Use of topical anesthesia is not recommended as vasoconstriction will reduce the target and make treatment less effective.

Choice of light source depends on the size and location of the telangiectasias. Short pulsed IPL and PDL are successful on diffuse redness and smaller vessels. Individually visible moderate-sized vessels respond almost equally well to IPL or PDL. In areas where the underlying skin is not flat, such as the nasal ala (wings of the nose). IPL is less successful, due to difficulty in placing the larger spot size. For thick bluish vessels, Nd:YAG has the advantage, though care must be taken to avoid scarring. In all cases, the clinical endpoint is a short-lived bluing

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b) (c)

Figure 43.11 Nasal telangiectasias within rhinophyma. (a) Before. (b) After multiple PDL, 40 ms, 7,5 J/cm^2 double pulse. (c) Subsequently: After YAG, ø3 mm, 35 ms, 254 J/cm^2.

of the vessel, frequently with a duration of less than 1 second. Treatment intervals are 1 month with PDL, IPL, or diode and 2 months with Nd:YAG.

Never forget: The use of covering makeup or corrective foundations can give a psychological boost to a patient waiting for or undergoing treatment. Consider sending the patient to a cosmetician or stylist to find the right color and the right application.

See also Video 43.2.

Granuloma Telangiectaticum (Pyogenic Granuloma)

Granulomas are benign vascular tumors that often ulcerate and bleed with trauma and are most commonly seen in children. They may occur after insect bites or minor trauma. Low fluence should be used because of the high incidence of posttreatment hypopigmentation and possible scarring.

This responds well to both diode and Nd:YAG lasers, though sometimes punch and suture are necessary.

Leg Veins and Telangiectasias

Although similar in appearance to facial vessels, leg telangiectasias are more difficult to treat in part due to hydrostatic pressure and in part due to increased depth and thicker lamina. While vein stripping may be required for the largest vessels, endovenous laser treatment, otherwise known as endovascular laser ablation therapy (ELT/EVLA) or sclerotherapy, can be considered for smaller vessels. Both diode and Nd:YAG laser possess the longer wavelengths enabling treatment of vessels with a diameter of 0.1–3 mm. Light-based treatment is the first choice for patients who have a fear for needles, as well as for the vessels around the ankles for which sclerotherapy is not suitable. IPL does not enjoy success for leg vessels, though may be useful to reduce hemosiderin or treat telangiectasial matting caused by other treatments. Clinical endpoint is a collapse of smaller vessels with loss of color or a blue flash lasting up to several seconds in larger vessels. The ideal treatment interval is 2 months.

Hereditary Hemorrhagic Telangiectasia (HHT, Morbus–Osler/Osler–Weber–Rendu Syndrome)

HHT presents as a series of telangiectasias, with epistaxis and a family history. In some cases, organs other than the skin may be affected. Treat frequently, every 3–4 weeks in the beginning. New lesions will develop with time. Diode laser treatment may leave a small hypopigmented depression as large as the telangiectatic papule after the treatment. Nd:YAG carries a lower risk of hypopigmentation or atrophic scarring (Figure 43.12).

Spider Angioma (Nevus Araneus)

These occur in up to 15% of normal adults and more frequently in children. They frequently occur in larger numbers during pregnancy. They are also characteristically found in liver disease; they may be a presenting sign. The main vessel of the spider is an arteriole. The blood flows from this to the periphery and then passes into a capillary network. If a little pressure can be applied on the angioma, it is possible to isolate the central arteriole (the body of the spider) from the surrounding capillaries (the legs) and target only this. The capillaries will then disappear without further treatment. Clinical endpoint is the disappearance or a bluing of the vessel.

The first choice id Nd:YAG and then IPL and PDL.

Poikiloderma of Civatte (Erythrosis Interfollicularis Colli)

Poikiloderma of civatte is a variant of telangiectasia combining vascular lesions with both areas of both hyper- and hypopigmentation and some symmetrical atrophy. Induced by sun exposure, often in the presence of a cosmetic sensitizer, poikiloderma of civatte is unresponsive to most standard forms of thaerapy. IPL is absolutely first treatment of choice and is popular with patients since there is less purpura, and due to the IPL applicator's large squared footprint there is no lattice pattern associated with PDL treatment. The clinical endpoint is a general light erythema in the treated area. If there is overlying htperpigmentation, then IPL treatment will result in a darkening of the pigment. It is important to reduce the energy on the neck and over bony areas of the chest. Generally, only 1–2 treatments are necessary.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 43.12 Hereditary hemorrhagic telangiectasia. (a, b) Before: spontaneously bleeding AVF causing social problems and low Hb. (c, d) After diode (causing hypopigmented scarring) and Nd:YAG air cooled.

Rosacea

Rosacea typically affects Caucasians but is reported in skin type III Hispanics, and begins in adulthood, presenting as a general redness on the central face across the cheeks, nose, or forehead and less commonly the neck, chest, ears, and scalp. The disease may progress to cause telangiectasias, papules, and/or pustules. In some advanced cases, rhinophyma may develop. If misdiagnosed, steroids may be given, and these tend to worsen the condition. The cause is not certain, though intestinal bacteria may be involved [10]. Figure 43.13 shows a 72 years old man who has suffered fro rosacea for more than ten years. He has been in permanent tetracycline treatment (2 × 300 mg daily), but stopped this treatment six months prior to light based treatment. Facial left side has been treated with the short pulsed Ellipse PR530 applicator (1.5–1.9 ms, 7.8–9.6 J/cm^2) and the right side was PDL treated (1.5 ms, 9 J/cm^2). After three treatments a significantly higher clearance could be observed on the IPL treated side compared to the PDL treated side.

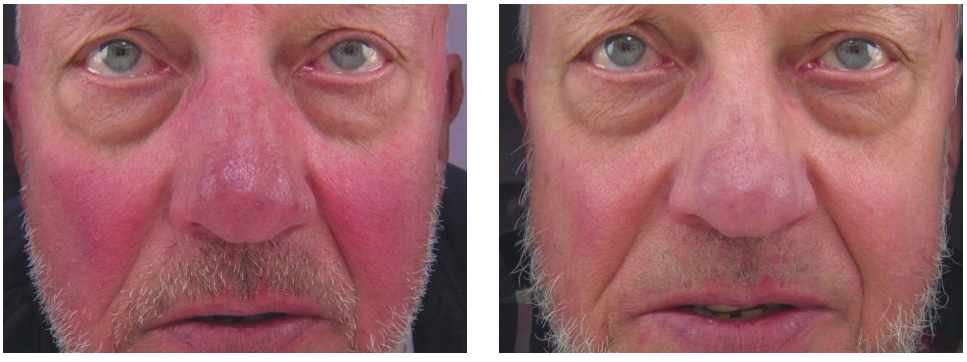


Figure 43.13 Rosacea.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 43.14 VM with swelling. (a) After 2 PDL, 2 YAG contact cooling, 1 diode 810 nm. (b) After xylocaine spray 1 YAG air cooling, 3 mm spot, 32 ms, 250 J/cm^2; less treatment on the red outside of the lip.

Rosacea can be treated with medication (systemic tetracycline and topical metronidazole and azelaic acid) but results (like those from laser or IPL treatment) are temporary. The condition responds very well to short pulsed IPL (Figure 43.13) nut PDL treatment also works well and 1–3 treatments is normally necessary. There are numerous triggers, both physical (heat, cold, certain foods) and emotional. Best results are obtained if treated in conjunction with trigger avoidance. It is important to recommend good cosmeceuticals developed for rosacea care.

Venous Lake

Venous lakes are generally solitary, soft, compressible papules, violet to dark blue in color, and 2–10 mm in diameter most commonly found on the lip or ear, most commonly as a result of sun exposure. The condition responds very well to Nd:YAG, requiring only a single treatment in over 90% of cases, and Nd:YAG treatment has a much lower risk of scarring than diode (Figure 43.14).

Acne

Acne is caused by the presence of multiplying *P. acnes* bacteria in sebaceous glands, which have been blocked by sebum. Over 90% of the population has experienced acne at some stage, usually in puberty, but in many cases, the condition is still present into the 30 s. Numerous medications are available, but photodynamic therapy seems to offer good, though not permanent results. IPL used in conjunction with adapalene seems to increase the speed of resolution, by both action of the light on the protoporphyrins contained within the *P. acnes* bacteria (especially when treatment is PDT enhanced) and by reducing sebum production through reducing the vascular supply to the sebaceous glands.

Red or Hypertrophic Scars

Collagen neogenesis following vascular injury will result in a flattened and less red scar, and this appears after treatment by PDL, and short pulsed IPL, though there is little published work on this. Treatment should commence a month or so after any steroid has been injected into the scar tissue. Typically, 4–6 treatments separated by 1 month intervals give the desired result.

VIDEOS

Video 43.1. Ellipse treatment of capillary malformation, with Dr. Michael Drosner: http://goo.gl/TD9mRr

Video 43.2. Ellipse treatment of telangiectasias, with Dr. Peter Bjerring: http://goo.gl/bLCPrs

REFERENCES

1. Dixon JA, Huether SE, Rotering SH. Hypertrophic scarring in argon of port-wine stains. *Plast Reconstr Surg* 1984; 73:771–779.
2. Anderson RR, Parrish JA. Selective photothermolysis: Precise microsurgery by selective absorption of pulsed radiation. *Science* 1993; 220:524–527.
3. Patterson MS, Wilson BC, Wyman DR. The propagation of optical radiation in tissue. II: Optical properties of tissues and resulting fluence distributions. *Lasers in Med Science* 1991; 6(3): 79–90.
4. Adamic M, Troilius A, Adatto M et al. Vascular lasers and IPLs: Guidelines for care from the European Society for Laser Dermatology (ESLD). *J Cosmet Laser Ther* 2007 June; 9(2):113–124.
5. Raulin C, Weiss RA, Schonermark MP. Treatment of essential telangiectasias with an intense pulsed light source. *Dermatol Surg* 1997; 23:941–945.
6. Bjerring P, Christiansen K, Troilius A. Intense pulsed light source for treatment of facial telangiectasias. *J Cosmet Laser Ther* 2001; 3:169–173.
7. Richter GT, Friedman AB. Hemangiomas and vascular malformations: Current theory and management. *J Pediatr* 2012; 2012:645678.
8. Bjerring P, Christiansen K, Troilius A. Intense pulsed light source for the treatment of dye laser resistant port-wine stains. *J Cosmet Laser Ther* 2003 April; 5(1):7–13.
9. Drosner M, Ellwanger J, Schöttle K et al. Comparison of intense pulsed light (IPL) and pulsed dye laser (PDL) in port-wine stain treatment. *Med Laser Appl* 2008; 23:133–140.
10. Parodi A, Paolino S, Greco A et al. Small intestinal bacterial overgrowth in rosacea: Clinical effectiveness of its eradication. *Clin Gastroenterol Hepatol* 2008 July; 6(7):759–764.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Laser and veins

Karin de Vries, Renate R. van den Bos, and Martino H.A. Neumann

INTRODUCTION

Several laser systems have been developed and used for vascular lesions. The argon laser, which emits continuous wave light with several wavelengths, was the first laser used in medicine. Shortly after its introduction in medicine, it was used for patients with vascular lesions such as port-wine stains. Due to the high incidence of textural changes and scarring, this laser is now seldom used [1].

At present, several laser systems with different wavelengths are available for treating vascular lesions (see Table 44.1). When treating vascular lesions using laser therapy, the targeted chromophore is hemoglobin, which has absorption peaks at wavelengths of 418, 542, and 577 nm. Wavelengths between 700 and 1100 nm are less but still significantly absorbed by hemoglobin [2,3]. Longer wavelengths, up to 1100 nm, penetrate deeper than shorter wavelengths. For longer wavelengths, penetration is limited because of absorption by water [4]. In addition to penetration depth, interference with other skin constituents, especially melanin, should be taken into account when choosing the appropriate wavelength.

For treating vessels, heating of blood is not sufficient, as damage to the endothelium and/or vessel wall is necessary for vessel clearance. By heating blood, heat will diffuse to the vessel wall. The goal is to reach a temperature in the vessel wall of around 65°C; this is the threshold for immediate protein denaturation, which irreversibly damages the vessel wall. To achieve sufficient damage, pulse duration should be longer than the thermal relaxation time of the vessel [5].

In addition to laser therapy of small vessels through an intact epidermis, lasers are also very useful when used in the setting of endovenous laser ablation (EVLA), which can be used for treating the great saphenous vein (GSV) and small saphenous vein (SSV) or, less commonly, the anterior accessory saphenous vein (AASV) or the posterior accessory saphenous vein (PASV) and perforator veins.

In this chapter, we will focus on laser treatment of facial telangiectasias and leg vessels. In addition, the use of laser systems in various skin disorders will be shortly addressed.

FACIAL TELANGIECTASIAS

Facial telangiectasias are small dilated vessels with a diameter between 0.1 and 1.0 mm and affect tens of millions of people worldwide [2]. They may be idiopathic but can also occur in several skin conditions, such as rosacea and photodamage or in association with hypertension or connective tissue disorders [1,2]. A significant proportion of procedures performed by laser surgeons is treatment of facial telangiectasias [1,2].

Recently, Hare McCoppin and colleagues reviewed the literature on laser treatment for facial telangiectasias. Laser treatment is very effective for facial telangiectasias, sometimes even after just one treatment session [2,6]. The pulsed dye laser (PDL) is widely used and regarded as safe and effective, with low incidence of pigment changes and scarring. After treatment, purpura may occur as a result of vessel rupture due to microvaporization of erythrocytes [2]. Purpura may last more than 7 days and decrease treatment acceptance.

Superficial telangiectasias can also be treated with a potassium titanyl phosphate (KTP) laser, which emits green light at a wavelength of 532 nm. This wavelength is close to the absorption peak of oxyhemoglobin at 542 nm and has the advantage of no postoperative purpura. This can possibly be explained by prevention of vessel rupture due to the slow heating of the vessel. An intravascular steam bubble is induced, which gradually expands and clears the vessel lumen. After the steam bubble has disappeared, the thermally damaged vessel wall collapses [7]. The major disadvantages of KTP lasers are their superficial penetration and interference with melanin. When vessels are located somewhat deeper or when they are larger than 1 mm, alexandrite laser, diode, or Nd:YAG lasers can be used. Alexandrite laser systems emit light at a wavelength of 755 nm, which has a higher absorption coefficient for melanin than for hemoglobin. Therefore, it can only be used in fair-skinned patients. It seems to have a better effect on blue vessels than on red vessels. Clinical endpoints are immediate stenosis or persistent bluing of the vessels without purpura [8]. For patients with darker skin types, the Nd:YAG laser can be used. This laser has a wavelength of 1064 nm and penetrates deeply into the skin. Absorption by hemoglobin is lower compared to a KTP laser or PDL. The advantage of lower absorption is that not all the energy will be absorbed in the most superficial part of the vessel, leading to a homogeneous heating of all vessels (no heat gradient). A disadvantage is that high energy and short pulse duration are needed to treat small vessels, increasing the risk for nonselective heating of the surrounding tissue and scarring [2,9].

VARICOSE VEINS OF THE LEG

Varicose veins are tortuous and enlarged veins due to weakening in the vein wall or valves. They are a part of chronic venous disease, which may lead to serious complications, such as leg ulcers. Chronic venous disease can be divided into primary chronic venous disorders and secondary chronic venous disorders, which are mostly due to postthrombotic syndrome and congenital malformations. They all share similar clinical

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Table 44.1 Vascular Laser Systems

Laser	Wavelength (nm)	Ideal Vessel Diameter (mm)	Penetration Depth in Fair-Skinned Patients (μm)[a]	Immediate Clinical Endpoint	Advantage	Disadvantage
Copper vapor/ bromide	578	0.1–0.3	400	Vessel blanching without epidermal changes	Effective and well tolerated	Results operator dependent, interference with melanin
Potassium titanyl phosphate (KTP)	532	<1	400	Vessel clearance	No postoperative purpura	High absorption by melanin, only superficial veins
Pulsed dye laser (PDL)	577, 585, 590, 595, 600	<1	400–600	Vessel clearance, mild purpura	Effective, safe	Postoperative purpura
Alexandrite	755	0.4–1.6	1300	Vessel clearance, persistent bluing	Deep penetration	Interference with melanin
Diode	800, 810, 940, 980	>0.4	Up to 3000	Vessel clearance	Deep penetration	
Nd:YAG 1064 nm	1064	>0.7	1600–3000	Vessel clearance	Deep penetration, homogeneous vessel heating, low absorption by melanin	Unselective heating of the surrounding tissues

Sources: Anderson RR, Laser-tissue interactions, in: Goldman MP, Fitzpatrick RE, eds., *Cutaneous Laser Surgery*, Mosby, St. Louis, MO, 1994, pp. 1–18; Ross EV et al., *Dermatol Surg*, 36, 470, 2010; Hsu J and Weiss R, Leg veins, in: Goldberg DJ, ed., *Procedures in Cosmetic Dermatology: Lasers and Lights*, Elsevier Saunders, Philadelphia, PA, 2005, pp. 29–40; Neumann RA et al., *J Invest Dermatol*, 99, 160, 1992; Owen WR and Hoppe E, *Australas J Dermatol*, 53, 281, 2012.

[a]Penetration depth not only depends on wavelength. It also depends on spot size and the concentration of targeted and interfering chromophores such as melanin.

symptoms, but their etiology differs. There are thought to be three important causes for developing varicose veins [13]:

1. A primary anomaly of the matrix of the vein wall may cause changes of its elasticity.
2. A primary anomaly of the cups of the valves may lead to white cell trapping, inflammation, and destruction of the cups.
3. Primary varicose veins as well as postthrombotic varicose veins may cause secondary changes to the valves. Primary varicose veins may cause incompetence of the valves in the superficial veins by dilatation of the vein. In postthrombotic syndrome, the valves of the deep veins may be damaged by the thrombotic process and this initially results in deep venous valvular incompetence. This causes secondary dilation of perforating veins and superficial varicose veins, which again induces valvular incompetence in the superficial veins.

The valves that are present in the veins are unable to perform optimally in the upright position. The insufficiency of valve functioning in the saphenofemoral or saphenopopliteal junction causes descending varicose veins. Insufficient tributaries and perforating veins, on the other hand, can cause saphenous insufficiency without incompetence of the junction in an ascending way.

The prevalence of varicose veins is high and is estimated to range from 2% to 40% [14–17] and increases with age. Four surveys of the general population, in which subjects were examined clinically for the presence of varicose veins, reported a prevalence of varicose veins in 10%–40% in men and 26%–32% in women [14,16,18,19]. Most important risk factors for the development of varicose veins include older age, history of leg injury, and deep vein thrombosis (DVT). The incidence of varicose veins increases with age in a linear manner. It is very difficult, if not impossible, to predict which patient with varicose veins will develop a leg ulcer. However, it has been estimated that about half of the venous leg ulcers are the result of superficial varicose veins [20]. The treatment of leg ulcers is very expensive; therefore, the treatment of varicose veins, which may reduce the incidence of leg ulcers by 50%, is likely to be cost-effective.

Although many individuals will consult their physician for cosmetic reasons, others will have serious complaints and visible complications. Classic symptoms associated with CVD are discomfort, heaviness, aching, muscle cramps, and itching. Clinical characteristics of CVD are varicose veins, edema, hyperpigmentation, eczema, induration, lipodermatosclerosis, white atrophy, nail changes, pachyderma, subcutaneous calcification, and venous ulcers. The gold standard of investigating the venous system is duplex ultrasound examination. Ultrasound examination is best performed with the patient standing so that the anatomy and hemodynamics can be investigated optimally. Both transverse and longitudinal views of the veins should be used during duplex ultrasound scanning because the transverse view provides the best view to visualize the venous anatomy and the longitudinal view gives most information on normal venous flow and reflux. Reflux in the groin is best assessed by Valsalva maneuver and by flow augmentation after releasing manual pressure of the leg. Reflux duration of >0.5 seconds is considered pathological.

The current treatment options for varicose veins are compression therapy, surgery, sclerotherapy, and endovascular thermal ablation techniques. The endovenous ablation therapies have many advantages compared to surgery and are nowadays considered the primary choice treatment. They have a very high success rate and very few complications and are

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

fast and easy to perform, and they can be performed in an outpatient setting. First, the anatomy and nomenclature of the leg veins will be explained briefly before EVLA and will be discussed in more detail.

ANATOMY AND NOMENCLATURE

Saphenous Veins and Tributaries

The superficial venous system is divided into saphenous and nonsaphenous veins. The saphenous veins are located within a fascial compartment. Tributaries are located more superficial in the subcutaneous tissue. The GSV drains blood from the dorsal foot and runs from the medial ankle to the groin where it ends in the femoral vein at the saphenofemoral junction. The SSV arises at the lateral ankle, runs within the saphenous compartment, and usually terminates in the popliteal vein around 2–5 cm above the popliteal fossa at the saphenopopliteal junction. There is a great variation between people, because the SSV may terminate higher in the thigh or gluteal region in a deep vein, via a perforator or in the GSV.

The AASV and the PASV belong to the saphenous veins, because they also run within the saphenous compartment, parallel to the GSV. When they leave the fascial compartment, they must be regarded as tributaries. Typically, the AASV is located laterally from the GSV and is in line with the femoral artery and vein, called the "alignment sign."

Perforator Veins

There are many perforator veins, and the interindividual variation is high. Some important perforator veins are located at the foot, the ankle, the leg at knee level, the thigh, and the gluteal muscles.

Endovenous Laser Ablation

EVLA can be performed under local tumescent anesthesia in an outpatient setting. Venous access is obtained by puncturing with a 16F or 18F needle or a cannula under ultrasound guidance. Most commonly, the insufficient GSV is entered at knee level and the SSV at midcalf [21]. After entrance to the vein is established, a guidewire is passed through the needle into the vein up to the level of the junction with the deep venous system. After checking the position of the guidewire with ultrasound, the needle is removed, and a small cutaneous incision of 3 mm is made. An introducer sheath is inserted over the guidewire and is positioned a few centimeters below the junction. Subsequently, the laser fiber (diameter ranges between 200 and 600 μm) is introduced after removing the guidewire. In some laser sets, there is no guidewire and the sheath is directly introduced through a cannula. The most pivotal step in the EVLA procedure is positioning the tip of the laser fiber 1–2 cm distally from the junction under ultrasound guidance, in longitudinal view. Tumescent anesthesia is administered into the perivenous space, again under ultrasound guidance using a syringe or mechanical infusion pump. Tumescent anesthesia is warranted, because it reduces pain, cools perivenous tissue, and decreases the venous diameter. After activation, the laser is pulled back in a continuous way (usually at about 3–5 mm/s, depending on the power and wavelength; with the 1320 nm laser, a pullback speed of 1 mm/s is commonly used) [22] or in a pulsed fashion, with the objective to administer about 30–60 J/cm. EVLA can be used for treating insufficient GSVs and SSVs. Because of the rigidity and size of the disposables, linear saphenous veins with a diameter of 5 mm or more are ideal for EVLA. EVLA can also be used for ablation of the AASV or the PASV and perforator veins [23,24]. The amount of delivered energy can be varied. By adjusting the pullback speed, the power, or both, the total amount of delivered energy per centimeter can be influenced. For small veins, only 20 J/cm can be used, whereas higher energy (i.e., 60 J/cm) can be used when treating large veins. Several wavelengths have been used for EVLA (810, 940, 1064, 1320, 1470, and 1500 nm), all with similar results. Although it has been suggested, no RCT has shown that one wavelength results in better outcomes than the others. Endovenous-simulated laser experiments showed no difference in the temperature profile between 940 and 1470 nm lasers, suggesting wavelength-independent temperature profiles [25]. The first large case series reported high success rates [26,27] and many series followed with comparable results. A recent, large randomized clinical trial performed by Rasmussen et al. [28] showed that EVLA, radio-frequency ablation, and stripping (under tumescent anesthesia) were all equally efficacious [28].

The side effects of EVLA are usually mild. Systematically studying all publications on EVLA showed that the most common side effects were ecchymoses and pain with or without induration (100%). Other side effects were less common: skin burns (<1%), dysesthesia (0%–22%), superficial thrombophlebitis (0%–25%), DVT (0%–6%), nerve injury (<1%), and hematoma [29]. Using a laser fiber with a modified tip (tulip or radial fiber) and avoiding very high energy dose may reduce postoperative pain [30]; however, there are no good comparative studies available.

TELANGIECTATIC AND RETICULAR LEG VEINS

Telangiectatic and reticular leg veins are very common. The etiology of telangiectatic leg veins is still unknown. Some researchers have proposed that telangiectatic leg veins originate similarly to larger varicose veins. Weiss found an association of telangiectatic veins with reticular veins on the thighs [31]; however, not all patients with telangiectatic leg veins have evidence of underlying venous insufficiency [32]. Many patients seek treatment often for cosmetic reasons [33].

The standard treatment for telangiectatic leg veins without underlying venous insufficiency is sclerotherapy. This therapy is used for many decades and is regarded as safe and effective [32]. Possible unwanted side effects of sclerotherapy are hyperpigmentation and telangiectatic matting. Another risk is the occurrence of ulceration, especially when treating vulnerable areas such as the ankle. Some vessels are too small to be cannulated with a needle. Furthermore, some patients do not tolerate the treatment because of sclerosant allergy or anxiety for needles [34].

From the aforementioned reasons, there has been a growing interest in finding an effective alternative that is equally safe as sclerotherapy. Many physicians have therefore implemented laser therapy. The effect of laser treatment of leg telangiectasias is somewhat disappointing compared to the treatment of facial vessels. More treatment sessions and higher fluences are needed to achieve a similar effect, resulting in a higher risk of complications [6,34]. Possible explanations for this difference are the higher hydrostatic pressure in the leg, thicker vessel walls, and a more heterogeneous mix of vessel diameters and blood flow rates [34]. Also, as matting is a possible side effect of treatment of leg veins, there may be angiogenesis after treatment.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 44.1 Clinically visible veins, originating from a feeder vein. (Courtesy of T.D. Wentel.)

The efficacy of laser therapy for leg veins has been compared to the efficacy of sclerotherapy in four studies. Lupton et al. [35] treated 20 women with two treatments with Nd:YAG 1064 nm in one leg and two treatments with sclerotherapy with injectable 0.25% sodium tetradecyl sulfate in the other leg. Sclerotherapy was more effective than laser with minimal adverse sequelae in both groups. Coles et al. treated 20 women with leg veins at two comparable sites. The veins were 0.25–3 mm in diameter. One site was treated with Nd:YAG laser 1064 nm. Nine patients were treated twice and one patient was treated four times. The other site was treated with injectable 0.6% Sotradecol®. Three months after the last treatment, they found that the results were similar [36]. Levy et al. treated four sites in 14 patients, using sclerotherapy with 0.5% polidocanol alone, Nd:YAG laser 1064 nm alone, sclerotherapy followed by Nd:YAG laser treatment, and Nd:YAG laser treatment followed by sclerotherapy. There were no significant differences between the four sites [37]. Recently, Munia et al. treated 30 patients with sclerotherapy using 75% glucose solution in one leg and Nd:YAG 1064 nm laser treatment in the other leg. Vessel clearance was better after laser therapy, but patients were more satisfied after sclerotherapy [38]. In conclusion, when treating leg veins, Nd:YAG laser therapy is a reasonable alternative to the current gold standard of sclerotherapy. For both treatment methods, it is important to pay attention to feeder veins (Figures 44.1 and 44.2). Cosmetically disturbing veins can be the tip of an iceberg; only the most superficial part is visible. If leg telangiectasias arise from a "feeder" vein, this feeder vein should be treated first. If not, there is a high risk of recurrence [33]. Our approach is to treat the feeder vein first using sclerotherapy with polidocanol 1% foam or liquid. The feeder vein can be found using a vein viewer (Figure 44.3). Then, smaller veins are treated with sclerotherapy using polidocanol 0.5% liquid. The third step is to treat residual veins using a combination of PDL and Nd:YAG 1064 nm (see the succeeding text).

Red Veins

As for facial telangiectasias, KTP laser and PDL are effective for small vessel up to 1 mm in diameter that are located less than 1 mm from the skin surface (Figures 44.4 and 44.5). Longer wavelength lasers such as alexandrite, diode, or Nd:YAG lasers are less useful for the smallest vessels up to 0.4 mm in diameter. A possible explanation for this finding is that longer wavelengths simply bypass the small vessels. Second, the number of hemoglobin-containing erythrocytes in the small vessel is low and absorption coefficient of hemoglobin is much lower for 1064 nm (Nd:YAG) than for 577–600 nm (PDL). For these reasons, high fluences are needed when treating small vessels with longer wavelength laser systems, leading to a higher risk of complications due to heating of the surrounding tissues [34].

Blue Veins

Larger vessels are a good target for the longer wavelength laser, especially 1064 nm Nd:YAG (Figures 44.6 through 44.8). This can be explained by their greater volume/surface ratio compared to small red veins. Coagulation and forming of methemoglobin

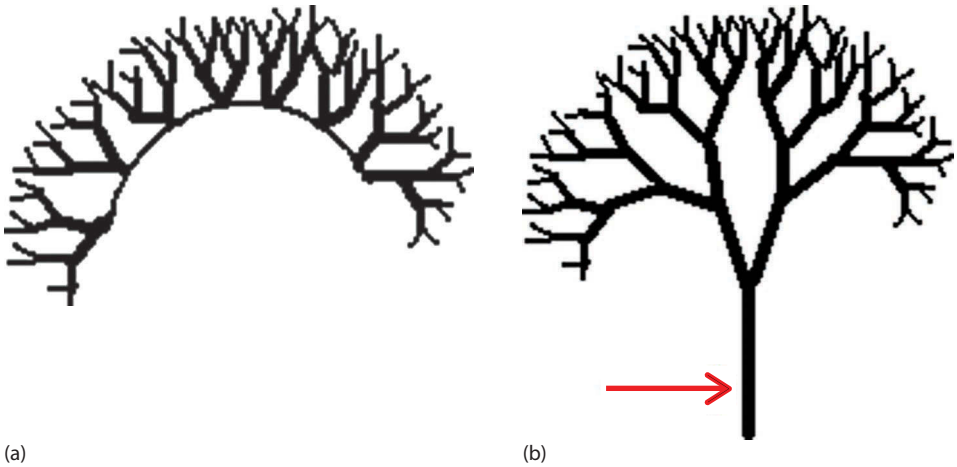


Figure 44.2 (a) Schematic view of clinically visible veins. (b) Clinically visible veins can originate from a feeder vein (red arrow). To achieve satisfactory results, the feeder vein has to be treated first.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

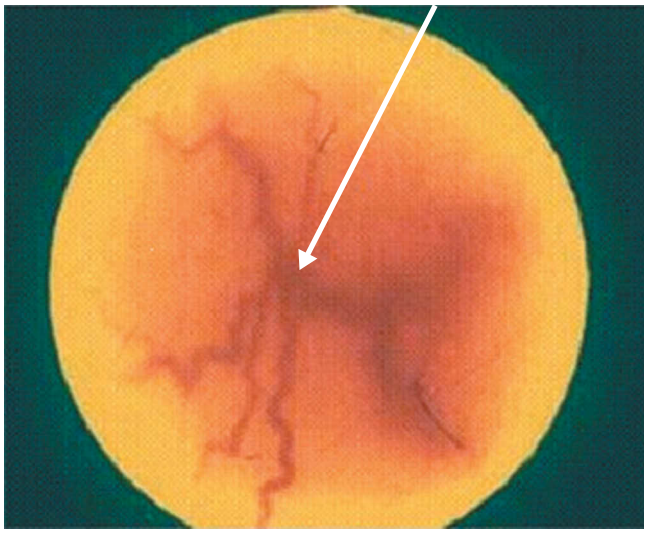


Figure 44.3 A feeder vein (white arrow) is visible with the vein viewer.

Figure 44.4 Small localized red telangiectasias.

occur at temperatures >70°C. The heat remains longer in larger vessels, because they have a larger volume compared to their surface. Also, as long as the temperature is high enough, methemoglobin is formed. This results in a higher absorption because the laser light of the Nd:YAG is better absorbed by methemoglobin than by oxyhemoglobin. The effect is better at the end of the pulse when oxyhemoglobin is converted into methemoglobin. Also, interference with melanin is lower after the conversion of oxyhemoglobin to methomeglobin [9].

One of the challenges when treating larger vessels is to deliver energy to the vessel without heating the tissue between

Figure 44.5 Small localized red telangiectasias, which show slight purpura immediately after treatment with pulsed-dye laser.

Figure 44.6 Telangiectatic leg veins, before treatment.

the skin surface and the vessel, which would result in undesirable side effects. Most larger vessels are situated somewhat deeper than smaller vessels. When using laser, a certain percentage of laser light is lost due to scattering. This percentage is much higher for small spot sizes than for large spot sizes. Therefore, when using larger spot sizes, laser energy will be

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 44.7 Telangiectatic leg veins: immediately after treatment with Nd:YAG 1064 nm.

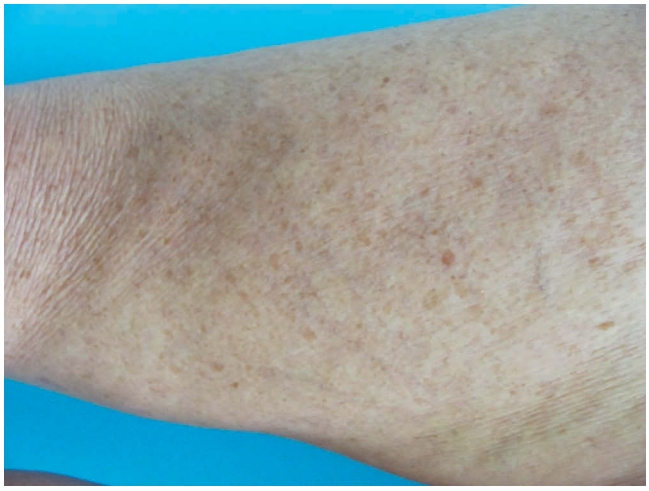


Figure 44.8 Telangiectatic leg veins: 2 months after treatment with Nd:YAG 1064 nm.

higher at any given depth in the dermis. It is therefore tempting to choose a spot size as large as possible to be able to reach the vessels. However, Baümler and colleagues showed that when using Nd:YAG laser with a wavelength of 1064 nm, larger spot sizes result in a higher risk of unselective heating of the surrounding tissues. This is the result of a relatively low absorption of 1064 nm laser light by hemoglobin [9]. Around the ankle, treatment with Nd:YAG should be used with caution, as penetration is deep and arterial vessels are relatively superficial in this area.

Improvement of Effect

A strategy to optimize effect in treating vascular lesions is to use the combination of laser systems, such as a combination of PDL and Nd:YAG or KTP and Nd:YAG. These combinations have shown to be effective at fluences that were not effective when used separately. After irradiation with PDL or KTP laser, methemoglobin is formed at a temperature range of 65°C–72°C and blood clot formation occurs at temperatures >80°C. When a fluence is used that causes the blood in the vessel to coagulate, but not to vaporize, erythrocytes will be tightly packed and so will the targeted chromophore. Both methemoglobin and blood clots have a high absorption band at approximately 1000 nm. This package can then be treated with the Nd:YAG laser. Thus, the combined treatment has a synergistic effect that can result in vessel damage with a relatively low incidence of complications, which may be caused, for example, by absorption of light by melanin [39–41].

Another possibility to increase the treatment effect of PDL is to use pulse stacking, which means the application of several pulses on top of each other (mostly three or four). This may lead to a synergistic effect and deeper penetration [42]. With Nd:YAG, pulse stacking can lead to unselective heating of the tissue surrounding the vessels and subsequent scarring.

Recently, Klein and colleagues reported improved effects of the combination of intravenous indocyanine green and diode laser therapy. Fluences of 100–110 J/cm^2 were most effective, with even better results if a second pass was performed. In this study, the combination of intravenous indocyanine green and diode laser was more effective than treatment with diode laser alone or PDL alone [43].

TREATMENT OF CUTANEOUS VESSELS IN VARIOUS SKIN DISORDERS

Telangiectasias can arise on other sites in the body than the face and legs in various clinical settings [44] and be treated with laser systems. Other vascular disorders such as spider nevi and venous lakes and can also be effectively treated. Other cutaneous disorders, such as psoriasis, chronic discoid lupus erythematosus, warts, and granuloma faciale, have also been treated with vascular lesions; however, results are variable [45–48].

COMPLICATIONS

Several complications may arise after laser therapy. As interference with melanin is one of the problems when treating vascular lesions, pigment changes are a relatively common complication. Both hyper- and hypopigmentation can occur. This can in part be prevented by adequate pre- and posttreatment cooling of the epidermis. However, a somewhat reduced effect on the most superficial vessels has been shown after precooling of the skin [49].

The risk of postinflammatory hyperpigmentation is higher in patients with darker skin types and in suntanned patients. In these patients, Nd:YAG may be the safest laser system, as absorption of this wavelength by melanin is very low. Purpura occurring after treatment of leg veins increases the risk of skin discoloration as a result of iron depositions in the dermis. Hyperpigmentation may be transient but can, in some patients, be persistent.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Bruising may be caused by vessel rupture instead of coagulation; this occurs more frequently when short pulses are used [50]. Ulceration is a seldom complication, which may occur when using too high fluences, too long pulse durations, or inadequate epidermal cooling. Also, patients may experience too much pain during treatment to tolerate the treatment.

The most common complications after EVLA are postoperative pain and ecchymoses. Also, phlebitis and sensible nerve injury may occur. Serious complications such as DVT are fortunately rare (<1%) [29].

CONCLUSIONS

Facial telangiectasias can effectively be treated with several laser systems. PDL is the most frequently used laser system, but other systems, especially Nd:YAG, can also be used for somewhat larger or deeper vessels. Leg telangiectasias are more difficult to treat with laser. It is very important to rule out the possibility of underlying chronic venous insufficiency before starting laser therapy. Also, feeder veins should be treated first. As both laser treatment and sclerotherapy have their advantages and disadvantages, a combination of both treatments may offer the best results. It is reasonable to use Nd:YAG for larger vessels (larger than 0.7 mm) and PDL or KTP for smaller vessels (up to 1.0 mm). Complications can in part be prevented with adequate choice of laser parameters and adequate cooling of the skin. To further reduce the risk of complications while enhancing efficacy, combined laser systems such as PDL and Nd:YAG or KTP and Nd:YAG can be used, as these combined systems have a synergistic effect.

ACKNOWLEDGMENT

Thanks to Professor Dr. E.P. Prens for his comments on this text.

REFERENCES

1. Astner S, Anderson RR. Treating vascular lesions. *Dermatol Ther* 2005; 18:267–281.
2. Hare McCoppin HH, Goldberg DJ. Laser treatment of facial telangiectases: An update. *Dermatol Surg* 2010; 36:1221–1230.
3. Anderson RR, Parrish JA. Microvasculature can be selectively damaged using dye lasers: A basic theory and experimental evidence in human skin. *Lasers Surg Med* 1981; 1:263–276.
4. Anderson RR. Laser-tissue interactions. In: Goldman MP, Fitzpatrick RE, eds. *Cutaneous Laser Surgery*. St. Louis, MO: Mosby, 1994, pp. 1–18.
5. Altshuler GB, Anderson RR, Manstein D, Zenzie HH, Smirnov MZ. Extended theory of selective photothermolysis. *Lasers Surg Med* 2001; 29:416–432.
6. Major A, Brazzini B, Campolmi P et al. Nd:YAG 1064 nm laser in the treatment of facial and leg telangiectasias. *J Eur Acad Dermatol Venereol* 2001; 15:559–565.
7. Cassuto DA, Ancona DM, Emanuelli G. Treatment of facial telangiectasias with a diode-pumped Nd:YAG laser at 532 nm. *J Cutan Laser Ther* 2000; 2:141–146.
8. Ross EV, Meehan KJ, Domankevitz Y, Trafeli JP, Annandono J, Jacoby M. Use of a variable long-pulse alexandrite laser in the treatment of facial telangiectasia. *Dermatol Surg* 2010; 36:470–474.
9. Baumler W, Ulrich H, Hartl A, Landthaler M, Shafirstein G. Optimal parameters for the treatment of leg veins using Nd:YAG lasers at 1064 nm. *Br J Dermatol* 2006; 155:364–371.
10. Hsu J, Weiss R. Leg veins. In: Goldberg DJ, ed. *Procedures in Cosmetic Dermatology: Lasers and Lights*. Philadelphia, PA: Elsevier Saunders, 2005, pp. 29–40.
11. Neumann RA, Knobler RM, Leonhartsberger H, Gebhart W. Comparative histochemistry of port-wine stains after copper vapor laser (578 nm) and argon laser treatment. *J Invest Dermatol* 1992; 99:160–167.
12. Owen WR, Hoppe E. Copper bromide laser for facial telangiectasia: A dose response evaluation. *Australas J Dermatol* 2012; 53:281–284.
13. Lim CS, Davies AH. Pathogenesis of primary varicose veins. *Br J Surg* 2009; 96:1231–1242.
14. Evans CJ, Fowkes FG, Ruckley CV, Lee AJ. Prevalence of varicose veins and chronic venous insufficiency in men and women in the general population: Edinburgh Vein Study. *J Epidemiol Community Health* 1999; 53:149–153.
15. Kurz X, Kahn SR, Abenhaim L et al. Chronic venous disorders of the leg: Epidemiology, outcomes, diagnosis and management. Summary of an evidence-based report of the VEINES task force. Venous Insufficiency Epidemiologic and Economic Studies. *Int Angiol* 1999; 18:83–102.
16. Abramson JH, Hopp C, Epstein LM. The epidemiology of varicose veins. A survey in western Jerusalem. *J Epidemiol Community Health* 1981; 35:213–217.
17. Brand FN, Dannenberg AL, Abbott RD, Kannel WB. The epidemiology of varicose veins: The Framingham Study. *Am J Prev Med* 1988; 4:96–101.
18. Coon WW, Willis PW III, Keller JB. Venous thromboembolism and other venous disease in the Tecumseh community health study. *Circulation* 1973; 48:839–846.
19. Criqui MH, Jamosmos M, Fronek A et al. Chronic venous disease in an ethnically diverse population: The San Diego Population Study. *Am J Epidemiol* 2003; 158:448–456.
20. Magnusson MB, Nelzen O, Risberg B, Sivertsson R. A colour Doppler ultrasound study of venous reflux in patients with chronic leg ulcers. *Eur J Vasc Endovasc Surg* 2001; 21:353–360.
21. van den Bos RR, Kockaert MA, Neumann HA, Nijsten T. Technical review of endovenous laser therapy for varicose veins. *Eur J Vasc Endovasc Surg* 2008; 35:88–95.
22. Goldman MP, Mauricio M, Rao J. Intravascular 1320-nm laser closure of the great saphenous vein: A 6- to 12-month follow-up study. *Dermatol Surg* 2004; 30:1380–1385.
23. Proebstle TM, Herdemann S. Early results and feasibility of incompetent perforator vein ablation by endovenous laser treatment. *Dermatol Surg* 2007; 33:162–168.
24. Bush RG, Hammond K. Treatment of incompetent vein of Giacomini (thigh extension branch). *Ann Vasc Surg* 2007; 21:245–248.
25. van den Bos RR, van Ruijven PW, van der Geld CW, van Gemert MJ, Neumann HA, Nijsten T. Endovenous simulated laser experiments at 940 nm and 1470 nm suggest wavelength-independent temperature profiles. *Eur J Vasc Endovasc Surg* 2012; 44:77–81.
26. Navarro L, Min RJ, Bone C. Endovenous laser: A new minimally invasive method of treatment for varicose veins—Preliminary observations using an 810 nm diode laser. *Dermatol Surg* 2001; 27:117–122.
27. Min RJ, Zimmet SE, Isaacs MN, Forrestal MD. Endovenous laser treatment of the incompetent greater saphenous vein. *J Vasc Interv Radiol* 2001; 12:1167–1171.
28. Rasmussen LH, Lawaetz M, Bjoern L, Vennits B, Blemings A, Eklof B. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins. *Br J Surg* 2011; 98:1079–1087.
29. Van Den Bos RR, Neumann M, De Roos KP, Nijsten T. Endovenous laser ablation-induced complications: Review of the literature and new cases. *Dermatol Surg* 2009; 35:1206–1214.
30. Doganci S, Demirkilic U. Comparison of 980 nm laser and bare-tip fibre with 1470 nm laser and radial fibre in the treatment of great saphenous vein varicosities: A prospective randomised clinical trial. *Eur J Vasc Endovasc Surg* 2010; 40:254–259.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

31. Weiss RA, Weiss MA. Doppler ultrasound findings in reticular veins of the thigh subdermic lateral venous system and implications for sclerotherapy. *J Dermatol Surg Oncol* 1993; 19:947–951.
32. Schwartz L, Maxwell H. Sclerotherapy for lower limb telangiectasias. *Cochrane Database Syst Rev* 2011; 12:CD008826.
33. Weiss RA, Dover JS. Leg vein management: Sclerotherapy, ambulatory phlebectomy, and laser surgery. *Semin Cutan Med Surg* 2002; 21:76–103.
34. McCoppin HH, Hovenic WW, Wheeland RG. Laser treatment of superficial leg veins: A review. *Dermatol Surg* 2011; 37:729–741.
35. Lupton JR, Alster TS, Romero P. Clinical comparison of sclerotherapy versus long-pulsed Nd:YAG laser treatment for lower extremity telangiectases. *Dermatol Surg* 2002; 28:694–697.
36. Coles CM, Werner RS, Zelickson BD. Comparative pilot study evaluating the treatment of leg veins with a long pulse ND:YAG laser and sclerotherapy. *Lasers Surg Med* 2002; 30:154–159.
37. Levy JL, Elbahr C, Jouve E, Mordon S. Comparison and sequential study of long pulsed Nd:YAG 1,064 nm laser and sclerotherapy in leg telangiectasias treatment. *Lasers Surg Med* 2004; 34:273–276.
38. Munia MA, Wolosker N, Munia CG, Chao WS, Puech-Leao P. Comparison of laser versus sclerotherapy in the treatment of lower extremity telangiectases: A prospective study. *Dermatol Surg* 2012 April; 38(4):635–639.
39. Trelles MA, Weiss R, Moreno-Moragas J, Romero C, Velez M, Alvarez X. Treatment of leg veins with combined pulsed dye and Nd:YAG lasers: 60 patients assessed at 6 months. *Lasers Surg Med* 2010; 42:609–614.
40. Saafan AM, Salah MM. Using pulsed dual-wavelength 595 and 1064 nm is more effective in the management of hemangiomas. *J Drugs Dermatol* 2010; 9:310–314.
41. Karsai S, Roos S, Raulin C. Treatment of facial telangiectasia using a dual-wavelength laser system (595 and 1,064 nm): A randomized controlled trial with blinded response evaluation. *Dermatol Surg* 2008; 34:702–708.
42. Tanghetti E, Sherr EA, Sierra R, Mirkov M. The effects of pulse dye laser double-pass treatment intervals on depth of vessel coagulation. *Lasers Surg Med* 2006; 38:16–21.
43. Klein A, Baumler W, Koller M et al. Indocyanine green-augmented diode laser therapy of telangiectatic leg veins: A randomized controlled proof-of-concept trial. *Lasers Surg Med* 2012; 44:369–376.
44. Baker C, Kelly R. Other vascular disorders. In: Bolognia JL, Jorizzo JL, Rapini RP, eds. *Dermatology*. St. Louis, MO: Mosby, 2008, p. 1621.
45. De Leeuw J, Van Lingen RG, Both H, Tank B, Nijsten T, Martino Neumann HA. A comparative study on the efficacy of treatment with 585 nm pulsed dye laser and ultraviolet B-TL01 in plaque type psoriasis. *Dermatol Surg* 2009; 35:80–91.
46. Erceg A, Bovenschen HJ, van de Kerkhof PC, de Jong EM, Seyger MM. Efficacy and safety of pulsed dye laser treatment for cutaneous discoid lupus erythematosus. *J Am Acad Dermatol* 2009; 60:626–632.
47. Schellhaas U, Gerber W, Hammes S, Ockenfels HM. Pulsed dye laser treatment is effective in the treatment of recalcitrant viral warts. *Dermatol Surg* 2008; 34:67–72.
48. Cheung ST, Lanigan SW. Granuloma faciale treated with the pulsed-dye laser: A case series. *Clin Exp Dermatol* 2005; 30:373–375.
49. Dai T, Diagaradjane P, Yaseen MA, Pikkula BM, Thomsen S, Anvari B. Laser-induced thermal injury to dermal blood vessels: Analysis of wavelength (585 nm vs. 595 nm), cryogen spray cooling, and wound healing effects. *Lasers Surg Med* 2005; 37:210–218.
50. Garden JM, Tan OT, Kerschmann R et al. Effect of dye laser pulse duration on selective cutaneous vascular injury. *J Invest Dermatol* 1986; 87:653–657.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Lasers and intense pulsed light for hair reduction

Valéria Campos, Luiza Pitassi, and Christine Dierickx

INTRODUCTION

For the last decade, removal of unwanted face and body hair employing laser or intense pulsed light technology has become a quite sought-after procedure due to this treatment method's success and efficacy. New equipment is launched in the market, allowing very fast epilations, making hair removal more accessible, safer, and more efficient each day [1,2].

The optimal hair removal method is the one that is practical and effective. Classical methods, such as electrolysis, shaving, tweezers, waxing, and hair removal creams, are still very popular, but none provide a permanent solution for hair removal. Their efficacy is limited; they may be painful, in addition to possible risks of side effects, such as skin irritation, infection, dermatitis, and scars [3].

Historically, hair removal has drawn great interest, since excessive hair, especially in patients with hypertrichosis or hirsutism, may bring major psychosocial effects, self-esteem problems, and even depression [4,5].

The first device for laser epilation, a 694 nm ruby laser, was approved in 1996 by the *Food and Drug Administration* (FDA) [6]. Since then, several other light-based technologies have been approved for hair removal, such as alexandrite lasers (755 nm), diode lasers (800–810 nm), neodymium:YAG lasers (1064 nm), and intense pulsed light sources (590–1200 nm). These devices with their technical specifications have constantly evolved through the years and are very effective for long-term hair reduction [1,7].

Photothermal hair destruction is based on the selective photothermolysis principle. By choosing a proper wavelength, pulse duration, and fluence, thermal injury will be specific to a target chromophore, in this case hair follicle melanin, with minimal thermal injury to the surrounding tissue [8].

Patients' response to treatment depends on individual factors, such as skin type and hair to be treated, hormonal influence, or the use of some drugs. Since these factors may impact treatment response by "new hair" appearance, the correct term to be used is long-term or semipermanent epilation. The optimal patient for treatment should have dark, thick hair and fair skin. Darker skin phototypes and tanned skin are relative contraindications for laser, since these show a higher risk of burns and unwanted side effects [2,9].

Most women with polycystic ovary syndrome have an 80% chance of developing hirsutism, with this being one of the most common reasons to pursue facial hair removal [10]. This hair may also be treated transiently with eflornithine hydrochloride cream, a drug delaying hair growth and also effective in patients with beard pseudofolliculitis [1,11].

Our experience shows a better efficacy when employing higher energies for the treatment, this observation being consistent with the literature [12]. Overall, the best treatment responses for hair reduction is found with diode and alexandrite lasers, followed by IPL and Nd:YAG lasers [13]; however, it is possible to achieve good outcomes with any wavelength as long as the energy provided by the equipment is enough to destroy the follicle.

The efficacy of laser epilation treatment varies considerably among patients, depending on the skin type, ethnicity, hair color, anatomical site, and window between treatments [2]. The first generation of lasers with short pulse duration (2–5 ms) limited the treatment safety to subjects with fair skin and dark and thick hair. With the development of lasers with longer wavelengths and longer pulse durations, patients with all skin types may be safely treated. Among lasers commonly used for hair reduction, the Nd:YAG (1064 nm) laser is considered the safest for unwanted hair treatment in dark skin patients [14].

Recently, a series of handheld laser and intense pulsed light devices have been developed for hair removal at home. In spite of being FDA approved, very few controlled studies related to the safety and efficacy of these devices have been conducted [14,15].

In the last few years, laser hair removal has become a quite sought-after procedure due to its treatment efficacy, allowing treatment of large areas of unwanted hair, with less discomfort and less complications. The best clinical outcomes became possible due to the high selectivity of laser and intense pulsed light systems toward the hair follicle. In addition to great technology employed for these equipments, light-based hair removal has become increasingly accessible (Table 45.1).

MECHANISMS OF HAIR FOLLICLE DESTRUCTION

Light-based treatment may damage hair follicles through three mechanisms: thermal (due to local heating), mechanical (through shock waves and violent cavitations), and photochemical (by creating toxic mediators, such as simple oxygen or free radicals) [17] (Table 45.2).

Photothermal destruction is based on the principle of selective photothermolysis [8]. The choice of wavelength, pulse duration, and fluence will be crucial for inducing selective thermal damage [17]. Melanin absorbs in the wavelength ranging from ultraviolet (400 nm) to infrared (1200 nm) [17]. Lasers or light sources using this range of wavelengths (ruby 694 nm, alexandrite 755 nm, diode 800 nm, neodymium:YAG 1.064, and intense pulsed light lamps) are selectively absorbed by melanin and deeply penetrate into the dermis [17]. While reaching the dermis, light causes an excessive heating of pigmented hair, causing full or partial hair follicle destruction. At the skin surface, this is observed as selective vaporization of hair shafts (Figures 45.1 and 45.2). The purpose of this process is to reach stem cells located in the bulge area [6].

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Table 45.1 Main Types of Laser and Intense Pulsed Light Sources with Their Specifications

Supplier	Product name	Device type	Wavelength (nm)	Energy output (J)	Pulse length
Alma Lasers	Soprano	CW diode	810	Up to 120 J/cm²	10–1,350 ms
	Harmony	In-motion AFT pulsed light/alexandrite/ Nd:YAG	650–950/755/1064	5–20 J/cm²/1–32 J/cm²/30–450 J/cm²	1, 3, 30 s/3 ms/10, 15, 45, 60 ms
Cutera	Xeo Platform	Long pulse Nd:YAG	1064	Up to 300 J/cm²	0.1–300 ms
	CoolGlide	Intense pulsed light	Programmable: 770–1100	5–35 J/cm²	Automatic, based on program
	ProWave 770			10–100 J/cm²	
	Solera Platform	Intense pulsed light	520–1100 nm	5–30 J/cm²	Automatic, based on program
	Opus		770–1100 nm	5–35 J/cm²	
			500–635	3–24 J/cm²	
Cynosure, Inc.	Apogee+	Alexandrite	755	Max. 50 J/cm²	0.5–300 ms
	Elite+	Alexandrite/Nd:YAG	755/1064	Max. 300 J/cm²	0.4–300 ms
	Elite MPX	Alexandrite/Nd:YAG/ MultiPlex/IPL	755/1064/530–1200	Up to 600 J/cm²	0.5–300 ms
	Acclaim	Nd:YAG	1064	Up to 600 cm²	0.4–300 ms
	PhotoSilk Plus	XE lamp	950	30 J/cm²	5–50 ms
	Cynergy PL	Pulsed light	560–950	16–30 J/cm²	5–50 ms
	Cynergy III	Pulsed dye	585	7–40 J/cm²	0.5–40 ms
		Nd:YAG	1064	35–300 J/cm²	0.3–300 ms
		Pulsed light	560–950	16–30 J/cm²	5–50 ms
Industra	Etherea	Intense pulsed light	400–1200	Up to 33 J/cm²	5–100 ms
	IPL-Sq	Square-wave pulse IPL	400–1200	Up to 33 J/cm²	5–100 ms
Lumenis	LightSheer Duet	Diode	800	10–100 J/cm²	5–400 ms
	LightSheer ST	Diode	800	10–40 J/cm²	5–100 ms
	LightSheer XT	Diode	800	10–100 J/cm²	5–400 ms
	IPL QuantumHR	Intense pulsed light	695–1200	20–45 J/cm²	6–18 ms
	Lumenis One	Intense pulsed light	515–1200	10–40 J/cm²	3–100 ms
		Multiapplication	IPL: 515–1200	10–40 J/cm²	3–100 ms
		Multitechnology	Nd:YAG: 1064	10–225 J/cm²	2–20 ms
		Modular platform	Diode: 800	10–100 J/cm²	5–400 ms
	M22	Multiapplication, Multitechnology	IPL: 515–1200	10–35 J/cm²	4–20 ms
		Modular platform	Nd:YAG: 1064	20–225 J/cm²	2–20 ms
Palomar	StarLux IPL Palomar Icon	Intense pulsed light	525–1200	Up to 70 J/cm²	5–500 ms
	MaxR handpiece	Optimized light	650–1200	Up to 46 J/cm²	1–100 ms
	MaxRshandpiece	Optimized light	650–1200	Up to 70 J/cm²	1–100 ms
	MaxY handpiece	Optimized light	525–1200	Up to 52 J/cm²	1–100 ms
	MaxYs handpiece	Optimized light	525–1200	Up to 81 J/cm²	1–100 ms
	1064 + Laser	Nd:YAG	1064	Up to 700 J/cm²	10–100 ms
	Vectus	Diode laser	800	Up to 100 J/cm²	5–300 ms
Quanta System	Duetto	Alexandrite	755	22 J/cm²	100 ms
		YAG	1064	400 J/cm²	1–100 ms
	Ultrawave 1064	Nd:YAG long pulse/ short pulse	1064	Up to 500 J/cm²	3–100 ms/0.3–0.8 ms
				Up to 46 J/cm²	
	Ultrawave 755	Alexandrite	755	Up to 120 J/cm²	3–100 ms
	Ultrawave I	Nd: long pulse/short pulse/Nd:YAG	1064/532	Up to 500 J/cm²	3–100 ms
				Up to 46 J/cm²	0.3–0.8 ms
		Nd:YAG F.D.		Up to 90 J/cm²	5–25 ms
	Ultrawave II	Alexandrite/Nd:YAG	755/1064	Up to 120 J/cm²	3–100 ms
		Long pulse/short pulse	1320/1064	Up to 500 J/cm²	0.3–0.8 ms
	Ultrawave III	Alexandrite/Nd:YAG	755/1064	Up to 120 J/cm²	3–100 ms
		Long pulse/short pulse/Nd:YAG F.D.	1320/1064	Up to 500 J/cm²	100 ms/0.3–0.8 ms/ 5–25 ms
			532	Up to 46 J/cm²	
	Eterna Giovinezza	Pulsed light	570–1200	Up to 40 J/cm²	3–240 ms
	Eterna Giovinezza Plus	Pulsed light	570–1200	Up to 40 J/cm²	3–240 ms
			625–1200		

(*Continued*)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Table 45.1 (*Continued*) Main Types of Laser and Intense Pulsed Light Sources with Their Specifications

Supplier	Product name	Device type	Wavelength (nm)	Energy output (J)	Pulse length
	Eterna Giovinezza Compact (table top)	Pulsed light	570–1200	Up to 40 J/cm^2	3–240 ms
Quantel/Alma	Leda	Diode	808–980	60 J/cm^2	6–60 ms
Syneron and Candela	eLaser DSL	Diode	810	Up to 50 J/cm^2	N/D
		RF		Up to 50 J/cm^3	
	eLight DS	Optical energy	680–980	Up to 45 J/cm^2	N/D
		RF		Up to 25 J/cm^3	
	eMax/eLaser DSL	Diode/RF electrical energy	810	Up to 50 J/cm^3	N/A
				Up to 50 J/cm^3	
	eMax/eLight DS	Optical energy/RF electrical energy	600–980	Up to 45 J/cm^3	N/A
				Up to 25 J/cm^3	
	GentleLASE (various models)	Alexandrite	755	Up to 100 J/cm^3	3 ms
	GentleYAG (various models)	Nd:YAG	1064	Up to 600 J/cm^3	0.250–300 ms
	GentleMax Configurable Workstation	Alexandrite/Nd:YAG	755/1064	Up to 600 J/cm^3	0.250–300 ms

Table 45.2 Mechanisms of Hair Follicle Destruction

Types of destruction	Devices used
Photothermal	Ruby laser (694 nm)
	Alexandrite laser (755 nm)
	Diode laser (800 nm)
	Nd:YAG laser (1064 nm)
	Intense pulsed light source (590–1200 nm)
Photomechanical	Q-switched Nd:YAG laser with carbon suspension
	Q-switched Nd:YAG laser
Photochemical	Photodynamic therapy

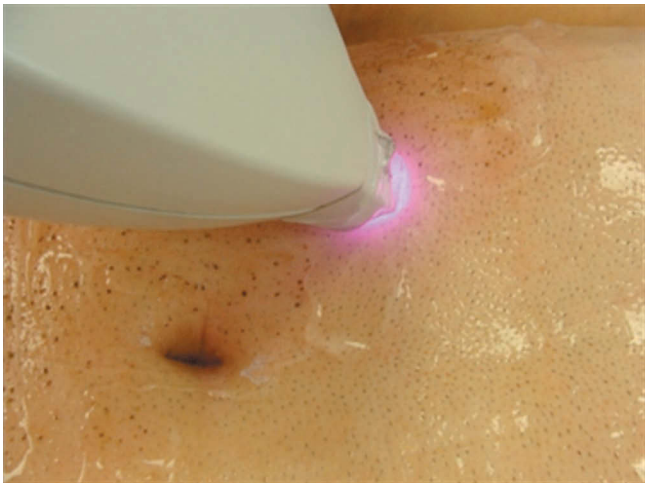


Figure 45.1 Photothermal hair destruction with an 800 nm diode laser (Lightsheer®).

Figure 45.2 Detail of photothermal hair destruction with selective vaporization of hair shafts.

However, melanin in the epidermis presents a competing site for absorption. Cooling of the epidermis before and during laser exposure has been shown to minimize epidermal injury. Cooling can be done by various means, including ice [18], a cooled gel layer [19], a cold glass window [20], a cold sapphire window [21,22], or a pulsed cryogen spray [23].

Laser pulse width (exposure duration) also plays an important role, as suggested by thermal transfer theory [24].

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Thermal conduction during the laser pulse heats a region around each microscopic site of optical energy absorption. The spatial scale of thermal confinement and resulting thermal or thermomechanical damage is therefore strongly related to laser pulse width. Q-switched (ns domain) laser pulses effectively damage individual pigmented cells within hair follicles by confinement of heat at the spatial level of melanosomes [25], leading, in animals, to leukotrichia but not to hair loss [26]. Consistent with this behavior, permanent hair loss has not been reported in humans after Q-switched laser treatments, despite a decade of using Q-switched ruby and Nd:YAG lasers widely for tattoo removal.

In theory, the optimal pulse duration for selective photothermolysis is approximately equal to the thermal relaxation time of the target structure. Thermal relaxation of human terminal hair follicles has never been measured but is estimated to range from about 10 to 100 ms [17,24], depending on the size. The optimal pulse duration should be longer than the estimated epidermal thermal cooling time (3–10 ms) and close to the hair follicle time (10–100 ms) [17].

Anatomically, the chromophore (melanin in the hair-shaft) and the target structure (bulge cells in the follicular epithelium) are separated. Therefore, the extended photothermolysis theory suggests that even longer pulse durations may increase the efficacy for destruction of coarse, terminal hair, by allowing thermal conduction throughout the follicular epithelium during each laser pulse. This conduction in the perifollicular area reaches stem cells in the bulge area and, thus, could favor the destruction of these cells [27].

Lasers and intense pulsed light follow the photothermal destruction principle. The efficacy of intense pulsed light, diode, and alexandrite lasers was studied in 232 patients with phototypes from II to IV. After 6 months, an excellent hair reduction was seen, with no significant differences among devices (intense pulsed light 66.9%, alexandrite 68.7%, diode 71.7%) [28].

Photomechanical hair destruction has been obtained with a very short pulse duration (nanoseconds) with Q-switched Nd:YAG (1064 nm) laser, with or without carbon suspension [29–31]. When these very short pulses are used to damage hair follicles, a fast chromophore (melanin) heating occurs, causing a photoacoustic shock wave. This process causes bulbar melanocyte destruction but does not destroy the hair follicle, since there is no time enough for the thermal energy to diffuse and reach target cells, this being clinically translated into a transient hair removal. The combination of a switched 1064 nm laser and an exogenous chromophore (carbon particles) may have a clinical benefit of inducing temporary hair removal for fine nonpigmented hairs [32,33].

Photochemical destruction is carried out through photodynamic therapy. The use of light along with a photosensitizer produces a photochemical reaction, thus allowing the therapeutic effect. Topical aminolevulinic acid (ALA) is a precursor in porphyrin synthesis, being converted in protoporphyrin IX (PPIX) by epidermis and follicular epithelium-derived cells. Hair removal with ALA was shown through a study evidencing hair loss by about 40% in 12 volunteers after a single exposure to light at 630 nm, 3 hours after ALA 20% skin application [34]. Because of substantial epidermal PPIX accumulation, these outcomes are obtained solely by using a great amount of energy, causing great pain and side effects. Further optimization of selective PPIX accumulation in hair follicles and/or sebaceous glands is being investigated [34].

FACE AND BODY EPILATION INDICATIONS AND CONTRAINDICATIONS

Seeking face or body epilation may be related to unwanted hair growth associated to various etiologies or simply to the wish of aesthetically removing hair in normal areas.

Laser and intense pulsed light hair removal is efficient for dark and thick hair; however, it is almost nonefficient for vellus hair. Major parameters, such as skin color and hair type, indicate the best system to be used and the best patient response to treatment (Table 45.3). Fairer skin and darker and thicker hair, in addition to areas such as the groin and axillae, show the best outcomes [1]. White, blond, and light hair show lack of melanin; therefore, these are not a good indication for the treatment, especially if accompanied by a darker skin [1]. Red hair do not respond well to treatment either.

Proper patient selection, preoperative preparation, informed consent form, and understanding laser and light source safety principles are key to treatment success [1,36,37].

It is very important to gather medical history so as to assess patients' expectations, hormone changes, the nature of the drugs being used, history of scars, local infections, and history of recent sunlight exposure (Table 45.4) [1,36,37]. Contraindications for laser hair removal are listed in Table 45.5.

Hirsutism is characterized by an excessive terminal hair growth in women, in anatomical sites with characteristic male

Table 45.3 Indications and Expected Efficacy for Lasers and Light Sources

Laser or light source	Phototype	Hair color	Hair diameter
Long-pulse ruby	I–III	Dark to light brown	Thick and thin
Alexandrite	I–IV	Dark to medium brown	Thick and thin
Diode	I–V	Dark to medium brown	Thick (thin[a])
Long-pulse Nd:YAG	I–VI	Dark	Thick (thin[a])
Q-switched Nd:YAG	I–VI	All	All
Intense pulsed light	I–VI	Dark to light brown	Thick

[a]Provided that system has short pulse durations with high fluence capacity.

Table 45.4 Medical History Assessment

Medical history: precautions

• Presence of conditions that may cause hirsutism and hypertrichosis:
  • Hormone
  • Family
  • Drug
  • Tumor

• History of local or recurrent skin infection
• History of herpes simplex, especially perioral
• History of genital herpes, key when treating the pubic area
• History of keloids/hypertrophic scar
• History of diseases such as vitiligo and psoriasis
• Recent tan or exposure to artificial tanning
• Photosensitizing drugs
• Sunburn

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Table 45.5 Contraindications for Using Laser

Contraindications
• Sudden onset of hirsutism or hypertrichosis without proper investigation
• Herpes simplex virus active infection in the area to be treated
• Pregnancy
• Use of gold salts
• Recent use of high-dose isotretinoin

distribution, including the mustache, beard, chest, and inner thigh (Figures 45.3 and 45.4). Increased hair growth seen in hirsute women is often triggered by an endocrine disorder characterized by hyperandrogenemia, the most common cause being polycystic ovary syndrome. Hypertrichosis is a disorder characterized by generalized and excessive growth of abnormal dark and long hair for the age, gender, and race, in areas usually rich in vellus hair. Acquired hypertrichosis; some metabolic diseases, such as hypothyroidism and porphyrias; or nutrition diseases, such as anorexia, malnutrition, or malabsorption syndromes may be caused by drug intake; Both hirsutism and hypertrichosis may be congenital or iatrogenic in nature and should be investigated for their etiology before treatment [38].

Figure 45.3 Pretreatment hirsutism with diode laser.

Figure 45.4 Results post treatment (3-year follow-up).

Figure 45.5 Groin pseudofolliculitis.

For patients with recurrent staphylococcal infection and herpes simplex, a proper prophylaxis is indicated, aiming at decreasing the probability of a new outbreak. The history of keloids or hypertrophic scars is not a contraindication for the treatment, but subjects with these conditions are treated less aggressively. While it has been reported that laser treatment for patients on oral isotretinoin would be safe, the issue is still controversial and, for caution, a 6-month period after ending the drug should be awaited to start the treatment for highly dosed patients. Topical retinoids and hydroquinone used in the treatment area may be stopped 2 days before the laser if there is skin irritation [1,36,37].

Hormone imbalances, such as polycystic ovary or menopause, in addition to drugs such as penicillamine, phenytoin, cyclosporine, and cortisone, may stimulate hair growth, with a possibility of new hair growth. In this case, the patient should be warned on the requirement of maintenance treatments [1,36,37].

Patients with vitiligo and psoriasis should be warned for the risk of the Köebner phenomenon after laser treatment [36,37,39].

Sunlight exposure should be avoided for a month before the procedure. Fair-skinned patients may be safely treated with any device, but tanned patients are advised to avoid treatment until the tan disappears, although devices with ultralong pulse durations may be safe options for tanned skins, bearing in mind that efficacy in these cases is lower and the pain is greater [36,37].

Chronic pseudofolliculitis (Figures 45.5 and 45.6), common in groin and leg areas of women and beard of men, is an excellent indication for treatment [40–43].

PATIENT EXPECTATIONS AND OUTCOME

Expectations and goals can be very different for each patient: temporary versus permanent and partial versus complete hair removal. All responses are clinically significant and may be separately desirable for different patients. Growth delay that

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 45.6 Pseudofolliculitis in beard region.

provides a few months of hairless skin is far more reliable. All laser systems have been shown to temporarily reduce hair growth. It occurs for all hair colors (except white) and at all fluences. Blonde-, red-, or gray-haired patients are unlikely to experience a long-term reduction, but hair loss in these patients can be maintained by treatment at approximately 1–3-month intervals.

Effectiveness for permanent hair reduction is strongly correlated with hair color and fluence. Research has shown that the ideal patient is the one with fair skin and dark hair [44]. A critical threshold fluence is also needed to obtain this effect. Currently, there are a number of options of lasers and light sources used for photoepilation. Research has shown that the average long-term hair loss per treatment is about 20%–30%. Multiple treatment sessions are therefore usually required to achieve the maximal level of hair reduction [45–48].

AREAS TO BE TREATED: REMARKS

The face is the most commonly treated area, both for beard removal in men and for unwanted hair in women [11,49].

Beard removal in men is challenging since the hair is thick and dense and a great amount of laser energy is absorbed, creating great heat and making the procedure quite uncomfortable [40–43].

Chest and breast hair in women are related to hormonal issues or racial predispositions but respond well to laser therapy [50]. Chest, abdominal, and dorsal back hair in men are dense and very sensitive, several times requiring topical anesthetics for treatment. Good efficacy has been obtained in these areas [51–54].

In axillae, hair follicles tend to respond better than in other body areas [50]. Patients tolerate well in this area since the treatment time is short and the area to be treated is small.

Groin hair respond quite well to treatment; furthermore, all areas may be treated, including perianal area. This area is usually more pigmented; thus, a higher wavelength is indicated for use in darker areas.

For leg hair, the response is good for both men and women [55,56]. Bone areas, including toes, feet, legs, and ankles, tend to be more sensitive.

Arms may have hair too thin or too thick, and the treatment efficacy will depend on the pulse duration and the presence of melanin in hair.

Ear and nose hair areas are treated safely by using a tip with a smaller diameter.

PREOPERATIVE AND POSTOPERATIVE CARE

Tools to measure the skin color in order to determine which laser or intense pulsed light technology may be used safely can be utilized [57]. Lasers with longer wavelength are deemed the safest for darker skin types [58,59]. Moreover, epidermal cooling decreases the odds of thermal injury, allowing the use of larger and more efficient fluences [1,18–23].

The area to be treated should be shaved due to the risk of skin burn and interference with laser energy absorption. Research has shown greater hair loss at shaved versus epilated sites, suggesting that light absorption by the pigmented hair shaft itself plays an important role [60]. Patients seeking for best outcomes should therefore avoid plucking hair through methods such as wax or electrolysis. Shaving and the use of epilation creams do not interfere with epilation outcomes [36,37].

Lidocaine cream may be used to reduce discomfort, being applied onto the area to be treated at least 30 minutes before the procedure [36,37,61].

If hair removal is planned in sun-exposed sites, it is recommended to avoid sunlight, in addition to applying a broad-spectrum sunscreen. Clarifying formulas with hydroquinone combined or not with retinoic acid and hydrocortisone may be prescribed for patients with darker skin or those recently exposed to sunlight [36,37].

After treatment, especially when effective fluence has been utilized, erythema and perifollicular edema are expected in the treated area (Figures 45.7 and 45.8); however, this reaction is less intense when superlong pulse duration is used. Cold dressings reduce postoperative pain, erythema, and edema. Using analgesics and corticoids decrease the pain and postinflammatory hyperchromia [62]. Refrain from pulling out crusts and avoid direct sunlight exposure. Damaged hair usually falls within the first weeks after treatment [1,36,37].

Figure 45.7 Postlaser erythema and perifollicular edema.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 45.8 Postlaser perifollicular edema.

Figure 45.9 Protection goggles.

PREOPERATIVE AND POSTOPERATIVE REMARKS

- A proper anamnesis should be carried out.
- A physical exam is performed to determine skin color, as well as hair color, diameter, and density.
- Instructions should be given to patients on care to be taken prior to treatment (e.g., clarifiers and sunscreen), as well as side effect risks (e.g., paradoxical hair increase in teenagers' facial sides), special attention to patients with unreal expectations.
- Procedures (treatment) are determined per skin and hair characteristics.
- Specific posttreatment care should be preferably provided in writing.

POTENTIAL RISKS FROM LASERS

The primary risk related to laser hair removal devices is from involuntary exposure to laser emission. Exposure may occur directly from the laser to the subject or from a beam reflected by a bright surface, such as a mirror, a ring, etc. The highest risk biological targets are eyes and skin, both for the client and for the operator performing laser hair removal procedures [36,37].

Hair removal laser radiation passes easily through cornea and eye lenses and is focused into the retina, creating a great amount of energy to be absorbed by a very small retinal area. The energy and/or potency per area unit on the retina may be increased by 10,000–100,000 times; therefore, retinal burn and other tissues around the impact area occur immediately. Consequently, it is extremely important that all who walk through or pass by the laser room wear specific protection goggles [36,37] (Figure 45.9).

Studies have shown that high potency lasers (classes 3B and 4) used to treat human tissues produce toxic gases and fumes, in addition to viruses that may also be released in the air. Other types of risk may exist, including electric shocks and light dispersion (all mirrors and windows of the procedure room should be covered) [63–65].

Esse é o mecanismo de atuação dos principais *lasers* e luz intensa pulsada Esse é o mecanismo de atuação dos principais *lasers* e luz intensa pulsada Diversas variantes devem ser consideradas ao se determinar se o tratamento à base Diversas variantes devem ser consideradas ao se determinar se o tratamento à base Parte inferior do formulário

POSTPROCEDURAL COMPLICATIONS

The most common side effects are pigmentary changes such as hypopigmentation or hyperpigmentation. It can be prevented if appropriate treatment fluences are chosen for a certain skin type. This problem is mostly seen in patients with darker skin types or when patients have had a recent tan [66–68].

Other posttreatment adverse effects include edema, erythema, scaling, blistering, scars, folliculitis, leukotrichia [69,70], livedo reticularis [71], pruritus, and urticaria [72,73], in addition to herpes outbreaks in patients with previous history.

The risk of bacterial infections is extremely low, but these may occur if the epidermis is damaged. Folliculitis may occur in treated areas after excessive sweating and intense physical exercise [70].

Scars are extremely rare, but these may occur when excessive energies are used [74].

Rare cases of paradoxical hypertrichosis (hair growth induction) were seen in several areas, but those are more frequent at the side of the face of young women with Fitzpatrick's phototype III or IV; these patients usually do not have a well-outlined hairline (Figure 45.10) [70,75–79]. The precise mechanism of paradoxical hair growth is unknown, but it is speculated that subtherapeutic thermal injury may cause induction and stimulation of the hair cycle. Subsequent application of cold packs surrounding the treatment area during treatment and treating the area with two passes has minimized the incidence of hair growth stimulaton [76].

Eye complications were reported with the treatment in areas close to the eyes; therefore, patients should wear a proper eye protector. There are reports of irreversible cataracts, atrophy, and iris synechiae in eyebrow epilation [80–86].

When treating areas close to tattoos [87,88], caution should be taken to avoid a possible color change or scar injury after treatment with laser or intense pulsed light at the site.

Exposure of melanin-containing skin lesions, especially congenital melanocytic nevi and dysplastic nevi, to laser and

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 45.10 Paradoxical hypertrichosis.

IPL should be avoided because of the risk of burn and potential scarring. Moreover, there has been a report of the appearance of clinically atypical nevi when nevus cells were treated in areas previously treated for hair removal. This should be kept in mind, especially in patients with the history of dysplastic nevi or with the personal or family history of malignant melanoma [89]. It is therefore advisable to avoid treating skin for hair removal when melanocytic nevi are present in this area.

IMPORTANT REMARKS

- Melanin is the target chromophore for hair removal.
- Identify endocrine changes before treatment.
- Delay the treatment in tanned skins.
- Multiple treatments may be required.
- Do not wax the area to be treated.
- Photograph areas before shaving.
- The informed consent form should be provided.
- Use sunscreens with a high protection factor.
- Skin whitening before treatment reduces pain and complications.
- Never use a dark marker onto the skin, since this may be absorbed by the laser.
- In brunette skins, perform a previous test to increase the procedure safety.
- Eye protection is mandatory for both the physician and the patient.
- Do not treat within periocular bone border.
- In case of epidermal injury, cooling should be increased and/or the energy level should be decreased and/or the pulse duration should be increased.
- Special care in pigmented genital areas.
- Use the highest amount of safe energy for best results.

CONCLUSIONS

With the progress of new technologies for hair removal through laser and pulsed light, the outcomes have become better and the treatment has become safer. For fair skin patients (phototypes I–III) and dark hair, all epilation systems available in the market may be used. However, for patients with darker phototypes (IV–VI), longer wavelengths and longer pulse durations should be used, in addition to skin cooling systems, thus increasing treatment safety. Although diode and alexandrite lasers may be used in such patients, Nd:YAG is deemed the safest laser for darker skin.

Laser epilation has currently become an accessible, fast, and less painful method, with less side effects. The main challenges with laser technology include advances to treat all hair types, lower number of sessions and pain-free treatments, and safe and cheaper equipment.

REFERENCES

1. Ibrahimi OA, Avram MM, Hanke CW, Kilmer SL, Anderson RR. Laser hair removal. *Dermatol Ther* 2011; 24:94–107.
2. Haedersdal M, Beerwerth F, Nash J. Laser and intense pulsed light hair removal technologies: From professional to home use. *Br J Dermatol* 2011; 165:31–36.
3. Olsen EA. Methods of hair removal. *J Am Acad Dermatol* 1999; 40:143–155.
4. Nouri K, Trent JT. Lasers. In: Nouri K, Leal-Khouri S, eds. *Techniques in Dermatologic Surgery*. St. Louis, MO: Mosby, 2003, Vol. 29, pp. 245–258.
5. Lipton MG, Sherr L, Elford J, Rustin MH, Clayton WJ. Women living with facial hair: The psychological and behavioral burden. *J Pysychosom Res* 2006; 61(2):161–168.
6. Grossman MC, Dierickx C, Farinelli W, Flotte T, Anderson RR. Damage to hair follicle by normal-mode ruby laser pulses. *J Am Acad Dermatol* 1996; 35:889–894.
7. Gold MH. Lasers and light sources for the removal of unwanted hair. *Clin Dermatol* 2007; 25(5):443–453.
8. Anderson RP, Parrish JA. Selective photothermolysis: Precise microsurgery by selective absorption of pulsed radiation. *Science* 1983; 220:524–527.
9. Serrano-Grau P, Campo-Voegeli A, Romero D. Fotodepilación. *Actas Dermosifiliogr* 2009; 100:351–361.
10. McGill DJ, Hutchison C, McKenzie E, McSherry E, Mackay IR. A randomised, split-face comparison of facial hair removal with the alexandrite laser and intense pulsed light system. *Lasers Surg Med* 2007; 39(10):767–772.
11. Lapidoth M, Dierickx C, Lanigan S, Paasch U, Campo-Voegeli A, Dahan S, Marini L, Adatto M. Best practice options for hair removal in patients with unwanted facial hair using combination therapy with laser: Guidelines drawn up by an expert working group. *Dermatology* 2010; 221(1):34–42.
12. Campos VB, Dierickx CC, Farinelli WA, Lin TY, Manuskiatti W, Anderson RR. Hair removal with an 800-nm pulsed diode laser. *J Am Acad Dermatol* 2000; 43(3):442–447.
13. Haedersdal M, Wulf HC. Evidence-based review of hair removal using lasers and light sources. *J Eur Acad Dermatol Venereol* 2006; 20(1):9–20.
14. Vachiramon V, Brown T, McMichael AJ. Patient satisfaction and complications following laser hair removal in ethnic skin. *J Drugs Dermatol* 2012; 11(2):191–195.
15. Thaysen-Petersen D, Bjerring P, Dierickx C, Nash J, Town G, Haedersdal M. A systematic review of light-based home-use devices for hair removal and considerations on human safety. *J Eur Acad Dermatol Venereol* 2012; 26(5):545–553.
16. Town G, Ash C, Dierickx C, Fritz K, Bjerring P, Haedersdal M. Guidelines on the safety of light-based home-use hair removal devices from the European Society for Laser Dermatology. *J Eur Acad Dermatol Venereol* 2012; 26(7):799–811.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

17. Anderson RP. Laser-tissue interactions. In: Goldaman MP, Fitzpatrick RE, eds. *Cutaneous Laser Surgery: The Art and Science of Selective Photothermolysis*. St. Louis, MO: Mosby, 1994, pp. 1–18.
18. Gilchrest BA, Rosen S, Noe JM. Chilling portwine stains improves the response to Argon laser therapy. *Plast Reconstr Surg* 1982; 69:278–283.
19. Lask G, Elman M, Slatkine M, Waldman A, Rozenberg Z. Laser-assisted hair removal by selective photothermolysis. *Dermatol Surg* 1997; 23:737–739.
20. Chess C, Chess Q. Cool laser optics treatment of large telangiectases of the lower extremities. *J Dermatol Surg Oncol* 1993; 19:74–80.
21. Zenzie HH, Altshuler GB, Smirnov MZ, Anderson RR. Evaluation of cooling methods for laser dermatology. *Lasers Surg Med* 2000; 26(2):130–144.
22. Altshuler GB, Zenzie HH, Erofeev AV, Smirnov MZ, Anderson RR, Dierickx C. Contact cooling of the skin. *Phys Med Biol* 1999; 44(4):1003–1023.
23. Nelson JS, Milner TE, Anvari B, Tanenbaum S, Kimel S, Svaasland L, Jacques S. Dynamic epidermal cooling during pulsed laser treatment of port-wine stain. *Arch Dermatol* 1995; 131:695–700.
24. Van Gemert MJC, Welch AJ. Time constants in thermal laser medicine. *Lasers Surg Med* 1989; 9:405–421.
25. Anderson RR, Margolis RJ, Watanabe S et al. Selective photothermolysis of cutaneous pigmentation by Q-switched Nd-YAG laser pulses at 1064, 532 and 355 nm. *J Invest Dermatol* 1989; 93:28–32.
26. Dover JS, Margolis RJ, Polla LL et al. Pigmented guinea pig skin irradiated with Q-switched ruby laser pulses: Morphologic and histologic findings. *Arch Dermatol* 1989; 125:43–49.
27. Altshuler GB, Anderson RR, Manstein D, Zenzie HH, Smirnov MZ. Extended theory of selective photothermolysis. *Lasers Surg Med* 2001; 29(5):416–432.
28. Toosi P, Sadighha A, Sharifian A, Razavi GM. A comparison study of the efficacy and side effects of different light sources in hair removal. *Lasers Med Sci* 2006; 21(1):1–4.
29. Rogers CJ, Glaser DA, Siegfried EC, Walsh PM. Hair removal using topical suspension-assisted Q-switched Nd:YAG and long-pulsed alexandrite lasers: A comparative study. *Dermatol Surg* 1999; 25(11):844–850.
30. Nanni CA, Alster S. Optimizing treatment parameters for hair removal using a topical carbon-based solution and 1064-nm Q-switched neodymium:YAG laser energy. *Arch Dermatol* 1997; 133(12):1546–1549.
31. Goldberg DJ, Littler CM, Wheeland RG. Topical suspension-assisted Q-switched Nd:YAG laser hair removal. *Dermatol Surg* 1997; 23(9):741–745.
32. Littler CM. Laser hair removal in a patient with hypertrichosis lanuginosa congenita. *Dermatol Surg* 1997; 23(8):705–707.
33. Bakus AD, Garden JM, Yaghmai D, Massa MC. Long-term fine caliber hair removal with an electro-optic Q-switched Nd:YAG laser. *Lasers Surg Med* 2010; 42(8):706–711.
34. Grossman MC, Wimberely J, Dwyer P, Flotte TJ, Anderson RR. PDT for hirsutism. *Lasers Surg Med* 1995; S7:44.
35. Sakamoto FH, Doukas AG, Farinelli WA, Tannous Z, Su Y, Smithj NA, Zurakowski D, Anderson RR. Intracutaneous ALA photodynamic therapy: Dose-dependent targeting of skin structures. *Lasers Surg Med* 2011; 43(7):621–631.
36. Drosner M, Adatto M. Photo-epilation: Guidelines for care from the European Society for Laser Dermatology (ESLD). *J Cosmet Laser Ther* 2005; 7:33–38.
37. Casey AS, Goldberg D. Guidelines for laser hair removal. *J Cosmet Laser Ther* 2008; 10:24–33.
38. Bode D, Seehusen DA, Baird D. Hirsutism in women. *Am Fam Physician* 2012; 85(4):373–380.
39. Sellheyer K. Mechanisms of laser hair removal: Could persistent photoepilation induce vitiligo or defects in wound repair? *Dermatol Surg* 2007; 33:1055–1065.
40. Emer JJ. Best practices and evidenced-based use of the 800 nm diode laser for the treatment of pseudofolliculitis barbae in skin of color. *J Drugs Dermatol* 2011; 10(12 Suppl.):s20–s22.
41. Schulze R, Meehan KJ, Lopez A, Sweeney K, Winstanley D, Apruzzese W, Ross E. Low-fluence 1,064-nm laser hair reduction for pseudofolliculitis barbae in skin types IV, V, and VI. *Dermatol Surg* 2009; 35(1):98–107.
42. Smith EP, Winstanley D, Ross EV. Modified superlong pulse 810 nm diode laser in the treatment of pseudofolliculitis barbae in skin types V and VI. *Dermatol Surg* 2005; 31(3):297–301.
43. Kauvar AN. Treatment of pseudofolliculitis with a pulsed infrared laser. *Arch Dermatol* 2000; 136(11):1343–1346.
44. Liew SH, Ladhani K, Grobbelaar AO, Gault DT, Sanders R, Green CJ, Linge C. Ruby laser-assisted hair removal success in relation to anatomic factors and melanin content of hair follicles. *Plast Reconstr Surg* 1999; 103(6):1736–1743.
45. Gan SD, Graber EM. Laser hair removal: A review. *Dermatol Surg* 2013; 39(6):823–838.
46. Haedersdal M, Matzen P, Wulf HC. Laser epilation: A systematic review of evidence-based clinical results. *Ugeskr Laeger* 2000; 162(50):6809–6815.
47. Haedersdal M, Wulf HC. Evidence-based review of hair removal using lasers and light sources. *J Eur Acad Dermatol Venereol* 2006; 20(1):9–20.
48. Haedersdal M, Gøtzsche PC. Laser and photoepilation for unwanted hair growth. *Cochrane Database Syst Rev* 2006; 18(4):CD004684.
49. Haak CS, Nymann P, Pedersen AT, Clausen HV, Feldt Rasmussen U, Rasmussen AK, Main K, Haedersdal M. Hair removal in hirsute women with normal testosterone levels: A randomized controlled trial of long-pulsed diode laser vs. intense pulsed light. *Br J Dermatol* 2010; 163(5):1007–1013.
50. Kutluba Z. Alexandrite laser hair removal results in 2359 patients: A Turkish experience. *J Cosmet Laser Ther* 2009; 11(2):85–93.
51. McDaniell DH, Lord J, Ash K, Newman J, Zukowski M. Laser hair removal: A review and report on the use of the long-pulsed alexandrite laser for hair reduction of the upper lip, leg, back, and bikini region. *Dermatol Surg* 1999; 25(6):425–430.
52. Xia Y, Moore R, Cho S, Ross EV. Evaluation of the vacuum-assisted handpiece compared with the sapphire-cooled handpiece of the 800-nm diode laser system for the use of hair removal and reduction. *J Cosmet Laser Ther* 2010; 12(6):264–268.
53. Amin SP, Goldberg DJ. Clinical comparison of four hair removal lasers and light sources. *J Cosmet Laser Ther* 2006; 8(2):65–68.
54. Adatto M. Hair removal with a combined light/heat-based photoepilation system: A 6-month follow-up. *J Cosmet Laser Ther* 2003; 5(3–4):163–167.
55. Davoudi SM, Behnia F, Gorouhi F, Keshavarz S, Nassiri Kashani M, Rashighi Firoozabadi M, Firooz A. Comparison of long-pulsed alexandrite and Nd:YAG lasers, individually and in combination, for leg hair reduction: An assessor-blinded, randomized trial with 18 months of follow-up. *Arch Dermatol* 2008; 144(10):1323–1327.
56. Lorenz S, Brunnberg S, Landthaler M, Hohenleutner U. Hair removal with the long pulsed Nd:YAG laser: A prospective study with one year follow-up. *Lasers Surg Med* 2002; 30(2):127–134.
57. Dolotov L, Sinichkin Y, Tuchin V, Utz S, Alshuler G, Yaroslavsky I. Design and evaluation of a novel portable erythema melanin meter. *Lasers Surg Med* 2004; 34:127–135.
58. Rao K, Sankar TK. Long-pulsed Nd:YAG laser-assisted hair removal in Fitzpatrick skin types IV-VI. *Lasers Med Sci* 2011; 26(5):623.
59. Nanda S, Bansal S. Long pulsed Nd:YAG laser with inbuilt cool sapphire tip for long term hair reduction on type-IV and V skin: A prospective analysis of 200 patients. *Indian J Dermatol Venereol Leprol* 2010; 76(6):677–681.
60. Dierickx CC, Grossman MC, Farinelli WA, Anderson RR. Permanent hair removal by normal-mode ruby laser. *Arch Dermatol* 1998; 134(7):837–842.
61. Akinturk S, Eroglu A. A clinical comparison of topical piroxicam and EMLA cream for pain relief and inflammation in laser hair removal. *Lasers Med Sci* 2009; 24(4):535–538.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

62. Aldraibi MS, Touma DJ, Khachemoune A. Hair removal with the 3-msec alexandrite laser in patients with skin types IV-VI: Efficacy, safety, and the role of topical corticosteroids in preventing side effects. *J Drugs Dermatol* 2007; 6(1):60–66.
63. Laser Institute of America. American National Standard for safe use of lasers in health care facilities (ANSI Z136.3). Orlando, FL, 81pp.
64. Castelluccio D. Implementing AORN recommended practices for laser safety. *AORN J* 2012; 95(5):612–624.
65. Plauntz L. Guidelines for staff administering laser therapy in an office setting. *Plast Surg Nurs* 2013; 33(1):29–35.
66. Fontana CR, Bonini D, Bagnato VS. A 12-month follow-up of hypopigmentation after laser hair removal. *J Cosmet Laser Ther* 2013; 15(2):80–84.
67. Liew SH. Laser hair removal: Guidelines for management. *Am J Clin Dermatol* 2002; 3(2):107–115.
68. Moreno-Arias GA, Camps-Fresneda A. Long-lasting hypopigmentation induced by long-pulsed alexandrite laser photo-epilation. *Dermatol Surg* 2003; 29(4):420–422.
69. Radmanesh M, Mostaghimi M, Yousefi I, Mousavi ZB, Rasai S, Esmaili HR, Khadivi HA. Leukotrichia developed following application of intense pulsed light for hair removal. *Dermatol Surg* 2002; 28(7):572–574.
70. Radmanesh M, Azar-Beig M, Abtahian A, Naderi AH. Burning, paradoxical hypertrichosis, leukotrichia and folliculitis are four major complications of intense pulsed light hair removal therapy. *Dermatolog Treat* 2008; 19(6):360–363.
71. Lapidoth M, Shafirstein G, Ben Amitai D, Hodak E, Waner M, David M. Reticulate erythema following diode laser-assisted hair removal: A new side effect of a common procedure. *J Am Acad Dermatol* 2004; 51(5):774–777.
72. Landa N, Corrons N, Zabalza I, Azpiazu JL. Urticaria induced by laser epilation: A clinical and histopathological study with extended follow-up in 36 patients. *Lasers Surg Med* 2012; 44(5):384–389.
73. Berstein EF. Severe urticaria after laser treatment for hair reduction. *Dermatol Surg* 2010; 36(1):147–151.
74. Ainomair N, Nazarian R, Marmur E. Complications in lasers, lights, and radiofrequency devices. *Facial Plast Surg* 2012; 28(3):340–346.
75. Desai S, Mahmoud BH, Bhatia AC, Hamzavi IH. Paradoxical hypertrichosis after laser therapy: A review. *Dermatol Surg* 2010; 36(3):291–298.
76. Willey A, Torrontegui J, Azpiazu J, Landa N. Hair stimulation following laser and intense pulsed light photo-epilation: Review of 543 cases and ways to manage it. *Lasers Surg Med* 2007; 39(4):297–301.
77. Lolis MS, Marmur ES. Paradoxical effects of hair removal systems: A review. *J Cosmet Dermatol* 2006; 5(4):274–276.
78. Alajlan A, Shapiro J, Rivers JK, Macdonald N, Wiggin J, Lui H. Paradoxical hypertrichosis after laser epilation. *J Am Acad Dermatol* 2005; 53(1):85–88.
79. Bernstein EF. Hair growth induced by diode laser treatment. *Dermatol Surg* 2005; 31(5):584–586.
80. Lee WW, Murdock J, Albini TA et al. Ocular damage secondary to intense pulse light therapy to the face. *Ophthal Plast Reconstr Surg* 2011; 27(4):263–265.
81. Carrim ZI, Chohan AW, Devlin HC. Iris damage and acute pigment dispersion following photo-epilation. *Eye* 2006; 20(12):1486–1488.
82. Halkiadakis I, Skouriotis S, Stefanaki C et al. Iris atrophy and posterior synechiae as a complication of eyebrow laser epilation. *J Am Acad Dermatol* 2007; 57:S4–S5.
83. Le JM, Autie M, Monnet D et al. Ocular complications after laser epilation of eyebrows. *Eur J Dermatol* 2007; 17:553–554.
84. Herbold TM, Busse H, Uhlig CE. Bilateral cataract and corectopia after laser eyebrow [corrected] epilation. *Ophthalmology* 2005; 112(9):1634–1635.
85. Shulman S, Bichler I. Ocular complications of laser-assisted eyebrow epilation. *Eye* 2009; 23:982–983.
86. Sheikh A, Hodge W, Coupland S. Diode laser-induced uveitis and visual field defect. *Ophthal Plast Reconstr Surg* 2007; 23:321–323.
87. Riml S, Larcher L, Grohmann M, Kompatscher P. Second-degree burn within a tattoo after intense-pulsed-light epilation. *Photodermatol Photoimmunol Photomed* 2013; 29(4):218–220.
88. Kluger N, Hakimi S, Del Giudice P. Keloid occurring in a tattoo after laser hair removal. *Acta Dermatol Venereol* 2009; 89(3):334–335.
89. Soden CE, Smith K, Skelton H. Histologic features seen in changing nevi after therapy with an 810 nm pulsed diode laser for hair removal in patients with dysplastic nevi. *Int J Dermatol* 2001; 40(8):500–504.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Photodynamic therapy for aesthetic indications

Colin A. Morton, Rolf-Markus Szeimies, and Lasse R. Braathen

Photodynamic therapy (PDT) is a noninvasive therapy with proven efficacy in nonmelanoma skin cancer (NMSC) and several additional indications including photorejuvenation. PDT involves the activation of a photosensitizing drug by visible light to produce activated oxygen species within target cells, resulting in their destruction or modification, accompanied by host inflammatory and immune responses; the relative contribution of these processes to the therapeutic effect depends on treatment indication.

In this chapter, we review the efficacy of topical PDT for current indications, with emphasis on the good cosmetic outcome achieved, as well as its effectiveness in improving fine wrinkles, mottled pigmentation, sallow complexion, skin texture, tactile roughness, telangiectasias, and facial erythema. A comprehensive evidence-based review of current and emerging indications for topical PDT can be found in European and international guidelines [1–3]. PDT is currently being explored for use in certain inflammatory and infectious indications, including acne, where high quality of cosmetic outcome is typical, although protocols to maximize efficacy await optimization. Treatment is generally well tolerated, but tingling discomfort or pain is common during PDT. Alterations in the way PDT is delivered, including the use of daylight or shorter photosensitizer application times, are associated with decreased discomfort, with reports indicating maintenance of efficacy. We consider current approaches to deliver treatment and potential adverse reactions.

TOPICAL PDT: DELIVERING TREATMENT

PDT is usually performed by topical application of precursors of the heme biosynthetic pathway, in particular 5-aminolevulinic acid (5-ALA) or its ester, methyl aminolevulinate (MAL), converted within target cells into photoactive porphyrins, especially protoporphyrin IX (PpIX). After the incubation period, the light of an appropriate wavelength activates the photosensitizer, promoting the photodynamic reaction. Before light illumination, it is possible to detect skin surface fluorescence, assisting lesion delineation.

Four agents are currently licensed for use in topical PDT: a 20% formulation of 5-ALA, Levulan (DUSA Wilmington, MA), is approved in North America and certain other countries for actinic keratoses (AKs), in a protocol that uses blue light. MAL (160 mg/g, Metvix®/Metvixia®) (Galderma, Lausanne, CH) is used along with red light to treat AK, squamous cell carcinoma (SCC) *in situ* and superficial basal cell carcinoma (sBCC) and nodular basal cell carcinoma (nBCC), although approvals vary between countries. A patch containing 5-ALA (Alacare® [Galderma Spirig AG, Egerkingen, Switzerland]) is approved for the treatment of mild to moderate AK in a single treatment session in combination with red light without pretreatment of the lesion. Furthermore, for AK, a nanoemulsion (Ameluz® [Biofrontera AG, Leverkusen, Germany]) is licensed for PDT in combination with red light.

There are no current approvals specifically for the use of topical PDT in aesthetic indications, although AKs often coexist with photo-damaged skin and many operators utilize treatment protocols based on clearing AKs while observing considerable improvement in signs of photoaging as discussed in the succeeding text.

Light-emitting diode (LED) devices are commonly used for topical PDT, although a range of suitable light sources exist, including filtered intense pulsed lights (IPLs) that have been successfully used in PDT for AK, acne, and photorejuvenation. Red narrowband LED sources, with a 630/635 nm activation peak of PpIX, are commonly used with the licensed agents described earlier, although the Levulan formulation of ALA is approved for use with a blue fluorescent lamp (Blu-U™, peak emission 417 nm) for AK. IPLs emit different spectra because of different filter technologies, resulting in a need to derive specific protocols to achieve identical radiant exposures.

Recently, daylight has be used as light source for PDT with application of MAL for 0.5 hour, followed by exposure to daylight for up to 2.5 hours, proving as effective as conventional PDT in treating AK, but with only minimal therapy-related pain. Research continues to optimize wearable light sources to achieve ambulatory PDT, using by either wearing a portable LED device or wearing optical fibers in a flexible textile structure that allows uniform light distribution even in curved surfaces. Dosimetry in PDT is usually estimated from the energy fluence delivered by the light source used, although it is more strictly defined by photosensitizer dose, drug-light interval, wavelength/wave band, irradiance (mW/cm^2), and fluence (J/cm^2).

In practice, it is usual to degrease the skin, remove scales/crust, and roughen the surface of epidermis overlying lesions before applying a 1 mm thick layer of photosensitizing cream to the lesion/area to be treated, or for Levulan ALA, apply the mixed solution by gently dabbing lesions and reapplying when dry, without lesion preparation. No preparation is required when using the ALA patch to treat AK. When treating Bowen's disease, sBCC, and nBCC, it is recommended to gently remove overlying crust and scale with a curette/blade, removing the intact epidermis overlying basal cell carcinoma (BCC). The treatment area is left nonoccluded with Levulan ALA-PDT and daylight PDT but is occluded in standard MAL-PDT and nanoemulsion ALA-PDT. Incubation time of 3 hours is recommended for standard MAL-PDT and PDT using the

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

nanoemulsion of ALA, 4 hours for the ALA patch, and up to 14–18 hours for Levulan ALA-PDT, although much shorter times of 1–3 hours are commonly used in the clinic. Following incubation period, the treatment sites are exposed to light, with treatment repeated after 1 week for MAL-PDT when treating SCC *in situ* and BCC, while otherwise, it is a common practice to review patients after 6–12 weeks to assess the need for repeat treatment for AKs.

Following topical PDT, localized photosensitivity can remain for up to 48 hours, ALA degrading with a half-life of about 24 hours, and MAL-induced PpIX clearing from the normal skin within 24–48 hours; hence, suitable sunlight protection is required, which are especially important when large fields have been treated. Limiting sun exposure during the 2 weeks following field PDT may also help reduce the risk of hyperpigmentation.

ADVERSE EVENTS

Pain/burning sensation is often experienced during PDT, usually developing within minutes of commencing light exposure, and probably reflects nerve stimulation and/or tissue damage by reactive oxygen species, possibly aggravated by hyperthermia. Most patients tolerate PDT without specific need for pain relief nor pause in illumination, but pain is more likely to be experienced if large fields are treated and is more common when treating AK than SCC *in situ*/BCC and, hence, should be anticipated when treating large facial fields containing multiple AK. Patients with sensitive skin types appear more prone to pain. It remains unclear whether there is a significant difference in pain experienced on account of photosensitizer used, with contradictory study results, and additional factors often make direct comparison difficult.

To date, topical anesthetics have not been shown to reduce pain significantly during PDT, but nerve blocks and cold air analgesia are effective, which are especially useful for large field treatment. Cold air analgesia, using a device to blow air at a temperature of –35°C, reduces pain duration and severity although cooling may slow down the photodynamic reaction. PDT using low-intensity light (daylight, ambulatory) is much less painful but results in prolonged treatment times, with a daylight PDT requiring favorable weather conditions to permit patient comfort as well as achieve PpIX-weighted daylight doses above 8 J/cm^2 and a maximum daytime temperature of 10°C to permit effective treatment. During conventional PDT, reduced pain during illumination has been observed when using a variable pulsed light or visible light plus water-filtered infrared A.

Erythema and edema are common post-PDT, with erosion, crust formation, and healing over 2–6 weeks. To avoid risk of UV-induced erythema, initial widespread application of an organic sunscreen (with an absorption spectrum that does not significantly overlap that of PpIX) is required, approximately 15 minutes later by lesion preparation. Urtication of treatment sites is rare and is probably an exaggeration of the normal inflammatory response to PDT. Postinflammatory hypo- and hyperpigmentation or clinically obvious scar formation are rarely observed when using PDT for approved indications. Hair loss is also possible, given concomitant sensitization of pilosebaceous units, but is more often observed focally with PDT for BCC than AK. There is a small risk of sensitization to the photosensitizer that might give an exaggerated response to patients receiving further PDT with the same drug formulation.

The long-term safety of PDT is encouraging with many thousands of patients treated by topical PDT over 20 years and little evidence to indicate risk of progression from sublethal injury to target cells. Case reports of melanoma within the field of previous PDT and of SCC developing following PDT for penile intraepithelial neoplasia could represent evidence of progression, but the melanomas may well have arisen coincidentally and the SCC development be due to incomplete response of a penile intraepithelial neoplasm. An observation that PDT might promote a more aggressive histological pattern of residual BCC is confounded by recognizing sampling error in biopsies, with no supportive evidence from several large studies with a 5-year follow-up.

PDT FOR ACTINIC KERATOSES

Thin and moderate-thickness AKs respond well to topical PDT, with initial clearance rates of 89%–91% approximately 3 months following therapy. Treatment-specific guidelines identify PDT as effective both as a lesion and field-directed treatment and suggest PDT has a role where AKs are multiple/clustered, at sites of poor healing, or where there has been a poor response to other topical therapies [4].

The favorable cosmetic outcome at sites of PDT for AK has been widely reported and best exemplified in intraindividual comparison studies. A randomized intraindividual study of 1501 face/scalp AK in 119 patients used this protocol to compare MAL-PDT with cryotherapy [5]. After the initial cycle of treatments, PDT resulted in a significantly higher cure rate than cryotherapy (87% versus 76%), but with equivalent outcome after nonresponders were retreated (89% vs. 86%). Investigators significantly preferred MAL-PDT over cryotherapy for cosmetic outcome (43% vs. 12%) and patients also significantly favored PDT over cryotherapy for overall outcome (cosmesis, efficacy, and skin discomfort; 49% versus 21%). In a U.S. multicenter study of MAL-PDT for AK, a good or excellent cosmetic outcome was recorded by the investigator in 97% of patients [6].

ALA-PDT using the BF-200 nanoemulsion has been shown to be superior to MAL in clearing thin and moderate-thickness AK from the face/scalp in patients with multiple AK, with clearance rates of 90% versus 83% of lesions (respective complete clearance rates of 78% vs. 64%) 12 weeks after one or two PDT treatments [7]. The cosmetic outcome was similar between ALA-PDT and MAL-PDT with a good/very good cosmesis grading in 43% and 45% subjects, respectively.

ALA-PDT using the self-adhesive patch cleared 82%–89% of mild or moderate AK in patients with 3–8 face/scalp lesions, superior to the 77% clearance rate in a comparator group receiving cryotherapy [8]. Twelve months after the single treatment, patch ALA-PDT remained superior in efficacy and cosmesis, with 31% of cryotherapy lesion sites still hypopigmented compared with 0%–3% of the PDT treatment sites [9].

Topical PDT is less effective for AK on acral sites, probably in part due to a higher proportion of thicker lesions on these sites, which remains an off-label indication.

PDT FOR BOWEN'S DISEASE (SQUAMOUS CELL CARCINOMA *IN SITU*)

Review of studies indicates clearance rates of 88%–100% for Bowen's disease (SCC *in situ*) 3 months after topical PDT, with 53%–89% of the treated lesions remaining clear over follow-up

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

periods of 17–60 months [2]. Topical PDT has been reported to clear digital, subungual, and Bowen's disease of the nipple and where it arises in a setting of poor healing (lower leg, epidermolysis bullosa, and radiation dermatitis).

In the largest comparison study reported, MAL-PDT using a broadband red light was compared with clinician's choice of cryotherapy or 5-fluorouracil in a large European study of 225 patients with 275 SCC *in situ* [10]. The lesion's complete response rates 3 months after the last treatment (1–2 treatment cycles) were similar with all regimens (93% for MAL-PDT, 86% for cryotherapy, 83% for 5-fluorouracil), but PDT gave superior cosmetic results. Cosmetic outcome at 3 months was good or excellent in 94% of patients treated by PDT compared with 66% with cryotherapy and 76% following 5-fluorouracil. Although 1-year sustained lesion clearance rates showed MAL-PDT to be superior to cryotherapy, rates for all three therapies were similar after 2 years with 68% of lesions cleared following PDT, 60% after cryotherapy, and 59% after 5-fluorouracil.

Red narrowband LED light is used most often for PDT treatment of SCC *in situ*; however, organic LEDs have been used in ambulatory PDT for small plaques of SCC *in situ* as well as sBCCs with an overall 84% response rate at 1 year [11].

PDT is a good treatment option, especially for both large and small plaques of Bowen on poor healing sites, representing the majority of lesions. Due to reduced efficacy of PDT for microinvasive and for nodular-invasive SCC, PDT currently cannot be recommended.

PDT FOR BASAL CELL CARCINOMA

MAL is currently the only photosensitizing agent approved for the treatment of sBCC and/or nBCC and is indicated where a patient is unsuitable for other available therapies due to possible treatment-related morbidity and poor cosmetic outcome.

Initial clearance rates are high for patients receiving PDT for primary sBCC, with 92%–97% 3 months after the last treatment and a 9% 1-year recurrence rate [12,13]. Clearance rates were equivalent when MAL-PDT was compared with cryotherapy for the treatment of sBCC, having 97% and 95% at 3 months, respectively, with overall clearance after 5 years identical at 76% of lesions initially treated, but more patients had an excellent cosmetic outcome following PDT (60% vs. 16%). In a comparison of PDT with excision surgery, efficacy rates were again comparable, but cosmetic outcome was superior—with 94% PDT treatment sites with excellent or good cosmetic outcome compared with 60% of surgical sites [13].

MAL-PDT cleared 93% of thin nBCC 3 months after treatment but was inferior to excision when recurrence rates are compared (14% and 4% recurrences at 5 years) [14]. Cosmetic outcome is superior following PDT compared with surgery, with 87% of the patients experiencing good or excellent cosmesis at 5 years compared with 54% following surgery.

ALA-PDT, although not currently licensed for treating BCC, has been widely used, with similar high efficacy to surgery in a recent comparison with simple excision, both therapies clearing 96% of lesions (sBCC and nBCC), with 2 lesions recurring in each group over 12 months. Cosmetic outcome was superior with 100% of PDT-treated patients having a good or excellent outcome at 12 months, compared with 89% following surgery [15].

Responsiveness of BCC is influenced by lesion thickness, with reduced efficacy and increasing tumor thickness. Lesion preparation is probably more important when treating BCC than AK by PDT, with a removal of intact epidermis overlying lesion advised in the treatment protocol. However, it is considered important for subsequent cosmesis that any debulking using a curette or blade should not extend beyond the rim of the lesion and, hence, promote a surgical scar. Lesions in the H-zone also have reduced sustained clearance rates.

Topical PDT is a good treatment for primary sBCC, but given that recurrence rates for nBCC are higher than surgery, PDT is best considered only for thin nodular lesions where surgical excision is relatively contraindicated or where patient preference, reflecting past therapy history, comorbidities, and/or cosmetic considerations, results in a willingness to accept higher risk of recurrence. PDT should not be used for high-risk BCC, including morphoeic subtype. As a nonsurgical therapy, review of patients for at least 1-year post-PDT for BCC is recommended.

Scar vascularity and pigmentation are the most predictive aspects of skin appearance determining physicians' opinion on cosmesis, while scar color is most important for the patient in aesthetic evaluation following noninvasive treatments for sBCC including PDT [16].

PDT FOR FIELD CANCERIZATION/ MULTIPLE NMSC

The presence of multiple NMSC, AK, dysplastic keratinocytes in sun-exposed areas, and field cancerization reflects the presence of multilocular clinical and subclinical cancerous lesions. PDT, with its selective sensitization and destruction of diseased tissue, is a good treatment option, permitting an office-based treatment where compliance is assured, with a shorter period of therapy-induced inflammation compared with prolonged application of drugs such as imiquimod, 5-fluorouracil, or diclofenac sodium (Figure 46.1) [17]. A recent consensus noted that PDT in field cancerization might also prevent new AKs and transformation of AK to invasive SCC in a secondary prevention strategy in organ transplant recipients, proposing cyclic PDT with at least two initial treatments repeated several times over a year, possibly at 3-month intervals [18]. The preventive potential of field PDT appears relevant also in the immunocompetent, with a single treatment of topical ALA-PDT to photo-damaged patients with facial AK, demonstrating a significant delay of about 6 months until new AK develops [19]. PDT can decrease expression of p53, a marker of early skin cancer, supporting its preventive indication in carcinogenesis [20,21].

PDT FOR HYPERTROPHIC AND KELOID SCARS

In addition to the overall high quality of cosmesis following PDT, there are reports of improvement in appearance of preexisting scars following PDT. Following PDT for field cancerization, significant improvement in the appearance of hypertrophic scars was observed in a small study of six patients after two to three PDT treatments [22]. Similar results were reported in further eight patients with hypertrophic scars, with marked improvement in five [23]. The effect of PDT in the treatment of hypertrophic scars is associated with a degradation of collagen and an increase in elastin fibers, suggesting an induction of

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 46.1 Photodynamic therapy of (a) field cancerization areas with actinic keratosis (AK), showing (b) healed and rejuvenated areas.

collagen-degrading enzymes [24]. Reduced pruritus and pain and improved pliability of keloids were demonstrated in 20 patients receiving MAL-PDT (3 treatments at weekly intervals) alone or subsequent to surgery [25].

PDT FOR PHOTOREJUVENATION

PDT: EFFICACY, PREVENTION, AND PHOTOREJUVENATION

In this chapter, we have highlighted the attributes of PDT that makes it an attractive option for NMSC and precancer lesions, affording high efficacy combined with a potential in secondary prevention of further lesions, complemented by high quality of cosmesis. The opportunity for PDT to be used for photorejuvenation is also attractive, given the frequent coexistence of clinical AKs and likely coexistence of subclinical lesions in patients with severe photodamage. Compliance is maximized as an office-based therapy. Post-PDT downtime is relatively short following PDT, in comparison with other approaches, although protocols that optimize efficacy, yet minimize treatment-related discomfort, are crucial to its wider adoption. However, the high quality of cosmesis consistently observed in PDT studies for NMSC indications including AK, combined with increasing emphasis on patient choice over therapy, is likely to see increased demand for topical PDT.

REFERENCES

1. Braathen Lasse R, Szeimies Rolf M, Basset Seguin N et al. Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: An international consensus. *J Am Acad Dermatol* 2007; 56:125–143.
2. Morton CA, Szeimies R-M, Sidoroff A, Braathen LR. European guidelines for topical photodynamic therapy. Part 1: Treatment delivery and current indications—Actinic keratoses, Bowen's disease, basal cell carcinoma. *J Eur Acad Dermatol Venereol* 2013; 27:536–544.
3. Morton CA, Szeimies R-M, Sidoroff A, Braathen LR. European guidelines for topical photodynamic therapy. Part 2: Emerging indications—Field cancerization, photorejuvenation and inflammatory/infective dermatoses. *J Eur Acad Dermatol Venereol* 2013; 27:672–679.
4. De Berker D, McGregor J, Hughes B. Guidelines for the management of actinic keratosis. *Br J Dermatol* 2007; 156:222–230.
5. Morton C, Campbell S, Gupta G et al. Intraindividual, right-left comparison of topical methyl aminolaevulinate-photodynamic therapy and cryotherapy in subjects with actinic keratoses: A multicentre, randomized controlled study. *Br J Dermatol* 2006; 155:1029–1036.
6. Pariser DM, Lowe NJ, Stewart DM et al. Photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: Results of a prospective randomized multicenter trial. *J Am Acad Dermatol* 2003; 48:227–232.
7. Dirschka T, Radny P, Dominicus R et al. Photodynamic therapy with BF-200 ALA for the treatment of actinic keratoses: Results of a multicentre, randomized, observer-blind phase III study in comparison with registered methyl-5-aminolaevulinate cream and placebo. *Br J Dermatol* 2012; 166:137–146.
8. Hauschild A, Stockfleth E, Popp G et al. Optimization of photodynamic therapy with a novel self-adhesive 5-aminolaevulinic acid patch: Results of two randomized controlled phase III studies *Br J Dermatol* 2009; 160:1066–1074.
9. Szeimies RM, Stockfleth E, Popp G et al. Long-term follow-up of photodynamic therapy with a self-adhesive 5-aminolaevulinic acid patch: 12 months data. *Br J Dermatol* 2010; 162:410–414.
10. Morton CA, Horn M, Leman J et al. A randomized, placebo-controlled, European study comparing MAL-PDT with cryotherapy and 5-fluorouracil in subjects with Bowen's disease. *Arch Dermatol* 2006; 142:729–735.
11. Ibbotson SH, Ferguson J. Ambulatory photodynamic therapy using low irradiance inorganic light-emitting diodes for the treatment of non-melanoma skin cancer: An open study. *Photodermatol Photoimmunol Photomed* 2012; 28:235–239.
12. Basset-Séguin N, Ibbotson SH, Emtestam L et al. Topical methyl aminolaevulinate photodynamic therapy versus cryotherapy for superficial basal cell carcinoma: A 5 year randomized trial. *Eur J Dermatol* 2008; 18:547–553.
13. Szeimies R, Ibbotson S, Murrell D et al. A clinical study comparing methyl aminolevulinate photodynamic therapy and surgery in small superficial basal cell carcinoma (8–20mm), with a 12-month follow-up. *J Eur Acad Dermatol Venereol* 2008; 22:1302–1311.
14. Rhodes LE, de Rie MA, Leifsdottir R et al. Five year follow up of a randomized prospective trial of topical methyl aminolevulinate-photodynamic therapy versus surgery for nodular basal cell carcinoma. *Arch Dermatol* 2007; 143:1131–1136.
15. Cosgarea R, Susan M, Crisan M, Senila S. Photodynamic therapy using topical 5-aminolaevulinic acid vs. surgery for basal cell carcinoma. *J Eur Acad Dermatol Venereol* 2013; 27:980–984.
16. Mosterd K, Arits AH, Nelemans PJ, Kelleners-Smeets NW. Aesthetic evaluation after non-invasive treatment for superficial basal cell carcinoma. *J Eur Acad Dermatol Venereol* 2013; 27:647–650.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

17. Braathen L, Morton C, Basset-Seguin N et al. Photodynamic therapy for skin field cancerization: An international consensus. International Society for Photodynamic Therapy in Dermatology. *J Eur Acad Dermatol Venereol* 2012; 26:1063–1066.
18. Basset-Seguin N, Baumann Conzett K, Gerritsen MJP et al. Photodynamic therapy for actinic keratoses in organ transplant recipients. *J Eur Acad Dermatol Venereol* 2013; 27:57–66.
19. Apalla Z, Sotiriou E, Chovarda E, Lefaki I, Devliotou-Panagiotidou D, Ioannides D. Skin cancer: Preventive photodynamic therapy in patients with face and scalp cancerization. A randomized placebo-controlled study. *Br J Dermatol* 2010; 162:171–175.
20. Bagazgoitia L, Cuevas Santos J, Juarranz A, Jaen P. Photodynamic therapy reduces the histologic features of actinic damage and the expression of early oncogenic markers. *Br J Dermatol* 2011; 165:144–151.
21. Szeimies RM, Torezan L, Niwa A et al. Clinical, histopathological and immunohistochemical assessment of human skin field cancerization before and after photodynamic therapy. *Br J Dermatol* 2012; 167:150–159.
22. Sakamoto F, Izikson L, Tannous Z, Zurakowski D, Anderson RR. Surgical scar remodelling after photodynamic therapy using aminolaevulinic acid or its methylester: A retrospective, blinded study of patients with field cancerization. *Br J Dermatol* 2012; 166:413–416.
23. Calzavara-Pinton PG, Rossi MT, Aronson E, Sala R; Italian Group For Photodynamic Therapy. A retrospective analysis of real-life practice of off-label photodynamic therapy using methyl aminolevulinate (MAL-PDT) in 20 Italian dermatology departments. Part 1: Inflammatory and aesthetic indications. *Photochem Photobiol Sci* 2013; 12:148–157.
24. Campbell SM, Tyrrell J, Marshall R, Curnow A. Effect of MAL-photodynamic therapy on hypertrophic scarring. *Photodiagn Photodyn Ther* 2010; 7:183–188.
25. Ud-Din S, Thomas G, Morris J et al. Photodynamic therapy: An innovative approach to the treatment of keloid disease evaluated using subjective and objective non-invasive tools. *Arch Dermatol Res* 2013; 305:205–214.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Nonsurgical skin tightening

Ashraf Badawi

Skin rejuvenation has gained a lot of attention during the past few years. It seems that the public awareness, heavy marketing, and the need to maintain a good and healthy look have encouraged both patients and practitioners toward the rejuvenation and body-shaping procedures.

Optimally, the outcome is restoring the natural appearance present 15 or 20 years earlier with no or minimal downtime and minimal detectability of surgical incisions.

Surgical procedures might be associated with immediate improvement of skin tone as in cases of face lift or abdominoplasty; however, many patients are willing to accept less dramatic improvement of their skin to avoid the risk of surgery by going for nonsurgical procedures for skin tightening.

As a matter of fact, nonsurgical skin tightening might be associated with less improvement of the skin tone; however, in the long term, it improves the structure and function of the skin, which gives the skin a much better complexion.

The ideal nonsurgical rejuvenation method for the aging skin depends on each patient's skin type, pathologies, rejuvenation objectives, recovery time acceptable to the patient, threshold for complications, and patient's expectations. Although these are very important factors, the physician's experience and familiarity with a particular rejuvenation modality play a vital role in selecting the technology and the treatment plan recommended for the candidates who aspire for skin tightening and rejuvenation. An ideal rejuvenation modality induces an improvement in the skin without causing injury to the epidermis.

CAUSES OF SKIN LAXITY

Skin laxity can attack all skin types and all age groups. Both men and women get skin laxity. As with all signs of aging, prevention should be the main focus. It is a lot easier to prevent something from occurring than to reverse it once it has happened. And since most people are not happy with the signs of aging showing visually on their faces, prevention really is the best way to go.

As with any other organ, the skin is subject to the gradual chronological senescence of aging. The biological consequences of aging are first apparent at the cellular level, where they act on a variety of targets. Even in persons as young as 30, aging has an effect at the cellular level, but it is only in mid to old age that the process becomes visible, as the microscopic structural and functional changes accumulate, forming wrinkles and folds, for example. Aging of the skin can be attributed to intrinsic and extrinsic factors, both of which manifest as surface and subsurface changes. Intrinsic aging is dictated by the genes of the person [1].

In skin aging, collagen and elastin are degraded and neocollagenesis is inhibited. The DNA of living cells is also damaged [2,3].

The intrinsic process of chronological aging results from thinning of the epidermis and dermis and loss of elasticity. This process affects all layers of the face, including subcutaneous tissue, the musculofascial system, the superficial musculoaponeurotic system, and the facial skeleton. The result is bony resorption, atrophy of subcutaneous fat, attenuation of the musculofibrous system, and alterations of skin surface. The dermal–epidermal junction flattens, which results in loss of rete ridges and a thinner appearance to the epidermis. The dermis also becomes thin, with a decrease in elastic fibers, collagen production, vascularity, and ground substance. The biochemical alterations in collagen and elastin result in a dermis that is more lax, yet less elastic and resilient. Collectively, these changes result in fine wrinkling of the skin and sagging of the tissues that overlay the facial skeleton [4].

Extrinsic photoaging causes degenerative changes in the skin that are superimposed on the normal chronologic aging process. Clinically, this process results in coarse and dry skin, deep wrinkles, sallowness, and dyschromia. Histologically, photo-aged skin is characterized by epidermal hyperplasia and dysplasia, a thickened dermis with solar elastosis, actinic vasculopathy, decreased collagen fibers, and increased ground substance [5].

MANAGING SKIN LAXITY

As we can conclude from the pathogenesis of the skin laxity, it is not a solitary pathology; hence, managing skin laxity should not be limited to skin-tightening procedures only. It is of utmost importance to deal with the skin as an organ composed of three layers: the epidermis, the dermis, and the subcutaneous fat and tissue.

Focusing on skin tightening only will not give the patient the optimum outcome.

It is important to combine the tightening treatment we perform with a treatment targeting the epidermis to decrease the hyperkeratosis, increase the population of epidermal living cells, increase the absorption of topically applied active substances, and restore the epidermal barrier function. Restoring the epidermal barrier function by itself should help in decreasing the transepidermal water loss, which in turn will improve the skin elasticity and tone. Treating the epidermis can be achieved by chemical peels, microdermabrasion, keratolytic skin products like vitamin A acids, or even superficial laser peels using the erbium:Yag 2940 nm laser.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

The microdermabrasion is considered superior to all other modalities targeting the improvement of epidermal structure: it has a mechanical rather than chemical effect, which is associated with less risk of irritation or pigmentery alterations. An additional benefit of the microdermabrasion is improved microcirculation and the lymphatic drainage that might be impaired due to the aging.

The next layer that needs attention in the course of treating skin laxity is the dermis. It is well known that starting from the age of 20 years, old human beings start to lose 1%–2% of the body collagen per year and this percentage doubles in sun-/UV-exposed areas [6,7].

With collagen loss, the skin tensile strength is becoming weak and this helps in developing wrinkles and skin laxity. Procedures known to induce neocollagenesis, such as nonablative Nd:YAG 20,164 nm laser [8,9], ablative and nonablative fractional lasers, collagen induction therapy, and microneedling radiofrequency (RF), are the most popular procedures now in the process of rejuvenation.

Although skin-tightening procedures induce neocollagenesis, when the pathology is at the level of the dermis and in the absence of skin laxity, the aforementioned technologies are the first choice.

As the topic of this chapter is nonsurgical skin tightening, the focus will be on the different technologies used for that indication.

TECHNOLOGIES USED IN SKIN TIGHTENING

Radiofrequency

RF devices have been widely used for skin tightening and are thought to lead to volumetric heating of the dermis, subcutaneous tissue including the fibrous septa strands, and fascia layers. It is well documented that one of the effects of dermal heating is an immediate change in collagen structure, followed by a long-term stimulation of neocollagenesis starting at 4–6 weeks after treatment [10]. These thermal effects can help to reduce the appearance of wrinkles and laxity and improve contours on both the face and body.

When the RF is used for tissue tightening, the main bulk of heat is in the hypodermis and deep dermis where more water content is associated with more heat production. The more superficial we go, the less water content is found, and consequently, less thermal effect will happen at the level of the epidermis. This makes the RF technology suitable for all skin types unlike some other light-based tightening modalities that cannot be used in darker skin types.

The first generation of the monopolar RF devices showed good effectiveness in skin tightening, but the main problem was the severe pain associated with the treatment. The treatment also involved expensive disposable transducers. When new treatment protocols with less aggressive power settings were introduced, the efficacy was hindered, but the cost did not go down. This motivated the development of the bipolar and tripolar RF devices.

The thermal effects of monopolar and bipolar RF have been proven to be beneficial in skin tightening. Nevertheless, these effects are often partial or unpredictable because of the uncontrolled nature and possible pain produced during monopolar or unipolar RF treatments and the superficial nature of energy flow for bipolar or tripolar configurations.

In addition, these first-generation RF therapy systems delivered frequently unpredictable results, possibly due to the large differences in individual skin impedance [11].

It is important to point out the fact that when using the RF the amount of heat generated will depend not only on the type of FR and whether it is monopolar, bipolar, or tripolar, the energy used, and the technique but also on the amount of subcutaneous fat present. That might be the reason behind the inconsistent results reported with the RF devices. In many cases, the RF fails to demonstrate good tightening effect in slim patients that could be explained by the presence of small amount of subcutaneous fat, hence less heat production and lack of effect.

Recently, a novel multisource phase-controlled RF system was introduced, which allows for enhanced energy penetration to the lower dermis and hypodermis, minimizing epidermal heating. To enhance predictability of energy delivery, the system employs a continuous real-time measurement of skin impedance, allowing delivery of constant energy to the patient skin independent of changes in its impedance. In 2013, Tanaka [12] treated twenty Japanese patients with a multisource phase-controlled RF device. Three-dimensional imaging was performed with a Canfield Scientific Vectra camera and software, and quantitative volume measurements were taken to evaluate the change in the posttreatment volume. The conclusion of the study was that the advantages of these multisource phase-controlled RF treatments are its high efficacy for skin tightening associated with minimal level of discomfort, minimal side effects, and low cost. Taken together, these characteristics facilitate the ability to give repeated treatments as a stand-alone treatment or adjunct to surgery. This study provides for the first time a qualitative and quantitative volumetric assessment, proving the ability of the technology to reduce the volume through noninvasive skin tightening [12] (Figures 47.1 and 47.2).

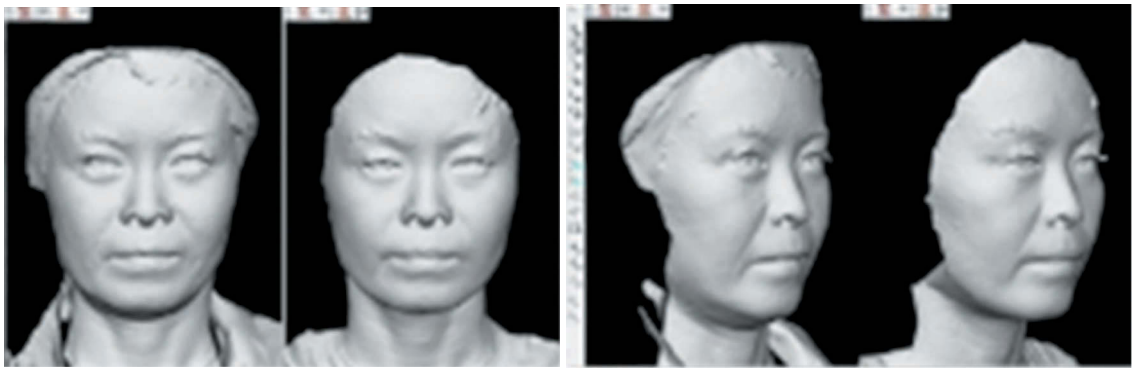
Focal Ultrasound

Since 2007, intense focused ultrasound has emerged as a novel technology for noninvasive skin tightening and lifting, offering promise for more consistent and superior efficacy compared to the preexisting devices [13]. An important feature of focused ultrasound that distinguishes it from other preexisting skin tightening technologies is its capability of producing small, microthermal lesions at precise depths in the mid to deep reticular dermis up to the fibromuscular layer causing thermally induced contraction of collagen and tissue coagulation with subsequent neocollagenesis while sparing the epidermis [14,15].

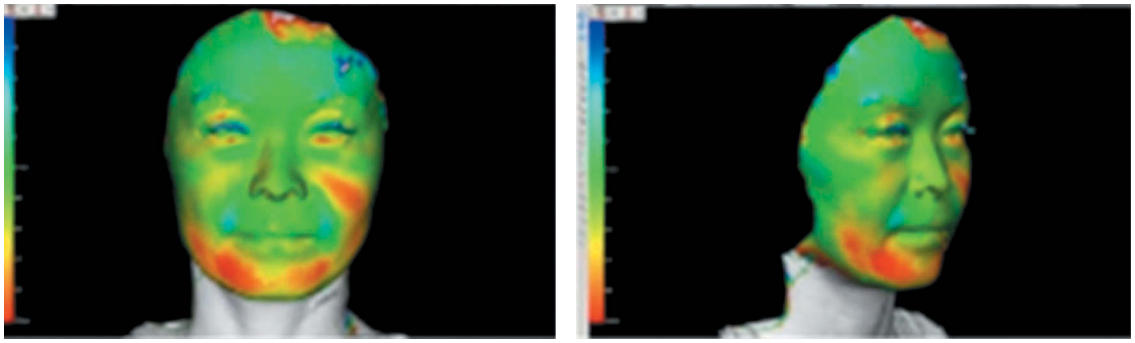
A novel device that incorporates the delivery of focused ultrasound energy with ultrasound imaging allows real-time visualization of subdermal boundaries during treatment. The efficacy and safety of this device for eyebrow lift after a single treatment have been shown in a prospective cohort study in Caucasians [16].

A unique feature of this technology is its ability to deliver geometrically microfocused ultrasound energy at precise and consistent depths on a prescribed tissue plane, which can be from the dermis deep down to even the subdermal connective tissue of the superficial musculoaponeurotic system (SMAS), depending on the selected transducers used [17]. Histological studies on porcine and human cadaveric tissues as well as some clinical studies demonstrated the formation of thermal injury zones of specific size and geometry, which led to

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a)



(b)

Figure 47.1 Representative photographs of tightening effects treated with a multisource phase-controlled RF treatment. Pretreatment (a, left); a 44-year-old Japanese woman exhibited skin laxity in the cheek, mental portion, and neck and wrinkles such as the nasolabial fold. Posttreatment (a, right); significant improvements were noted in both skin laxity and wrinkles. Three-dimensional color schematic representation shows the varying degrees of tightening achieved in colors yellow to red (b). Green areas remain unchanged. These images indicate significant improvements in appearance, skin laxity, and wrinkles after the treatments. (Reprinted from Tanaka Y, *J Cosmet Dermatol Sci Appl*, 3, 110, 2013. With permission.)

(a) (b) (c)

Figure 47.2 Patient treated with a tripolar RF device. (a) Before treatment. (b) Immediately after treating the right side of the face only with clear tightening effect. (c) One month after the treatment of the right side of the face with clear sustained tightening effect after a single session.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

thermal collagen denaturation with subsequent tissue shrinkage and tightening while sparing the intervening tissues and the epidermis [14,15,17,18]. In a prospective clinical study by Alam et al. in Caucasian patients, significant eyebrow lift from skin tightening was achieved with a single treatment [16]. The device has also been shown to be safe, with transient erythema and edema being the commonest side effects [14,16].

For dark skin, postinflammatory hyperpigmentation associated with laser and light-source treatment is always a concern.

As the ultrasound energy is not absorbed by melanin, noninvasive skin tightening with focused ultrasound is considered safe in all skin types including patients with dark skin.

This novel technology has gained a lot of ground specially in the United States during the past few years; however, the pain associated with the first protocols recommended by the manufacturers and the high cost of the transducers were the main limiting factors for the wide spread of this technology. Recently, less aggressive protocols are recommended; the treatment passes have increased and so did the lines obtained by the transducers of the machine; thus, the cost did not go up.

During the treatment, there are certain areas that should not be treated to avoid nerve injuries and paresthesia, which is a temporary complication of this treatment.

Chan et al. [13] reported mild perioral numbness in one patient at 7 days posttreatment, and it was resolved spontaneously within a month. Even though focused ultrasound can potentially penetrate much deeper than preexisting nonablative skin-tightening devices, the focal depth is predetermined by the transducers used. For transducers with a fixed focal depth of 4.5 mm (7.0 or 4.0 MHz), the nominal depth to which most of the energy is delivered in the tissue has been shown to be limited to approximately 5.0 mm [15], which is more superficial than the mean depths of facial nerve in different facial regions described in the literature [19]. No long-term nerve dysfunction has so far been reported with this device in published data [13].

In conclusion, the focused ultrasound is considered an effective toll in the nonsurgical-tightening armamentarium with a high degree of reproducibility and it is suitable for all skin types; however, the pain associated with the treatment and the high cost are the two main limiting factors for the wide use of this technology.

Figure 47.3 (a, c) Neck laxity before treatment. (b, d) Neck after IR light session with residual erythema. Clear tightening effect.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Infrared Light

Laser/light energy in the near- and mid-infrared locations on the spectrum is weakly attracted to melanin and is mainly absorbed by water. When epidermal melanin is bypassed more efficiently, patients with all skin types can be treated with a reduced risk. Also, by extending the wavelength of the selected laser to the infrared and mid-infrared areas, deeper energy penetration can be achieved, and laser energy can be delivered to the dermis. The epidermis is bypassed, and the heat that is produced by laser energy is nonselectively deposited in the dermis. Theoretically, heat-induced dermal injury eventually results in the activation of dermal fibroblasts and the induction of a healing response. An inflammatory response within the dermis to the laser-generated heat hypothetically initiates a reaction that leads to collagen remodeling and an improvement in the appearance of facial rhytides.

When the infrared laser or light is emitted with long pulse duration, the result will be deep tissue heating and collagen fiber shrinkage, leading to tissue tightening.

An infrared light with wavelength around 1100 nm has been used by a couple of laser manufacturers for skin tightening. The technique involved contact cooling for epidermal protection. This technology has been in the market for over 10 years; however, the lack of reproducibility was one of the obstacles that did not allow the widespread use of the infrared light in the indication of tightening, which is the only indication for those devices (Figure 47.3).

On the other hand, the extended pulse 1064 nm Nd:YAG laser is a safe and proven technology that has been effectively used in laser epilation in patients of all skin types and colors. Similar to the 1320 nm Nd:YAG laser, the 1064 nm wavelength deposits nonselective heat into the dermis with a minimal affinity for melanin. The advantages of this modality for wrinkle reduction include the technical ease of performing the procedure, minimal to no patient discomfort, and the ability to treat all skin types with little risk of epidermal injury [6].

Recently, Nd:YAG 1064 nm laser has been released with superextended pulse duration. Utilizing this feature, the laser can be used for skin tightening in an effective and safe way.

The technique involves using relatively high fluence exceeding 60 J/cm^2 with 10 mm spot size and 2 or more hertz repetition rate in a continuous motion technique. The results are impressive; however, the long-term efficacy is still to be proven (Figure 47.4).

NONABLATIVE Er:YAG LASER FOR PERIORBITAL SKIN TIGHTENING

One of the most impressive recent developments is the ability to induce tightening of the periocular skin in a very conservative manner with almost no downtime. This is achieved by using the fractional Er:YAG laser 2940 nm in treating the skin around the eye. The procedure does not lead to ablation: the pulse duration used is extremely long, which leads to thermal coagulation of the

Figure 47.4 (a, b) Right and left sides of the face before treatment. (c, d) After Nd:YAG 1064 nm laser treatment for skin tightening with clear lifting effect and improvement of the jawline.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

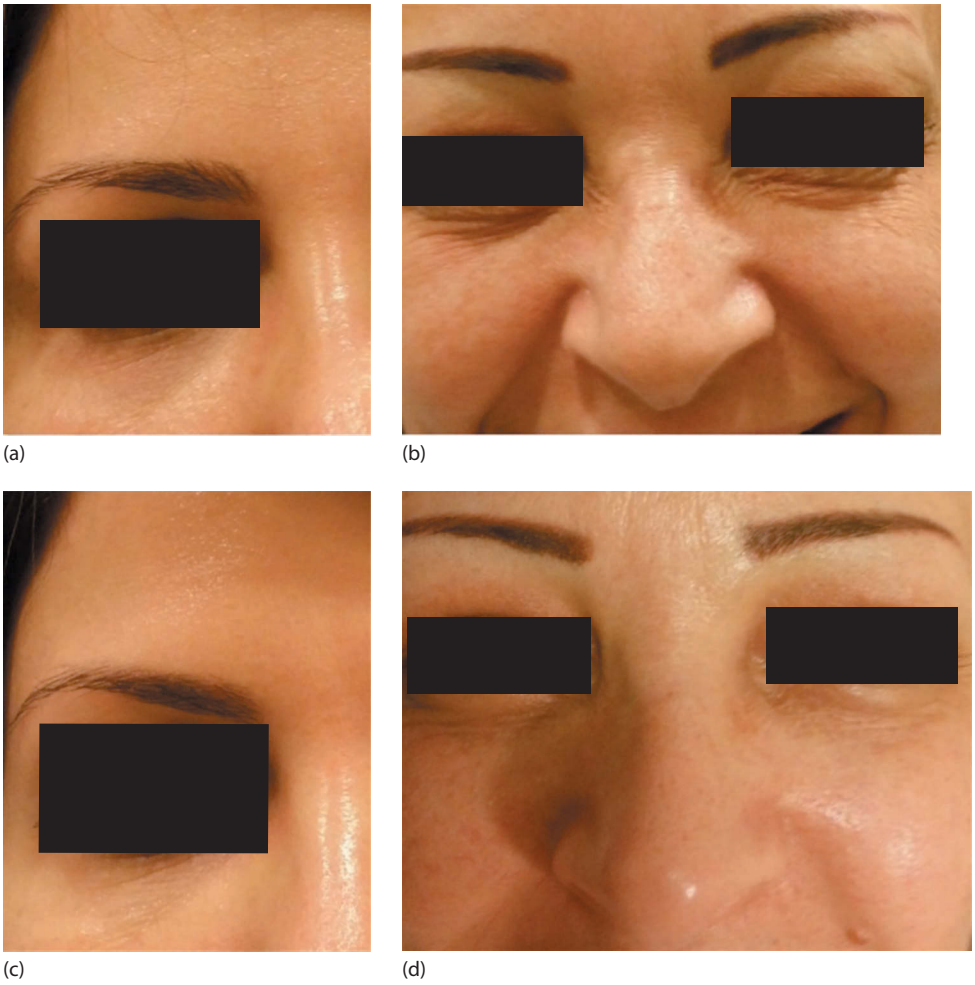


Figure 47.5 (a, b) Before treatment. (c, d) After 2 sessions of nonablative fractional Er:YAG laser with long pulse duration.

subcutaneous tissue with minimal surface effects (Figure 47.5). Although the initial results of this method are impressive, longer-term follow-up in a large number of patients is required to prove the efficacy and safety of a potentially impressive procedure.

CONCLUSION

It is clear that there are several modalities for nonsurgical skin tightening. Most of them can work effectively and safely on almost all skin types. The key for success is achieving patient's satisfaction, and this can never be attained unless the practitioner is able to properly assess the patient's skin issues, understand the patient's psychology, discuss the treatment options and required combinations, limit the patient's expectations, and explain the process of skin aging and the need for ongoing rejuvenation program to combat the dynamic ongoing aging process.

REFERENCES

1. Moschella S, Hurley H. Aging and its effects on the skin. In: Moschella S, Hurley H, eds. *Dermatology*, 3rd ed. Philadelphia, PA: W.B. Saunders, 1992.
2. Fisher GJ. The pathophysiology of photoaging of the skin. *Cutis* 2005; 75:5–9.
3. Fisher GJ, Wang ZQ, Datta SC et al. Pathophysiology of premature skin aging induced by ultraviolet light. *N Engl J Med* 1997; 337:1419–1428.
4. White CR, Bigby M, Sangueza OP. What is normal skin? In: Arndt KA, ed. *Cutaneous Medicine and Surgery: An Integrated Program in Dermatology*. Philadelphia, PA: W.B. Saunders, 1996, pp. 3–41.
5. Coopman SA, Garmyn M, Gonzalez-Serva A. Photodamage and photoaging. In: Arndt KA, ed. *Cutaneous Medicine and Surgery: An Integrated Program in Dermatology*. Philadelphia, PA: W.B. Saunders, 1996, pp. 732–750.
6. Badawi A. Role of lasers in rejuvenation. *G Ital Dermatol Venereol* 2012 June; 147(3):285–293.
7. Shuster S. Osteoporosis, a unitary hypothesis of collagen loss in skin and bone. *Med Hypotheses* 2005; 65(3):426–432.
8. Badawi A, Tome M, El Morsy I, Atteya A, Sami N. Retrospective analysis of non-ablative scar treatment in dark skin types using the sub-millisecond Nd:YAG 1064 nm laser. *Laser Surg Med* 2011; 43:130–136.
9. Badawi A, Tome M, Turely A, Kemeny L. Successful treatment of chicken pox in dark skin using the microdermabrasion and the Nd:YAG 1064 nm laser. *J Cosmet Dermatol* 2011; 24:389–394.
10. Sadick N, Sorhaindo L. The radiofrequency frontier: A review of radiofrequency and combined radiofrequency pulsed light technology in aesthetic medicine. *Facial Plast Surg* 2005; 21(2):131–138.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

11. Harth Y, Lischinsky D. A novel method for realtime skin impedance measurement during radiofrequency skin tightening treatments. *J Cosmet Dermatol* 2011; 10(1):24–29.
12. Tanaka Y. Objective assessment of skin tightening using multisource, phase-controlled radiofrequency in Asians. *J Cosmet Dermatol Sci Appl* 2013; 3:110–116.
13. Chan N, Shek S, Yu C et al. Safety study of transcutaneous focused ultrasound for non-invasive skin tightening in Asians. *Lasers Surg Med* 2011; 43:366–375.
14. Gliklich RE, White WM, Slayton MH, Barthe PG, Makin IR. Clinical pilot study of intense ultrasound therapy to deep dermal facial skin and subcutaneous tissues. *Arch Facial Plast Surg* 2007; 9(2):88–95.
15. White WM, Makin IR, Barthe PG, Slayton MH, Gliklich RE. Selective creation of thermal injury zones in the superficial musculoaponeurotic system using intense ultrasound therapy: A new target for noninvasive facial rejuvenation. *Arch Facial Plast Surg* 2007; 9(1):22–29.
16. Alam M, White LE, Martin N, Witherspoon J, Yoo S, West DP. Ultrasound tightening of facial and neck skin: A rater-blinded prospective cohort study. *J Am Acad Dermatol* 2010; 62(2):262–269.
17. White WM, Makin IR, Slayton MH, Barthe PG, Gliklich R. Selective transcutaneous delivery of energy to porcine soft tissues using Intense Ultrasound (IUS). *Lasers Surg Med* 2008; 40(2):67–75.
18. Laubach HJ, Makin IR, Barthe PG, Slayton MH, Manstein D. Intense focused ultrasound: Evaluation of a new treatment modality for precise microcoagulation within the skin. *Dermatol Surg* 2008; 34(5):727–734.
19. Rudolph R. Depth of the facial nerve in face lift dissections. *Plast Reconstr Surg* 1990; 85(4):537–544.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Cellulite and non-surgical fat destruction

Philippe Blanchemaison and Jade Frucot

INTRODUCTION

Cellulite can be defined by a simple clinical criterion: a spontaneous orange-peel appearance when the skin is pinched. The two most common sites in the body where cellulite appear are the outer thighs (femoral fat, saddlebags) and inner knees [1]. This particular fat, "compacted" by fibrous septa, is much more difficult to remove especially in obese people: it is particularly resistant to a low-calorie diet that reaches femoral reserve fat as a last resort [2].

Although the term cellulite, literally means "inflammation of the cells," poorly reflects its pathophysiology, it should be kept as it has been adopted all around the world. It must be distinguished from cellulitis, which is a severe and progressive infective disease that can lead to skin necrosis [3].

Cellulite is primarily an excess of fat content in adipocytes. The adipocyte changes, a water retention phenomenon related to poor venolymphatic circulation and potential hormonal imbalance between estrogen and progesterone, influence capillary permeability. Finally, fibrosis may occur gradually over time, resulting in induration [4].

These three factors adiposity (increased number and size of adipocytes), water retention, and fibrosis are now quantifiable.

DEFINITION DIAGNOSIS

Cellulite corresponds to an increase in the number and/or size of adipocytes. So this is a superficial lipodystrophy, which in other words is an increase in the volume or the number of fat cells that sit in the surface of the hypodermis. The main misunderstanding comes from a frequent confusion between the terms cellulite, lipodystrophy, and steatomery. Lipodystrophy is the transformation of the subcutaneous adipose tissue, in excess or in deficiency. When adipocytes concerned are located in the superficial part of the hypodermis, it is called cellulite. When it is located in the deep part of the hypodermis, we talk about steatomery. The steatomeries are deep localized lipodystrophy, while obesity is a deep diffuse lipodystrophy.

CLASSIFICATIONS

In 1929, Lageze [5] talked about cellulite with water retention, through interstitial edema located in the connective tissue between the fat cells, which gradually evolves to a fibrous structure.

In 1940, Allen [6] proposed the concept of lipoedema: it is a chronic edematous infiltration, a water retention, which affects the lower limbs from the root of the thighs to the ankles, but which do not reach the foot, unlike lymphedema or phlebedema (edema associated with venous insufficiency).

In 1972, Braun and Falco observed fluid "microlakes" between adipocyte lobules containing a protein-rich liquid, which showed vascular involvement in cellulite phenomenon.

In 1978, Nürnberger [7] demonstrated, on a set of biopsies of the hypodermis, the existence of adipocyte lobules separated by connective tissue septa. These septa are parallel in women and polygonal in men. According to the author, it is this particular structure of female cellulite fat that gives the orange peel-like appearance. Cellulite may be classified in three stages (Box 48.1).

In 1979, Curri and Merlen [8], using biopsy and video capillaroscopy direct observation of interadipocyte vessels, concluded that cellulite or "edemafibrosis paniculopathy" is a true vascular disease, classified into four stages [9,10] (Box 48.2).

These classifications, based on excellent visual observations, describe a linear evolution. What will primarily interest the treating physician faced with a patient who consults for his or her cellulite is to determine the importance of the three main actors, fibrosis, adiposity, and water retention, on the day of the visit.

Thus, different types of cellulite appear, fat, fibrous, or edematous, following the predominance of one of the three players.

In 2000, Blanchemaison [11], based on this reasoning, proposed a new classification called R-FAT classification of cellulite: water retention, fibrosis, and adipose tissue. This classification is based on the development of a water retention index (WRI) for quantifying, by high-frequency ultrasound, the water retention phenomenon. This index has been validated in a prospective study of 48 patients [12]. Each of the three players of cellulite can then be defined according to the pathophysiology.

In 2009, Hexsel [13] established a new scale based on standardized photographs of 55 patients with cellulite. Five key morphological aspects of cellulite were identified and validated. The five key morphological features of cellulite identified were number of depressions, depth of depressions, appearance of raised lesions, presence of flaccidity, and grade of cellulite. Each item was graded from 0 to 3, allowing final classification of cellulite as mild, moderate, and severe [14].

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

BOX 48.1

- *Stage I*: Orange peel only appears when the skin is pinched.
- *Stage II*: Spontaneous orange peel appearance is visible only in the standing position.
- *Stage III*: Spontaneous orange peel appearance is visible in standing and lying positions.

BOX 48.2

- *Stage I*: Simple water retention defined by a greater capillary filtration than reabsorption according to Starling's law
- *Stage II*: Increasing adipocyte size with adipocyte micronodule formation
- *Stage III*: Fibrosis
- *Stage IV*: Adipocyte macronodule formation with liposclerosis expansion

PHYSIOPATHOLOGY

Cellulite is the result of a chronic imbalance of the adipocyte (adiposity) and its surrounding tissue, especially the microcirculation (water retention) and collagen (fibrosis) (Figure 48.1).

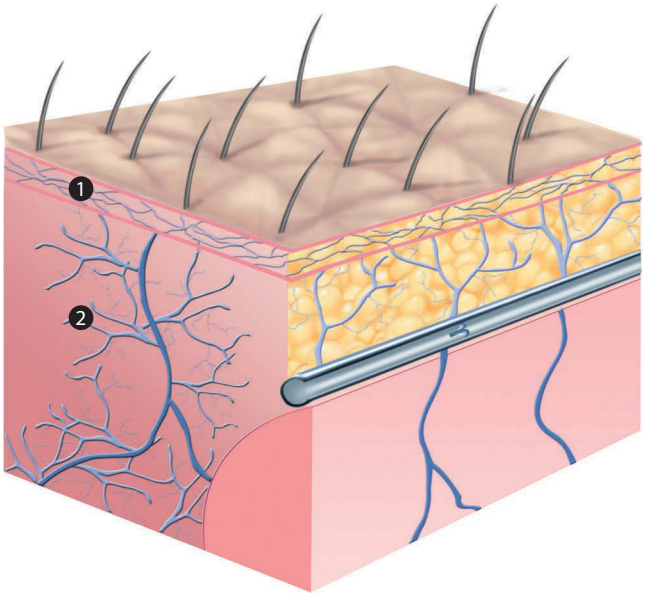


Figure 48.1 The three players in cellulite: subcutaneous adipose tissue (2), water retention (1 and 2), and subcutaneous fibrosis (2).

Adiposity

It corresponds to an increase in the number or size of adipocytes associated with chronic dysfunction in their metabolism. This dysfunction has been well described [15,16] through mechanisms of lipogenesis (triglyceride synthesis) and lipolysis (lysis of glycerol and fatty acids in triglycerides) alteration.

Lipogenesis is associated with alterations in the operation of a key enzyme, lipoprotein lipase, and leptin, a newly discovered hormone. These alterations may be genetic, hormonal, or vascular. There may be a disorder of glucose uptake by adipocytes, controlled by insulin, playing a fundamental role in lipogenesis. This mechanism explains the detrimental effect of excessive consumption of industrial sugar on the formation of cellulite.

Finally, catecholamines (norepinephrine and epinephrine) are the most potent physiological factors acting on the lipolysis-lipogenesis balance, which may explain the negative effect of stress on cellulite. Dysfunction of alpha-2 adrenergic receptor and prostaglandins PGE1 and PGE2 or PYY receptor was also found in the adipocyte membrane of cellulite patients. The abundance of these receptors could be partly responsible for the low lipolytic activity of adipocytes in cellulite patients. This mechanism acts on one of the most potent lipolytic pharmacological factors known as caffeine [17,18].

The constant balance between lipolysis and lipogenesis can be summarized by the concept of "adipostat," analogous a thermostat, a control system leading to a thermal equilibrium avoiding excess or heat failure. On the one hand, this system involves a set of actors such as peptides secreted by adipocytes (leptin, adiponectin, prostaglandins, TNF-α, angiotensinogen, etc.); on the other hand, it involves adipocyte membrane receptors to insulin, catecholamine, prostaglandins, and estrogens [19–24].

Water Retention

Every day, more than 20 L of water is filtered through our arterial capillaries and then it is reabsorbed by our venous and lymphatic capillaries [25]. This daily washing of our cells requires a perfect balance between the amount of water that is filtered from the arteries to the fatty tissue and the amount of water that is reabsorbed into the fatty tissue and lymph veins (see WRI). If there is a poor venous or lymphatic insufficiency, or capillary permeability changes due to hormonal imbalance, a portion of the filtered water will remain in the interstitial tissues, and, in the case of cellulite, in fatty tissue, hence, the famous "fluid lakes" observed by Lageze, Allen, Braun and Falco, and Merlen and Curri. This water retention concerns the dermis and the hypodermis. It is possible to measure it in the dermis, the part most accessible to the high-frequency ultrasound [26].

Fibrosis

Fibrosis is the sequel to the passage through interadipocyte tissues of water and high-molecular-weight proteins. The poor resorption by the lymphatic system of these proteins stimulates fibroblasts to produce collagen fibers. Fibrosis may follow water retention, but may appear several years later.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Another mechanism of fibrosis is the glycation of collagen [27]. This consists of proteins of collagen being bridged by glucose molecules, which leads to a loss of skin tissue support and subcutaneous support (skin sagging) or, in other cases, leads to rigidity and loss of tissue elasticity.

This phenomenon of glycation, favored by excess sugar, causes a chain reaction: progressive formation of reversible intermediate products, dehydration, condensation, and organization that gradually leads to irreversible compounds called advanced glycation end products (AGEs). These AGEs cause permanent connections between molecules, altering their physicochemical and biological properties.

Another concept is the balance between the production of collagen by fibroblasts and its elimination by metalloproteinases.

Identified recently and secreted by our adipocytes, metalloproteases are enzymes (ases) directed against the proteins (proteo), which operate with cofactors, trace metals, such as zinc or selenium (metallo).

These metalloproteinases (matrix metalloproteases) are normally secreted to clear aged collagen, and their dysfunction has a role in the overproduction of collagen fibers by fibroblasts (fibrosis) or, on the contrary, in the abnormal destruction of healthy collagen fibers (tissue sagging). Their dysfunction leads to disorganization of the extracellular matrix and promotes the colonization of the fat tissue by new adipocytes. Thus, they play a role in the differentiation of preadipocytes into adipocytes thereby worsening cellulite.

Finally, when fibroblast cells are stressed, or under the influence of certain stimuli, they can secrete large quantities of abnormal collagen, which also leads to fibrosis, in other words, dermal and hypodermic induration. The cellulite fat becomes "compacted" by fibrosis that makes it difficult to remove.

ETIOPATHOGENESIS

While the mechanisms of cellulite are now better understood, it is not the same for the causes. Five causes are usually recognized [28]:

1. *Genetic* (determination of the activity of lipolytic enzymes genetically determined, which explains the injustice for one woman rather than another, despite similar dietary patterns).
2. *Hormonal*: First, estrogens condition gynoid fat distribution (unlike android distribution, which is related to testosterone or estrogen deficiency), and second, the balance between estrogen and progesterone affects capillary permeability and, therefore, water retention.
3. *Vascular*: Venolymphatic stasis acts on both adipose and water retention and can change the appearance of the dermis and hypodermis (lipodermatosclerosis lesions of insufficiency).
4. *Nutrition*: According to a quantitative point of view, if the energy balance is not at an equilibrium point, excess contributions over expenses will lead to storage of fat reserves, aggravating cellulite. From a qualitative point of view, some fats, like transfats, tend to store, and industrial sugar (sucrose) may act through insulin receptors on the adipocyte membranes.
5. *Neurological*: Increasing retroperitoneal fat was observed in rats subjected to an electrical stress, repeatedly suggesting a link between lipogenesis, retroperitoneal fibrosis, and stress. The main recognized causes and mechanisms of cellulite are summarized in Table 48.1.

Table 48.1 Causes and Mechanisms of Cellulite

Causes	Mechanism	Means of Evaluation
Genetic	Adiposity	Ultrasound 10 MHz
Hormonal	Adiposity	Densitometry Impedance calculation
Vascular	Water retention	Ultrasound 20 MHz Volumetry
Nutritional	Fibrosis	Palpation
Neurological	Fibrosis	Tonometry

CELLULITE DIAGNOSIS

The positive diagnosis does not raise any difficulties: cellulite is recognized by inspection or palpation and is evident when there is a spontaneous orange-peel appearance when the skin is pinched. (Figure 48.2). It can be localized to the outer surface of the thighs and the inner side of the knees but can also be diffused over the whole of the hypodermis of the abdomen and lower limbs and sometimes the upper limbs or back, usually found in women and sometimes found in men and young children.

The different nosological approaches that have been proposed, such as lipoedema or "paniculopathies edematofibrosis," are not true differential diagnoses. In fact, the three actors (adipose, water retention, and fibrosis) may be present in different degrees. According to the predominance of one or the other of these actors, it will be referred to as *cellulite with water retention* or *hydrolipodystrophy*, *fibrous cellulite* or *fibrolipodystrophy*, and *adipose cellulite* or *lipodystrophy*.

CELLULITE ASSESSMENT

Even if cellulite accumulation is not considered a disease, because it does not cause any complications, cellulite generates severe pain in patients with cancer, and it is a frequent reason for consultation and concern for women. Some authors have

Figure 48.2 Clinical appearance of cellulite.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

spoken of a "disease that does not exist" [29]; it remains true that everyone recognizes, patients and doctors, and its clinicopathological reality is now fully objectified. Evaluation can be carried out by WRI and Liposcore®.

Water Retention Index (WRI)

Proposed in 2000 [12], this method quantifies water retention through the use of high-frequency ultrasound [30–32].

This measures the thickness of the femoral dermis whose variations over short periods of time are related to the water retention phenomenon. Then, this measure is compared to the thickness of the dermis of the anterior aspect of the forearm, where it is relatively thin and constant (Figure 48.3).

The WRI is defined by the ratio of the thickness of the dermis of the forearm to the dermis of the thigh (Box 48.3).

In healthy subjects, the skin of the forearm has a thickness ranging from 0.9 to 1.5 mm and the thigh from 1.3 to 2.3 mm.

Measuring the thickness of the dermis in absolute value is of no interest because of its variability from one individual to another. However, the ratio of the dermis of the forearm to the dermis of the thigh in the subject free from any water retention is consistently above 0.7; in other words, the thigh skin is thicker than the forearm skin, but this change does not exceed 30%.

When the WRI is less than 0.7, this corresponds to a dermal infiltration of water from the capillaries.

The systolic pressure index quantifies arteritis of the lower limbs, the WRI quantifies edematous tissue infiltration.

Cellulite without water retention has a WRI greater than 0.7; cellulite with water retention has a WRI less than 0.7 (Figure 48.3). Reproducibility of the measurement is 2.6% on the forearm and 4.2% on the thigh. So the water retention index is simple, rapid, and reproducible. It differentiates hydrolipodystrophies from lipodystrophy (cellulite with water retention).

Liposcore®

This is a questionnaire that assesses each patient's type of cellulite (Table 48.2). This simple self-administered questionnaire allows a clinical orientation, confirmed by an examination and measurement of the WRI.

BOX 48.3

$$\text{WRI} = \frac{\text{Thickness of the dermis of the forearm (mm)}}{\text{Thickness of the dermis of the thigh (mm)}}$$

THERAPEUTIC STRATEGY

Cellulite is a dysfunction, there are no complications and no morbid character. This is an aesthetic problem whose impact may be important to the quality of life.

It is a chronic disorder that can be improved by medical, surgical, or paramedical treatments, and will require long-term care.

The long-term goal is control.

The modern treatment of cellulite is based on a combination of different tactics (new methods used, techniques, equipment).

In practice, the proposed treatments include the following five components:

1. Cosmetic treatments (slimming creams)
2. Paramedical treatment (physiotherapy institutes)
3. Hydrotherapy treatments (spas, and thalassotherapy)
4. Medical treatment (injection lipolysis focused ultrasound, or laser)
5. Surgical treatment (liposuction, liposculpture)

Cellulite with water retention requires drainage methods: manual lymphatic drainage, pressure therapy, and lymphatic aquadrainage. Topical cosmetics used contain active ingredients such as horse chestnut, pilosella, butcher's broom, ivy, ginkgo biloba, and visnaga vera.

Adipose cellulite can be surgically removed by injection lipolysis, ultrasound or laser, or liposuction. Cosmetic active ingredients such as caffeine, wrack, geranium, and forskolin

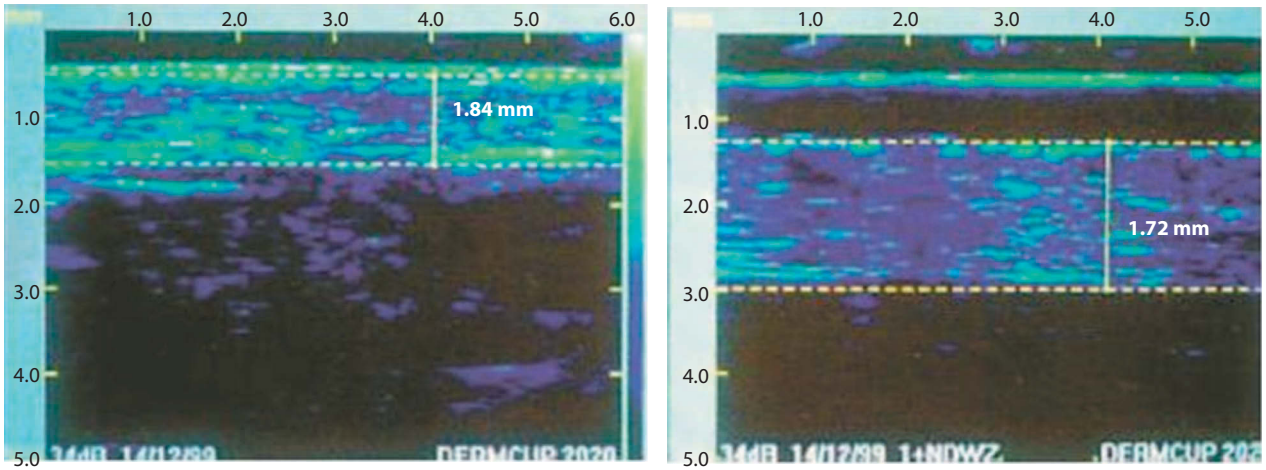


Figure 48.3 High-frequency (20 MHz) ultrasound allows one to measure the water retention index (normal, >0.7).

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Table 48.2 Liposcore® Test: Assessment of Our Type of Cellulite in 20 Questions

1. You are	
Less than 30 years old	A
Between 30 and 50 years old	B
More than 50 years old	C
2. In your family, you already heard about other women complaining of	
Swelling of the legs	A
Overweight	B
Entrenched cellulite	C
3. Your cellulite is located	
On one part of your body (hips, or inner knee, etc.)	A
Or diffusely on the hips and legs	B
4. Do you have excess weight compared to your "ideal weight" (the one where you feel fit)?	
Yes, but variable from one week to another	A
Yes, but variable to an age to another (teenage, pregnancy, menopause, etc.)	B
Yes, remains stable or increasing	C
5. Do you suffer from a feeling of	
Ankle swelling	A
Heavy legs	B
Pain when the leg skin is pinched	C
6. Do you observe the appearance of	
Veinlets visible on your legs	A
Lumpy fat	B
Indurated areas in the lower part of the body relative to the upper portion	C
7. You think you have cellulite for	
Less than 1 year	A
Between 1 and 5 years	B
More than 5 years	C
8. In your diet, you prefer	
Salty food	A
Fatty food	B
Sweet food	C
9. In the balance of your meals, you eat	
Especially in the morning	A
Especially in the evening	B
Between meals	C
10. Do you practice any sport?	
No sport endurance	B
No sweating sport	A
Less than 1 hour walking a day	C
11. Can your weight vary from 1 to 3 kg in less than 48 hours?	
Yes	A
12. If you wear socks, does a mark remain on your skin?	
Yes	A
13. Is your menstruation very abundant or irregular?	
Yes	A
14. Do you feel pain in the pelvis when you have your period?	
Yes	A
15. Do you often have bruising on the legs even for light knock?	
Yes	A
16. Do you experience feelings of hunger during the day?	
Yes	B
17. When you are upset, do you eat more than usual?	
Yes	B
18. Have you ever put on weight after taking the contraceptive pill or hormone treatment?	
Yes	B
19. Do you experience hunger or fatigue during the day?	
Yes	C
20. If you follow a strict diet, do you lose weight from the upper body but rarely from lower limbs?	
Yes	C
Count the letters you selected:	A: __ B: __ C: __

Results:

Mostly A: Cellulite with water retention.
Mostly B: Adipose cellulite.
Mostly C: Fibrous cellulite.
Tied A and B: Adipose cellulite mixed with water retention.
Tied B and C: Adipofibrosis cellulite.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

extract of *Coleus*, which acts like caffeine, will be used as stimulants of lipolysis, associated with substances limiting the transformation of preadipocytes into adipocytes such as *Garcinia cambogia*.

A fibrous cellulite can be improved by a pinch-roll technique, laser that acts on collagen, and creams that act on collagen such as madecassic acid, gluconolactone, and oligomeric proanthocyanidins extracted from grape seeds.

PARAMEDICAL TREATMENT

Used in beauty parlors or by physiotherapists, paramedical treatments stimulate physiological lipolysis (slow) as opposed to "fast" lipolysis methods. In the past 2 years, various systems have been proposed, some constitute genuine innovations and some involve two or three older techniques. Among these devices are the following:

Cellu-M6® (Figure 48.4)

Dynamic pinch-roll method helps fibrosis and water retention. The quality of results is directly dependent on the indication.

An innovation of LPG, Cellu-M6®, used at home is called Wellbox®. Regarding the Cellu-M6, there is a study published by Professor Ortonne confirming the protocol and the results of this technique [33] and a clinical and *in vitro* study led by Humbert [34].

Manual Lymphatic Drainage

Used as a reference method for several years, it is active on the water retention and edema, whether from venous or lymphatic origin. Its complement, the tyre lymphatic drainage or pressure therapy, is also often used [35].

Bodysculptor®

It uses electromagnetic waves at low frequencies that stimulate lipolysis associated with a manual draining massage late in the session. According to the manufacturer, it was shown that "ELF electromagnetic waves are able to specifically stimulate the β-adrenergic receptors and thus may promote … adipocyte lipolysis." The scientific case then presents a study conducted by a physician. The promise is the average loss of two clothing sizes after 12 treatment sessions.

Figure 48.4 Cellu-M6® device.

Vacu-Step®

Originally from Germany, it is a machine with a step. The patient performs step movements in a standing position in a large apparatus that creates a negative air pressure, which is exerted on the entire lower part of the body. The concept is clever: when performing physical exercise of the lower limbs, the blood flows in the muscle. The airspace created by the device will increase the blood flow in the skin and subcutaneous fatty tissue, which can accelerate fat metabolism. It yet remains to demonstrate clinical efficacy study.

Cellusonic®

This is a device that combines two ancient techniques: vacuotherapy, a device creating a localized suction on the skin under the probe, and unfocused ultrasound positioned at the bottom of the probe. Its action is probably very limited and remains to be demonstrated.

Spa Jet

It is a multifunctional box that combines water jet massaging, vibration, affusion showers, and infrared lights, all finished with 2 minutes of cold water jets to firm the tissues. Relaxing and toning are very likely with circulatory stimulation, but the lipolytic action remains to be seen.

Technical Alice®

Using infrared filters of short wavelength, the apparatus seeks transcutaneous thermolipolysis. The argument focuses on the fact that infrared whose wavelength is greater than 1.5 μm is completely absorbed by the water of the superficial layers of the skin. Thus, manufacturers decided to only use the shortest wavelengths associated with electrical muscle stimulation with power modulated in a train of sine waves of 20 Hz. These currents would be particularly active on the deep muscular fibers and would assist in the removal of mobilized fat. A good press release was attached to the system with a clinical study. However, there is no published medical reference.

Inovo Body

This is a device that emits "long infrared" after application of a spray containing a ceramic powder. This powder would be a long infrared vector allowing the absorption of radiation of a wavelength "between 4 and 14 μm." The technique is then followed by massage with a caffeine-based gel and "reed." Promises are 3.2 kg weight loss after 15 sessions of 60 minutes and 2.9 cm average loss of thigh circumference. There are neither published medical studies nor references to the action of the infrared and the ceramic powder on human adipose tissue.

Strange Methods

Many other techniques are proposed such as "anticellulite laser 'class ALS' 3A" named "soft laser" that would have "a dramatic decrease in the ptosis and strengthening action of the skin"; Celluderm®, an electrolipolysis method using an electrotherapy device; and "luxopuncture" that combines traditional energy and current biophysical science.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Electrotherapy

Mainly active on the perivenous muscle (Datavein®, Veino®), it has also been proposed, a few years ago, to accelerate the melting of fatty tissue under the term electrolypolysis. Today, the methods of perivenous muscle electrotherapy are still used in patients who are unable to perform physical exercises.

Starvac

This medical equipment exerts a vacuum effect, which induces a mechanical movement on the skin that we name "cell stretching." This stretching induces a mechanical signal that causes biochemical stimuli. The latter increases the synthesis of collagen, elastin, and hyaluronic acid [34,36].

HYDROTHERAPY TREATMENTS

The development of spas, thalassotherapy centers, and thermal cures, as well as recent work on muscle physiology, led to the development of new hydrotherapy techniques. Two of them stand out.

Lymphatic Aquadrainage

Lymphatic aquadrainage is a new method of lymphatic drainage of the lower limbs that can be performed in a pool at 30°C.

This is an active drainage because it is not the hand of the therapist that works on a passive patient but the patient himself who makes aquatic gymnastics facing underwater jets.

Protocol is based on the bed rest studies whose results have shown that to improve venous and lymphatic return in the lower limbs, it

- Is better to act on the postural muscles
- Is with fascial stretching movements
- Works against resistance
- Involves agonist and antagonist muscles

Postural muscles include the psoas and piriformis in the pelvis, adductors in the thigh, and soleus in the calf. There is a link between the tone of these muscles and the quality of venous return. The flexibility of the fascia, the aponeurotic envelopes of muscles, acts on the venous blood drainage from the surface to the deep.

Muscular work against resistance, which involves agonist and antagonist muscles, is best achieved in water.

A protocol has been validated in a study of 41 patients with vascular edema of the lower limbs from venous or lymphatic origin, evaluated by centimetry, water volume, and high-frequency ultrasound.

The control group consisted of 24 patients performing two sessions per week for 6 weeks of classic aquagymnastics. The evaluated group included 17 patients who completed two sessions per week of lymphatic aquadrainage in a pool, for 6 weeks. Patients in the treatment group reported a significantly greater improvement in their edema, with thinning of 0.6 ± 0.2 cm at the instep of the foot, 0.9 ± 0.3 cm in the ankle, 1.1 ± 0.3 cm in the calf, and 2.2 cm to approximately 0.5 cm at the thigh. The weight loss was 1.5–3.8 kg in the group treated with lymphatic aquadrainage. Improved water retention was evaluated regarding the improvement of the WRI measured by high-frequency ultrasound. It showed an improvement from 0.18 in the treated group compared to 0.07 in the control group.

The treatment protocol combines a 10 minute water gymnastic session with 15 minutes of pedaling on an aquatic bicycle, legs facing the underwater jets. It assists deep drainage of hypodermic tissues of the thighs, calves, and ankles. Water gymnastic movements particularly exercise postural muscles, agonists and antagonists. It is active lymphatic drainage, which combines postural water gymnastics to aquatic bicycle sessions; it is effective on water retention and edema [37].

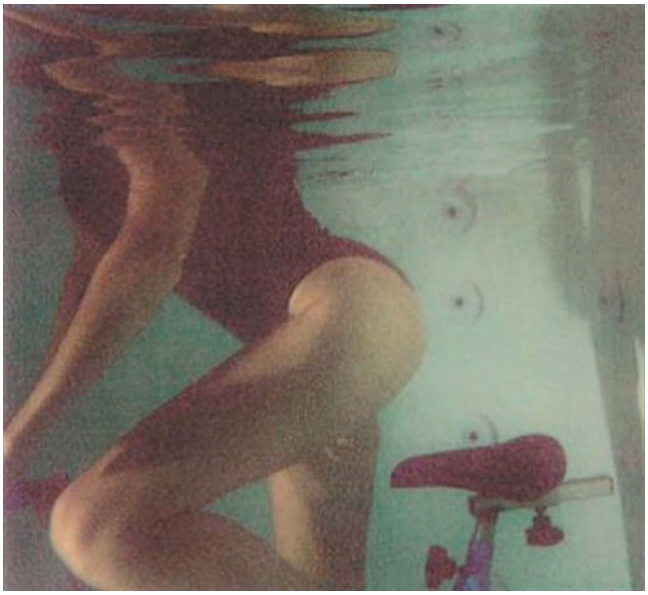


Figure 48.5 Aquatic bicycle.

Aquatic Bicycle

In terms of a usable machine in a paramedical center, the new Hydrobike® aquatic bicycle system that can be used in a special bath 1.2 m deep containing 320 L of water is, in our opinion, one of the best innovations. It meets the criteria of aquadrainage already used by hydrotherapy centers, which have been the subject of a clinical evaluation with a published study. This is an active drainage combining the benefits of hydrotherapy with muscle contractions and causing an average loss of thigh circumference of 0.8 cm (Figure 48.5).

MEDICAL TREATMENT

Lipolysis techniques, fast or slow, act on the adiposity and must be associated with active treatment of water retention or fibrosis. What fast methods of lipolysis are available today?

Injection Lipolysis

Lipolysis is a physiological phenomenon that mobilizes fat storage in case of energy requirement. It can be stimulated by certain drugs such as caffeine, which acts on the alpha-2 adrenergic receptors and causes inhibition of the phosphodiesterase enzyme. Other lipolytic substances include thyroxine, prolactin, conjugated linoleic acid [39–41], *Garcinia* [42,43], guarana, forskolin, geranium, and cangzhu [44].

Recently, three techniques of lipolysis via injections have been proposed: phosphatidylcholine (PPC) injections, injections of hypoosmolar solutions, and injections of lipolytic cocktails or mesotherapy (mésolipolyse). Regarding PPC or

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Lipostabil®, several publications have reported its effectiveness in lipolysis of localized fat deposits [45–50]. However, other publications have reported potential long-term side effects related to its detergent effect. It suggests caution since no marketing authorization (MA) has established its context of use and protocol. In particular, its association with deoxycholate causes muscle risk [48]. Moreover, PPC stimulates the production of P-selectin by the platelets, which can increase the risk of venous thrombosis [51]. Finally, the mixture with electrolytes causes desolubilization of PPC. Injectable preparations contain PCP and therefore should not be associated with electrolytes. But the interstitial medium is rich in electrolytes, which explains the risk of inflammatory reaction with free radical production, whereas this product should have an antioxidant action. Despite these reservations, the technique is already used in general practice and is the subject of a "lipolysis network" on the Internet (with registration and training days available to doctors).

In osmotic lipolysis, the adipose tissue is injected with a solution that is hypo-osmolar compared to the plasma (osmolality between 90 and 18 milliosmoles/L). Proposed in the United States by Dr. Hoefflin, this technique benefits from recent adjustments to the calculation of the density and volume of adipose tissue.

Finally, there is a technique called "lipolysis mesotherapy" using a cocktail containing mannitol, theophylline, buflomedil, rutin, cyclodextrin, and silicon.

Laser Lipolysis (Lipolaser)

Another state-of-the-art technique, it consists of introducing a laser fiber, by a catheter transcutaneous directly into the fatty tissue (Figure 48.6).

Several high-level publications in journals referenced in Medline show a real lipolytic effect observed *in vitro* and *ex vivo* [52–56]. The fat is liquefied by a desorption phenomenon. At a temperature of 65°C, the fat cells enter a phase transition that distorts their wall, validated by measurements carried out on the enthalpy *ex vivo* fat. Measurements on *ex vivo* fat have shown that for a power of 3.2 W, the treated volume is a cone 640 mm^3 (Figure 48.7). For 6.4 W, the treated volume was 9050 mm^3 [44]. At this power, no burning or charring was obtained with an Nd:YAG laser (the laser Deka™) or with a laser diode at 980 nm (the laser Osyris™) (Figure 48.8). A clinical study with a long-pulsed 1064 nm Nd:YAG laser led by Truitt shows mild or moderate improvement in some subjects as rated by blinded evaluators [57].

Figure 48.6 Laser lipolysis; light is visible through the skin.

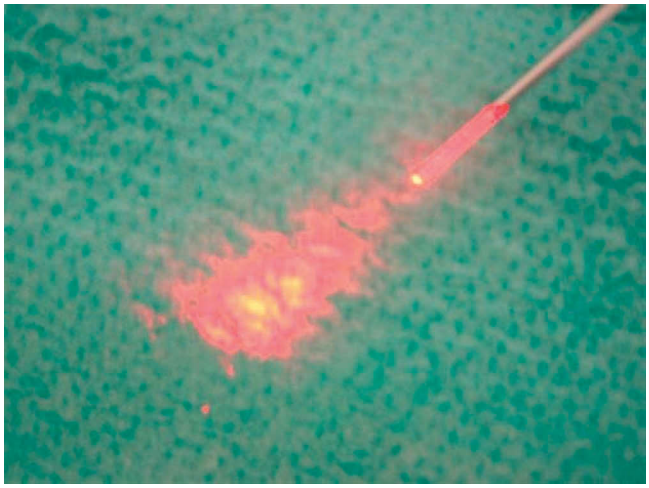


Figure 48.7 Cone area treated by a laser.

Figure 48.8 Laser lipolysis device (Osyris™, Deka).

The penetration depth of the laser beam in the adipose tissue is 12.5 mm for a laser diode of 980 nm wavelength.

Over an area corresponding to the outer side of the thigh, the total volume of mobilized fat is up to 400 mL, which raises the problem of the evacuation of the amount of fat in the

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

venous and lymphatic system. It may induce hepatic steatosis or restocking overflow of fatty acids into adipocytes.

Therefore, given the demonstrated effectiveness of the laser on the fatty tissue, we believe it can grow as a technique that we called "the microlipolysis by lipolaser," which takes place over several sessions, allowing the progressive metabolism of fat released.

Microlipolysis by Lipolaser or Technical ML3

This is a treatment for cellulite and fat deposits by laser lipolysis, which we called lipolaser. The laser is applied directly to adipocytes by way of transcutaneous catheterization. This nonsurgical technique is similar to an injection of laser light, without any removal of substance. It can be done in a medical setting.

Radio-Frequency Lipolysis

It is also a thermal lipolysis obtained by molecular vibrations that are similar to the effect of a microwave. But radio frequency (RF), already tried for a number of years in this indication, is less well controlled than laser. Exactly like a microwave oven, certain areas are hotter than other areas.

RF currently used either unipolar, bipolar, or dermal current alone or in combination with infrared. But its action is best demonstrated on sagging skin and collagen as lipolysis [58–61].

Infrared Lipolysis

Several devices have recently been developed using an infrared light in the range of 700–1800 nm. Their action has mostly been demonstrated on collagen and sagging skin (Titan™ Cutera® of fractionated infrared light from StarLux™ Palomar®). More focused on cellulite, the most successful of these devices is the VelaSmooth™, which combines a bipolar RF probe with infrared light-emitting diode and a system of mechanical rolling massage.

The combination of these three systems in one device acts on two of the three components of cellulite, water retention and fibrosis, which can improve the dimpled appearance of orange peel [62].

Low-Level Laser Therapy

This low-level laser therapy (LLLT) is a stand-alone procedure using green 532 nm diodes for improving the appearance of cellulite in the thighs and buttocks. In a double-blind study, 55.88% of subjects in the LLLT group achieved a decrease of one or more stages on the Nurnberger-Muller grading scale versus three subjects (8.82%) in the placebo-treated group [63]. Future studies will assess the long-term benefits of LLLT for the treatment of cellulite.

Focused Ultrasound Lipolysis

It is a focused ultrasound system (UltraShape® system) (Figure 48.9). This system is innovative and must be differentiated from conventional ultrasound, which is not focused. Ultrasound focusing can concentrate energy on a specific point, leading to a rise in temperature and cavitation behind the rupture of the membrane of adipocytes and the release of triglycerides. Ultrasound focus is a real technical advance but only active at a depth of 15 mm under the skin. So this

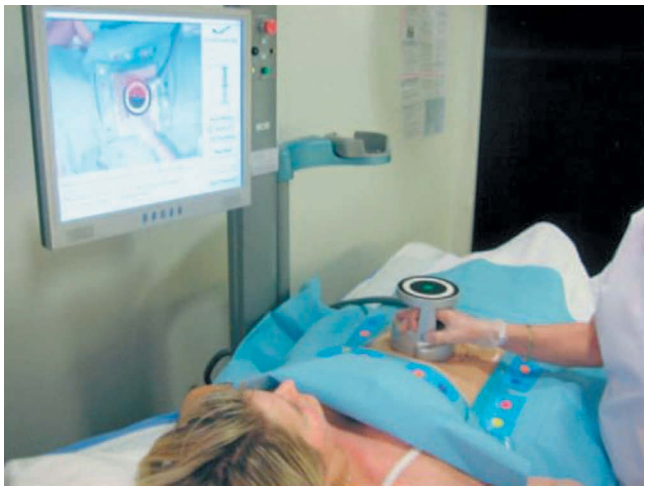


Figure 48.9 Lipolysis by focused ultrasound (UltraShape™, Syneron Candela).

is a treatment for steatomeries. Histological studies showed a selective lipolysis without the involvement of vessels, nerves, and collagen fibers [64]. This tissue selectivity is provided by mechanically dominant effect on the intracellular fat. The effect is primarily mechanical, the ultrasonic acoustic waves converging at a focus volume. The promise of this technology is an average reduction of 2 cm in body circumference after a single session. Two to three sessions are required. An extremely clever digital system avoids overlapping the points of impact. Currently, lipolysis-focused ultrasound with the laser is the most serious alternative to liposuction for the treatment of localized fat deposits.

Cryolipolysis

Ice-shock lipolysis is a noninvasive procedure for reducing subcutaneous fat volume and fibrous cellulite in areas that would normally be treated by liposuction. It uses a combination of acoustic waves and cryolipolysis. Shock waves, used normally in the treatment of renal calculi and musculoskeletal disorders, are focused on the collagen structure of cellulite skin. When used on the skin and underlying fat, they cause a remodeling of the collagen fibers, improving the orange-peel appearance typical of the condition. Cryolipolysis, on the other hand, is a noninvasive method used for the localized destruction of subcutaneous adipocytes, with no effects on lipid or liver marker levels in the bloodstream. The combination of the two procedures causes programmed cell death and slow resorption of destroyed adipocytes. A study conducted on 50 women showed a mean reduction in fat thickness after treatments (3.02 cm). Body circumference was reduced by a mean of 4.45 cm, and the reduction in fat thickness was accompanied by a significant improvement in microcirculation [65].

Mesotherapy

This is the intradermal injection of draining or lipolytic substances. Due to the absence of products having an MA for a lipolytic action injection, most cocktail-injected mesotherapy

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

contains draining substances. However, some clinical studies revealed case of oleoma on the thighs and buttocks that appeared 2 years after the injection of mesotherapy substance for improvement of cellulite, which requires that serious and peer-reviewed investigations must be performed to certify the efficacy and safety of this procedure [66,67].

SURGICAL TREATMENTS

Used as a reference method that acts on fatty tissue, liposuction is most effective on steatomeries. It must be combined with methods acting on the superficial fat, water retention, and fibrosis [68,69].

FOOD TIPS AND AN ANTI-CELLULITE DIET

We must reduce the amount of saturated fatty acids, triglycerides, and sucrose in the diet. In the cellulite fat, a disorder of glucose uptake by adipocytes controlled by insulin, playing a fundamental role in lipogenesis, may be highlighted. Hence, there is a need to reduce consumption of industrial sugar.

In addition, it is necessary to promote the consumption of antioxidant nutrients such as vitamins E and C, beta-carotene, zinc, and selenium. Indeed, the negative action of free radicals on the vascular walls is regularly mentioned.

Foods rich in dietary fiber can prevent a constipation-aggravating factor for venous stasis. Flavonoids, polyphenols, and grape seed derivatives promote drainage action. Foods like garlic, onions, and grapefruit improve blood flow. Finally, high biological value proteins are needed to maintain good muscle tone.

Taking into account all these elements provides a true anti-water retention regimen.

EVOLUTION AND MONITORING

Cellulite must be regarded as a chronic dysfunction. Although not a disease, it does not change unless it is of long term and requires a balance.

To balance cellulites as we balance diabetes or arteriosclerosis, it will require action on all the aggravating factors: power, muscle tone, stress, hormonal imbalance, etc.

The doctors will offer a one-time treatment (laser, focused ultrasound, injections, or liposuction) to mobilize stored fat locally. The method will be selected according to the type of cellulite diagnosed. Then, in the long term, a balanced diet and muscle balance should be sought to avoid a gradual recurrence. Psychological work on body image and self-esteem should not be neglected in order to avoid excessive requests. Cellulite is in no way a health risk, and the appreciation of the aesthetic disgrace should be regularly reduced to a reasonable level.

CONCLUSION

From this multifactorial approach of cellulite, it becomes possible to orient women with cellulite to methods to directly attack the fat: injection of lipolytic products, laser, focused ultrasound, application of caffeine creams, and liposuction.

When it comes to edematous cellulite with water retention, all methods of drainage will help: manual lymphatic drainage, lymphatic aquadrainage, Cellu-M6, pressure therapy, and draining creams.

When the fibrous component of cellulite dominates, giving it an indurated consistency, only certain methods that claim to act on fibrosis are useful, such as the Cellu-M6 or laser.

In all cases, the action on the muscle is important. The doctor may advise new methods of active vascular gymnastics, acting preferentially on the deep postural muscles, to improve venous circulation.

Finally, improving the quality of food and clearing of eating disorders are needed in all cases.

REFERENCES

1. Illouz YG. *La sculpture chirurgicale par lipoplastie*. Paris, France: Arnette, 1988.
2. Elia D, Raison J. *La composition corporelle*. Paris, France: Flammarion, 2001.
3. Blanchemaison P. Érysipèle et cellulite infectieuse des membres inférieurs. *Phlebologie* 1998; 51:509–511.
4. Blanchemaison P, Elia D, Hagege JC et al. *La cellulite*. Paris, France: Edition Privat, 1997.
5. Lagèze P. Sciatique et infiltration cellulalgique (thèse de médecine). Lyon, France, 1929.
6. Allen EW. Lipoedema of the leg: Syndrome characterized by fat leg and oedema. *Proc Staff Meet Mayo Clin* 1940; 15:184.
7. Nürnberger F, Müller G. So-called cellulite: An invented disease. *J Dermatol Surg Oncol* 1978; 4:221–229.
8. Merlen JF, Curi FB, Sarteel AM. La cellulite, affection microvasculoconjonctive. *Phlebologie* 1979; 3:279–282.
9. Merlen JF, Curri SB. Raisons anatomo-pathologiques de la cellulite. *J Mal Vasc* 1984; 9:53–54.
10. Curri SB, Merlen JF. Troubles micro-vasculaires du tissu adipeux. *J Mal Vasc* 1986; 11:303–309.
11. Blanchemaison P. La cellulite de la physiopathologie à la classification IFAT. *Actual Vasc Int* 2000; 85:15–19.
12. Blanchemaison P, Diridollou S, Cauquil J, Poulain D. L'indice de rétention d'eau: Une nouvelle méthode de quantification par échographie de haute fréquence de la cellulite. *Actual Vasc Int* 2000; 85:6–11.
13. Hexsel DM, Dal'forno T, Hexsel, CL. A validated photonumeric cellulite severity scale. *J Eur Acad Dermatol Venereol* 2009 May; 23(5):523–528.
14. Knobloch K, Joest B, Vogt PM. Cellulite and extracorporeal shockwave therapy (CelluShock-2009)—A randomized trial. *BMC Womens Health* 2010; 10:29.
15. Lafontan M, Berlan M. Fat cell adrenergic receptors and the control of white and brown fat cell function. *J Lipid Res* 1993; 34:1057–1091.
16. Lafontan M. Régulation adrénergique de la lipolyse et de la vascularisation du tissu adipeux. *Rev Prat* 1994; 44:19–23.
17. Lafontan M, Berlan M. Evidence for the alpha2-nature of the alphaadrenergic receptor inhibiting lyposis in human fat cells. *Eur J Pharmacol* 1980; 66:87–93.
18. Galitzky J, Lafontan M, Nordenström J, Amer P. Role of vascular alpha2-adrenoceptors in regulating lipid mobilization from human adipose tissue. *J Clin Invest* 1993; 91:1997–2003.
19. Trayhurn P, Beattie JH. Physiological role of adipose tissue: White adipose tissue as an endocrine and secretory organ. *Proc Nutr Soc* 2001; 60:329–339.
20. Van Dijk G. The role of leptin in the regulation of energy balance and adiposity. *J Neuroendocrinol* 2001; 13:913–921.
21. Hoffstedt J, Arvidsson E, Sjolin E, Wahlen K, Arner P. Adipose tissue adiponectin production and adiponectin serum concentration in human obesity and insulin resistance. *J Clin Endocrinol Metab* 2004; 89:1391–1396.
22. Bulló M, García-Lorda P, Peinado-Onsurbe J et al. TNF-alpha expression of subcutaneous adipose tissue in obese and morbid obese females: Relationship to adipocyte LPL activity and leptin synthesis. *Int J Obes Relat Metab Disord* 2002; 26:652–658.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

23. Emanuele E, Minoretti P, Altabas K, Gaeta E, Altabas V. Adiponectin expression in subcutaneous adipose tissue is reduced in women with cellulite. *Int J Dermatol* 2011 April; 50(4):412–416.
24. Lafontan M, Langin D. Lipolysis and lipid mobilization in human adipose tissue. *Prog Lipid Res* 2009 September; 48(5):275–297.
25. Blanchemaison P. Physiopathologie et classification des oedèmes vasculaires. *Angiologie* 2000; 52:47–50.
26. Blanchemaison P. Trois formes de cellulite, trois programmes de traitement: La méthode R-Fat. *J Med Esthet Chir Derm* 2005; 32(128):221–230.
27. Blanchemaison P. D'où viennent la fibrose et le relâchement des tissus dans la cellulite? *J Med Esthet Chir Derm* 2006; 33(131):175–179.
28. de la Casa Almeida M, Suarez Serrano C, Rebollo Roldán J, Jiménez Rejano JJ. Cellulite's aetiology: A review. *J Eur Acad Dermatol Venereol* 2013 March; 27(3):273–278.
29. Grosshans E. Les traitements de la cellulite: Inutiles ou dangereux ! *Rev Prat Med Gen* 1993; 214:13–15.
30. Perin F, Pittet JC, Schnebert S. Ultrasonic assessment of variations in thickness of subcutaneous fat during the normal menstrual cycle. *Eur J Ultrasound* 2000; 11:7–14.
31. Diridollou S, Berson M. An in vivo method for measuring the mechanical properties of the skin using ultrasound. *Ultrasound Med Biol* 1998; 24:215–224.
32. Blanchemaison P. L'échographie de haute fréquence en phlébologie. *Phlebologie* 2000; 53:271–273.
33. Ortonne JP, Queille-Roussel C, Duteil L. Traitement de la cellulite: Efficacité et rendement à 6 mois de l'endermologie. *Nouv Dermatol* 2004; 23:261–269.
34. Humbert P, Fanian F, Lihoreau T, Jeudy A, Elkhyat A, Robin S, Courderot-Masuyer C, Tauzin H, Lafforgue C, Haftek M. Mécano-Stimulation™ of the skin improves sagging score and induces beneficial functional modification of the fibroblasts: Clinical, biological, and histological evaluations. *Clin Interv Aging* 2015 February 2; 10:387–403.
35. Bayrakci Tunay V, Akbayrak T, Bakar Y, Kayihan H, Ergun N. Effects of mechanical massage, manual lymphatic drainage and connective tissue manipulation techniques on fat mass in women with cellulite. *J Eur Acad Dermatol Venereol* 2010 February; 24(2):138–142.
36. Huang C, Miyazaki K, Akaishi S, Watanabe A, Hyakusoku H, Ogawa R. Biological effects of cellular stretch on human dermal fibroblasts. *J Plast Reconstr Aesthet Surg* 2013 December; 66(12):e351–e361.
37. Blanchemaison P. L'aquadrainage lymphatique: Une nouvelle méthode de traitement de la rétention d'eau et de l'oedème des membres inférieurs. *Phlebologie* 2004; 57:75–80.
38. Blankson H, Stakkestad JA, Fagertun H, Thom E, Wadstein J, Gudmundsen O. Conjugated linoleic acid reduces body fat mass in overweight and obese humans. *J Nutr* 2000; 130:2943–2948.
39. Fantino AS. Acides linoléiques conjugués et composition corporelle: Étude pilote de l'efficacité et de la tolérance chez le sujet humain (thèse de doctorat en médecine). Université Claude Bernard, Lyon I, France, 2001, 105pp.
40. Riserus U, Berglund L, Vessby B. Conjugated linoleic acid (CLA) reduced animal adipose tissue in obese middle-aged men with signs of the metabolic syndrome: A randomised controlled trial. *Int J Obes Relat Metad Disord* 2001; 25:1129–1135.
41. Petridou A, Mougios V, Sagredos A. supplementation with CLA: Isomer incorporation into serum lipids and effect on body fat of women. *Lipids* 2003; 38:805–811.
42. Hasegawa N. Garcinia extract inhibits lipid droplet accumulation without affecting adipose conversion in T3-L1 cells. *Phytother Res* 2001; 15:172–173.
43. Heymsfield SB, Allison DB, Vasselli JR, Pietrobelli A, Greenfield D, Nunez C. *Garcinia cambogia* (hydroxycitric acid) as a potential antiobesity agent: A randomized controlled trial. *JAMA* 1998; 280:1596–1600.
44. Franchi J, Pellicier F, André P, Schnebert S. Adipocyte and the story of slimming products. *Pathol Biol* 2003; 51:244–247.
45. Hexsel D, Serra M, Mazzuco R, Dal'Forno T, Zechmeister D. Phosphatidylcholine in the treatment of localized fat. *J Drugs Dermatol* 2003; 2:511–518.
46. De Goursac C. Nouvelle mésothérapie de la cellulite avec la lécithine de soja. *J Med Esthet Chir Derm* 2005; 32(126):105–109.
47. Rotunda AM, Ablon G, Kolodney MS. Lipomas treated with subcutaneous deoxycholate injections. *J Am Acad Dermatol* 2005; 53:973–978.
48. Rotunda AM, Suzuki H, Moy RL, Kolodney MS. Detergent effects of sodium deoxycholate are a major feature of an injectable phosphatidylcholine formulation used for localized fat dissolution. *Dermatol Surg* 2004; 30:1001–1008.
49. Kadowaki H, Patton GM, Robins SJ. Effect of phosphatidylcholine molecular species on the uptake of HDL triglycerides and cholesteryl esters by the liver. *J Lipid Res* 1993; 34:180–189.
50. Takahashi M, Okazaki H, Ogata Y, Takeuchi K, Ikeda U, Shimada K. Lysophosphatidylcholine induces apoptosis in human endothelial cells through a p38-mitogen-activated protein kinase-dependent mechanism. *Atherosclerosis* 2002; 161:387–394.
51. Murohara T, Scalia R, Lefer AM. lysophosphatidylcholine promotes P-selectin expression in platelets and endothelial cells. Possible involvement of protein kinase C activation and its inhibition by nitric oxide donors. *Circ Res* 1996; 78:780–789.
52. Neira R, Arroyave J, Ramirez H et al. Fat liquefaction: Effect of low-level laser energy on adipose tissue. *Plast Reconstr Surg* 2002; 110:912–922.
53. Ichikawa K, Miyasaka M, Tanaka R, Tanino R, Mizukami K, Wakaki M. Histologic evaluation of the pulsed Nd:YAG laser for laser lipolysis. *Lasers Surg Med* 2005; 36:43–46.
54. Kuwahara K, Gladstone HB, Gupta V, Kireev V, Neel V, Moy RL. Rupture of fat cells using laser-generated ultra short stress waves. *Lasers Surg Med* 2003; 32:279–285.
55. Badin AZ, Gondek LB, Garcia MJ, Valle LC, Flizikowski FB, de Noronha L. Analysis of laser lipolysis effects on human tissue samples obtained from liposuction. *Aesthetic Plast Surg* 2005; 29:281–286.
56. Badin AZ, Moraes LM, Gondek L, Chiaratti MG, Canta L. Laser lipolysis: Flaccidity under control. *Aesthetic Plast Surg* 2002; 26:335–339.
57. Truitt A, Elkeeb L, Ortiz A, Saedi N, Echague A, Kelly KM. Evaluation of a long pulsed 1064-nm Nd:YAG laser for improvement in appearance of cellulite. *J Cosmet Laser Ther* 2012 June; 14(3):139–144.
58. Krueger N, Sadick NS. New-generation radiofrequency technology. *Cutis* 2013 January; 91(1):39–46.
59. Boisnic S, Branchet MC. Ex vivo human skin evaluation of localized fat reduction and anti-aging effect by TriPollar radio frequency treatments. *J Cosmet Laser Ther* 2010 February; 12(1):25–31.
60. Trelles MA, van der Lugt C, Mordon S, Ribé A, Al-Zarouni M. Histological findings in adipocytes when cellulite is treated with a variable-emission radiofrequency system. *Lasers Med Sci* 2010 March; 25(2):191–195.
61. Trelles MA, Mordon SR. Adipocyte membrane lysis observed after cellulite treatment is performed with radiofrequency. *Aesthetic Plast Surg* 2009 January; 33(1):125–128.
62. Sadick NS, Mulholland RS. A prospective clinical study to evaluate the efficacy and safety of cellulite treatment using the combination of optical and RF energies for subcutaneous tissue heating. *J Cosmet Laser Ther* 2004; 6:1–4.
63. Jackson RF, Roche GC, Shanks SC. A double-blind, placebo-controlled randomized trial evaluating the ability of low-level laser therapy to improve the appearance of cellulite. *Lasers Surg Med* 2013 March; 45(3):141–147.
64. Knobloch K, Joest B, Vogt PM. Focused ultrasound for non-invasive body contouring in cellulite. *Plast Reconstr Surg* 2010 February; 125(2):751.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

65. Ferraro GA, De Francesco F, Cataldo C, Rossano F, Nicoletti G, D'Andrea F. Synergistic effects of cryolipolysis and shock waves for noninvasive body contouring. *Aesthetic Plast Surg* 2012 June; 36(3):666–679.
66. Ramos-e-Silva M, Pereira AL, Ramos-e-Silva S, Piñeiro-Maceira J. Oleoma: Rare complication of mesotherapy for cellulite. *Int J Dermatol* 2012 February; 51(2):162–167.
67. Rotunda AM, Avram MM, Avram AS. Cellulite: Is there a role for injectables? *J Cosmet Laser Ther* 2005 December; 7(3–4):147–154.
68. Toledo LS. Syringe liposculpture: Two-year experience. *Aesthetic Plast Surg* 1991; 15:321–326.
69. Illouz YG. Complications de la lipoaspiration. *Ann Chir Plast Esthet* 2004; 49:614–629.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Cryolipolysis

Hernán Pinto

INTRODUCTION

Historical Background

During the 2000s, significant studies were carried out, laying the methodological groundwork for leveraging the combined application of vacuum and heat extraction for the treatment of localized adiposities. Such studies have given rise to a new therapy, initially called cryolipolysis but nowadays found in the literature indistinctly referred to as cryolipolysis, lipocryolysis, or selective cryolysis [1–3]. Although the first records of lipocryolysis as such date back to the early twenty-first century, these have appeared almost 40 years after the first publication that already and unknowingly hinted at the effectiveness of the future technique. In the 1970s, inflammatory lesions of the adipose tissue of the face (cheeks) of children after eating popsicles were described. These were the first cases of a condition later known as popsicle panniculitis [4,5]. Almost 10 years after the works on popsicle panniculitis, other physiopathologically identical cases appeared in women with inflammatory lesions of their inner thighs after horseback riding in cold weather. This new syndrome was named equestrian panniculitis [6–8]. Both popsicle panniculitis and equestrian panniculitis turned out to be clinical manifestations in different age groups of a single condition: cold panniculitis. This panniculitis is sometimes referred to as Haxthausen's disease (not to be confused with *keratoderma climacterium*, sometimes also called Haxthausen's disease [9]), after Danish H. Haxthausen, who described the first cases in 1937, though he mentioned in his 1941 work that Hochsinger et al. had already described a "probably identical condition" in 1902 [6]. This is believed to be the first bibliographical mention or description of a case of cold panniculitis as a clinical manifestation of an effect of the cold on adipose tissue.

Nomenclature

In the past few years, the literature has created some confusion regarding the name of this procedure, often arbitrarily changing prefixes and suffixes to call it something else, and other times using the same terms to refer to techniques based on some of its physical principles but which are radically different. Thus, we can currently find multiple synonyms for this technology: the already mentioned *Cryolipolysis*™ [1], *lipocryolysis* [10], *or selective cryolysis* [11] and any other combination of the words "cold," "lysis," and "selective" and the prefixes or suffixes "cryo," "lipo," and "vacuum." In addition, some of these names are under commercial protection, and often the general public has been misled to believe that the words used in certain trademarks are the name of the technique, and vice versa. In this chapter, we will use the name lipocryolysis.

At a time when lipocryolysis is so in fashion, when the market's thirst for the latest novelty is sky-high, and when the consumers' demand for technologies that actually work is at its peak, it is not surprising to see a proliferation of platforms combining all kinds of principles of action—often absurd and even antagonistic but always promising and having miraculous results. For this reason, what is truly important is to understand the basis of this treatment in order to be able to set good and effective lipocryolysis equipments apart from those that are not. At the time of its inception, lipocryolysis was a true revolution and one of the most novel techniques. Nowadays, it has paved its own way and found a place within the therapeutic arsenal that doctors specialized in aesthetic medicine can offer their patients [12].

PHYSICS BEHIND THE TECHNOLOGY

Overview of Heat Transfer

It is widely known that a cup of hot tea left on a table will cool down, while the opposite will happen if what we leave on the table is a jar of jam right out of the refrigerator [13]. This is due to a transfer of energy from the medium with the higher temperature to the medium with the lower temperature. Heat is the form of energy that can be transferred from one system to another [13]. Thermodynamics is the science that studies the amount of heat transferred as a system goes from one equilibrium state to another. Heat transfer is the science that seeks to determine the reasons behind such transfer [13].

Heat Transfer Mechanisms

Radiation is the energy emitted by matter in the form of electromagnetic waves as a result of changes in the electronic configurations of atoms and molecules.

Convection is the transfer of energy between a solid surface and the liquid or gas moving around it. It involves the combined effects of conduction and fluid flow [14]. The greater a fluid's flow rate, the greater the heat transfer by convection.

Conduction (thermal conductivity) is a property of matter in any of its states. Although the mechanism of action is not identical in liquids, gases, and solids, it can be described as a transfer of heat from the more energetic particles in a certain material to its less energetic particles. This is the main mechanism underlying heat transfer by lipocryolysis. The speed or rate of heat conduction through a medium will be based on its geometric configuration, its thickness, the material it is made of, and the temperature difference through it [15]. The variables playing a role in and affecting heat conduction are naturally summarized in Fourier's Law, named after Jean Baptiste Joseph Fourier, who developed the mathematical basis for the understanding of heat conductivity [16]. It can be deducted from his law that heat conduction through a material will be greater the greater its surface, the greater the temperature difference through it, and the smaller its thickness.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Cooling or Cooling Down?

The cooling power of lipocryolysis machines has been used and abused as a marketing tool. The cooling down capability of a machine is a completely different issue from its tissue cooling capability. Unwitting physicians normally believe that machines are more powerful because they cool down way beyond 0°C. But skin cannot tolerate these freezing temperatures for a long time. Firms use devices like a gel pad or a special cloth that they often characterize as "antifreezing." Their claims are diverse, but these devices always act as a barrier. Lipocryolysis exchanges temperature between patient and machine by conduction (convection and irradiation are negligible). By using these "antifreezing" devices, heat conduction gets impaired, and thus, machine operational temperature (the temperature to which tissues are exposed) falls into the temperature range allowed by the skin (which is absolutely obvious, mandatory, and the only option we all have).

Physical Principles of Lipocryolysis

Lipocryolysis platforms are usually configured as a base and an applicator head, joined by a hose. The base houses several components and usually has a touch screen as an interface between the user and the device. The applicator head has a long cavity specially designed to hold the tissue to be treated. Inside the cavity, there are stainless steel plates and a hole for vacuum application.

Heat Extraction

For this purpose, Peltier devices (PDs) are used. PDs were named after Jean Charles Athanase Peltier, who invented them and discovered the physical principle by which electric currents can create great differences in temperature in materials with certain characteristics [17]. PDs use electrothermal conversion to create a temperature gradient to cool one of the device's faces and heat the opposite one. This was initially a significant technical disadvantage when it came to building the first lipocryolysis machines but now is a major advantage for the new generation of contrast lipocryolysis equipments using tempering technology [18]. Thermal contrast equipments work by alternating heat and cold cycles. This can be easily obtained by reversing the polarity of the current flowing through the PD; the same face of the cell cools down or heats up as necessary.

Lipocryolysis affects adipocytes by changing their temperature. Machines extract heat until the target temperature is detected. At that time, the energy of the "Peltier" device is downregulated so that it will not extract any further heat from tissues. As tissues reheat, machines increase their energy to extract again a few tenths of a degree. This "push–pull" regulation mechanism continues throughout the session, during which high-quality machines measure tissue or Peltier–epidermis interface temperature every second. This strict temperature control enables the best therapeutic result possible while maintaining full safety and protection of surrounding tissues [19]. Heat extraction should be performed in a fully controlled manner. By maintaining the target temperature over time, adipose tissue is cooled down to a temperature equal to or lower than the temperature described in the literature as the minimum necessary to trigger the stimulus that will cause the therapeutic effect, namely, 10.38°C [11].

Heat extraction will be achieved more or less quickly based on the energy that can be created by the machine. This has been a very significant factor in the past for differentiating state-of-the-art machines because it translated into shorter sessions. However, although this factor is still significant today, it is not as relevant. First, it is because most machines have greatly improved in terms of the power delivered, and practically all of them can achieve top rates. And second, it is because now we know that the speed at which adipocyte temperature is lowered (°C/min) does not only condition results it is but is crucial [20] (Figure 49.1). Second-generation lipocryolysis machines or contrast lipolysis machines pay great attention to this variable and have ended the "race" to create higher extraction power and shorter sessions. The main reason is that, although original lipocryolysis studies showed intra-adipocyte crystallization at temperature reduction speeds around 10°C/min [11], today we know that smaller temperature reduction speeds lead to better results, both in terms of direct cell lysis and intra-adipocyte crystallization [20] (Figure 49.2).

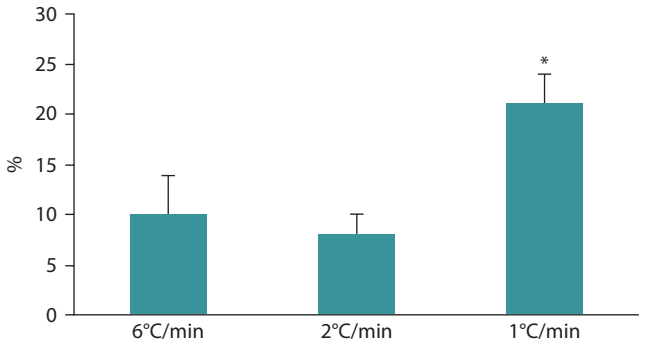


Figure 49.1 Percentage of damaged cells after exposure to different cooling speeds. In samples subjected to a cooling rate of 6°C/min, there was a 10% ± 4% of cell damage. When the cooling rate was 2°C/min, the cell damage was similar, 8% ± 2%, and when a cooling rate of 1°C/min was used, the percentage of cell damage raised to 21% ± 3%. *ANOVA p = 0.0168. (From Pinto H and Melamed G, *J Surg*, 3(1–1), 11, 2015. With permission.)

Other types of equipment use a different but equally safe mechanism for temperature control: gradient calculation. They use algorithms to calculate session time and apply the original push–pull mechanism during only part of the treatment. The difference between these and the original equipments is that they use a "temperature floor," which is basically a maximum emission time. Once this time as elapsed, the machine cuts heat extraction power regardless of the temperature reached by tissues. The "temperature floor" is an added safety measure [21]. The purpose of lipocryolysis is to lower the temperature of adipocytes until certain intracellular changes leading to their death have taken place. This technology is exclusively based on cell thermal conditioning.

Vacuum

Lipocryolysis leverages the physical properties of vacuum. Every session of lipocryolysis begins with the machine creating a vacuum in the area to be treated. The negative pressure of vacuum ensures the correct positioning inside the applicator of the tissue from which heat will be extracted, as well as a reduction of blood flow in the area, resulting in lower thermal contribution [11]. A lower thermal contribution makes it easier to reduce temperature in the tissues suctioned inside the applicator, which is the factor enabling a much greater heat extraction than achieved in the past by any other nonvacuum

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

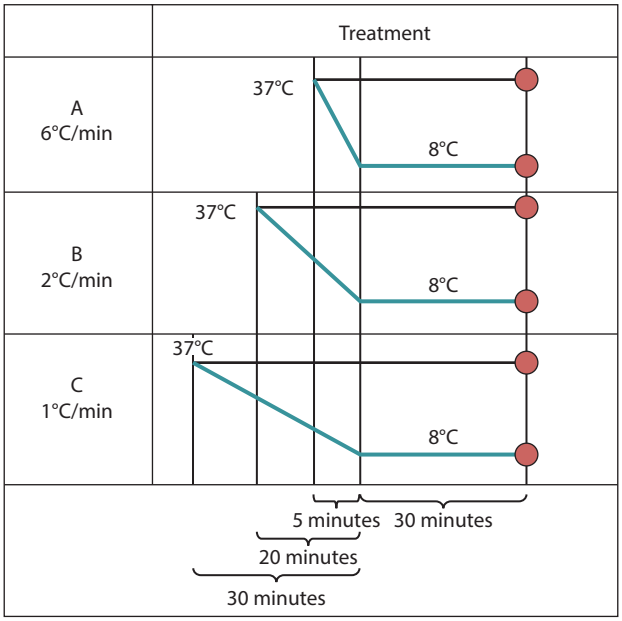


Figure 49.2 Three tempering conditions: from 37°C to 8°C, at cooling speeds of 6°C/min, 2°C/min, and 1°C/min and 30 minutes at 8°C (blue line). Control groups for each condition: 37°C (black line). (From Pinto H and Melamed G, *J Surg*, 3(1–1), 11, 2015. With permission.)

technology [11]. Vacuum is critical to achieve the best results! However, the use of vacuum also entails some determinants for the lipocryolysis technique:

1. *Pain*: Although lipocryolysis machines typically create suction pressure below one atmosphere, suction can be very uncomfortable for the patient if not applied gradually. At first, the machine suctions only as much as necessary to position tissues inside the applicator. Then, it increases suction pressure because the cold applied during the first few minutes in the session has an anesthetic effect. Regulation of this process is fully automatic. Although the best machines available offer a way to adjust vacuum administration, this is rarely necessary.
2. *Friction*: Tissue suction inside the head can entail unwanted friction between the walls of the applicator and the tissues between them. Gel is always used to prevent any irritation or discomfort. This product does not have any special features other than being a gel. Its conductor, echogenic, and thermal properties are irrelevant. However, the gel should be as unaggressive as possible. Hypersensitivity to this type of product has been described [22]. Although extremely rare, it should always be ruled out at the time of taking the patient's medical history. The use of gels with added substances, whether lipolytic or any other kind, has also been proposed. Although this idea is sensible and very attractive, several issues keep us from putting it into practice. First, there is an unlikely chance that a physical interaction will take place when the temperature of the active ingredient is subsequently lowered. In other words, we do not know what will happen to the product when it is cooled down. Second, even if we could be sure that no such interaction will take place, we should be certain that neither the vacuum nor the cold will increase penetration of the active ingredient. For the aforementioned reasons, I believe that this practice does not make any sense.
3. *Immobility*: Due to suction, the head of the machine should remain fixed on the area to be treated throughout the session. Skin temperature is lowered to the target temperature, but there is a very important safety margin, as cold burns and other issues would multiply if an application temperature below 0°C was achieved and maintained during too many minutes. This is why temperature should be lowered in a controlled manner and measured to the nearest 10th of a degree. This is also why heads are static and cannot move during the lipocryolysis session. Vacuum is created for the same reason. On the other hand, those platforms that work with temperatures below 0°C should move the head constantly because the skin should not be subjected to such low temperatures for long. Because the head moves, vacuum cannot be created and therefore, blood flow is not interrupted. The paradoxical consequence of all of these is that platforms working at extremely low temperatures are usually less effective, because they extract less heat from adipose tissue than machines that lower tissue temperature less but with simultaneous vacuum. What actually happens is that this type of platform cools down to a lower temperature but extracts less heat from tissues. A platform's ability to cool down to a lower temperature does not mean it will achieve better results since better results are only associated with a greater ability to extract heat from adipose tissue. Results are proportional to the heat extracted from tissue, not the temperature to which the machine cools down. There is a temperature limit (TL) below which the stimulus leading to therapeutic results is triggered. Ultimately, if adipocyte temperature can be lowered below this TL, the results of lipocryolysis will be observed; conversely, if temperature of the target tissue is not lowered below this TL, there will be no adipocytolytic results. In conclusion, a machine unable to lower the temperature of the target tissue below the TL is not a lipocryolysis machine. It is not a question of cooling down to a greater extent by means of brute force, but of extracting more heat from tissues in an efficient, controlled, dynamic, and safe manner.
4. *Coloring*: When the session is completed and the heat is removed, the treated area can display a color from light red to dark purple [23]. Darker colors can frighten the patient, who should be warned that this situation is normal and almost immediately reversible; in a few seconds, the color of the treated area will turn to red and then pink. One hour after the lipocryolysis session, in general, the remaining erythema will not be different than that which may be caused by any other treatment.
5. *Adverse effects*: The frequency and severity of bruising will be directly proportional to application time and vacuum intensity [23].

ACTION MECHANISM

For a long time, white adipose tissue (WAT) was believed to be a rather passive tissue that served as a store of energy in the form of triacylglycerols (TAGs) to be provided to the rest of the body in case of energy deficit. In recent years, our understanding of the physiopathology of WAT has progressed remarkably, and it has been shown that it is not merely a fat reserve, but a significant endocrine organ that plays an active role not only in

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

maintaining energy homeostasis but also in regulating various physiological processes, such as controlling blood glucose, the immune system, and reproduction.

There are multiple ways to act on the regulation of the body's adipose tissue content, including intake control, central nervous system regulation, energy expenditure, endocrine system regulation, and direct fatty tissue removal. That local fat tissue removal was the only level at which lipocryolysis acted was a fact taken for granted. Today, this concept is under review [20]. The main two processes for noninvasive fat elimination are lipolysis and adipocytolysis. Lipolysis is a normal, reversible physiological process of a marked metabolic, molecular, or chemical nature. Adipocytolysis, on the other hand, is an irreversible cellular process that is mainly physical.

Apoptosis and necrosis occur. The apoptotic hypothesis was originally accepted in the absence of evidence partly because of a delayed fat reduction response after procedure and partly because no severe posttreatment inflammatory response was observed. But we already reported some immediate cellular damage after cold exposure [20], and it is not clear whether the crystallization observed would result in later apoptosis or in immediate necrosis. New studies addressing the apoptosis process should be performed.

Adipocytes are the specific cells that make up adipose tissue. Although they have some particular features, adipocytes are capable of reproducing just like any other type of cell. An increase in the number of a certain type of cell is called hyperplasia. In addition, however, adipocytes are capable of increasing in content and therefore in size. An increase in the size of a certain type of cell is called hypertrophy. The adipose tissue disorders of the great majority of our patients will be associated with adipocyte hypertrophy.

Three concepts are extremely important to fully understand lipocryolysis action mechanisms:

Lipolysis

Lipolysis is a well-studied, natural, chemical, molecular, and reversible metabolic process [24]. It takes place in our bodies all the time and it is strictly regulated. Lipolysis is a central pathway for the disposal of energy and for the regulation of the metabolic state of the body. When specific receptors are stimulated, a cascade-type pathway is activated, where several intermediate enzymes are phosphorylated and undergo changes until they eventually stimulate any lipase. Lipases acting on TAGs release fatty acids and glycerol (Figure 49.3). Those released fatty acids that are not reesterified into TAGs may be involved in a specific type of oxidation called β-oxidation. In few words, β-oxidation can be described as a sequence of four basic reactions where a fatty acid loses two carbon atoms in the form of an acetyl CoA molecule. Each new round of β-oxidation extracts a new molecule of acetyl CoA from the β-oxidized fatty acid, and the fatty acid is shortened. Acetyl CoA can follow various metabolic pathways based on external stimuli and on the body's energy and structure requirements. Such pathways typically include (1) entering the tricarboxylic acid cycle (Krebs cycle) to be fully oxidized and produce energy through ATP, GTP, and NADH+; (2) generating ketone bodies (ketogenesis) through acetoacetyl CoA and hydroxymethylglutaryl CoA to export energy to peripheral tissues; (3) resynthesizing fatty acids; or (4) taking part in the synthesis of ketogenic or "nonglucogenic" amino acids. At the cellular level, the effect of lipolysis is expressed as adipocyte hypotrophy.

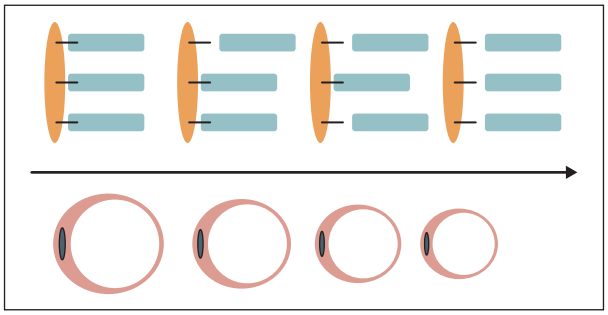


Figure 49.3 Lipolysis: lipases act on TAGs and release fatty acids and glycerol. Adipocytes are reduced in size: hypotrophy.

The cell is not destroyed and its contents are not released; it only metabolizes its lipid load [25]. Therefore, lipolysis does not trigger any inflammatory reaction, and treatments seeking to stimulate or speed up this pathway do not have any adverse effects associated with inflammation.

Adipocytolysis

Adipocytolysis, unlike lipolysis, is a predominantly physical, cellular, local, and irreversible process. From the molecular point of view, there is no local catalytic activity mediated by any enzyme nor is there any metabolic change [26–28]. Systemic action is different. For study purposes, I have subclassified these procedures based on the process triggered in adipocytes:

1. Clastic adipocytolysis is the result of the mechanism of action of substances such as sodium deoxycholate (DC) or phosphatidylcholine (PPC) [29–32], grouped under the biological detergent category [33] (Figure 49.4).
2. Phagocytic adipocytolysis is the result of the mechanism of action of technologies that, although adipocytolytic, do not destroy adipocytes directly (Figure 49.5). By means of various physical principles, these technologies seek to cause structural changes in several elements of adipocytes in order to induce apoptotic responses. Unlike what takes place in clastic adipocytolysis processes, apoptosis performs its function without triggering an inflammatory response, for adipocytes will be finally phagocytized.

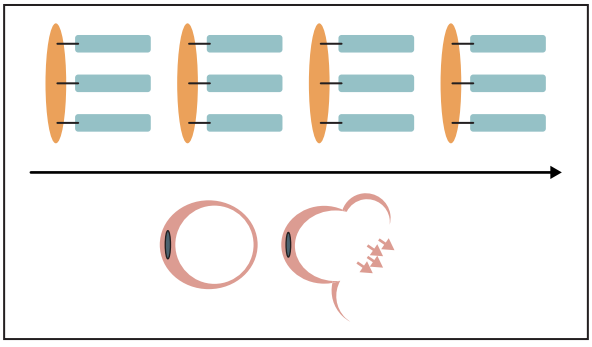


Figure 49.4 Clastic adipocytolysis: lipases do not act on TAGs. Cell membrane is destroyed. Adipocytes are reduced in number: hypoplasia.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

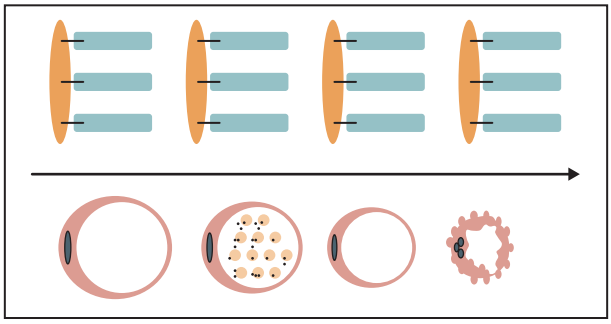


Figure 49.5 Phagocytic adipocytolysis: lipases do not act on TAGs. Cell membrane remains intact. Adipocytes are reduced in number: hypoplasia.

Crystallization

Lipid crystallization is the main process underlying the adipocyte destruction caused by lipocryolysis (Figure 49.6). It is a physical process first discovered many years ago, often used by multiple industries, most notably the food industry [34,35]. Lipid crystallization is not a deleterious process in itself, among other reasons, because it is mostly reversible and to a certain extent controllable. The situation is different, however, in complex systems such as live cells. Studies performed by the food industry usually take into account systems with a small number of phases, where few TAGs are mixed, crystallized, or otherwise modified. Under this type of system, X-ray diffraction (XRD) shows that TAGs are generally crystallized in one way or another and based on multiple environmental factors.

Postlipocryolysis lipid crystallization is not an exception, although we have observed in prior studies that traditional lipocryolysis crystallized TAGs into more than one polymorphism [36] (lipid polymorphisms are the different solid phases of the same chemical composition, which result in an identical liquid phase when they melt [37], which is to say, that they are the different ways in which the cell may pack triglycerides). This makes sense because, among other things, a live cell is a multiphase system in which a great number of TAG varieties should coexist. Interaction of all of these phases among themselves and with the environment creates a virtually infinite number of combinations. The structure of lipid crystals can be extremely complex [38,39] and requires very specific physicochemical knowledge, like "d" and "l" spacing and Miller indices, to fully understand it (Figure 49.7). Although this level of knowledge exceeds the needs of any aesthetic physician during daily practice, a brief introduction is necessary in order to discuss the mechanism of action of lipocryolysis and to explain how and why we have evolved toward new technologies such as contrast lipocryolysis.

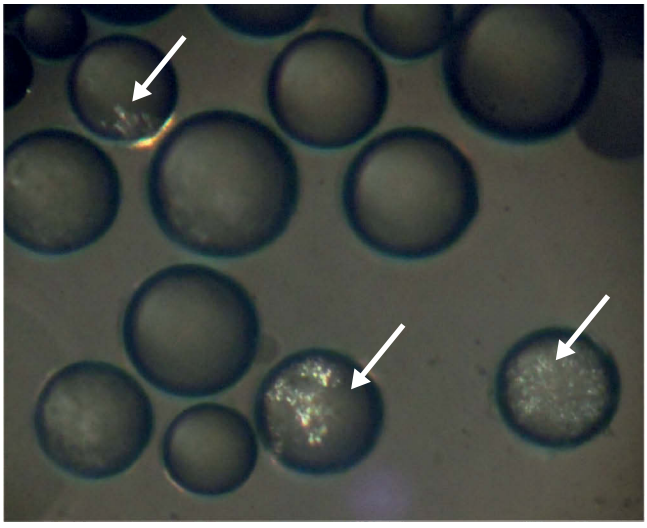


Figure 49.6 Crystals inside adipocytes (white arrows). (From Pinto H et al., *Cryo Lett*, 34(6), 619, 2013. With permission.)

The overall shape of a crystal is mainly determined by the relative growth rates of each part of its surface (Figure 49.8). The anisotropism that is typical of triglyceride crystals creates large differences between the growth rates of different parts of the surface of a crystal [40]. There are three traditional forms of molecular packing (polymorphism) of TAGs: α, β′, and β, which differ in terms of stability, melting temperature, and density. The alpha form is the most unstable and therefore the most prone to convert into other forms. Microscopically, α-polymorphism usually looks like an amorphous mass of small crystals, while the β′ form has a bulky shape or looks like spherulites, and the β form looks like needlelike crystals [41]. Interconversion of a polymorphism into another (transformations between liquid, α, β′, and β phases) is a significant process for the industrial handling and storage of fats, but it is also very attractive from the point of view of aesthetic medicine. Such transformation can take place with or without prior melting. The process is referred to as melt-mediated transformation in the first case and solid-state transformation in the second case [42,43]. All three polymorphisms can be created indistinctly by melt-mediated transformation. However, since fats exhibit monotropic polymorphism, solid-state transformations can only take place in forms with growing stability. This means that the only direction possible is that the α form will be transformed into the β′ form, and the β′ form will be transformed into the β form. Melt-mediated crystallization can be understood as the melting of a less stable form followed by the nucleation and growth of more stable forms. Mass transfer occurs in the liquid created by melting of the less stable forms [44], and overlapping makes it very difficult to measure each process separately [40]. Lipid crystallization may be affected by multiple variables including (1) chain length and purity of fatty acids; (2) presence, number, and location of double bonds (saturation vs. unsaturation); (3) configuration (*cis* vs. *trans*); (4) stereospecific positioning with respect to general TAG structure [45]; (5) temperature; (6) mechanical stress; (7) exposure time; (8) cooling speed; (9) presence of seeds; (10) solvent; (11) impurities; and (12) isothermal cooling. Some of these variables can be controlled by the new contrast lipocryolysis machines. This is the direction currently followed by R&D efforts in the field of lipocryolysis.

Both the structure of TAGs and their crystalline behavior are very sensitive to temperature. This entails potential alterations in the mechanical properties, as well as the fluid properties and texture of TAGs [46]. Controlling the crystallization process has been crucial for the food industry, but it is also of particular interest to medicine, because these alterations could imply, among other things, cell death (which is in fact the goal and basis of lipocryolysis). Larger crystals, with different degrees of insolubility and greater

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

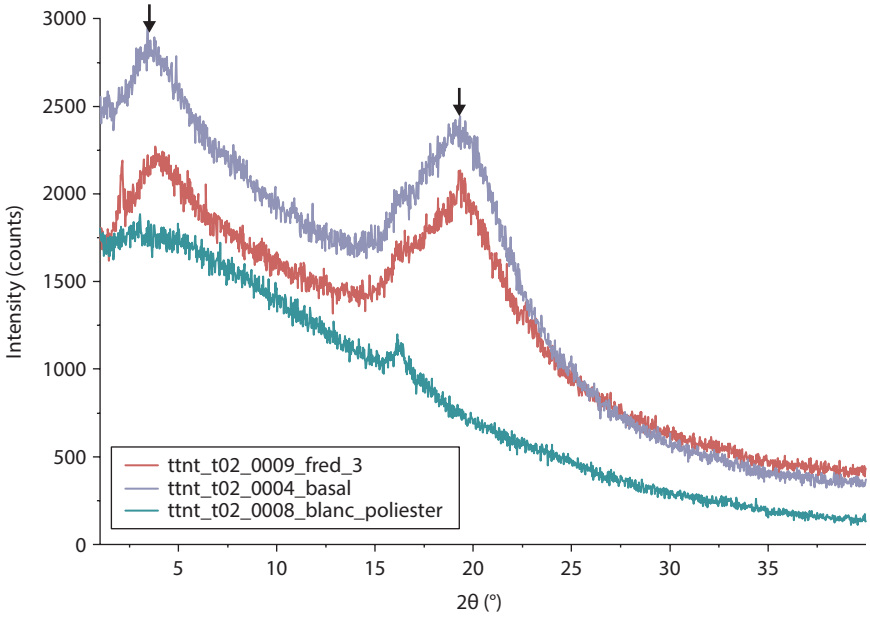


Figure 49.7 XRD: sample analysis (position vs. counts) showing peaks A and B (arrows). (From Pinto H et al., *Cryo Lett*, 34(6), 619, 2013. With permission.)

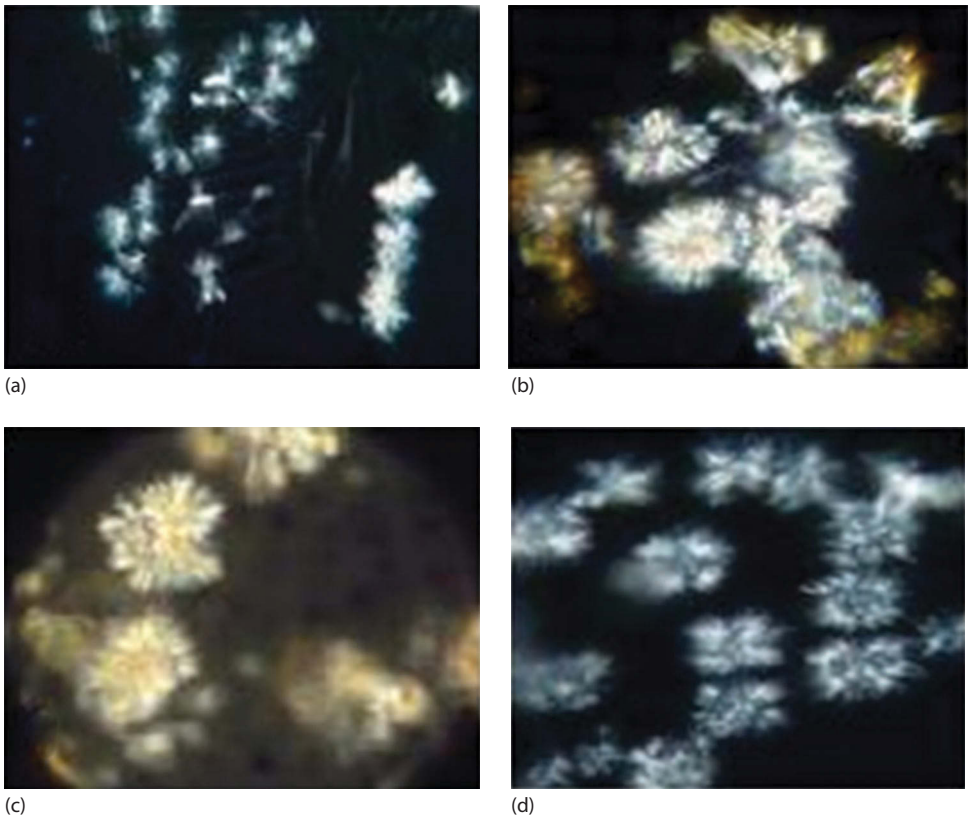


Figure 49.8 Lipid crystals: (a) adipocyte exposed to 8°C for 10 minutes; (b) adipocyte exposed to 8°C for 25 minutes; (c and d) adipocytes reheated at room temperature (22°C) for 2 hours. (From Pinto H et al., *Cryo Lett*, 34(1), 100, 2013. With permission.)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

irregularity, could determine greater apoptosis induction, a higher degree of fat necrosis, or both.

This has been the original line of thinking for the development of "contrast lipocryolysis," the natural evolution of traditional lipocryolysis. The name "contrast" refers to the fact that this technique aims to condition adipocytes by heating them up before and after conventional lipocryolysis: thermal contrast. Cells are subjected to a complex thermal stimulus comprising one hot cycle, one cold cycle, and a second hot cycle. The results we have seen are very promising. Compared to conventional lipocryolysis, contrast lipocryolysis has shown in *in vitro* mouse models that it is capable of (1) destroying more adipocytes directly, (2) creating more crystals in those adipocytes that do not die immediately, and (3) creating larger crystal structures [18]. In addition, contrast lipocryolysis has shown significant improvements in clinical results in a 10-case pilot study [47] (Figure 49.9).

Crystals can be created directly, by modifying variables such as the speed of cooling or supercooling throughout the tempering process, or indirectly, by interconversion into more stable packing forms. The speed of cooling is the force governing the formation of precrystal nuclei (nucleation), and it is a variable on which lipocryolysis machines can have incidence. When a triglyceride mix is cooled below the melting point of any of the triglycerides, the mix is oversaturated with that TAG and the crystallization force established will be directly proportional to the cooling force. Original lipocryolysis studies [11] reported crystallization with fat cooling below 10.38°C. Fat must usually be cooled between 5°C and 10°C for crystallization to begin. When the magnitude of crystallization force is low to moderate, secondary nucleation takes place layer by layer, in an orderly fashion such that a new layer will be formed only when the previous layer has been completed. On the other hand, elevated magnitudes will force secondary nucleation processes in several layers of the spherulite at the same time, resulting in more diffuse structures [40]. The same is sought by the application of tempering (heating and cooling) cycles in order to create more stable crystal forms by means of melt-mediated polymorphic transformations. Cells subjected to TAG crystallization can die in one of two ways: by the triggering of an apoptotic stimulus (presumably generated by crystals of any shape and size) or by rupture of their cell membranes (presumably due to large crystals destroying the cell immediately [35]).

However, there are also a large number of cells that do not crystallize and a third set of cells that do not die despite crystallization [35]. The reason why one adipocyte dies while the contiguous adipocyte remains alive after a session of lipocryolysis is still unknown. Due to the highly complex nature of the crystallization process, assimilating its mechanisms has been—and still is—a task requiring maximum commitment. Understanding how crystallization works in order to ultimately use it in our favor is the main objective of any researcher in the field of lipocryolysis. Analyzing the thermodynamic characteristics of the TAG crystallization process helps us determine the stability of different polymorphisms, as well as quantify crystallization force, giving us a benchmark for crystal nucleation and growth models [40]. On the other hand, analyzing the kinetic characteristics of the TAG crystallization process helps us explain polymorphic crystallization and its final morphology [40]. Understanding how TAGs interact and are structured is crucial if we want to understand the behavior of fatty tissue at macroscopic level [37].

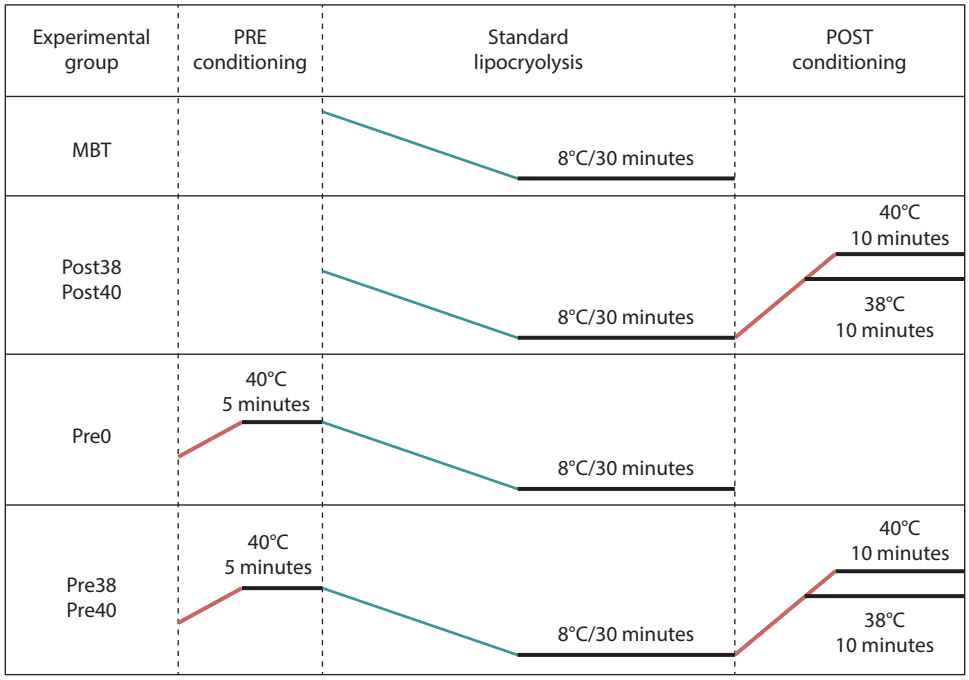


Figure 49.9 Temperature treatment patterns (TTPs). Heating (red line), cooling (blue line), and stabilized temperature (black line). 40°C during preconditioning, 8°C during standard lipocryolysis, and 38°C or 40°C during postconditioning. Control groups (constant room temperature) are not shown. MBT, modified basal treatment. (From Pinto H et al., *Cryo Lett*, 35(2), 154, 2014. With permission.)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

CLINICAL INTERACTION

Indication

Few technologies have a clearer or more precise indication than lipocryolysis. The only indication currently accepted is localized adiposity in any of its clinical presentations [10,47]. Of course, any other local-regional lipodystrophy could also in theory be reduced by applying this technology; such is the case of lipomas and certain types of cellulite. However, the following must be made very clear: lipocryolysis improves cellulite only because it reduces local fat accumulation. The cases of cellulite are not all the same, and neither are the levels of incidence of each physiopathological factor determining the situation of each patient. The multiple factors that play a role in cellulite physiopathology make it critical to assess each case individually and in depth, in order to make the right therapeutic decision.

Contraindications

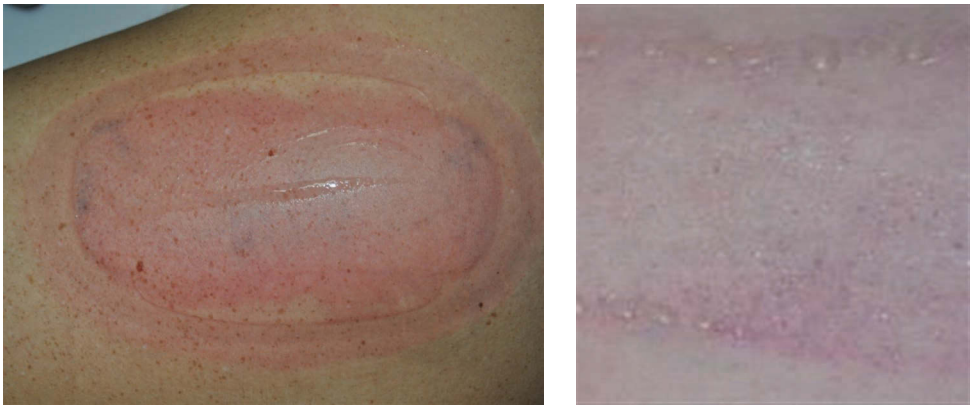
The following list of contraindications is under no circumstance thorough or final. It is important to understand why each contraindication has been included in each section so that the list may be used as a dynamic tool where practitioners can include new pathologies in the future. I like to classify lipocryolysis contraindications into four groups [12]:

1. *Legal*: These are usually the same to virtually all aesthetic medicine treatments. The reason for the contraindication does not lie in any actual problem posed by the treatment, but in impediments of a different nature. Classic examples in this group are minors and the mentally disabled, both of which groups are legally incapable of giving informed consent. Pregnant women are the third paradigmatic collective in this group.
2. *Local*: This group gathers pathologies locally affecting the area to be treated, including, among others, recent wounds, skin infections (i.e., Herpetoviridae family), hernias, blisters, scars, and ulcers. We might also include "fat layer thickness" in this group. Areas where fat panicles are less than 1.5 cm are normally contraindicated. In these patients, the cost/benefit rate is not favorable, since results will be discrete and sessions will be more painful and with a higher hematoma incidence. On the other hand, patients with very thick fat panicles are to be carefully assessed, since the thicker the panicle, the higher the probability of a mistaken indication (lipodysmorphia—overweight—instead of a localized adiposity).
3. *Specific*: This is a group of rare pathologies originated by or associated with any of the physical principles governing lipocryolysis (i.e., essential cryoglobulinemia, Raynaud's disease, and keratoderma climacterium). In general, they are all cold-associated disorders.
4. *Pathological*: This group includes those conditions that are associated with the patient's clinical status rather than with the treatment itself. Systemic diseases or disorders with severe organ compromise include liver, kidney, or heart failure; recent cerebral or myocardial infarction; neoplasias; and systemic autoimmune diseases. Although most of these pathologies are presumed to be fully compatible with lipocryolysis treatment, they are usually contraindicated automatically because no studies with sufficient or high-level evidence are available to back the potential indication or therapeutic application in this type of patient. Anticoagulated patients, whether artificially with medication or due to any pathology, are also strict contraindications.

While groups 1, 2, and 3 will expand to include a greater number of items in the future, group 4 should be significantly reduced as research develops.

Adverse Effects

Lipocryolysis can have complications like any other treatment. Luckily, the complications in this case are mild. In addition, there is evidence that any potential complication will be transient. It is important to note that since lipocryolysis is noninvasive, there is no chance of infection. The most frequent complications are those associated with the trauma caused by suction: erythema, edema, hot sensation after the session, and hematomas. There is clearly no allergy or rejection. Like any other medical or surgical procedure, lipocryolysis can entail some risk. Fortunately, in the case of this technology, the risk is minimal and the benefits greatly outweigh the potential problems, which are certainly few. There is very little evidence regarding the adverse effects of lipocryolysis: mild standard inflammatory is accepted (i.e., erythema, hematoma, pain) (Figure 49.10).



(a) (b)

Figure 49.10 Adverse effects observed immediately after session: (a) erythema and (b) traction blisters.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

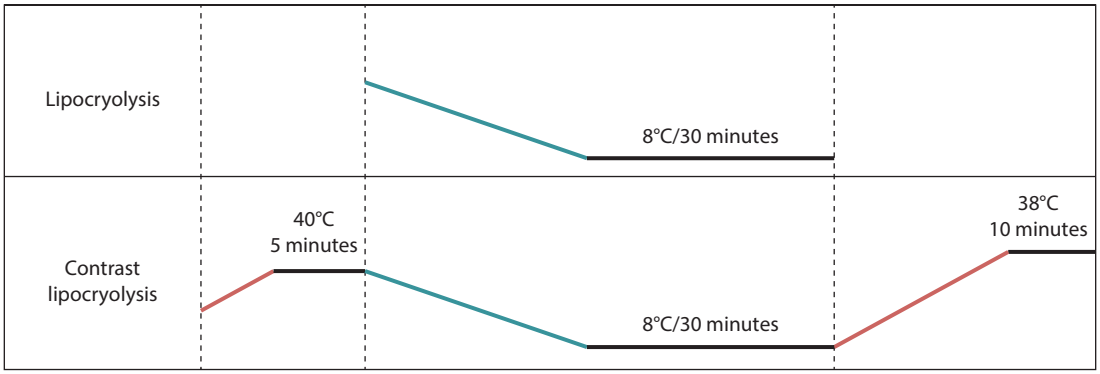


Figure 49.11 Tempering: standard vs. contrast lipocryolysis. Heating (red line), cooling (blue line), and stabilized temperature (black line). Min: minutes. (From Pinto H et al., *Adipocyte*, 3(3), 212, 2014. With permission.)

In addition, the few studies that have explored adverse effects have been designed with representative, but small, samples. Compared to the great number of subjects who have undergone lipocryolysis treatment around the world in the past five years, the total population on which adverse effects have been studied is tiny. The mild, reversible, and usual adverse effects of lipocryolysis are well known. However, are these an appropriate sample of post-treatment complications or is it that these adverse effects are the only ones we know because the sample we have surveyed is too small? The reality is that thousands of lipocryolysis treatments are performed around the world every day, and even if only empirically, no evidence of greater or different issues comes up.

There have been no reports of infection, wounds, or ulcers. Late-onset pain has been described [48]. Lipocryolysis is a noninvasive procedure. Scientific studies have provided conclusive data regarding the reversibility of adverse effects and the harmless nature of the procedure. In terms of systemic markers, there are no elevations of liver or kidney enzymes or variations in blood count. Other studies have applied lipocryolysis on flanks, observing a mild and reversible decrease in HDL concomitant with a discrete and reversible increase in serum triglycerides [49,50].

Coleman et al. have assessed biopsies from patients with postsession hypoesthesia and shown the absence of any structural damage or changes in peripheral nerve fibers, as well as that the process is reverted in 100% of cases, in 3.6 weeks [2]. Lastly, a few rare adverse effects have been reported, including two cases of paradoxical adipose hyperplasia (PAH), which had never been reported before associated with a lipocryolysis session. The frequency of PAH is extremely low [51].

Although the vast majority of patients do not experience any severe complications [52], the procedure should not be underestimated, and the indication of lipocryolysis should be correctly assessed. New adverse effects studies with specific designs should be carried out in order to provide definitive data in this respect. Based on the current status of our knowledge of the adverse effects of lipocryolysis, we believe that prospective, observational, and simple studies enabling the assessment of a great number of subjects with very good follow-up capabilities are needed.

PROTOCOL AND FINAL COMMENT

Protocol

Lipocryolysis is applied on a monthly basis and though session length can be adjusted, it is fully automatized. Standard lipocryolysis sessions' length will vary according to the platform used: between 30 and 60 minutes. Contrast Lipocryolysis session time is 60 minutes. Future studies will surely change current lipocryolysis application protocol (Figure 49.11).

Patient Expectations

Lipocryolysis is a great noninvasive local fat reducer technology and contrast lipocryolysis is even better. Still invasive procedures, from which liposuction is the gold standard, will face more risks but also will achieve better results. In addition, nonresponders do exist. To be able to establish an estimation of the percentage of nonresponders, new studies with specific designs are required. In my experience, nonresponders represent approximately 10%–15% of the patients. The leveling of patient expectations is a must for every physician. If expectations are correctly managed, even mediocre results may satisfy our patients. On the other hand, when expectations are not realistic, even the best results the treatment can offer may not be sufficient.

REFERENCES

1. Avram MM, Harry RS. Cryolipolysis™ for subcutaneous fat layer reduction. *Las Surg Med* 2009; 41:703–708.
2. Coleman S, Sachdeva K, Egbert B, Preciado JA, Allison J. Clinical efficacy of non-invasive Cryolipolysis™ and its effects on peripheral nerves. *Aesth Plast Surg* 2009; 33:482–488.
3. Nelson AA, Wasserman D, Avram MM. Cryolipolysis™ for reduction of excess adipose tissue. *Semin Cutan Med Surg* 2009; 28:244–249.
4. Epstein EH Jr., Oren ME. Popsicle panniculitis. *N Engl J Med* 1970; 282(17):966–967.
5. Rajkumar SV, Laude TA, Russo RM, Gururaj VJ. Popsicle panniculitis of the cheeks: A diagnostic entity caused by sucking on cold objects. *Clin Pediatr* 1976; 15:619–621.
6. Haxthausen H. Adiponecrosis e frigore. *Brit J Dermatol* 1941; 53:83–88.
7. Beacham BE, Cooper PH, Buchanan CS, Weary PE. Equestrian cold panniculitis in women. *Arch Dermatol* 1980; 116(9):1025–1027.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

8. Pekki A, Sauni R, Vaalasti A, Toivio P, Huotari-Orava R, Hasan T. Cold panniculitis in finnish horse riders. *Acta Derm Venerol* 2011; 91(4):463–464.
9. Deschamps P, Leroy D, Pedailles S, Mandard JC. Keratoderma climactericum (Haxthausen's disease): Clinical signs, laboratory findings and etretinate treatment in 10 patients. *Dermatologica* 1986; 172(5):258–262.
10. Pinto H, García-Cruz E, Melamed G. Study to evaluate the action of lipocryolysis. *Cryo Lett* 2012; 33(3):176–180.
11. Manstein D, Laubach H, Watanabe K, Farinelli W, Zurakowski D, Anderson R. Selective cryolysis: A novel method of non-invasive fat removal. *Las Surg Med* 2008; 40:595–604.
12. Pinto H. Lipocriolisis. In: Pinto H, ed. *Principios de Medicina Estética*. Albacete, Spain: Ruiz del Ámo, 2013.
13. Çenjel Y, Ghajar A. *Transferencia de calor y masa*, 4th ed. Mexico: McGraw Hill, 2011.
14. Lestina T, Serth R. *Process Heat Transfer: Principles, Applications and Rules of Thumb*. Amsterdam, the Netherlands: Academic Press, 2010.
15. Incropera F, De Witt D, Dewitt D. *Fundamentals of Heat and Mass Transfer*, 3rd ed. Hoboken, NJ: John Wiley & Sons, 1990.
16. Fourier J. *Théorie analytique de la chaleur*. Paris, France: Firmin Didot Père et Fils, 1822.
17. Peltier JA. Nouvelles experiences sur la caloricite des courants electriques. *Ann Chim* 1834; 56:371.
18. Pinto H, Ricart-Jané D, Pardina E. Pre and post lipocryolysis thermic conditioning enhances rat adipocyte destruction. *Cryo Lett* 2014; 35(2):154–160.
19. Pinto H, Aredondo E, Ricart-Jané D. Study for the evaluation of adipocytic changes after a simil-lipocryolysis stimulus. *Cryo Lett* 2013; 34(1):100–105.
20. Pinto H, Melamed G. Lipocryolysis cooling speed affects adipocyte survival. *J Surg* 2015; 3(1–1):11–13.
21. Pinto HR. *Principles of Lipocryolysis and Adipocyte Destruction by Thermic Contrast*, 1st ed. Albacete, Spain: Ruiz del Amo, 2014.
22. Verdelli A, Francalanci S, Palleschi GM. Contact allergic dermatitis due to Kathon CG contained in ultrasound gel. *Dermatitis* 2014 January–February; 25(1):35–36.
23. Vidal R, Segura L, Vergara P, Pinto H. Adverse effects of lipocryolysis: Analysis of 28 cases. *J Surg* (*special issue*) 2015; 3(1–1):6–7.
24. Rutkowski JM, Stern JH, Scherer PE. The cell biology of fat expansion. *J Cell Biol* 2015 March 2; 208(5):501–512.
25. Motolese P. Phospholipids do not have lipolytic activity: A critical review. *J Cosmet Laser Ther* 2008 June; 10(2):114–118.
26. Bobkova VI, Lokshina LI, Korsunskii VN, Tananova GV. Metabolic effect of Lipostabil forte. *Kardiologiia* 1989; 29:57–60.
27. Hasengschwandtner F. Phosphatidylcholine treatment to induce lipolysis. *J Cosmet Dermatol* 2005; 4(4):308–313.
28. Yagima Odo ME, Cucé LC, Odo LM, Natrielli A. Action of sodium deoxycholate on subcutaneous human tissue: Local and systemic effects. *Dermatol Surg* 2007; 33(2):178–188; discussion 188–189.
29. Cohen BM, Lipinski JF, Altesman RI. Lecithin in the treatment of mania: Double blind, placebo controlled trials. *Am J Psychiatry* 1982; 139:1162–1164.
30. Little A, Levy RP, Chua-Kidd P, Hand D. A double blind, placebo controlled trial of high dose lecithin in Alzheimer's disease. *J Neurol Neurosurg Psychiatr* 1985; 48:736–742.
31. Lieber CS, Robins SJ, Li J et al. Phosphatidylcholine protects against fibrosis and cirrhosis in the baboon. *Gastroenterology* 1994; 106:152–159.
32. Salti G, Ghersetich I, Tantussi F, Bovani B, Lotti T. Phosphatidylcholine and sodium deoxycholate in the treatment of localized fat: A double-blind, randomized study. *Dermatol Surg* 2008 January; 34(1):60–66.
33. Rotunda A, Suzuki H, Moy R, Kolodney MS. Detergent effects of sodium deoxycholate are a major feature of an injectable phosphatidylcholine formulation used for localized fat dissolution. *Dermatol Surg* 2004; 30:1001–1008.
34. Garside J. General principles of crystallization. In: Blanshard J, Lillford P. eds. *Food Structure and Behavior*. London, U.K.: Academic Press, 1978.
35. Hartel R. Nucleation. In: Hartel R, Frederik M, eds. *Crystallization in Foods*. Gaithersburg, MD: Aspen Publishers Inc., 2001.
36. Pinto H, Pardine E, Ricart-Jané D. X-ray diffraction analysis confirms intra-adipocitary lipid crystallization after a lipocryolysis-like stimulus. *Cryo Lett* 2013; 34(6):619–623.
37. Marangoni AG, Wesdorp LH. In: Marangoni AG, Wesdorp LH, eds. *Structure and Properties of Fat Crystal Networks*, 2nd ed. Boca Raton, FL: CRC Press/Taylor & Francis Group, 2013.
38. Chapman D. The polymorphism of glycerides. *Chem Rev* 1962; 63:433–456.
39. Clarkson CE, Marklin T. Alternation in long chain compounds. Part II: An x-ray and thermal investigation of the triglycerides. *J Chem Soc* 1934; 666–671.
40. Himawan C, Starov VM, Stapley AGF. Thermodynamic and kinetic aspects of fat crystallization. *Adv Colloid Interf Sci* 2009; 122:3–33.
41. Sato K, Ueno S. In: Garti N, Sato K, eds. *Crystallization Processes in Fats and Lipid Systems*. New York: Marcel Dekker, 2001.
42. Hagemann JW. In: Garti N, Sato K, eds. *Crystallization and Polymorphism of Fats and Fatty Acids*. New York: Marcel Dekker, 1988.
43. Dafler JR. Polymorphism behaviour in fully hydrogenated mono acid triglycerides *J Am Oil Chem Soc* 1977; 54:249.
44. Sato K. Solidification and phase transformation behaviour of food fats—A review. *Fett/Lipid* 1999; 101:467.
45. Small DM. *The Physical Chemistry of Lipids*. New York: Plenum Press, 1986.
46. Campos R, Marangoni AG. Molecular composition dynamics and structure of cocoa butter. *Cryst Growth Des* 2010; 10: 205–217.
47. Pinto H, Melamed G. Contrast lipocryolysis: Pre and post session tempering improves clinical results. *Adipocyte* 2014; 3(3): 212–214.
48. Krueger N. Cryolipolysis for noninvasive body contouring: Clinical efficacy and patient satisfaction. *Clin Cosmet Investig Dermatol* 2014; 7:201–205.
49. Riopelle J, Tsai MY, Kovack B. Lipid and liver function effects of the cryolipolysis procedure in a study of male love handle reduction. *Laser Surg Med* 2009; S21:82.
50. Klein KB, Zelickson B, Riopelle JG, Okamoto E, Bachelor EP, Harry RS, Preciado JA. Non-invasive cryolipolysis for subcutaneous fat reduction does not affect serum lipid levels or liver function test. *Surg Med* 2009 December; 41(10):785–790.
51. Jalian HR, Avram MM, Garibyan L, Mihm MC, Anderson RR. Paradoxical adipose hyperplasia after cryolipolysis. *JAMA Dermatol* 2014 March; 150(3):317–319.
52. Dierickx CC, Mazer JM, Sand M, Koenig S, Arigon V. Safety, tolerance, and patient satisfaction with noninvasive cryolipolysis. *Dermatol Surg* 2013 August; 39(8):1209–1216.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Botulinum toxins: Uses in cutaneous medicine

Uwe Wollina

SCIENTIFIC BACKGROUND

Botulinum toxin (BoTN) is produced by *Clostridium botulinum* as a complex mixture of seven neurotoxic polypeptides and nontoxic protein components. Synthesized as a single-chain polypeptide of ~150 kD, BoTN has relatively little potency until it is cleaved by trypsin or bacterial enzymes into two chains: a heavy chain of 100 kD responsible for binding to the target structure and a light chain of 50 kD known as the toxifying chain. BoTN serotypes act as zinc-dependent endopeptidases. The best characterized toxins are BoTN-A and BoTN-B, both are used therapeutically and commercially available [1,2].

When BoTN is injected into a target tissue, the heavy chain of the molecule binds to glycoproteins expressed specifically on cholinergic nerve endings. After internalization of the whole molecule by pinocytosis, the chains are cleaved intracytoplasmatically. The light chain binds with high specificity to the soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs) essential for exocytosis. SNARE is involved in transportation of acetylcholine from the cytosol into the synaptic cleft. It consists of a vehicle-associated protein (v-SNARE or synaptobrevin) and two target (t-SNARE) proteins: plasma membrane synaptosome-associated protein (SNAP-25) and syntaxin. The light chain exerts a multisite substrate binding imparting the protease with exquisite specificity [3]. This explains why additional proteins or other components used in commercially available products will not cause different modes of action after BoTN pinocytosis by target cells.

BoTN-A cleaves SNAP-25 [4], whereas BoTN-B cleaves synaptobrevin [5]. The proteolytic cleavage of SNARE proteins inhibits the docking of acetylcholine vesicles on the inner surface of the nerve terminal and results in a blockade of vesicle fusion. When the target structure is a muscle, paresis with chemical denervation occurs. When the target tissue is a sweat gland, the secretion is inhibited.

In Europe and North America, three different types of BoTN-A are commercially available: Botox® (Allergan), Dysport® (Speywood-Ipsen), and Xeomin® (Merz), which are identical with Vistabel® (Allergan), Azzalure® (Galderma), and Bocouture® (Merz), respectively. Their chemical composition and production are different although all contain BoTN-A as the active compound. Furthermore, the relative units differ between Botox/Xeomin® and Dysport/Azzalure. Frevert [6] analyzed the content of BoTN-A in vials of the three pharmaceutical brands. According to his study, the mean concentration of BoNT-A was 0.73 ng/100 unit vial in Botox; 3.24 ng/500 unit vial in Dysport, corresponding to 0.65 ng in 100 units; and 0.44 ng/100 unit vial in Xeomin. The specific potency of the 150 kD BoTN-A neurotoxin was calculated as 137 units/ng Botox, 154 units/ng Dysport, and 227 units/ng Xeomin.

MUSCULAR EFFECTS

Principally, muscular atrophy can be induced by usage of BoTN for prolonged periods of time, but it seems to occur very inconsistently. Muscular hypertrophy can be normalized with repeated injections of BoTN-A [7]. There are some muscular targets that show extreme dose insensitivity with respect to the therapeutic outcome and adverse effects like blepharospasm or spasmodic dystonia [8].

BoTN also affects the spinal stretch reflex of muscles. When a muscle is stretched, afferent signals from the muscle spindle organ are transmitted by Ia and II fibers. That excites not only alpha motoneurons of the stretched muscle but also interneurons of the antagonistic muscle, inhibiting their alpha motoneurons. Gamma motoneurons of the stretched muscle are inhibited by alpha motoneuron collaterals. In animal models, it was demonstrated that BoTN causes atrophy of both extrafusal and intrafusal muscle fibers of the biceps femoris of Wistar rats [9]. Gamma motoneurons of isolated rat masseter muscles could be blocked by BoTN without affecting muscle strength [10]. The antidystonic effect of BoTN may be explained by target muscle paresis and spinal reflex inhibition.

Investigations following a single BoTN injection into the sternocleidomastoid muscle of mice demonstrated the development of temporary nerve sprouts that eventually were capable of exocytosis with subsequent upregulation of adjacent nicotinic receptors of the muscle fiber, forming a functional synapse [11]. The kinetics of this process, however, cannot explain the longer duration of BoTN efficacy, for instance, in hyperhidrosis.

BoTN actions on hyperactive smooth muscles like anal sphincter are mediated by action on the autonomic nervous system.

EFFECTS ON EXOCRINE GLANDS

BoTN can be used to treat hyperactivity of sweat glands, lacrimal glands, and salivary glands. It acts also by inhibition of acetylcholine release.

The dose-effect relationship is different for each of these target tissues. The lowest doses to gain an anhidrotic effect are 2 U of BoTN-A (Botox). The dose-response does not seem to be linear for sweat glands and the same seems to be true for the dose-duration effect. Very low doses (<10 U of Botox) have a limited temporary effect with a relapse of 100% within 3 months in axillary hyperhidrosis [12]. Intermediate doses of 50–100 U of Botox produce a duration of about 9–12 months, whereas higher doses of 200 U of Botox produce an anhidrotic effect in a part of patients that can last longer than 15 months [13,14].

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

In patients suffering from Frey's syndrome, lower doses are needed compared with axillary hyperhidrosis, for instance, and longer durations have been obtained [12].

CENTRAL NERVOUS SYSTEM EFFECTS

BoTN cannot pass the blood-brain barrier because of its molecular weight of 150 kD. A retrograde axonal transport has been documented by radioactively labeled BoTN in cats after intramuscular injection. Because the transport was so slow, it seems likely that BoTN-A was inactivated before reaching the central nervous system (CNS) [15]. In cultured spinal cord cells, BoTN-A light chains persist for more than 11 weeks [16]. On the other hand, BoTN injection into muscles has indirect effects on CNS activity [17,18]. Human studies have suggested that BoTN could alter the functional organization of the CNS indirectly through peripheral mechanisms. BoTN-A-induced reduction in spindle signals could, therefore, alter the balance between afferent input and motor output changing cortical excitability. BoTN can interfere with and modify spinal, brainstem, and cortical circuits by altering spindle afferent inflow directed to spinal motoneurons or to the various cortical areas. It has been assumed that some of the long-term clinical benefits of BoTN-A treatment may also reflect plastic changes in motor output after the reorganization of synaptic density [19].

PAIN

Pain relief has been reported after injection of BoTN into hyperactive muscles. In addition, in animal models, muscular pain induced by formalin can also be reduced by BoTN-A, suggesting a direct analgesic effect [20]. In rabbit iris muscles and dorsal root ganglia neurons, substance P, a neuropeptide involved in pain reception and neurogenic inflammation, can be blocked together with acetylcholine [21,22].

Enkephalin gene expression is upregulated after BoTN injection into the gastrocnemius muscle, while acidic fibroblast growth factor genes become downregulated [23]. Of all seven BoTN serotypes, BoTN-A produced the strongest effects.

BoTN also inhibits the neurotransmitter glutamate involved in nociception [24]. Furthermore, the release of calcitonin gene-related peptide (CGRP) in autonomic vascular nerve terminals [25] and noradrenaline in PC12 cells [26] by BoTN has been demonstrated.

In myofascial pain syndrome, 10–20 U BoTN-A improved pain pressure thresholds, pain score, and visual analogue scores more effectively than dry needling [27]. In an experimental setting in humans, intracutaneous application of 100 U BoTN-A (Dysport) was compared with pure saline. Ultraviolet-B-induced sunburn spots were used as an inflammatory model. BoTN-A did not have an effect on inflamed and noninflamed human skin as measured by heat pain threshold, cold pain threshold, area of secondary hyperalgesia, and mechanical sensitivity [28].

PRURITUS

Itch is a sensation different from pain. In skin, cutaneous C-fibers conduct itch. They are sensitive to neurotransmitters, histamine, and other inflammatory mediators like substance P, vasoactive intestinal peptide, and CGRP. Intradermal injections of prostaglandin E2, bradykinin, serotonin, or interleukin-2 are known to produce itch [29].

Observations of an antipruritic activity of BoTN-A come from clinical investigations in lichen simplex [30] and dyshidrotic hand eczema [31,32]. A prospective trial with eight patients with dyshidrotic hand eczema and left-right comparison (one hand with topical steroids, the other with steroids and 100 U of Botox) showed that pruritus disappeared more quickly on the BoTN-A hand [31]. The same observation was made in a study on 10 patients with dyshidrotic hand eczema. Itch as measured by visual analogue scale was reduced by BoTN-A by 39% versus an increase of itch on the untreated side by 52% [32]. The exact mechanisms are yet not known, but inhibition of substance P and CGRP might be involved.

IMMUNE EFFECTS

While most patients continue to respond to repeated BoTN treatments, some become unresponsive as a result of the development of neutralizing or blocking antibodies. Only antibodies against the heavy chain block the function of the neurotoxin [33]. Immunization seems to be a higher risk in younger patients receiving higher doses more frequently as in neuromuscular diseases [34]. In a recent meta-analysis involving 16 studies with more than 3000 subjects treated with BoTN-A (Botox), 0.5% converted to antibody positive but only three patients became unresponsive to BoTN-A [35]. The rate of antibody positive subjects was 0.3% among those treated for glabellar lines and 0.5% for axillary hyperhidrosis. Due to the higher diffusion rate of BoTN-B, there might be no alternative in this indication [36].

POSSIBLE INDICATIONS FOR BOTULINUM TOXIN IN DERMATOLOGY

Hyperhidrosis and Related Disorders

Severe hyperhidrosis affects almost 3% of the adult population. It has negative effects on professional and private life. BoTN is effective in all types of focal hyperhidrosis. Analysis of relapse-free time after BoTN treatment in axillary and palmar hyperhidrosis revealed the following: the duration of therapeutic effect of BoTN-A is not significantly influenced by age, sex, extent of hyperhidrotic area, site of involvement, disease-induced impairment of life quality, number of previous therapies, or site of involvement. In palmar hyperhidrosis, patients with a longer disease history show a shorter duration of BoTN-A effect [37].

In patients with axillary hyperhidrosis, 120 units of BoTN-A per axilla (Dysport) produced significant reduction of sweating for between 6 and 24 months [38].

Several randomized controlled trials have been conducted for axillary hyperhidrosis ([39–44]; Table 50.1). One way to reduce the relapse rate after a single BoTN-A treatment is to increase dosage from 50 to 200 units of Botox per axilla. The longest duration of anhydrotic efficacy was 29 months. The relapse rate within 12 months after treatment was only 11.8% [13,14].

In a single-center, randomized, parallel, open-label 12-week trial, BoTN-A was compared to topical 20% aluminum chloride. At week 4, 92% of patients treated with BoTN and 33% of those treated topically showed a response. This major difference was maintained throughout the whole study period [47]. In axillary hyperhidrosis of female patients, 35 units of BoTN-A per axilla seemed to be a reasonable starting dose with some cost reduction [46].

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Table 50.1 Randomized Controlled Trials for Axillary Hyperhidrosis

No. of patients	Treatment arms	Duration	Outcome	Reference
322	BoTN-A (Botox) 75 or 50 units per axilla vs. placebo	52 weeks	75% improvement with BoTN duration of 197 days (75 units) and 205 days (50 units).	Lowe et al. [39]
43	BoTN-A (Dysport) 200 or 100 units per axilla	48 weeks	Both doses are equally effective.	Heckmann et al. [40]
207	BoTN-A (Botox) 50 units per axilla vs. placebo for up to three times	16 months	Response rates after first to third BoTN are 96.1%, 91.1%, and 83.3%; response rate after placebo at week 4 is 34.7%. Mean response duration for BoTN 7 months.	Naumann et al. [41]
307	BoTN-A (Botox) 50 units per axilla vs. placebo	16 weeks	Response rate at week 16 82% (BoTN) vs. 21% (placebo).	Naumann and Lowe [42]
145	BoTN-A (Dysport) 200 units per axilla vs. placebo; 2 weeks later, 100 units was injected into the placebo-treated axilla	24 weeks	After 24 weeks, both doses showed a significant sweat reduction compared to placebo; the difference between the two doses was not significant.	Heckmann et al. [43]
13	BoTN-A (Dysport) 200 units per axilla vs. placebo	13 weeks	Significant reduction of sweating compared to placebo.	Schnider et al. [44]

Another common indication for BoTN is palmar hyperhidrosis. Table 50.2 summarizes randomized controlled trials in palmar hyperhidrosis [47–50]. Palmar hyperhidrosis was treated by injections of 30 units of BoTN in 27 Japanese patients with moderate-to-severe hyperhidrosis. In a left-right comparison, BoTN was able to reduce the amount of sweat in the treated hand by 80% with a slight decrease on the contralateral, nontreated hand. Six months after injection, the sweat amount was still only 50% of the amount before treatment [51]. In an open trial, 10 patients with severe palmar hyperhidrosis were treated with 200 units of BoTN-A (Botox) per palm with markedly increased response duration. In six patients, a mean duration of 12.3 months could be achieved [52].

In a study from Greece, 36 patients with palmar hyperhidrosis were treated with 100 units of BoTN-A per palm. Significant improvement lasted 6.2 months. Surprisingly, 12 patients also had a marginal improvement in their plantar hyperhidrosis [53].

BoTN also works in plantar hyperhidrosis. There are, however, some limitations: the injections are very painful, it is hard to get enough BoTN into the dermis due to the thicker horny layer, and the effect is not as long lasting as for other types of focal hyperhidrosis [54].

Patients with focal hyperhidrosis who do not completely respond to BoTN-A may benefit from additional aluminum chloride 15% in a salicylic acid 2% gel base [55]. On the other hand, BoTN-A is effective for severe compensatory hyperhidrosis on the trunk after sympathectomy. The dosages used were in the range of 100–500 units [56].

Compared to thoracoscopic T2–T3 sympathectomy for palmar hyperhidrosis, BoTN-A injection is less effective at 6 and 12 months after treatment [57].

BoTN-A can also be used successfully to control facial or scalp hyperhidrosis [58].

Residual limb hyperhidrosis in amputees is a major problem causing immobility, infection, malodor, pruritus, or burning sensations. BoTN-A is effective in this complaint with only minor adverse effects. Duration is between 6 and 12 months depending on the severity of hyperhidrosis and the dosage of BoTN-A used [59,60].

Nine patients with lower limb amputation and focal hyperhidrosis received 1750 units of BoTN-B. Sweating was significantly decreased at 4 weeks and 6 months. Steadiness of gait, quality of life, and work performance increased accordingly, and skin problems decreased but not significantly. Stump pain was also reduced [61].

Frey's syndrome is a common complication after parotidectomy characterized by facial sweating and flushing after gustatory stimuli. In a prospective randomized controlled study, 20 patients with Frey's syndrome were treated with 2 or 3 units BoTN-A/cm^2 and followed for 12 months. All patients with the higher dosage achieved a complete response lasting at least 12 months [62].

Table 50.2 Randomized Controlled Trials for Palmar Hyperhidrosis

No. of patients	Treatment arms	Duration	Outcome	Reference
20	BoTN-B (Myobloc) 5000 units per palm vs. placebo	6 months	Mean significant improvement for 3.8 months	Baumann et al. [47]
24	BoTN-A (Botox) 50 or 100 units per palm	6 months	100% responders, after 6 months 75% response rate	Saadia et al. [48]
19	BoTN-A (Botox) 50 units per palm vs. placebo	28 days	100% response rate with BoTN-A, 12% with placebo	Lowe et al. [49]
11	BoTN-A (Dysport) 120 units per palm vs. placebo	13 weeks	Sweat reduction 26%–31% by BoTN	Schnider et al. [50]

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

In a study of seven patients with Frey's syndrome, 80 units of BoTN-B (Myobloc) was injected per cm^2 with a mean total dose of 2354 units. Six of seven patients had a complete response after 1 month. Improvement was notable in all patients during 12 months of follow-up [63].

Apocrine chromhidrosis is a rare disorder characterized by excretion of colored sweat. The underlying mechanisms are poorly understood. BoTN-A has been used in individual cases successfully [64].

Osmidrosis is a disorder more commonly seen in patients of Asian background. Injection of BoTN-A was effective in a series of 50 patients from China [65].

Inflammatory Disorders

Lichen simplex is a disorder within the atopic dermatitis spectrum that is characterized by intense but localized pruritus. The disease is an example of how itching and scratching can aggravate cutaneous inflammation and lead to hyperplastic epidermis, lichenification, and quite often hyperpigmentation or depigmentation. The injection of corticosteroids, topical high-potency corticosteroids (under occlusion), tar, and PUVA therapy have each been used. There is one study about four patients with lichen simplex that were treated with BoTN-A [30]. Intracutaneous injections of 20 U Dysport were evenly distributed over the plaques reaching a total dose between 20 and 80 U (about 20 U Dysport/4 cm^2). After 1 week, three of four patients felt no more itching, and one had a remarkable improvement using a visual analogue scale. After 4 weeks, five of six lesions had cleared without any other treatment. After 12 weeks, three patients were still in complete remission.

Dyshidrotic hand eczema or pompholyx is common. A hallmark of this disease is its tendency to relapse in response to various provoking factors including wet work, occlusion, and hyperhidrosis [66,67]. Dyshidrotic hand eczema was treated with BoTN-A as an adjunct to topical corticosteroids in a prospective trial [31]. Eight patients were included in a side-by-side comparison either with topical corticosteroids alone or with steroids plus 100 U of Botox per palm. The eczema was classified using the dyshidrotic eczema area and severity index (DASI). Six patients were evaluated for final analysis. The mean DASI score was reduced from 28 to 17 within 8 weeks of topical steroids alone and from 36 to 3 with adjuvant BoTN-A.

This study was confirmed by another on 10 patients with dyshidrotic hand eczema [32]. One side was treated with 162 U Botox, while the other remained untreated. After 5–6 weeks, 7 of 10 patients reported a marked improvement for both morphologic symptoms and itching on the treated side.

All studies confirmed that BoTN-A has an antipruritic effect that cannot be explained by acetylcholine inhibition but by inhibition of two other neurotransmitters, i.e., substance P and glutamate [21,22].

A study on 15 patients suffering from inverse psoriasis that was treated with 50–100 units of BoTN-A demonstrated improvement within 12 weeks of erythema, infiltration, and extension in 87% of patients [68]. There is no evidence available that BoTN-A works in other types of psoriasis except for pruritus [69]. BoTN-A injections, however, may induce a Koebner phenomenon due to mechanical trauma [70].

In conclusion, BoTN is a valuable alternative in certain limited types of inflammatory skin diseases due to its antipruritic and anhidrotic effects [71].

In a pilot trial, seven patients with alopecia areata were treated with BoTN-A injections (10 units three times per lesion), but no improvement could be observed [72].

BTX in Bullous Disease

Hailey-Hailey disease is an autosomal-dominant blistering disease affecting intertriginous skin. The treatment of choice is surgery or laser ablation leading to complete remission. Aggravation by heat and sweating are well known.

In the literature, several case reports of successful usage of BoTN-A have been published [73–77]. The mechanism is the anhidrotic efficacy of BoTN-A. In one study, BoTN-A was compared with either ablative laser or dermabrasion and found to be as effective as the two other modalities [75]. On the other hand, we do not know yet how long the remissions will last and some patients do not respond. We do not know why.

Painful blistering is a common problem in genetic bullous diseases like epidermolysis bullosa simplex and pachyonychia congenita. Focal hyperhidrosis is an aggravating factor. Multiple plantar injections of either BoTN-A or BoTN-B (a total of 76 treatments in 14 patients) resulted in improvement with a mean duration of 3 months [78,79].

Anal and Vaginal Disorders

Chronic anal fissures are common. Anal fissures are common complaints frequently developing along the posterior midline of the anoderm. Mean maximum anal resting pressure is directly related to the activity of the smooth muscles of the internal and external sphincters and has been found to be increased in patients with anal fissure. Muscular spasticity of the anal sphincter is accompanied by fissures, but it is unclear whether it is the cause or the consequence. High sphincter pressure may perpetuate fissuring by secondary local ischemia. Severe pain leads to a significant loss of quality of life in patients suffering from anal fissures [80]. By examining nerve fiber density in tissues surrounding chronic anal fissure and in normal anal mucosa, Horsch et al. [81] found markedly increased pan-neural innervation and growth-associated protein 43 immunoreactivity in tissues of anal fissures. These authors claimed that neural proliferation is involved in the pathogenesis of anal fissures and may also be responsible for pruritus and severe pain.

Erectile dysfunction is a possible complication of chronic anal fissures and their surgical treatment. Clinically longitudinal or elliptical tears or ulcers are observed in the distal anal canal. The most common site for both genders, however, is the midline posteriorly. The fissures typically present with severe pain after defecation, red rectal bleeding, and sometimes itch. Anal fissures are associated with high resting anal pressure and local ischemia of the cracked anal lining; however, the etiology is basically unknown [82].

The most widely used application of BoTN-A is the intramuscular injection into the internal sphincter. BoTN-A is significantly better than placebo and topical glyceryl trinitrate 0.2% ointment, but like all other medical treatments, the efficacy is higher in acute versus chronic fissures [83].

The BoTN doses used vary remarkably. Jost injected either 5 units of Botox or 20–40 units of Dysport and achieved a healing rate at 6–8 weeks of 76%–82% [84]. Higher doses with 20–50 (to 100) units of Botox can result in higher healing rates without increasing the risk of adverse effects significantly. Healing

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

rates of up to 96% have been observed [85]. On the other hand, costs are increasing with high-dose therapy so a balanced view between benefits and costs is yet to be defined.

In a small series of 10 patients with anal fissures, we found that focal perianal hyperhidrosis can also aggravate the symptoms and contribute to chronicity. Hence, we treated not only the sphincter muscle with 20–25 units of Botox but the perianal skin as well using a total dose of 30–50 units of Botox. After 5 months, five of five patients treated with intramuscular and perianal intradermal injections were free of symptoms but only two of five patients treated only intramusculary were [86].

In a review on pharmacological sphincterotomy by BoTN, the short-term healing rate (first half year after injection) was 60%–90%. The first effect is pain relief, whereas the fissure healing takes some time. More than 50% of patients achieved a complete response in more than a year. The adverse effects are temporary and mild, but the relapse rate is higher than with lateral sphincterotomy [85].

Hemorrhoidectomy is a common procedure. One of the adverse effects is postoperative pain. In a double-blind, randomized study on 50 patients undergoing Milligan-Morgan hemorrhoidectomy, it could be demonstrated that intramuscular application of 20 U of Botox significantly reduces postoperative pain within the first week [87]. This has been confirmed in another trial with 30 patients, where not only pain was reduced but also wound healing was improved [88]. The mechanisms behind this positive effect might be similar to anal fissure.

Provoked vestibulodynia is a difficult-to-treat disorder with severe pain perceptions not allowing sexual intercourse with negative impact on quality of life and sexual function. By electromyography, hyperactive muscles could be demonstrated. After injection of 50 units of BoTN-A bilaterally into the bulbospongiosus muscle, 80% of patients treated reported significant decreased pain after 3 and 6 months and 72% of the patients were able to have sexual intercourse after this treatment [89].

Proctalgia fugax is defined as sudden painful attacks in the anal region lasting for seconds or minutes. The complaint occurs slightly more often in women than men. There is a report on a 52-year-old woman with proctalgia fugax responding to 25 U of Botox injected in four sides along the sphincter ani muscle. She was completely free of symptoms for 4 months and responded well to a second injection of the same dose [90]. In a series of five patients, all responded well to BoTN-A 25–75 units [91].

Benign Eccrine Tumors and Cysts

Blugerman et al. [92] reported on the use of repeated BoTN-A injections for the treatment of multiple facial eccrine hidrocystomas. A total dose of 10 U of Botox was injected intradermally into the affected areas and the hidrocystomas disappeared within 1 week. During a follow-up of 6 months, no recurrence was noted. These results have been confirmed by another report on two female patients with multiple facial eccrine hidrocystomas. These authors suggested that BoTN should be the first-line treatment since it bears no risk of scarring [93]. In an uncontrolled trial, 18 patients were treated with 6–12 units of BoTN-A (Dysport) around each lesion, with a second possible injection in case of partial response after 3–4 weeks. Thirteen patients responded to a single injection; others responded after a second treatment. The effect lasted 5–7 months [94]. In a female patient, larger cysts refilled by 6 weeks [95].

Barco et al. [96] reported on successful therapy of a patient with eccrine angiomatous hamartoma with BoTN.

Apocrine hidrocystomas may also benefit from BoTN [97].

Neurogenic Pruritus and Facial Flushing

Kavanagh and Tidman [98] reported on successful treatment of brachioradial pruritus by BoTN injections. Weinfeld [99] observed relief of notalgia paresthetica after BoTN-A.

In a split-face study with BoTN-B, a significant improvement of facial flushing was documented by mexameter measurements 8 weeks after injection, but there was no difference to the control site [100]. Odo et al. [101] found improvement using BoTN-A for the treatment of hot flushes in a pilot study.

Scar Management

From animal studies, it is known that BoTN-A can normalize collagen formation and deposition in hypertrophic scar models. Collagen fibers become less thickened and better oriented [102]. Furthermore, it could be demonstrated that the deposition of collagen type I and III is diminished by BoTN-A and cellularity is also decreased [103].

This seems not to be due to alterations of cytokine expression by normal dermal fibroblasts of microvascular endothelial cells [104]. In cell cultures with fibroblasts from hypertrophic scars, however, BoTN-A decreased proliferation and tumor growth factor beta-1 protein and stimulated the expression of connective tissue growth factor in a dose-dependent manner [105,106].

Painful keloids can be treated by BoTN-A which reduces the discomfort [107].

In an open trial of 19 patients with hypertrophic scars, 2.5 units of BoTN-A/cm^3 of scar tissue was injected and repeated every 4 weeks for a total of three treatments. Erythema, pruritus, and pliability improved as measured by 6 months [108].

BoTN has been used to minimize scar formation after surgery by treatment of neighboring muscles [109,110]. In a blinded, prospective, randomized trial, 31 patients with traumatic forehead lacerations or surgical excisions were treated by intramuscular BoTN-A injections adjacent to the sutures within the first 24 hours after injury. Blinded photographs were scored using a 10 cm visual analogue scale. Healing and cosmesis was improved by this procedure [111]. Wilson [112] had used BoTN-A during revisions of ugly facial scars in 40 patients. Ninety percent of patients had an improved outcome with the combination of surgical scar revision and temporary muscular paralysis. Last but not least, BoTN-A has been used to improve acne scars [113].

Various Disorders

Vitiligo affects about 2% of the world's population. Acetylcholine concentration is increased in depigmentated patches. BoTN-A was used to treat vitiligo in 10 patients by intralesional, intradermal injections. There was no repigmentation initiated during 6 months of follow-up, indicating that BoTN is ineffective [114].

Three patients with leonine facies due to pachydermoperiostosis have been treated with BoTN-A (70–89 units) for the upper face. The response was faint to excellent at week 6 [115].

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Table 50.3 Level of Evidence for BoTN-A Indications in Dermatology

Indication	Level of evidence	Comments
Idiopathic axillary hyperhidrosis	Ia	BoTN is the most effective nonsurgical treatment.
Idiopathic palmar hyperhidrosis	Ib	The number of patients in the studies was low.
Frey's syndrome	Ib	Low doses and long duration of effect.
Other types of idiopathic focal hyperhidrosis or compensatory hyperhidrosis		
Hyperhidrosis	III	There is a need for trials.
Apocrine chromhidrosis	IV	
Osmidrosis	III	
Atopic dermatitis	III	Localized types only.
Pompholyx	IIb	Not for podopompholyx.
Inverse psoriasis	IV	
Hailey–Hailey disease	IV	It is not working in all cases.
Epidermolysis bullosa simplex and pachyonychia congenta	IV	For painful foot blisters.
Anal fissures	Ib	Doses vary remarkably. Higher doses produce longer efficacy.
Wound healing and pain after hemorrhoidectomy	IV	
Provoked vestibulodynia	IV	
Proctalgia fugax	IV	
Multiple eccrine hidrocystomas	IV	
Prevention and improvement of hypertrophic scars and keloids	IIb–III	

Granulosis rubra nasi is a rare entity, mainly seen in childhood. Focal hyperhidrosis is a major feature. The disease has been treated by BoTN-A injections successfully [116].

Aquagenic keratoderma is a rare disease occurring after water immersion. One 60-year-old male patient was treated with 50 units of BoTN-A leading to a significant improvement within 2 weeks. The complaint recurred after 6 months but responded to a second course of BoTN [117].

Cutaneous leiomyomas are painful benign tumors. Pain is precipitated by cold or trauma. BoTN injections were analgesic in a patient with the disease reducing the amount of other painkillers needed [118]. Another patient with multiple piloleiomyomas experienced a rapid and sustained decrease of pain after 200 units BoTN-A given every 3 months [119].

Intertrigo is a possible complication of Darier's disease. BoTN-A was used as a preventive measure in a single patient [120].

In a patient with palmar hyperhidrosis and Raynaud disease, 100 U BoTN-A reduced sweating, swelling, erythema, and digital pain. The authors speculated that the combined effect of BoTN on acetylcholine, substance P, noradrenaline, CGRP, and glutamate release from nerve endings might be involved [121].

CONCLUSIONS AND OUTLOOK

BoTN has become a safe drug therapy not only in the case of aesthetic indications but in a number of other dermatological conditions. When we score the clinical evidence for efficacy and safety of BoTN therapy among the various possible indications, the picture is unhomogeneous [122]. Table 50.3 provides the evidence-based levels available for major indications and demonstrates where more and better trials are necessary. On the other hand, there is progress in pharmaceutical technologies in the production process. A complexing protein-free BoTN-A is available now in the market and topical formulations for pain-free application of the active compound are under trial [123,124]. In the near future, BoTN will stay as an interesting and fascinating drug for cutaneous disorders and complaints.

REFERENCES

1. Brin MF. Botulinum toxin: Chemistry, pharmacology, toxicity, and immunology. *Muscle Nerve* 1997; 20(Suppl 6):S146–S168.
2. Setler PE. Pharmacology of botulinum toxin type B. *Eur J Neurol* 2001; 8(Suppl 4):9–12.
3. Breidenbach MA, Brunger AT. New insights into clostridial neurotoxin-SNARE interactions. *Trends Mol Med* 2005; 11:377–381.
4. Adler M, Keller JE, Sheridan RE, Deshpande SS. Persistence of botulinum neurotoxin A demonstrated by sequential administration of serotypes A and E in EDL muscle. *Toxicon* 2001; 39:233–243.
5. Schiavo G, Matteoli M, Montecucco C. Neurotoxins affecting neuroexocytosis. *Physiol Rev* 2000; 80:717–766.
6. Frevert J. Content of botulinum neurotoxin in Botox®/Vistabel®, Dysport®/Azzalure®, and Xeomin®/Bocouture®. *Drugs R D* 2010; 10:67–73.
7. Al-Muharraqi MA, Fedorowicz Z, Al Bareeq J, Al Bareeq R, Nasser M. Botulinum toxin for masseter hypertrophy. *Cochrane Database Syst Rev* 2009; (1):CD007510.
8. Jimenez-Shahed J. A new treatment for focal dystonias: IncobotulinumtoxinA (Xeomin®), a botulinum neurotoxin type A free from complexing proteins. *Neuropsychiatr Dis Treat* 2012; 8:13–25.
9. Rosales RL, Arimura K, Takenaga S, Osame M. Extrafusal and intrafusal muscle effects in experimental botulinum toxin-A injection. *Muscle Nerve* 1996; 19:488–496.
10. Filippi GM, Errico P, Santarelli R, Bagolini B, Manni E. Botulinum A toxin effects on rat jaw muscle spindles. *Acta Otolaryngol* 1993; 113:400–404.
11. DePaiva A, Meinier FA, Molgo J, Aoki KR, Dolly DO. Functional repair of motor endplates after botulinum neurotoxin type A poisoning: Biphasic switch of synaptic activity between nerve sprouts and their parent terminals. *Proc Natl Acad Sci USA* 1999; 96:3200–3205.
12. Naumann M. Evidence-based medicine: Botulinum toxin in focal hyperhidrosis. *J Neurol* 2001; 248(Suppl 1):I/31–I/33.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

13. Karamfilov T, Konrad H, Karte K, Wollina U. Lower relapse rate of botulinum toxin A therapy for axillary hyperhidrosis by dose increase. *Arch Dermatol* 2000; 136:487–490.
14. Wollina U, Karamfilov T, Konrad H. High-dose botulinum toxin A therapy for axillary hyperhidrosis markedly prolongs the relapse-free interval. *J Am Acad Dermatol* 2002; 46:536–540.
15. Wiegand H, Erdmann G, Wellhoner HH. 125I-labelled botulinum toxin A neurotoxin: Pharmacokinetics in cats after intramuscular injection. *Nauyn Schmiedebergs Arch Pharmacol* 1976; 292:161–165.
16. Keller JE, Neale EA, Oyler G, Adler M. Persistence of botulinum neurotoxin action in cultured spinal cord cells. *FEBS Lett* 1999; 456:137–142.
17. Gilio F, Curra A, Lorenzano C, Modugno N, Manfredi M, Berardelli A. Effects of botulinum toxin type A on intracortical inhibition in patients with distonia. *Ann Neurol* 2000; 48:20–26.
18. Dressler D, Eckert J, Kukowski B, Meyer B. Somatosensory evoked potentials in writer's cramp: Pathological findings reversed by botulinum toxin therapy. *EEG Clin Neurophysiol* 1995; 94:59.
19. Palomar FJ, Mir P. Neurophysiological changes after intramuscular injection of botulinum toxin. *Clin Neurophysiol* 2012; 123:54–60.
20. Cui M, Aoki KR. Botulinum toxin type A (BOTN-A) reduces inflammatory pain in the rat formalin model. *Cephalgia* 2000; 20:414.
21. Ishikawa H, Mitsui Y, Yoshitomi T, Mashimo K, Aoki S, Mukuno K, Shimizu K. Presynaptic effects of botulinum toxin type A on the neuronally evoked potentials of albino and pigmented rabbit iris sphincter and dilator muscles. *Jpn J Ophthalmol* 2000; 44:106–109.
22. Purkiss J, Welch M, Doward S, Foster K. Capsaicin-stimulated release of substance P from cultured dorsal root ganglion neurons: Involvement of two distinct mechanisms. *Biochem Pharmacol* 2000; 59:1403–1406.
23. Humm AM, Pabts C, Lauterburg T, Burgunder JM. Enkephalin and aFGF are differentially regulated in rat spinal cord motoneurons after chemodenervation with botulinum toxin. *Exp Neurol* 2000; 161:361–372.
24. Cui M, Li Z, You S, Khanjiou S, Aoki R. Mechanisms of the antinociceptive effect of subcutaneous Botox: Inhibition of peripheral and central nociceptive processing. *Arch Pharmacol* 2002; 365:R17.
25. Morris J, Jobling P, Gibbins I. Differential inhibition by botulinum neurotoxin A of cotransmitters released from autonomic vasodilator neurons. *Am J Physiol Heart Circ Physiol* 2001; 281:2124–2132.
26. Shone CC, Melling J. Inhibition of calcium-dependent release of noradrenalin from PC12 cells by botulinum type-A neurotoxin: Long-term effects of the neurotoxin on intact cells. *Eur J Biochem* 1992; 207:1009–1016.
27. Kamanli A, Kaya A, Ardicoglu O, Ozgocmen S, Ozkurt Zengin F, Bayik Y. Comparison of lidocaine injection, botulinum toxin injection, and dry needling to trigger points in myofascial pain syndrome. *Rheumatol Int* 2005; 25:604–611.
28. Sycha T, Samal D, Chizh B, Lehr S, Gustorff B, Schnider P, Auff E. A lack of antinociceptive or antiinflammatory effect of botulinum toxin A in an inflammatory human pain model. *Anesth Analg* 2006; 102:509–516.
29. Wallengren J. Neuroanatomy and neurophysiology of itch. *Dermatol Ther* 2005; 18:292–303.
30. Heckmann M, Heyer G, Brunner B, Plewig G. Botulinum toxin type A injection in the treatment of lichen simplex: An open pilot study. *J Am Acad Dermatol* 2002; 46:617–619.
31. Wollina U, Karamfilov T. Adjuvant botulinum toxin A in dyshidrotic hand eczema: A controlled prospective pilot study with left-right comparison. *J Eur Acad Dermatol Venereol* 2002; 16:40–42.
32. Swartling C, Naver H, Lindberg M, Anveden I. Treatment of dyshidrotic hand dermatitis with intradermal botulinum toxin. *J Am Acad Dermatol* 2002; 47:667–671.
33. Dolimbek BZ, Jankovic J, Atassi MZ. Cross reaction of tetanus and botulinum neurotoxins A and B and the boosting effect of botulinum neurotoxins A and B on a primary anti-tetanus response. *Immunol Invest* 2002; 31:247–262.
34. Hanna PA, Jankovic J. Mouse bioassay versus Western blot assay for botulinum toxin antibodies. Correlation with clinical response. *Neurology* 1998; 50:1624–1629.
35. Naumann M, Carruthers A, Carruthers J et al. Meta-analysis of neutralizing antibody conversion with onabotulinumtoxin A (BOTOX®) across multiple indications. *Mov Disord* 2010; 25:2211–2218.
36. Stengel G, Bee EK. Antibody-induced secondary treatment failure in a patient treated with botulinum toxin type A for glabellar frown lines. *Clin Interv Aging* 2011; 6:281–284.
37. Campanati A, Sandroni L, Gesuita R, Giuliano A, Giuliodori K, Marconi B, Ganzetti G, Offidani A. Treatment of focal idiopathic hyperhidrosis with botulinum toxin type A: Clinical predictive factors of relapse-free survival. *J Eur Acad Dermatol Venereol* 2011; 25:917–921.
38. Moffat CE, Hayes WG, Nyamekye IK. Durability of botulinum toxin treatment for axillary hyperhidrosis. *Eur J Vasc Endovasc Surg* 2009; 38:188–191.
39. Lowe NJ, Glaser DA, Eadie N, Daggett S, Kowalski JW, Lai PY, North American Botox in Primary Axillary Hyperhidrosis Clinical Study Group. Botulinum toxin type A in the treatment of primary axillary hyperhidrosis: A 52-week multicenter double-blind, randomized, placebo-controlled study of efficacy and safety. *J Am Acad Dermatol* 2007; 56:604–611.
40. Heckmann M, Plewig G, Hyperhidrosis Study Group. Low-dose efficacy of botulinum toxin A for axillary hyperhidrosis: A randomized, side-by-side, open-label study. *Arch Dermatol* 2005; 141:1255–1259.
41 Naumann M, Lowe NJ, Kumar CR, Hamm H; Hyperhidrosis Clinical Investigators Group. Botulinum toxin type a is a safe and effective treatment for axillary hyperhidrosis over 16 months: a prospective study. *Arch Dermatol* 2003; 139(6):731–736.
42. Naumann M, Lowe NJ. Botulinum toxin type A in treatment of bilateral primary axillary hyperhidrosis: Randomised, parallel group, double blind, placebo controlled trial. *BMJ* 2001; 323:596–599.
43. Heckmann M, Ceballos-Baumann AO, Plewig G, Hyperhidrosis Study Group. Botulinum toxin A for axillary hyperhidrosis (excessive sweating). *N Engl J Med* 2001; 344:488–493.
44. Schnider P, Binder M, Kittler H, Birner P, Starkel D, Wolff K, Auff E. A randomized, double-blind, placebo-controlled trial of botulinum A toxin for severe axillaryhyperhidrosis. *Br J Dermatol* 1999; 140:677–680.
45. Fianagan KH, King R, Glaser DA. Botulinum toxin type a versus 20% aluminium chloride for the treatment of moderate to severe primary focal axillary hyperhidrosis. *J Drugs Dermatol* 2008; 7:221–227.
46. Marcella S, Goodman G, Cumming S, Foley P, Morgan V. Thirty-five units of botulinum toxin type A for treatment of axillary hyperhidrosis in female patients. *Aust J Dermatol* 2011; 52:123–126.
47. Baumann L, Slezinger A, Halem M, Vujevich J, Mallin K, Charles C, Martin LK, Black L, Bryde J. Double-blind, randomized, placebo-controlled pilot study of the safety and efficacy of Myobloc (botulinum toxin type B) for the treatment of palmar hyperhidrosis. *Dermatol Surg* 2005; 31:263–270.
48. Saadia D, Voustianiouk A, Wang AK, Kaufmann H. Botulinum toxin type A in primary palmar hyperhidrosis: Randomized, single-blind, two-dose study. *Neurology* 2001; 57:2095–2099.
49. Lowe NJ, Yamauchi PS, Lask GP, Patnaik R, Iyer S. Efficacy and safety of botulinum toxin type a in the treatment of palmar-hyperhidrosis: A double-blind, randomized, placebo-controlled study. *Dermatol Surg* 2002; 28:822–827.
50. Schnider P, Binder M, Auff E, Kittler H, Berger T, Wolff K. Double-blind trial of botulinum A toxin for the treatment of focal hyperhidrosisof the palms. *Br J Dermatol* 1997; 136:548–552.
51. Yamashita N, Shimizu H, Kawada M, Yanagishita T, Watanabe D, Tamada Y, Matsumoto Y. Local injections of botulinum toxin A for palmar hyperhidrosis: Usefulness and efficacy in relation to severity. *J Dermatol* 2008; 35:325–329.
52. Wollina U, Karamfilov T. Botulinum toxin A for palmar hyperhidrosis. *J Eur Acad Dermatol Venereol* 2001; 15:555–558.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

53. Gregoriou S, Rigopoulos D, Makris M, Liakou A, Agiosofitou E, Stefanaki C, Kontochristopoulos G. Effects of botulinum toxin-a therapy for palmar hyperhidrosis in plantar sweat production. *Dermatol Surg* 2010; 36:496–498.
54. Wollina U. Botulinum toxin: Non-cosmetic indications and possible mechanisms of action. *J Cutan Aesthet Surg* 2008; 1:3–6.
55. Woolery-Lloyd H, Valins W. Aluminium chloride hexahydrate in a salicylic acid gel base: A case series of combination therapy with botulinum toxin type A for moderate to severe hyperhidrosis. *Cutis* 2011; 88:43–45.
56. Kom WO, Kil HK, Yoon KB, Noh KU. Botulinum toxin: A treatment for compensatory hyperhidrosis in the trunk. *Dermatol Surg* 2009; 35:833–838.
57. Ambrogi V, Campione E, Mineo D, Paternò EJ, Mineo TC. Bilateral throracoscopic T2 to T3 sympathectomy versus botulinum toxin injection in palmar hyperhidrosis. *Ann Thorac Surg* 2009; 88:238–245.
58. Komericki P, Ardjomand N. Hyperhidrosis of face and scalp: Repeated successful treatment with botulinum toxin type A. *Ind J Dermatol Venereol Leprol* 2012; 78:201–202.
59. Wollina U, Konrad H, Graefe T, Thiele J. Botulinum toxin A for focal hyperhidrosis in leg amputees: A case report. *Acta Derm Venereol* 2000; 80:226–227.
60. Gratrix M, Hivnor C. Botulinum toxin A treatment for hyperhidrosis in patients with prosthetic limbs. *Arch Dermatol* 2010; 146:1314–1315.
61. Kern U, Kohl M, Seifert U, Schlereth T. Botulinum toxin type B in the treatment of residual limb hyperhidrosis for lower limb amputees: A pilot study. *Am J Phys Med Rehabil* 2011; 90:321–329.
62. Nolte D, Gollmitzer I, Loeffelbein DJ, Hölzle F, Wolff KD. Botulinum toxin for treatment of gustatory sweating. A prospective randomized study. *Mund Kiefer Gesichtschir* 2004; 8:369–375.
63. Cantarella G, Berlusconi A, Mele V, Cogiamanian F, Barbieri S. Treatment of Frey's syndrome with botulinum toxin type B. *Otolaryngol Head Neck Surg* 2010; 143:214–218.
64. Pérez-Tato B, Zamora-Martínez E, Sánchez-Albisua B, Pérez-González YC, Polimón-Olabarrieta I, Marinero-Escobedo S, Fernández-López P. Facial and axillary apocrine chromhidrosis. *Dermatol Online J* 2012; 18:13.
65. Li WW, Liu ZF, Cui YN, Zeng A. Comparison study on the efficacy of three methods for the treatment of osmidrosis. *Zhonghua Zheng Xing Wai Ke Za Zhi* 2010; 26:348–350.
66. Wollina U. Pompholyx: What's new? *Expert Opin Investig Drugs* 2008; 17:897–904.
67. Wollina U. A review of clinical features, differential diagnosis, and management. *Am J Clin Dermatol* 2010; 11:305–314.
68. Zanchi M, Favot F, Bizzarini M, Piai M, Donini M, Sedona P. Botulinum toxin type-A for the treatment of inverse psoriasis. *J Eur Acad Dermatol Venereol* 2008; 22:431–436.
69. Wang TS, Tsai TF. Intralesional therapy for psoriasis. *J Dermatolog Treat* 2013; 24:340–347.
70. Bowden JB, Rapini RP. Psoriasiform eruption from intramuscular botulinum A toxin. *Cutis* 1992; 50:415–416.
71. Wollina U, Konrad H, Petersen S. Botulinum toxin in dermatology—Beyond wrinkles and sweat. *J Cosmet Dermatol* 2005; 4:223–237.
72. Cho HR, Lew BL, Lew H, Sim WY. Treatment effects of intradermal botulinum toxin type A injection on alopecia areata. *Dermatol Surg* 2010; 36(Suppl 4):2175–2181.
73. Lapiere JC, Hirsh A, Gordon KB, Cook B, Montalvo A. Botulinum toxin type A for the treatment of axillary Hailey-Hailey disease. *Dermatol Surg* 2000; 26:371–374.
74. Kang NG, Yoon TJ, Kim TH. Botulinum toxin type A as an effective adjuvant therapy for Hailey-Hailey disease. *Dermatol Surg* 2002; 28:543.
75. Konrad H, Karamfilov T, Wollina U. Intracutaneous botulinum toxin A versus ablative therapy of Hailey-Hailey disease—A case report. *J Cosmet Laser Ther* 2001; 3:181–184.
76. Koeyers WJ, Van Der Geer S, Krekels G. Botulinum toxin type A as an adjuvant treatment modality for extensive Hailey-Hailey disease. *J Dermatolog Treat* 2008; 19:251–254.
77. Bessa GR, Grazziotin TC, Manzoni AP, Weber MB, Bonamigo RR. Hailey-Hailey disease treatment with botulinum toxin type A. *An Bras Dermatol* 2010; 85:717–722.
78. Swartling C, Karlqvist M, Hymnelius K, Weis J, Vahlquist A. Botulinum toxin in the treatment of sweat-worsened foot problems in patients with epidermolysis bullosa simplex and pachyonychia congenital. *Br J Dermatol* 2010; 163:1072–1076.
79. Abitbol RJ, Zhou LH. Treatment of epidermolysis bullosa simplex, Weber-Cockayne type, with botulinum toxin type A. *Arch Dermatol* 2009; 145:13–15.
80. Jonas M, Scholefield JH. Anal fissure. *Gastroenterol Clin North Am* 2001; 30:167–181.
81. Horsch D, Kirsch JJ, Weihe E. Elevated density and plasticity of nerve fibres in anal fissures. *Int J Colorectal Dis* 1998; 13:134–140.
82. Zaghiyan KN, Fleshner P. Anal fissure. *Clin Colon Rectal Surg* 2011; 24:22–30.
83. Nelson RL, Thomas K, Morgan J, Jones A. Non surgical therapy for anal fissure. *Cochrane Database Syst Rev* 2012; 2:CD003431.
84. Jost WH. Ten year's experience with botulinum toxin in anal fissure. *Int J Colorectal Dis* 2002; 17:298–302.
85. Wollina U. Pharmacological sphincterotomy for chronic anal fissures by botulinum toxin A. *J Cutan Aesthet Surg* 2008; 1:58–63.
86. Wollina U, Konrad H. Botulinum toxin A in anal fissures: A modified technique. *J Eur Acad Dermatol Venereol* 2002; 16:469–471.
87. Davies J, Duffy D, Boyt N, Aghahoseini A, Alexander D, Leveson S. Botulinum toxin (botox) reduces pain after hemorrhoidectomy: Results of a double-blind, randomized study. *Dis Colon Rectum* 2003; 46:1097–1102.
88. Patti R, Almasio PL, Muggeo VM, Buscemi S, Arcara M, Matranga S, Di Vita G. Improvement of wound healing after hemorrhoidectomy: A double-blind, randomized study of botulinum toxin injection. *Dis Colon Rectum* 2005; 48:2173–2179.
89. Pelletier F, Parratte B, Penz S, Moreno JP, Aubin F, Humbert P. Efficacy of high doses of botulinum toxin A for treating provoked vestibulodynia. *Br J Dermatol* 2011; 164:617–622.
90. Katsinelos P, Kalomenopoulou M, Christodoulou K, Katsiba D, Tsolkas P, Pilpilidis I, Papagiannis A, Kapitsinis I, Vasiliadis I, Souparis T. Treatment of proctalgia fugax with botulinum A toxin. *Eur J Gastroenterol Hepatol* 2001; 13:1371–1373.
91. Sánchez Romero AM, Arroyo Sebastián A, Pérez Vicente FA, Serrano Paz P, Candela Polo F, Calpena Rico R. Treatment of proctalgia fugax with botulinum toxin: Results in 5 patients. *Rev Clin Esp* 2006; 206:137–140.
92. Blugerman G, Schavelzon D, D'Angelo S. Multiple eccrine hidrocystomas: A new therapeutic option with botulinum toxin. *Dermatol Surg* 2003; 29:557–559.
93. Correia O, Duarte AF, Barros AM, Rocha N. Multiple eccrine hidrocystomas—From diagnosis to treatment: The role of dermatoscopy and botulinum toxin. *Dermatology* 2009; 219:77–79.
94. Ebrahimi A, Radmanesh M. Botulinum toxin type-A (BT-A) for the treatment of multiple eccrine hidrocystomas. *J Dermatolog Treat* 2010; 21:80–82.
95. Woolery-Lloyd H, Raipara V, Nijhawan RI. Treatment for multiple periorbital eccrine hidrocystomas: Botulinum toxin A. *J Drugs Dermatol* 2009; 8:71–73.
96. Barco D, Baselga E, Alegre M, Curell R, Alomar A. Successful treatment of eccrine angiomatous hamartoma with botulinum toxin. *Arch Dermatol* 2009; 145:241–243.
97. Vashi N, Mandal R. Giant multi-loculated apocrine hidrocystomas. *Dermatol Online J* 2010; 16:16.
98. Kavanagh GM, Tidman MJ. Botulinum A toxin and brachioradial pruritus. *Br J Dermatol* 2012; 166:1147.
99. Weinfeld PK. Successful treatment of nostalgia paresthetica with botulinum toxin type A. *Arch Dermatol* 2007; 143:980–982.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

100. Oh YJ, Lee NY, Suh DH, Koh JS, Lee SJ, Shin MK. A pslit-face study using botulinum toxin type B to decrease facial erythema index. *J Cosmet Laser Ther* 2011; 13:243–248.
101. Odo ME, Odo LM, Farias RV, Primavery RA, Leão L, Cucé LC, Juliano Y. Botulinum toxin for the treatment of menopausal hot flushes: A pilot study. *Dermatol Surg* 2011; 37:1579–1583.
102. Xiao Z, Qu G. Effects of botulinum toxin type a on collagen deposition in hypertrophic scars. *Molecules* 2012; 17:2169–2177
103. Wang L, Tai NZ, Fan ZH. Effect of botulinum toxin type A injection on hypertrophic scar in rabbit ear model. *Zhonghua Zheng Xing Wai Ke Za Zhi* 2009; 25:284–287.
104. Haubner F, Ohmann E, Müller-Vogt U, Kummer P, Strutz J, Gassner H. Effects of botulinum toxin A on cytokine synthesis in a cell culture model of cutaneous scarring. *Arch Facial Plast Surg* 2012; 14:122–126.
105. Xiao Z, Zhang F, Lin W, Zhang M, Liu Y. Effect of botulinum toxin type A on transforming growth factor beta1 in fibroblasts derived from hypertrophic scar: A preliminary report. *Aesthetic Plast Surg* 2010; 34:424–427.
106. Xiao Z, Zhang M, Liu Y, Ren L. Botulinum toxin type A inhibits connective tissue growth factor expression in fibroblasts derived from hypertrophic scar. *Aesthetic Plast Surg* 2011; 35:802–807.
107. Uyesugi B, Lippincott B, Dave S. Treatment of a painful keloid with botulinum toxin type A. *Am J Phys Med Rehabil* 2010; 89:153–155.
108. Xiao Z, Zhang F, Cui Z. Treatment of hypertrophic scars with intralesional botulinum toxin type A injections: A preliminary report. *Aesthetic Plast Surg* 2009; 33:409–412.
109. Liu A, Moy RL, Ozog DM. Current methods employed in the prevention and minimization of surgical scars. *Dermatol Surg* 2011; 37:1740–1746.
110. Viera MH, Amini S, Valins W, Berman B. Innovative therapies in the treatment of keloids and hypertrophic scars. *J Clin Aesthet Dermatol* 2010; 3:20–26.
111. Gassner HG, Brissett AE, Otley CC, Boahene DK, Boggust AJ, Weaver AL, Sherris DA. Botulinum toxin to improve facial wound healing: A prospective, blinded, placebo-controlled study. *Mayo Clin Proc* 2006; 81:1023–1028.
112. Wilson AM. Use of botulinum toxin type A to prevent widening of facial scars. *Plast Reconstr Surg* 2006; 117:1758–1766.
113. Goodman GJ. The use of botulinum toxin as primary or adjunctive treatment for post acne and traumatic scarring. *J Cutan Aesthet Surg* 2010; 3:90–92.
114. Bin Saif GA, Al Samary A, Al Mohizea S. Failure of botulinum toxin treatment for localized vitiligo. *J Drugs Dermatol* 2010; 9:1092–1094.
115. Ghosn S, Uthman I, Dahdah M, Kibbi AG, Rubeiz N. Treatment of pachydermoperiostosis pachydermia with botulinum toxin type A. *J Am Acad Dermatol* 2010; 63:1036–1041.
116. Grazziotin TC, Buffon RB, da Silva Manzoni AP, Libis AS, Weber MB. Treatment of granulosis nasi with botulinum toxin type A. *Dermatol Surg* 2009; 35:1298–1299.
117. Houle M-C, Al Dhaybi R, Benohanian A. Unilateral aquagenic keratoderma treated with botulinum toxin A. *J Dermatol Case Rep* 2010; 1:1–5.
118. Onder M, Adişen E. A new indication of botulinum toxin: Leiomyoma-related pain. *J Am Acad Dermatol* 2009; 60:325–328.
119. Sifaki MK, Krueger-Krasagakis S, Koutsoupoulos A, Evangelou GI, Tosca AD. Botulinum toxin type A—Treatment of a patient with multiple cutaneous piloleiomyomas. *Dermatology* 2009; 218:44–47.
120. Santiago-et-Sánchez-Mateos JL, Beà S, Fernández M, Pérez B, Harto A, Jaén P. Botulinum toxin type A for the preventive treatment of intertrigo in a patients with Darier's disease and inguinal hyperhidrosis. *Dermatol Surg* 2008; 34:1733–1737.
121. Kossinetseva I, Barankin B. Improvement in both Raynaud disease and hyperhidrosis in response to botulinum toxin type A treatment. *J Cutan Med Surg* 2008; 12:189–193.
122. Sackett DL, Rosenberg WM, Richardson WS, Haynes RP. Evidence-based medicine: What it is and what it isn't. *Br J Med* 1996; 312:71.
123. Dressler D. Five-year experience with in cobotulinum toxin A (Xeomin(®)): The first botulinum toxin drug free of complexing proteins. *Eur J Neurol* 2012; 19:385–359.
124. Glogau R, Blitzer A, Brandt F, Kane M, Monheit GD, Waugh JM. Results of a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of a botulinum toxin type A topical gel for the treatment of moderate-to-severe lateral canthal lines. *J Drugs Dermatol* 2012; 11:38–45.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Cosmetic botulinum toxin treatment

Christopher M.E. Rowland Payne and Wolfgang G. Philipp-Dormston

INTRODUCTION

Botulinum (BTX) provides many opportunities for therapeutic benefit. Apart from dynamic rhytids, BTX can benefit focal hyperhidrosis, migraine, and tension headache as well as many other disorders, as wide ranging as cerebral palsy, stroke with upper motor neuron spasticity, blepharospasm, strabismus, torticollis, myofascial pain, esophageal spasm and achalasia, anal fissure, bladder detrusor overactivity, vaginismus, temporomandibular joint dysfunction, bruxism, masseter muscle hypertrophy (MMH), and even depression.

BTX not only diminishes unwanted muscular hyperactivity and hyperhidrosis, it also results in measurable improvements in skin quality, for example, BTX treatment decreases transepidermal water loss (TEWL) and increases stratum corneum hydration [15].

HISTORY

In nature, BTX is produced by the bacterium Clostridium BTX. BTX is the chemical mediator of botulism, which is a food poisoning-induced muscular paralysis.

In 1980, Alan Scott used BTX on a patient for the treatment of strabismus [14]. In 1992, Carruthers and Carruthers reported the use of BTX for the treatment of glabellar wrinkles caused by frowning [2]. The cosmetic use of BTX has been well recorded (e.g., [5,6,11]).

MODE OF ACTION

At the neuromuscular junction, stimulated nerve endings release a neurotransmitter, acetylcholine (ACh). ACh binds to the ACh receptor on the muscle fiber, stimulating a cascade that eventuates in muscle contraction. BTX blocks the release of ACh from the nerve ending and so inhibits muscle contraction.

The release of ACh is triggered by the action of membrane proteins located within the terminal nerve endings. By binding to these specific proteins, BTX blocks the release of ACh. Each of the BTX serotypes cleaves to a different membrane protein, thus, exerting a different clinical effect. Only five serotypes of BTX affect the human nervous system: BTX-A, B, E, F, and G.

The clinical effect of BTX-A begins to be apparent after 48 hours, reaches its maximum after 1–2 weeks, and lasts for 3–6 months. Its action wanes as new collateral nerve endings sprout from the original damaged nerve endings. This begins 4 weeks after treatment. Later, the damaged original nerve endings themselves regenerate and regain their function. Then the new collateral sprouts retract and disappear.

WRINKLES AND RHYTIDS

Not all wrinkles or rhytids are undesirable, for example, in the case of Sir Winston Churchill (1874–1965), determination and empathy were conveyed by contraction of the corrugator.

A wrinkle may be defined as a skin crease that disappears at rest; a rhytid may be defined as a skin crease that persists at rest.

Wrinkles and rhytids may result from

1. Gravity (*gravitational*)
2. Sleep (*compression*)
3. Muscle contraction (*dynamic*)

Wrinkles and rhitids due to gravity or sleep are not the concern of this chapter.

Dynamic facial wrinkles are skin creases that occur when a facial muscle contracts and disappear when it relaxes. Dynamic *wrinkles* disappear because the muscle relaxes and skin quality is unimpaired.

Dynamic facial *rhytids*, on the other hand, are skin creases that occur when the muscle contracts but do not entirely disappear when it relaxes. They persist at rest because of

1. Excessive muscular contraction
2. Impaired skin quality

Excessive muscular contraction may be the result of excessive resting muscle tone or repeated and/or prolonged muscle contractions. Normal healthy striated muscles, including facial muscles, have the capacity to contract at the conscious will of the subject, e.g., closing the jaw or creating a facial expression. In full extreme contraction, the jaw is very tightly closed and the face contorted. At rest, the muscles relax but not completely; there is some unconscious residual contraction, known as resting tone, which occurs without the conscious will of the subject. If they were not, the jaw would fall open and the face would look featureless, as in death. Resting tone is greater in those who are subject to stress or suffering from anxiety or depression; in these people, muscle tone may be excessive at rest. Muscular contraction is repeated and prolonged in patients with hyperdynamic faces (such patients also often suffer from stress) and also in those who have repeatedly screwed up their eyes when being exposed to strong sunlight or other adverse weather conditions. Furthermore, constant and repeated unconscious contraction leads the muscles to hypertrophy, so gradually worsening the rhytids.

Impaired skin quality is usually mainly due to photodamage, with thinning of the dermis and reduced elasticity. Intrinsic ageing (chronoageing) also thins the skin somewhat. In a small minority of patients, impaired skin quality is due to scarring, such as acne scars. In photodamaged skin with its UV-induced loss of dermal thickness, when the facial muscles cease contracting, the skin is less able to spring back to an unwrinkled

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

state and the wrinkles persist as dynamic rhytids. Rhytids like these are almost as much a consequence of photodamage as of excessive muscular contraction (irrespective of whether the muscular contraction has been due to excessive resting tone or repeated and/or prolonged muscle contractions).

Dynamic rhytids are usually a product of both excessive muscular contraction and impaired skin quality. Typically, patients who seek treatment for dynamic rhytids have elements of both impaired skin quality and excessive muscular contraction. Most are white and affected by photodamage. Many exhibit a degree of anxiety or depression.

By reducing muscle strength, BTX brings improvements in dynamic rhytids not only for those with excessive muscular contraction but also for those with impaired skin quality combined with "normal" muscular contraction.

AESTHETIC INDICATIONS FOR BTX

Aesthetic indications for BTX are legion. Many relate to the rebalancing of resting muscle tone. Relative overactivity of one muscle or muscle group can be reduced using BTX.

Good indications for BTX are

1. Rhytids resulting from unwanted or excessive muscular contraction (with or without photodamage)

Poor indications for BTX are

1. Fine rhytids from photodamage alone or chronoageing alone
2. Gravitational rhytids
3. Sleep rhytids

In certain parts of the world, abolition of frontal and glabella movement is the goal. In other parts of the world, the aim is a more natural look with a reduction in resting rhytids without impairment of expressions of animation. This more natural result can be achieved by using lower doses of BTX, applied in a more tailor-made fashion. This is the goal of multi-mini BTX (M-M BTX) [12].

PRETREATMENT CONSULTATION

As with all elective procedures, the good physician remembers that mutual trust and good communication are at the heart of a successful doctor–patient relationship, which is itself, like patient selection, an important determinant of patient satisfaction with treatment. Verbal exchange and eye contact are essential steps in these processes. All this is much more easily achieved if the initial consultation follows the classical medical model with clinical history, physical examination, and diagnosis followed by a discussion with the patient of the treatment options. All the better for the patient and the patient's confidence in you if your consultation also reveals other matters of a non-cosmetic nature that you can help the patient with, e.g., an incidental skin malignancy.

PSYCHOLOGICAL CONSIDERATIONS

BTX is a medical treatment. It requires a medical, including a psychological, assessment of the patient. "Botox parties" are unlikely to provide the ideal setting in which psychological factors may best be assessed. It is important to look behind the expression of the patient and to remember that 49% of cosmetic surgery patients have a body image disorder and 19% a personality disorder [4]. Of cosmetic rhinoplasty patients, 41% have an associated psychiatric disorder and 25% have body dysmorphic disorder (BDD) [1]. Of persons seeking appearance-enhancing treatment, such as cosmetic surgery or dermatological/minimally invasive treatments, 5%–15% have BDD [3,13].

Sometimes, patients seeking BTX may be better treated psychologically. On the other hand, in certain circumstances, BTX itself may be used as a psychological treatment.

> *Smile and the world smiles with you.*

An improvement in facial appearance may affect the way that a person is treated by others. It may also result in an improvement in self-confidence or mood.

Depression is unconsciously displayed in facial expression. In some patients, treatment of facial expression may result in an improvement in depression. BTX treatment of the face improves major depression [7,10], even in patients whose depression did not respond to oral antidepressant therapy [16].

BRANDS AND STORAGE OF BTX

In Europe, three companies sell three different preparations of BTX-A. Allergan sells Botox® (also known as Vistabel®), Merz sells Xeomin® (also known as Bocouture®), and Speywood/Galderma sells Dysport® (also known as Azzalure®). Prior to reconstitution, Botox/Vistabel and Dysport/Azzalure should be stored in a refrigerator. Xeomin/Bocouture may be stored at room temperature.

UNIT EQUIVALENCE

There is controversy, but, broadly speaking, the unit equivalence is that 1 unit of Dysport/Azzalure is equivalent to 0.4 unit of Botox/Vistabel/Xeomin/Bocouture (i.e., 1 Speywood unit = 0.4 Allergan/Merz unit).

This is the same as saying that 1 unit of Botox/Vistabel/Xeomin/Bocouture is equivalent to 2.5 units of Dysport/Azzalure (i.e., 1 Allergan/Merz unit = 2.5 Speywood units).

All BTX preparations have to be diluted with normal saline (N/S). Different doctors choose different dilutions. An equipotent (volume for volume) solution of BTX may be prepared using the formulae outlined in Table 51.1.

For the sake of simplicity, all doses stated in this chapter refer exclusively to Speywood units.

For ease of clinical use, 0.10 mL of this solution (20 Speywood units ≈ 8 Allergan/Merz units) is drawn up into each of a number of 0.3 mL insulin syringes with bonded 30 gauge needles.

PLANNING BTX TREATMENT

The patient is asked to sit upright, gazing into infinity. The lighting is adjusted so that it shines from above downward in the most unflattering way, in the style of "elevator lighting."

The patient should be observed at rest and in animation. Using a hand mirror, it is helpful to demonstrate to the patient any facial asymmetries. Often, patients are entirely unaware of quite major facial asymmetries.

Once the choice of treatment has been decided upon, the patient should give verbal and, if possible, written informed consent. Patient advice sheets may be useful. The more that can be explained to a patient preoperatively about what to expect, the less that needs to be explained postoperatively.

> *Preoperative explanation is "knowledge." Postoperative explanation is "excuses."*

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Table 51.1 Botulinum: Preparation of an Equipotent Solution of the Different Brands

1× Dysport 500 / 2.5 mL normal saline	=	1× Azzalure 125 / 0.63 mL normal saline	=	1× Vistabel 50 / Bocouture 50 / 0.63 mL normal saline	=	1× Botox 100/Xeomin 100 / 1.25 mL normal saline	
1 Speywood unit / 0.005 mL normal saline	=	0.4 Allergan unit / 0.4 Merz unit / 0.005 mL normal saline					
2.5 Speywood units / 0.0125 mL normal saline	=	1.0 Allergan unit / 1.0 Merz unit / 0.0125 mL normal saline					

Attention to all these steps increases patient confidence. The patient who is confident and positive in his or her approach to treatment will find the experience of the treatment session more easy and often less uncomfortable than the patient who is more diffident or doubtful. A patient who has confidence in the doctor is more likely to tolerate well any minor inconveniences of the treatment, such as small bruising.

MINIMIZING BRUISING AND DISCOMFORT

To minimize bruising, patients are asked to avoid aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) for 14 days preoperatively. For 2 days before treatment, patients may also avoid ginkgo, vitamin C, vitamin E, and supplements of fish oil or garlic. (Cooked garlic in food need not be avoided.) If pain relief is needed during the 14 days prior to treatment, patients are asked to use only paracetamol (= acetaminophen) or codeine or cocodamol (which is a combination of both codeine and paracetamol).

Ideally, the first day of the menses and the day before that are avoided as pain tolerance is less during that 48 hours.

Ideally, the patient should arrive 20 minutes early and be neither rushed nor tired. The makeup should be removed. Topical anesthetic, such as EMLA, is applied when the patient arrives and then again 2–5 minutes before treatment.

For the comfort of the patient, efforts should be made to avoid dulling the needle tip prior to making the injections. Therefore, the rubber bung of the ampoule is first removed, and then the treatment syringe with its bonded needle is filled directly from the ampoule without letting the needle tip touch the glass.

During treatment, the patient should be kept at their ease by talking. *Vocal anesthesia* is most effective if it is the patient who does the talking rather than the doctor. Discomfort is related to the sharpness of the needle, the number of injections, and the angle of the injections. Perpendicular injections minimize discomfort and lessen the risk of bruising. To avoid the increased discomfort that would come from using a dulled needle, no one needle should make too many injections. Risk of bruising is related to the number of injections and the depth of the injections. Superficial injections reduce the risk of bruising as any bleeding from a superficial injection is immediately apparent and can be prevented from progressing to a bruise by immediate pressure. It is more difficult to recognize deeper bleeding as swiftly or easily. It is very helpful to have an assistant who can exert pressure as soon as any bleeding is observed and who can also use a large diagram of the face on which to make detailed contemporaneous notes of the exact location and dose of each injection. Such notes are helpful at follow-up and at subsequent treatment sessions.

TECHNIQUE CONTROVERSIES

In certain respects, M-M BTX is at variance with the edicts of conventional product license–based practice.

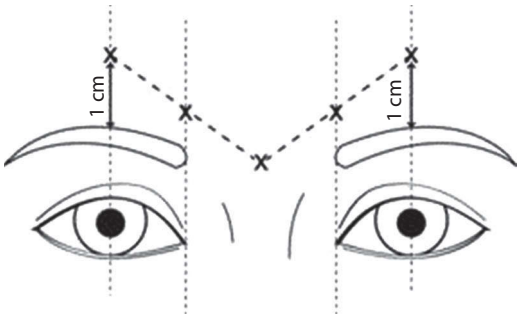


Figure 51.1 Conventional teaching: Azzalure injection sites.

- *Edict 1*: Conventional teaching is that the corrugator muscle can only be reached by deep injection.
- *Edict 2*: Conventional teaching concerning cosmetic BTX injection sites at the glabella recommends two single injections in "the region of each corrugator" and one into the procerus (i.e., the combined left and right sides receive a total of five injections, each of 10 Speywood units, totaling 50 Speywood units) (Figure 51.1).
- *Edict 3*: Conventional teaching is that BTX injections inferior to the eyebrow cause blepharoptosis.
- *Edict 4*: Conventional teaching is that cosmetic BTX injections should not be given within the orbital rim.

Following the standard teaching often gives very good results. However, in the opinion of the authors, more natural results can be achieved and smaller doses used when these four edicts are disobeyed.

RATIONALE OF MULTI-MINI BTX [12]

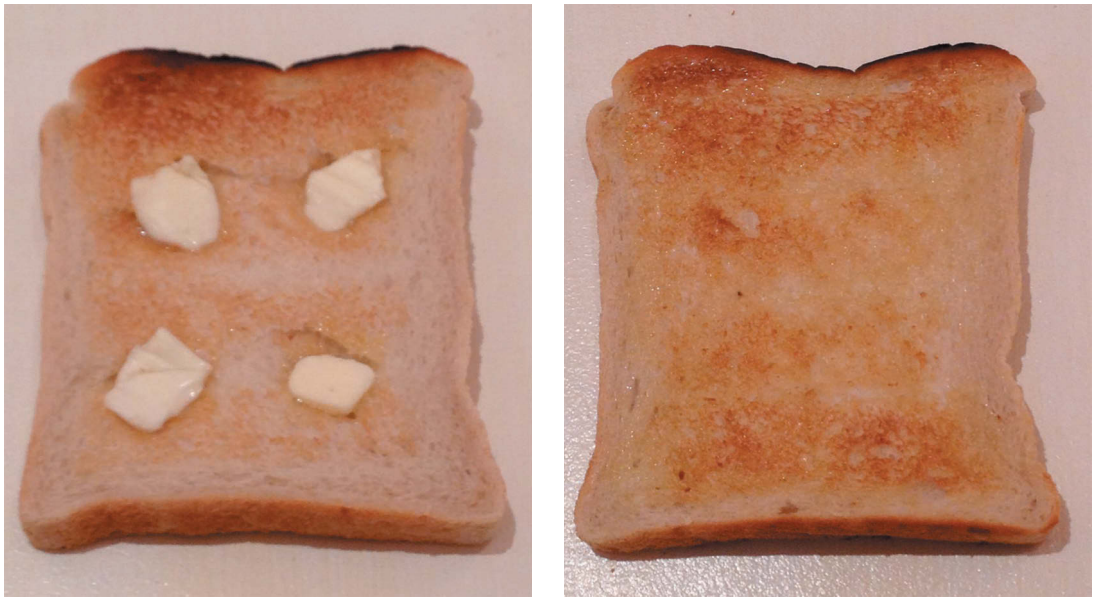
Toast may be buttered either with three or four largish blobs of butter or with a smaller amount of butter that is spread very thinly and evenly across the whole surface of the toast (Figure 51.2).

The latter is the principle of M-M BTX. M-M BTX uses multiple mini-dose injections of BTX, i.e., more injections, each of a much lower dose.

M-M BTX has the advantages of a more even and natural result and uses smaller amounts of BTX, and its beneficial effect lasts 5½ months (except in the most hyperdynamic of faces in which it lasts only 3–4 months). M-M BTX has the disadvantage of requiring more injections, which means a longer procedure time with somewhat more discomfort. BTX injections are usually best made into muscle. Since many of the facial muscles insert into skin, BTX can often be given as a subdermal injection, which helps minimize bruising.

The greater number of injections used in M-M BTX increases the risk of small bruising, but their mainly superficial placement

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b)

Figure 51.2 (a) Toast may be buttered like this or (b) like this. (Reproduced from Rowland Payne CME, Multi-mini botulinum, in: Redaelli A, ed., *Botulinum Toxin A in Aesthetic Medicine*, 2nd ed., Officiana Editoriale Oltrarno, Florence, Italy, 2013, pp. 185–198.)

reduces the risk of later larger ecchymoses, which are a risk of the deeper injections used in conventional cosmetic BTX treatments.

M-M BTX placement and dose are determined by observation and palpation of the relevant muscles in animation, such that the treatment is matched to the patient's own expressions. There is no textbook injection plan or dose that can be applied to every patient. In any cosmetic unit, several low-dose M-M BTX injections (each of 1–2 Speywood units) are made rather than one or two larger conventional dose BTX injections (each of 5–10 Speywood units). Typically, M-M BTX injections are less than 1 cm apart.

M-M BTX differs from conventional BTX most markedly at corrugator and in the region of orbicularis oculi (OO).

Rationale of M-M BTX at Corrugator Superciliaris

The brow elevator (frontalis) is opposed by the brow depressors (procerus, corrugator supercilii, OO, and depressor supercilii) as well as by the depressor effect of gravity and by the squashing and drawing downward effect of sleeping on the side of the face/brow (Figure 51.3).

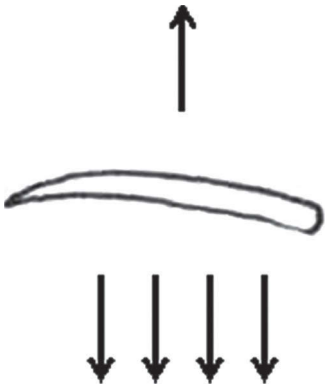


Figure 51.3 Eyebrow elevation by frontalis muscle is opposed by four depressor muscles (procerus, corrugator supercilii, OO, and depressor supercilii) as well as by gravity and sleep.

Conventional BTX injections, as illustrated in Figure 51.1, treat frontalis rather than corrugator. Frontalis is the only brow elevator. Inevitably, therefore, conventional BTX results in a degree of brow ptosis, especially at the medial eyebrows.

Conventional teaching is that corrugator can only be reached by deep injection. This is not so. It can be reached by superficial injections. Like most muscles of expression, corrugator originates from bone and inserts into skin.

Corrugator originates from the medial part of the superciliary arch. Most of its origin lies deep to the medial end of the eyebrow where the skin and subcutaneous tissues are thick. Part of its origin is just inferomedial to the medial end of the eyebrow where the overlying skin and subcutaneous tissue are thin. Thus, this part of the origin of corrugator is more or less subdermal and therefore amenable to superficial injection. The action of this part of corrugator is apparent when frowning, if the medial part of eyebrow is first immobilized by a digit.

Corrugator inserts into skin superior to the eyebrow. The skin superior to the eyebrow may be considered in sevenths with the first seventh being the most medial and the seventh seventh the most lateral. Corrugator inserts into the second, third, fourth, and fifth sevenths of the skin superior to the eyebrow. These cutaneous insertions of corrugator can be detected even in a child. They are apparent when frowning as three or four dimples, superior to the eyebrow (Figure 51.4). These dimples are amenable to superficial injection.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 51.4 (a) Corrugator dimples (aged 8 years); (b) Corrugator dimples (aged 24 years). (Reproduced from Rowland Payne CME, Multi-mini botulinum, in: Redaelli A, ed., *Botulinum Toxin A in Aesthetic Medicine*, 2nd ed., Officiana Editoriale Oltrarno, Florence, Italy, 2013, pp. 185–198.)

Corrugator also inserts into the inferior border of the eyebrow. The inferior border of the eyebrow may be considered in thirds. In the medial third, the eyebrow hairs exit the skin more or less vertically. Corrugator inserts into the lateral part of the medial third of the inferior border of the eyebrow. This is apparent when frowning if the rest of the eyebrow is first immobilized with a digit. This insertion is amenable to superficial injection. This injection may also helpfully serve to slightly inhibit the brow depressor activity of OO and its slip, depressor supercilii.

Rationale for Avoiding Eyebrow Ptosis

Eyebrow ptosis results from inhibition of frontalis.

In M-M BTX, *eyebrow* ptosis is avoided by ensuring that the superior-to-the-eyebrow mini-injections of BTX are injected in the minimum effective dose subdermally and *accurately into the corrugator dimples that correspond to the cutaneous insertions of corrugator*, so reducing any unwanted inhibition of frontalis, whose fibers blend with corrugator in this region.

Rationale for Avoiding Eyelid Ptosis (Blepharoptosis)

Eyelid ptosis (blepharoptosis) results from inhibition of levator palpebrae superioris (LPS). LPS originates from the sphenoid bone and runs anteriorly between the globe of the eye and the superior orbital rim, its tendon inserting into the tarsal plate of the upper eyelid (Figure 51.5).

In MM-BTX, *eyelid* ptosis (blepharoptosis) is avoided by

1. Ensuring that the superior-to-the-eyebrow mini-injections of BTX intended for corrugator are injected in the minimum effective dose *subdermally* and not preperiosteally. Injections made in the preperiosteal plane risk tracking inferiorly and into the LPS muscle.
2. Ensuring that the mini-injections of BTX intended for frontalis are made *subdermally* and not preperiosteally. Injections made in the preperiosteal plane risk tracking inferiorly and into the LPS muscle.
3. Ensuring that the inferior-to-the-eyebrow mini-injections of BTX intended for corrugator-depressor supercilii is injected accurately into the lateral part of the first third of the inferior border of the eyebrow, which corresponds to that particular cutaneous insertion of corrugator-depressor supercilii. This injection is made superficially and *in the medial limbal line*. The injection is not made more laterally than this in order to minimize the risk of blepharoptosis, which would follow any (unintended) inhibition of LPS, which lies more deeply and in the mid/medial pupillary line.

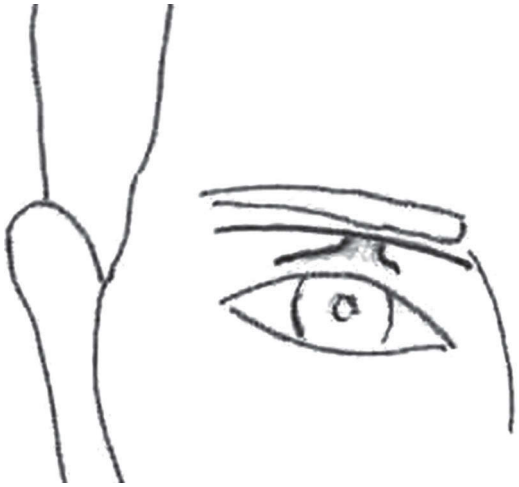


Figure 51.5 Levator palpebrae superioris (LPS) runs from under the superior orbital rim over the top of the eyeball. If botulinum (BTX) affects this muscle, the consequence is blepharoptosis.

Rationale of M-M BTX at OO

OO is a circumferential muscle. Tone in one part of the muscle is balanced by tone in the opposing part. The lateralmost fibers are opposed by the medialmost fibers. The innermost fibers are opposed by the outermost fibers.

If the lateralmost fibers are relaxed by BTX, there will be bunching of the medialmost fibers, i.e. effacement of crow's feet laterally leads to excessive wrinkling medially at the bunny lines.

If the outermost fibers are relaxed by BTX, there will be bunching of the innermost fibers, i.e. effacement of crow's feet

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

and bunny lines favors increased wrinkling of the eyelids themselves.

M-M BTX allows the possibility of treating lateralmost and medialmost as well as outermost and innermost fibers of OO.

M-M BTX: HOW TO DO IT?

Best results are achieved by using a bespoke approach that is determined by inspection and palpation. There is no M-M BTX formula that suits all patients. Each patient is treated differently. Described here is the range of injections that comprise M-M BTX. Not all M-M BTX injections are used in each patient. For simplicity, for each site, a typical dose is stated, but in practice the dose may be half or double that indicated; the dose of each injection varies from patient to patient.

Unless otherwise specified, M-M BTX injections are given superficially, i.e., *immediately subdermally* (or even intradermally). As a rule, injections are usually given into the cutaneous insertions of the treated muscles rather than into the bellies of these muscles.

Procerus

The patient reclines on a couch. The doctor stands behind the patient's head. The patient is asked to frown. The relative movements of the different parts of the glabella are observed. Both eyebrows are then immobilized by the operator's fingers and the patient is again asked to frown. The movement of the procerus muscle becomes apparent. The superior points of maximum movement, ¼ cm either side of the midline (corresponding to the cutaneous insertions of procerus), are injected superficially, usually 1 Speywood unit each side of the midline. Matching injections are made at the inferior points of maximum movement, either side of the midline at the bridge of the nose (nearer the bony origin of the muscle), usually 1 Speywood unit each side of the midline (Figures 51.6 through 51.8).

Sometimes, in patients with a narrow glabella, the left and right injections are merged into single midline injections.

Often, another point of movement can be identified, typically lying 1 cm superomedial to the superomedial border of

(a) (b)

Figure 51.6 (a) Glabella at rest and (b) frowning.

(a) (b)

Figure 51.7 (a) With corrugator immobilized at rest and (b) when frowning. The action of procerus is demonstrated.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

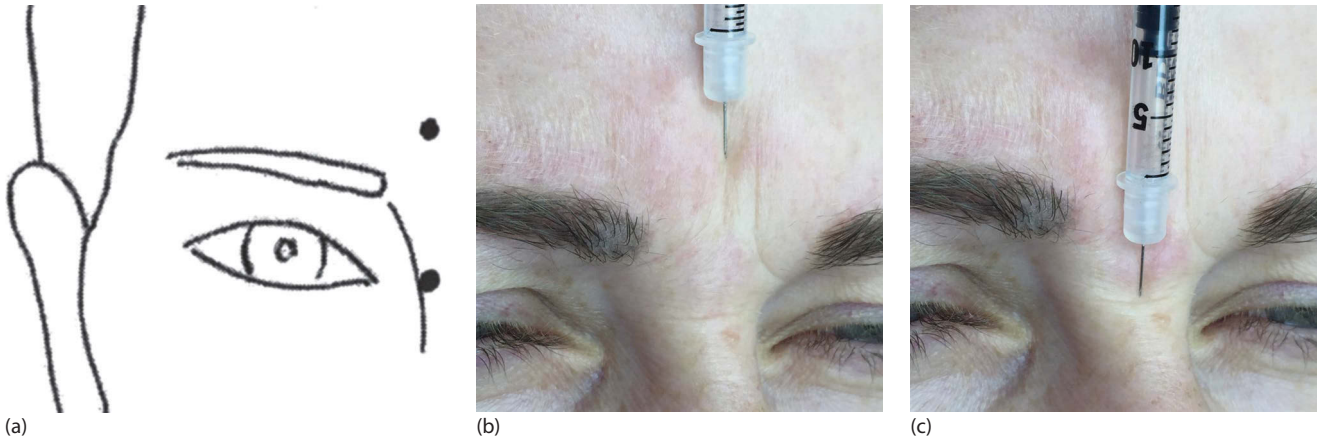


Figure 51.8 (a) Procerus. Each injection is 1 Speywood unit. (b) The superior zone of greatest movement, the insertion of procerus, is injected. (c) The inferior zone of greatest movement, the origin of procerus, is injected.

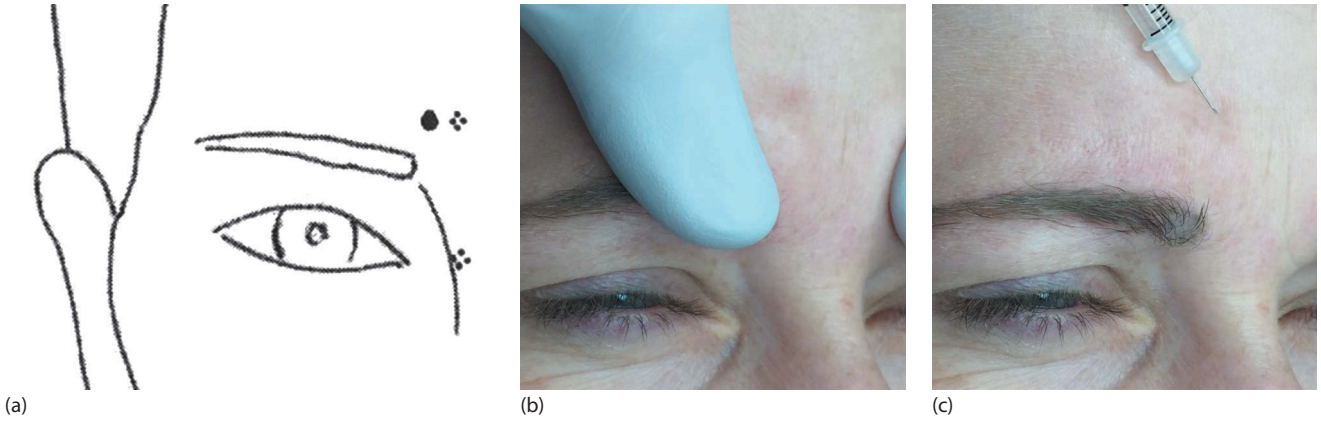


Figure 51.9 (a) Lateral procerus. This injection is 1 Speywood unit. (b) With corrugator and midline procerus immobilized, the patient is asked to frown. (c) The lateral part of the insertion of procerus is injected.

the eyebrow (corresponding to the lateral part of the insertion of procerus). The injection is made superficially (Figure 51.9).

This injection is not intended for corrugator (which lies deeper and more inferior).

Corrugator: Origin

The area that has just been injected is immobilized by the operator's fingers and so is one eyebrow. The patient is asked to frown. The skin between the two fingers is watched closely. The point of maximum movement is injected superficially, with 1 or 2 Speywood units. Usually, this point lies just inferomedial to the inferomedial border of the eyebrow (Figure 51.10).

This point corresponds to part of the origin of the corrugator muscle. Although most of the origin of corrugator lies deep to the medial part of the eyebrow, where the skin and subcutaneous tissues are thick, this medial part of the origin of corrugator is covered by skin and subcutaneous tissues that are thinner, such that this part of the origin of the muscle is more or less subdermal and therefore amenable to superficial injection. Injection at this point lessens the activity of corrugator without impairing frontalis, i.e., it avoids medial eyebrow ptosis.

Sometimes, a second point of movement is apparent. Typically, it lies halfway between the sites of the injections illustrated in Figure 51.9c and Figure 51.10e. This point is injected superficially with 1 Speywood unit (Figure 51.11).

Corrugator: Insertions

The operator's index finger immobilizes the area that has just been injected and also the eyebrow. The patient is asked to frown. The skin immediately superior to the eyebrow is observed. Puckering (i.e., dimpling) is seen superior to the eyebrow where corrugator inserts into the skin. Usually, there are three or four pucker points or dimples superior to each eyebrow. To lessen the frown, each of these corrugator dimples is injected subdermally (or even intradermally), each with 1 (or 2) Speywood units (Figures 51.12 and 51.13).

Sometimes, the lateralmost corrugator dimple lies in closer relation to the eyebrow or even in the eyebrow. In such cases, an injection of 1 Speywood unit is made into the eyebrow.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a)

(b)

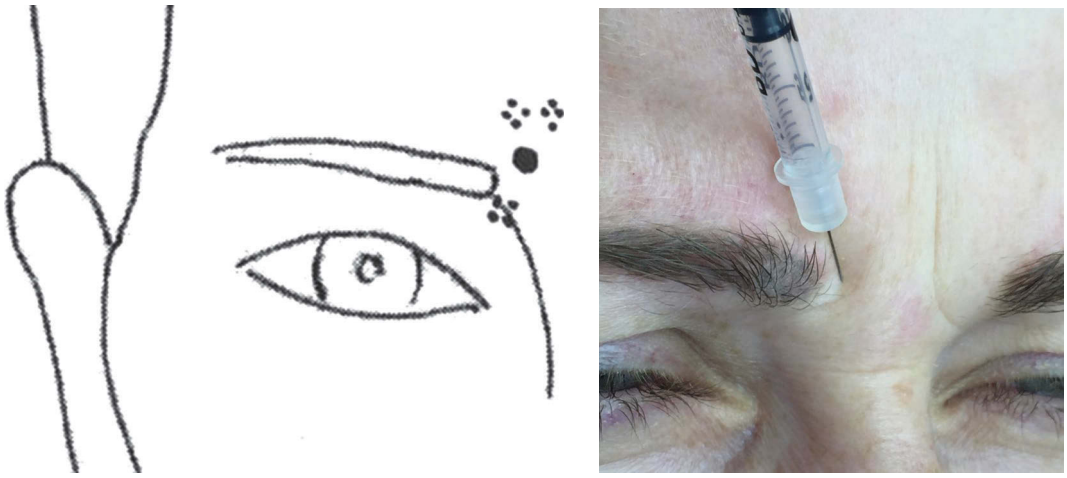
(c)

(d)

(e)

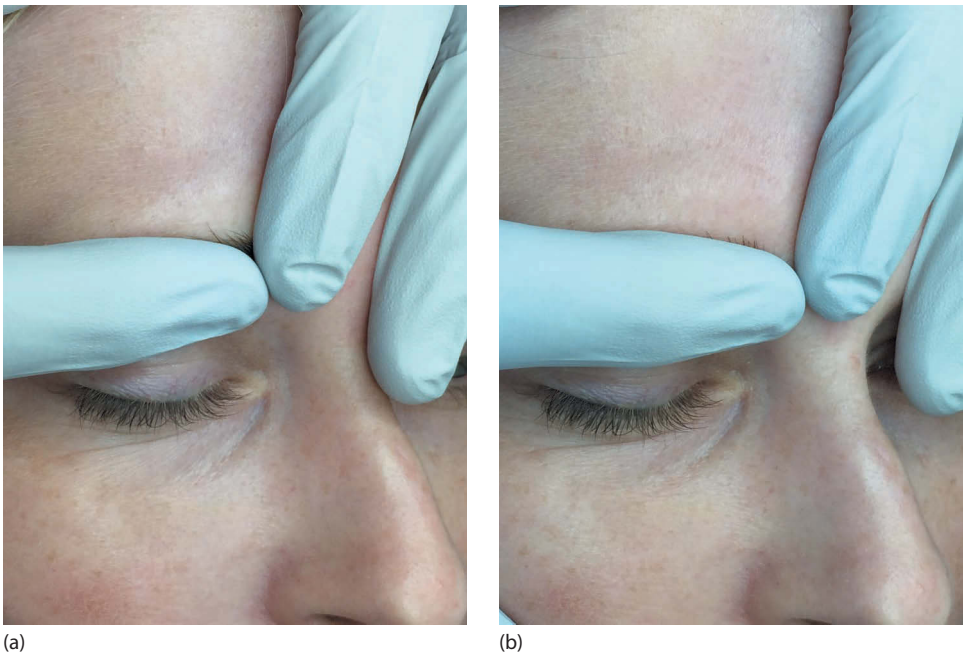
Figure 51.10 (a) Corrugator origin. This injection is 1 Speywood unit. (b) The medial part of the body of corrugator is demonstrated at rest (c) and when contracted. (d) The origin of corrugator is injected. (e) Some prefer to administer this injection in a superolateral direction.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b)

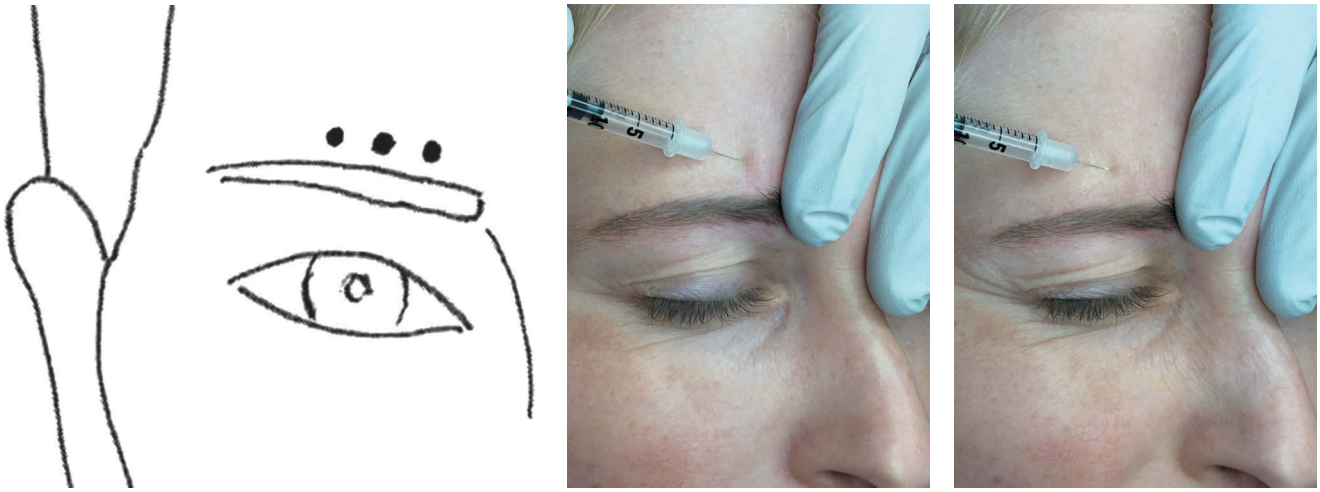
Figure 51.11 (a) Corrugator–procerus. This injection is 1 Speywood unit. (b) Sometimes an injection is also made into corrugator–procerus, midway between the injection points indicated in Figures 51.9c and 51.10e.



(a) (b)

Figure 51.12 (a) Procerus and one eyebrow are immobilized. (b) "Frown." The corrugator insertions are demonstrated.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b) (c)

Figure 51.13 (a) Corrugator insertions. Each injection is 1 Speywood unit. (b) The medialmost of the superior insertions of corrugator is injected. (c) The next insertion of corrugator is injected.

Corrugator-Depressor Supercilii Complex

Next, the eyebrow and the points that have just been injected are immobilized and the patient is asked to frown again. The skin inferior to the medial third of the eyebrow is observed. The point of maximum movement is usually at the inferior edge of the eyebrow, usually in the lateral part of the medial third. This represents a cutaneous insertion of corrugator–depressor supercilii. A superficial injection of 1 Speywood unit is made at this point (Figure 51.14).

(To avoid unwanted inhibition of LPS, this injection should be made no more laterally than the medial limbal line.) This injection may also helpfully serve to inhibit slightly the brow depressor activity of OO. In many patients, this inferior edge of the eyebrow injection is, by a small margin, the least comfortable of all the MM-BTX injections.

If the medial eyebrow lies too high, then the inferior edge of the eyebrow injection may be lessened or made into the eyebrow; this can be useful in rebalancing one eyebrow to better match its neighbor.

Procerus–Corrugator Complex Comment

In MM-BTX, the procerus region (left and right combined) usually needs only 2–9 Speywood units spread over two to six injections.

In MM-BTX, the corrugators (left and right combined) usually need only 8–14 Speywood units spread over 8–12 injections.

In MM-BTX, the procerus–corrugator complex (left and right combined) usually needs only 10–23 Speywood units spread over 10–18 injections.

Heresy 1: Conventional teaching is that corrugator muscle can only be reached by deep injection. Corrugator *can* be reached by superficial injection. Indeed, corrugator is *best* reached by superficial injection into the skin overlying the inferomedial part of its bony *origin* and by superficial injections into the cutaneous dimples that correspond to its cutaneous *insertions*.

(a) (b) (c)

Figure 51.14 (a) Corrugator–depressor supercilii. This injection is 1 Speywood unit. (b) The rest of the corrugator is immobilized. (c) The patient frowns and this cutaneous insertion of corrugator–depressor supercilii is injected (no more laterally than the medial limbal line).

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

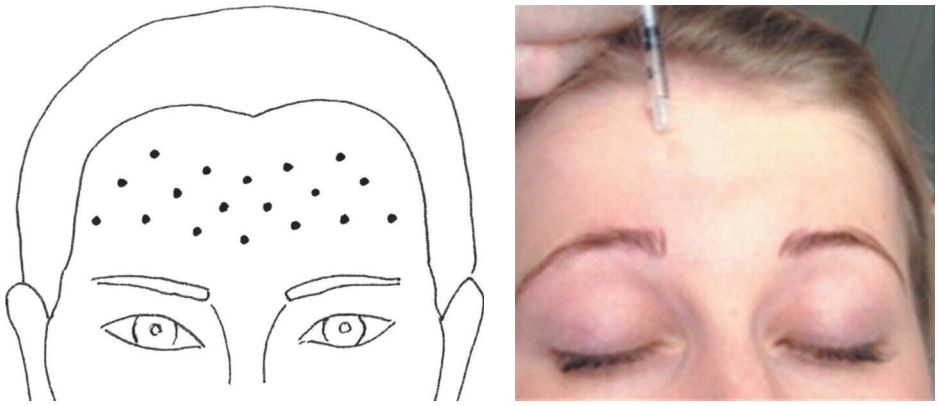


Figure 51.15 (a) Frontalis. Each injection is 1 Speywood unit. (b) Frontalis is injected.

Heresy 2: Conventional teaching recommends five injections, each of 10 Speywood units, to the combined left and right procerus–corrugator complex with a total dose of 50 Speywood units. M-M BTX uses 10–18 mini-injections to the same area with a total dose of 10–23 Speywood units.

Brow

Frontalis is the only brow elevator and is responsible for transverse rhytids of the brow. To lessen transverse rhytids of the brow, the patient is asked to raise their eyebrows, and, at the midline, usually just superior to the valley of the most inferior of the transverse rhytids of the brow, the first injection is made. Moving laterally and slightly superiorly, further superficial injections are made at about 1–2 cm intervals.

Typically, the lowest horizontal rank of brow injections would include one midline injection and three or four to each side of the midline. Each injection would usually be 1 Speywood unit. Subsequent ranks of injections are given 0.75–1 cm higher and interdigitating with the previous rank such that there is no midline injection for the second rank but there is again for the third rank. With the eyebrows raised, injections across the brow are made into the ridges rather than the valleys of the brow. If the rhytids are deep, some of the injections in the second rank may be of 1.5 rather than 1 Speywood unit each. Injections are distributed across all parts of the brow that wrinkle when the patient's eyebrows are raised. A third and sometimes a fourth or even a fifth rank of injections are sometimes necessary in those with the highest and most mobile of brows (Figure 51.15).

A typical bilateral brow treatment may require 20 superficial mini-injections, each of 1 Speywood unit, but the range is wide (14–32 Speywood units in bilateral total). Some relatively unwrinkled foreheads require as few as six or seven mini-injections. Some large and hyperkinetic foreheads may require as many as 34 mini-injections.

To prevent brow ptosis, frontalis injections are avoided within a finger's breadth of the eyebrows (although corrugator and eyebrow tail injections are made within that finger's breadth area, as detailed in this chapter).

Sand Point [12]

To lessen wrinkling near the palpebral opening and to assist in reducing crow's feet, the patient is asked to "Look into the distance. Imagine you are driving a car and that sand is blowing into your eyes." The patient squints but does not entirely close the palpebral fissure. In most patients, 1–2 mm superior and 5 mm lateral to the outer canthus, there is bunching of the OO. At this "sand point," 1 Speywood unit is injected superficially (Figure 51.16).

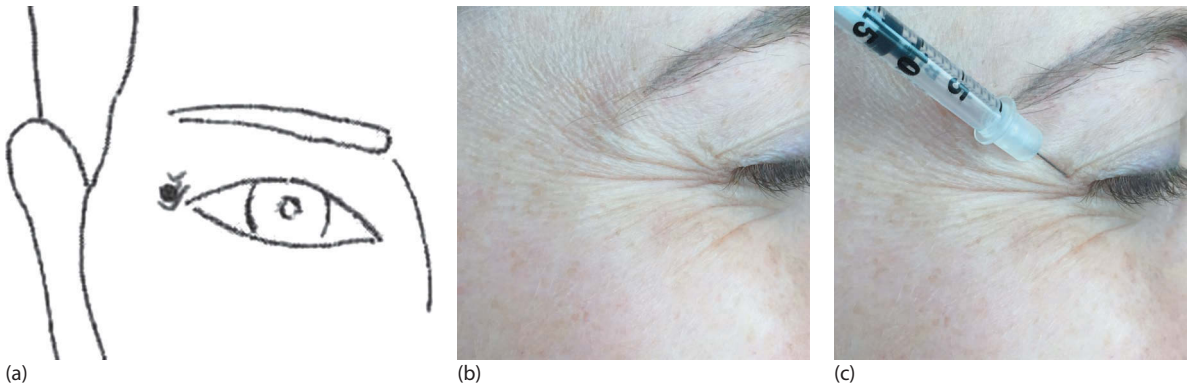


Figure 51.16 (a) The "sand point." This injection is 1 Speywood unit. (b) "Imagine you are driving and sand is blowing into your eyes." (c) Inject at the "sand point."

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 51.17 (a) The "lower sand point." This injection is 1 Speywood unit. It is seldom indicated. (b) "Imagine you are driving and sand is blowing into your eyes." (c) Inject at the "lower sand point."

One unit at the "sand point" is worth 3–4 units at the crow's feet.

Lower Sand Point

Occasionally, the "sand" exercise reveals bunching inferior to the almost lateralmost part of the lower eyelid, "the lower sand point." When present, the "lower sand point" usually lies 0.5–0.75 cm inferior and 0.5 cm medial to the lateral canthus. Only occasionally does an inferior sand point require injection. It can be treated with 0.5 Speywood unit (Figure 51.17).

"Puffy" lower eyelids are a risk with lower sand point injections.

Crow's Feet

To lessen crow's feet, the OO is injected superficially in three to four sites in its lateral part. The first of these OO injections is made in the canthal line. Usually, the next two injections are made superior to this. Each of these OO injections is of 1–2 Speywood units and very occasionally, one or two of the injections might be 4 Speywood units (Figure 51.18).

The sand point injection also helps to lessen crow's feet.

Any OO injections made inferior to the canthal line are seldom more than 1 Speywood unit each (and are often omitted); otherwise, the tarsal plate–inferior OO complex may become weakened allowing the inferolateral intraorbital fat pad to herniate anteriorly, giving an appearance of a "waterlogged" or "puffy" lower eyelid. Also, weakening the inferolateral part of OO risks allowing the malar fat pad to protrude as a "puffy pommette" (which, in time, may prolapse as malar crescent or even a malar festoon).

To avoid inhibition of zygomaticus major, the lower lateral injections are best made superficially and not more than 1½ cm from the orbital rim.

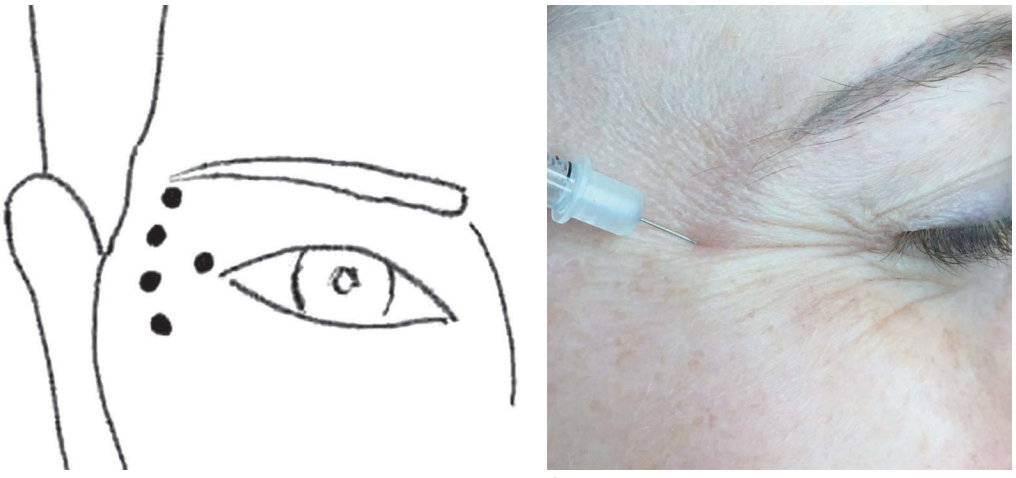


Figure 51.18 (a) Crow's feet. (b) Inject the crow's feet at the orbital rim in several places. (*Continued*)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(c) (d)

Figure 51.18 (*Continued*) (c–d) Inject the crow's feet at the orbital rim in several places.

Raising the Eyebrow Tail

To raise the lateral eyebrow by 1–2 mm, OO is injected superficially with 1 Speywood unit, 1–2 mm inferior to the lateralmost part of the eyebrow. Sometimes, another 1 Speywood unit is injected 0.5–1 cm medial to that (Figure 51.19).

The lateral eyebrow can be made to rise a further 1–2 mm by increasing the amount of BTX used in these lateral inferior-to-tail of the eyebrow injections and/or by lessening the injections made superior to the lateral eyebrow.

Avoiding the "Tell-Tail" Sign

After making these inferior-to-tail of the eyebrow injections, the patient is asked to raise the eyebrows maximally. If when doing this, on the superior side of the eyebrow, there is a "tell-tail" fine rhytid running parallel to the eyebrow, then matching superficial ultramini-injections of 0.5 Speywood unit are made into frontalis at the points of maximum movement on the superior side of the eyebrow (Figure 51.20).

These points are usually less than 1 cm superior to the eyebrow.

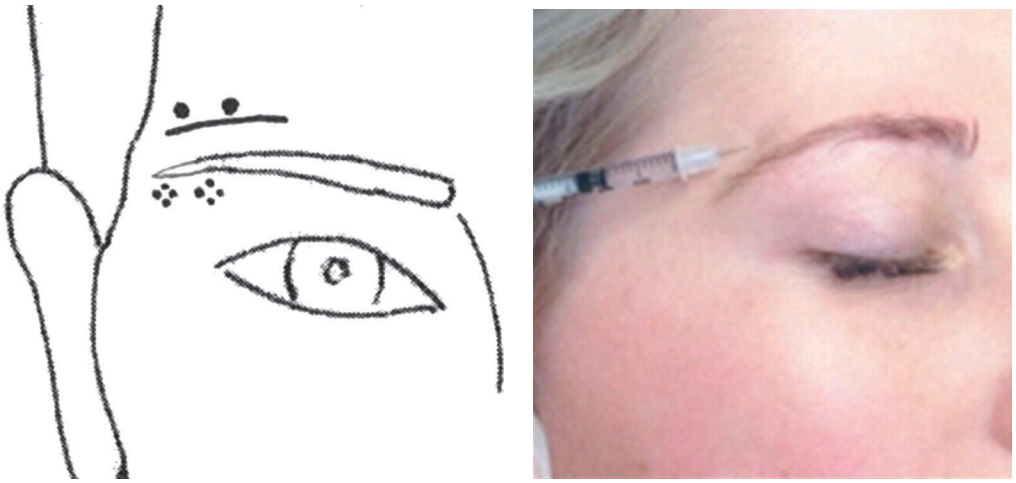
Inferior-to-the-Eyebrow Comment

Heresy 3: Conventional teaching is that BTX injections inferior to the eyebrow cause blepharoptosis. With caution, low-dose subdermal M-M BTX *can* be given inferior to the eyebrow without causing blepharoptosis. Indeed, inferior-to-the-eyebrow M-M BTX inhibits the brow depressors and so results in brow *elevation*. (Inferior-to-the-eyebrow injections in the middle and medial pupillary line are usually best avoided.)

(a) (b) (c)

Figure 51.19 (a) Eyebrow tail. Each injection is 1 Speywood unit. (b) Inject inferior to the tail of the eyebrow (c) and sometimes also just medial to that.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b)

Figure 51.20 (a) Eyebrow "tell tail." Each injection is 0.5 Speywood unit. (b) To avoid the "tell-tail" sign, also inject superior to the eyebrow.

Bunny Lines

The patient is asked to "make a bunny nose" (i.e. to wrinkle their nose). Nasalis is injected subdermally with 1 Speywood unit (Figure 51.21).

If the lateral part of the outermost fibers of OO is relaxed by crow's feet injections, unopposed contraction of the medial part of the outermost fibers of OO (and nasalis) will result in bunching at the bunny lines. Thus, if the crow's feet are injected, it is usually best also to inject the bunny lines.

"Owwee" Point [12]

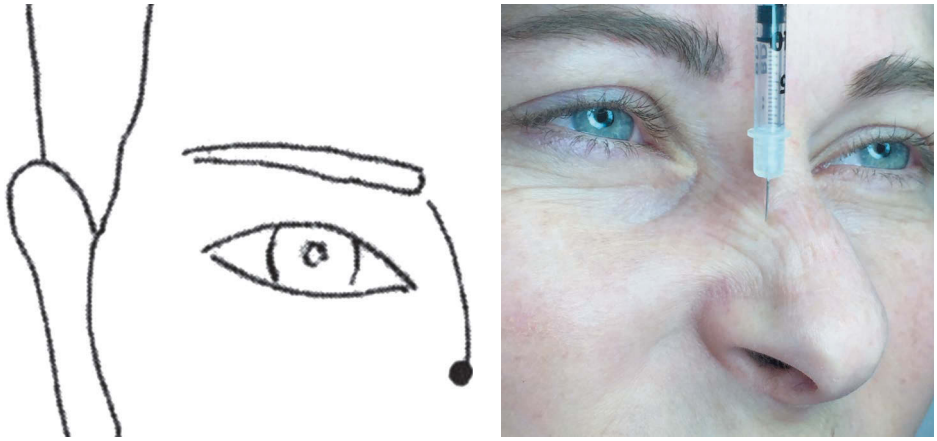
The patient is asked to screw up their eyes completely. There may be bunching of OO at the medial part of the lower eyelid. To lessen this bunching, 1 Speywood unit is injected most superficially into the bunched area, which is known as "the owwee point" (Figure 51.22).

The OO muscle is opposed by itself. Thus, if the lateral part of its innermost fibers is relaxed by an injection at the "sand point," unopposed contraction of the medial part of the innermost fibers may result in bunching at the "owwee point." Therefore, if the sand point is injected, it is often desirable also to inject the owwee point. Also if the inferolateral OO is generously injected, unopposed contraction of the inferomedial OO results in bunching at the "owwee point," which this injection will correct.

Lower Eyelid Margin

To increase the palpebral opening, 0.5 Speywood units may be injected superficially into OO, 1–2 mm inferior to the lid margin of the lower eyelid (Figure 51.23).

Scleral show is a risk with this injection. The lower eyelid pinch and snap back test is helpful. If there is not an excellent snap back, this injection is best avoided.



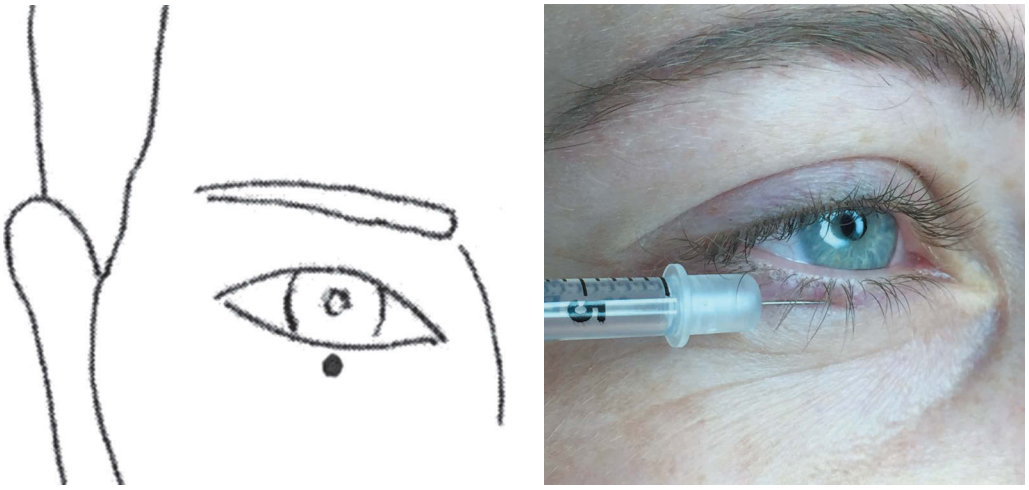
(a) (b)

Figure 51.21 (a) Bunny lines. This injection is 1 Speywood unit. (b) To lessen bunny lines.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 51.22 (a) "Owwee point." This injection is 1 Speywood unit. (b) Inject at the "owwee point."



(a) (b)

Figure 51.23 (a) Lower eyelid margin. This injection is 1 Speywood unit. (b) To increase inferior iris show.

Orbicularis Oculi Bands

A rare indication for BTX is to lessen OO bands in the lower eyelid. Typically, OO bands lie 1 cm inferior to the eyelid margin; 0.5 Speywood unit can be injected superficially (Figure 51.24).

If there is *any* tendency for herniation of the inferior intraorbital fat, this injection is best avoided; otherwise, the tarsal plate–inferior OO complex will become weakened, allowing the intraorbital fat pads to herniate, giving an appearance of "waterlogged" or "puffy" lower eyelids. These risks also exist, but less so, with the owwee point injection.

Orbicularis Oculi Comment

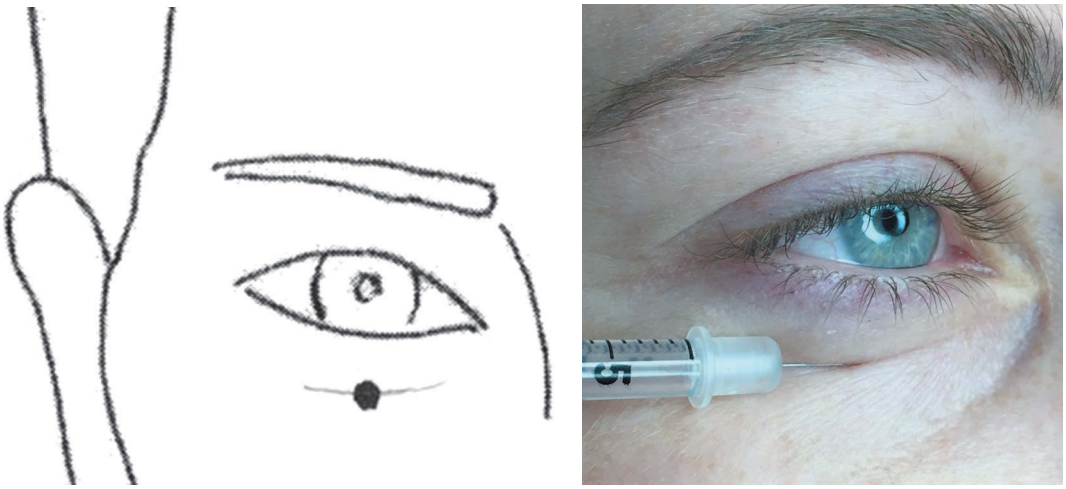
The sand point, owwee point, and the lower lid margin injection point illustrated in Figure 51.23b all lie well within the orbital rim.

Heresy 4: Conventional teaching is that cosmetic BTX should not be used within the orbital rim. For best results, injections usually *should* be made within the orbital rim.

Levator Labii Superioriset Alæque Nasi

This is the snarl muscle. Contraction causes retraction of the upper lip, inward rotation of the tip of the nose, and deepening of the ala nasi shadows. If the ala nasi fossa shadow is deep or dark or if the smile is overgummy, this injection may be helpful. Overlying this muscle, the skin relatively thick. The doctor's index and middle fingers should be placed on each side of the patient's nose, just superior to the ala nasi fossa, on the inferior slope of where the prominence of the cheek joins the side of the nose. The patient is asked to "Screw up your face." The doctor's fingertips can detect the point of maximum

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b)

Figure 51.24 (a) Orbicularis oculi (OO) bands. This injection is 1 Speywood unit. It is seldom indicated. (b) To reduce OO banding.

(a) (b)

Figure 51.25 (a) Levator labii superioris et alæque nasi. Each injection is 1 Speywood unit. (b) "Screw up your face." Palpate the zone of maximal muscle contraction. Inject subdermally to reach the body of levator labii superioris et alæque nasi.

muscular contraction. This is the point of injection. At this site, 1 Speywood unit is injected perpendicularly to the skin and relatively deeply on each side of the nose (Figure 51.25).

Dilator Naris

Injection of 1 Speywood unit into the dilator naris part of the nasalis muscle may be used to reduce nostril flare and help flatten an overarched lateral nostril margin. To do this, the lateral nasal sulcus is observed. The patient is asked to sniff sharply. That part of the sulcus that is most drawn in by the sniff, usually at the posterolateral end of the sulcus, is the point chosen for the injection (Perez F, personal communication, 2014) (Figure 51.26).

Depressor Septi Nasi

To raise the tip of the nose, depressor septi nasi may be injected with 1 Speywood unit. This is a deep injection that is made at an oblique angle to the skin (Figure 51.27).

Orbicularis Oris

For perioral rhytids, one or two injections, each of 0.5 Speywood units, may be made into one or two rhitids in each quadrant. These injections are made 1–2 mm away from the vermillion border (Figure 51.28).

This is uncomfortable. Difficulty with whistling and with swishing toothpaste is a hazard if higher doses are used for these injections.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

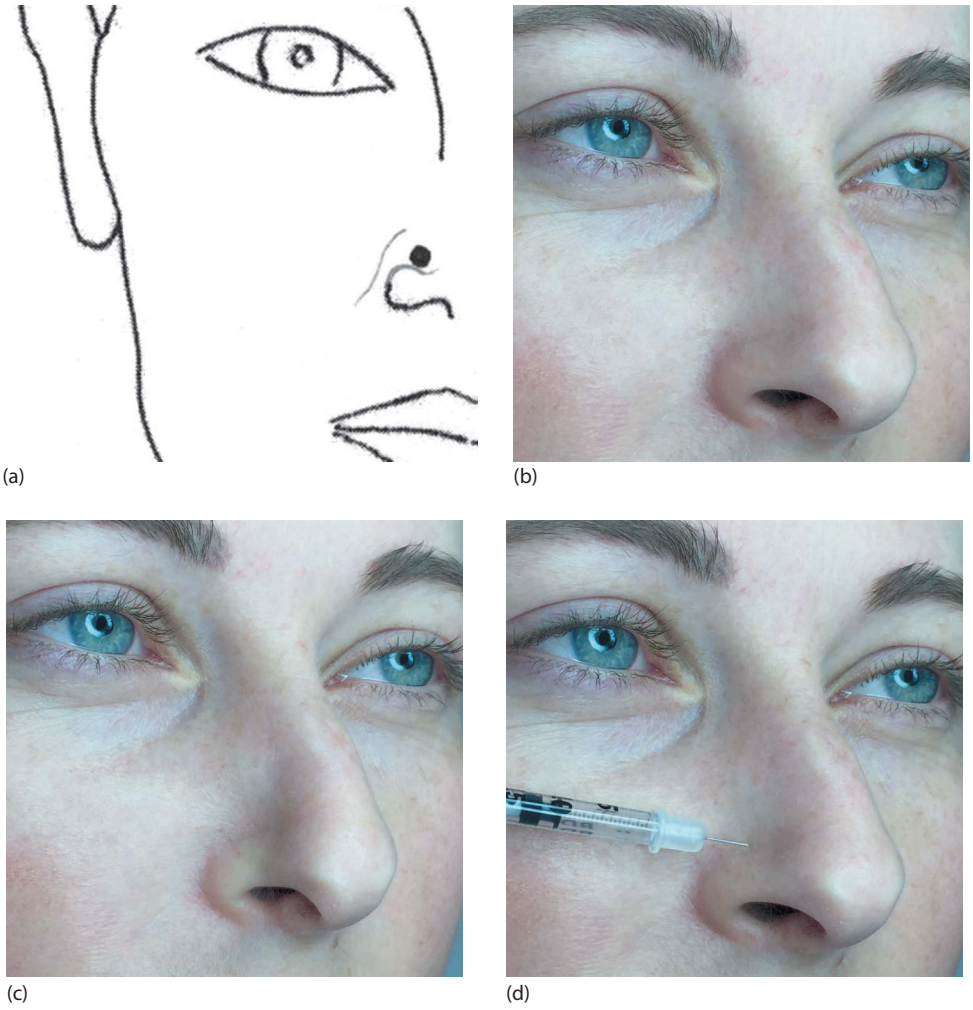


Figure 51.26 (a) Dilator naris. This injection is 1 Speywood unit. (b) At rest. (c) "Sniff." (d) Inject at Perez's sniff point to reach dilator naris.

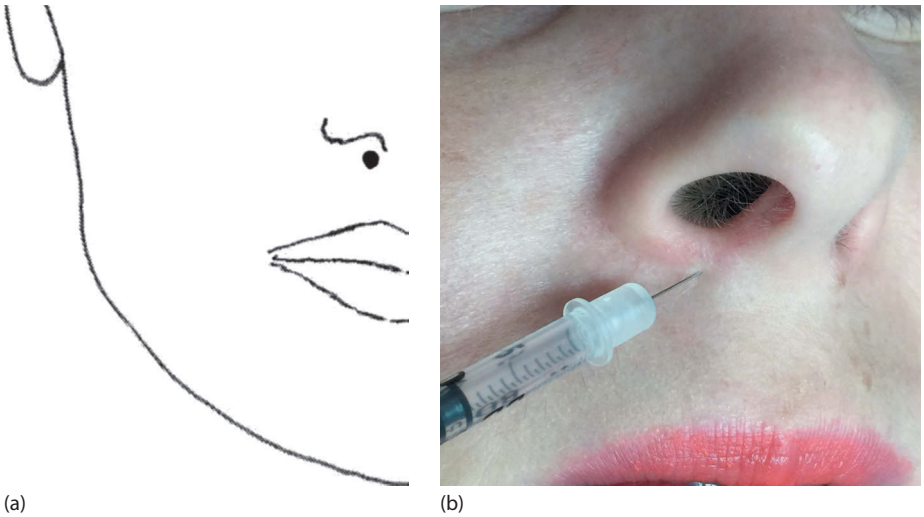


Figure 51.27 (a) Depressor septi nasi. This injection is 1 Speywood unit; it is a deep and oblique injection. (b) To lift the nasal tip.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 51.28 (a) Orbicularis oris. Each injection is 0.5 Speywood unit. (b) Inject near the vermillion border or in the radial rhytids.

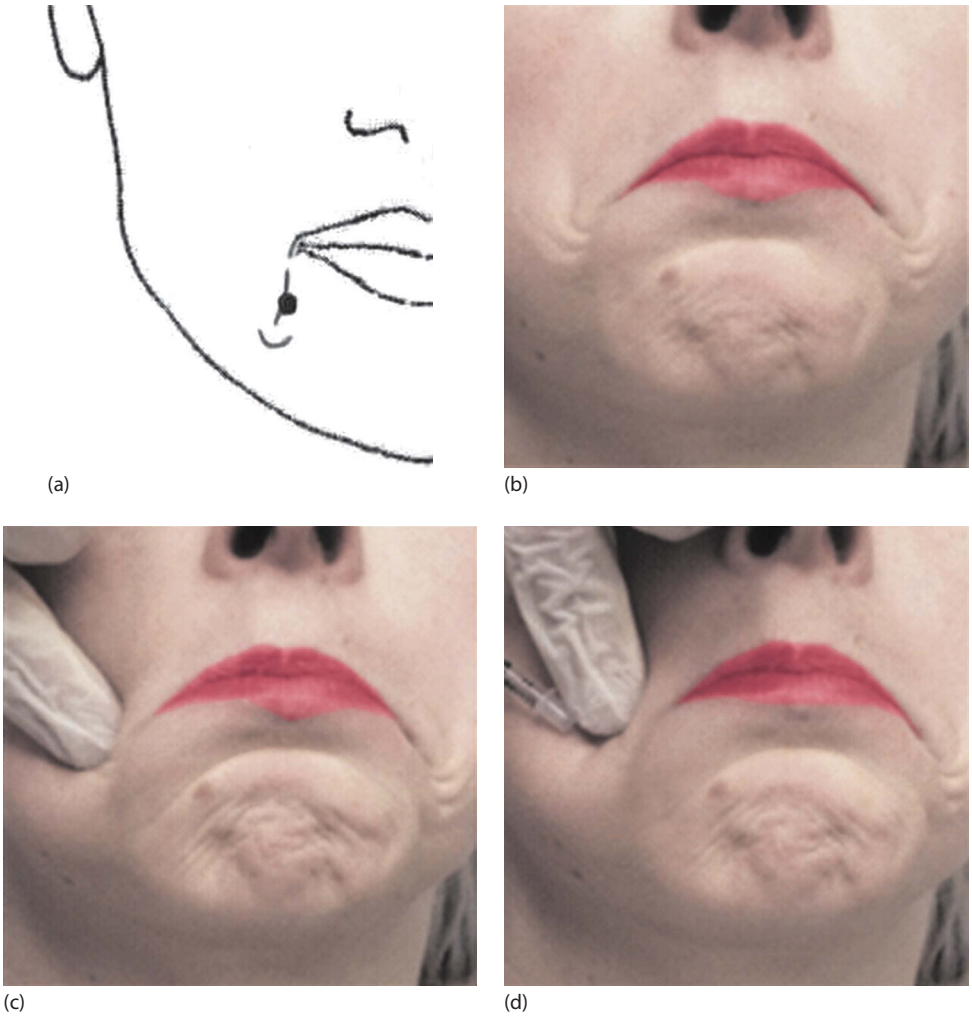


Figure 51.29 (a) Depressor anguli oris (DAO). This injection is 1 Speywood unit; it is a deep and oblique injection. (b) "Downturn your mouth." (c) Palpate the lateral border of DAO. (d) Inject obliquely and deeply to reach body of DAO.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Depressor Anguli Oris

The patient is asked to "Downturn your mouth." While doing this, the operator's finger fits neatly into the sulcus that lies at the lateral border of depressor anguli oris (DAO). At an oblique angle, 1 Speywood unit is injected into the lateral side of the maximal area of muscle contraction of the DAO. This lessens any downturning of the angle of the mouth. DAO lies relatively deep beneath the skin, so this is a deep injection (Figure 51.29).

If the injection is too medial, the depressor labii inferioris may be affected, which results in a lopsided smile.

Mentalis

Cobblestoning of the chin and/or a deep mentolabial sulcus may be treated by four to six superficial injections into mentalis. Injections are made superficially and usually symmetrical, each of 1 Speywood unit, into the deepest puckers, which correspond to the principal cutaneous insertions of mentalis (Figure 51.30).

These chin injections may be helpful in some patients with rosacea mentalis (rosacea of the chin) as overuse of this muscle causes "touching of the skin from the inside," which, just like touching from the outside, favors rosacea by causing increased blood flow to the skin of the chin.

Masseter

MMH causes "squaring" of the jaw. Masseter BTX helps reovalize the face. This treatment is very popular in the Far East.

Bruxism (teeth grinding or jaw clenching) is usually a sign of anxiety. Bruxism leads to an increase in both unconscious masseter muscle activity and resting tone. In due course, MMH follows. MMH is the rule in teeth grinders, jaw clenchers, and in those who overuse chewing gum. In time, jaw clenching and teeth grinding lead either to temporomandibular joint dysfunction or to cracking of teeth, early dental caries, broken teeth, crowns, root canal infection, dental abscesses with recourse to endodentistry, and, ultimately, dental implants. Masseter BTX helps prevent this undesirable and pathological evolution.

To lessen MMH, the patient is asked to clench the teeth. Masseter is palpated. Where the muscle is hardest and fullest, four to eight perpendicular injections are made deeply into the body of each muscle. Each injection is 4–6 Speywood units. This muscle lies relatively deep beneath the skin (Figure 51.31).

Figure 51.30 (a) Mentalis. Each injection is 1 Speywood unit. (b) "Pucker your chin." (c–e) Inject puckers, which are the principal insertions of mentalis.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

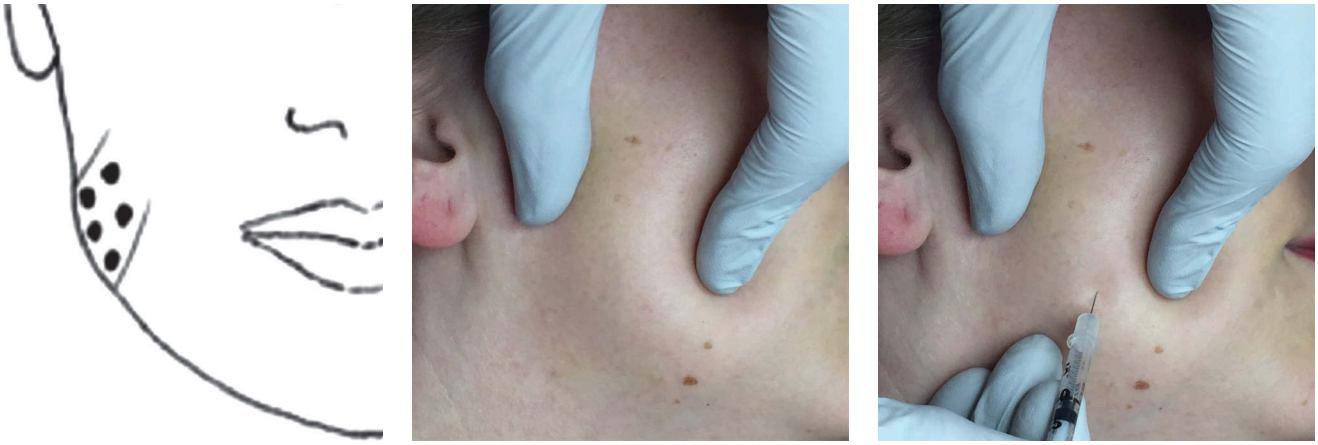


Figure 51.31 (a) Masseter. Each injection is 4–6 Speywood units; this is a deep injection. (b) "Clench the jaw." (c) Inject deeply into the body of masseter.

Nefertiti Lift

Before frank jowling occurs, the jawline begins to lose definition. To improve jawline definition, platysma may be inhibited by three or four superficial injections, each of 2–4 Speywood units, made just inferior to the mandibular edge, the "Nefertiti lift" [9] (Figure 51.32).

Early Jowling

When early or incipient jowling is evident, three intermediate depth injections are made, just inferior to the curve of the incipient jowl. Each injection might be 4–6 Speywood units (Figure 51.33).

Venus Rings

In many people, the action of platysma results in transverse creases at the neck without any platysmal bands. In "tech neck," an additional ring is seen inferolaterally on the dominant side (i.e., right side of the neck in a right-handed person) from repeated downward gaze at tablets and smart phones. To lessen Venus rings (and/or tech neck), 1 Speywood unit is injected superficially every 2 cm along each Venus ring. For best results, these injections are made 2–3 mm superior to each Venus ring. These injections are also safe in the midline (Figure 51.34).

Platysmal Bands

Platysmal bands are best displayed by tensing the neck muscles. Platysmal bands are usually strongest in their superior

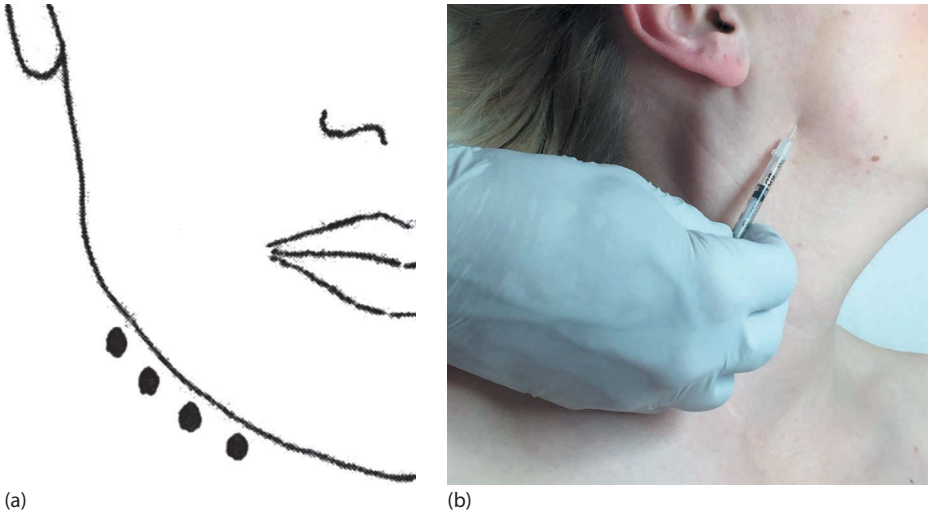


Figure 51.32 (a) The Nefertiti lift. Each injection is 2–4 Speywood units. (b) Inject platysma's attachment to the mandible.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

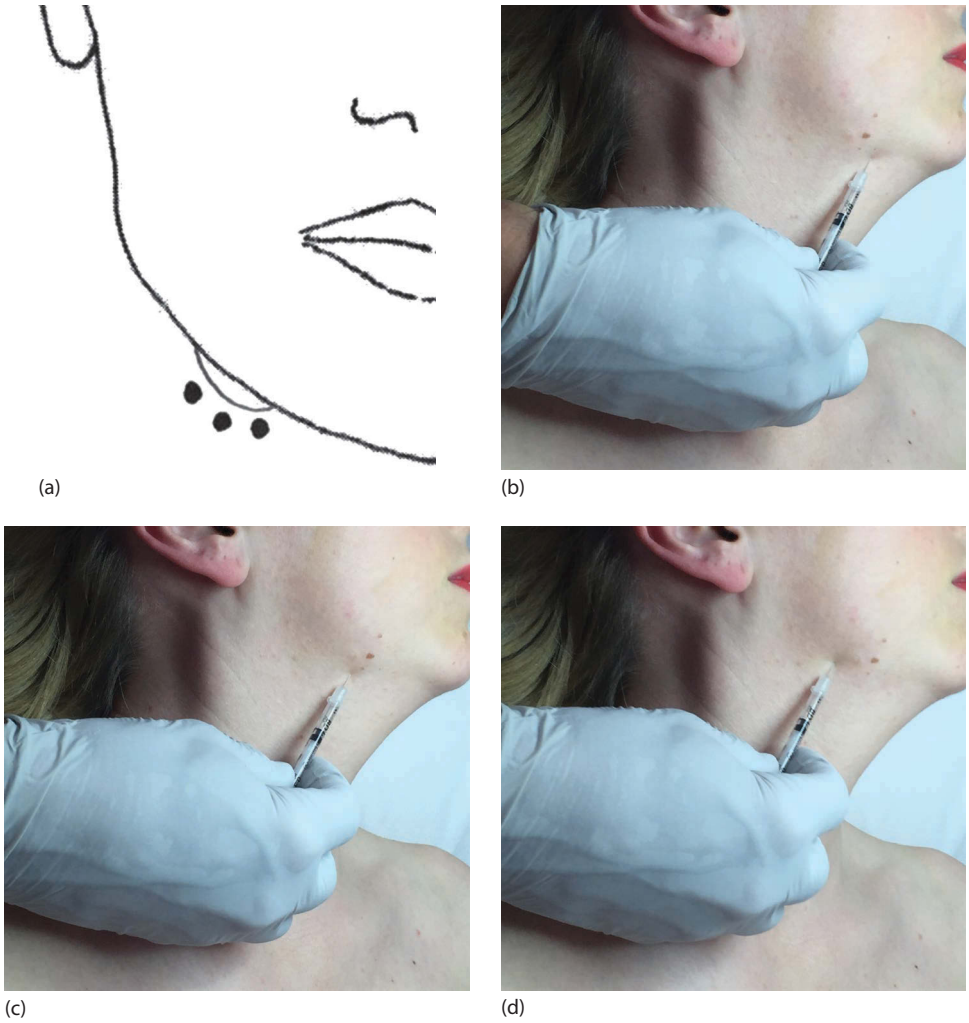


Figure 51.33 (a) Early jowling. Each injection is 4–6 Speywood units. (b–d) "Tense your neck muscles." Inject just inferior to the incipient jowl in an arc.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

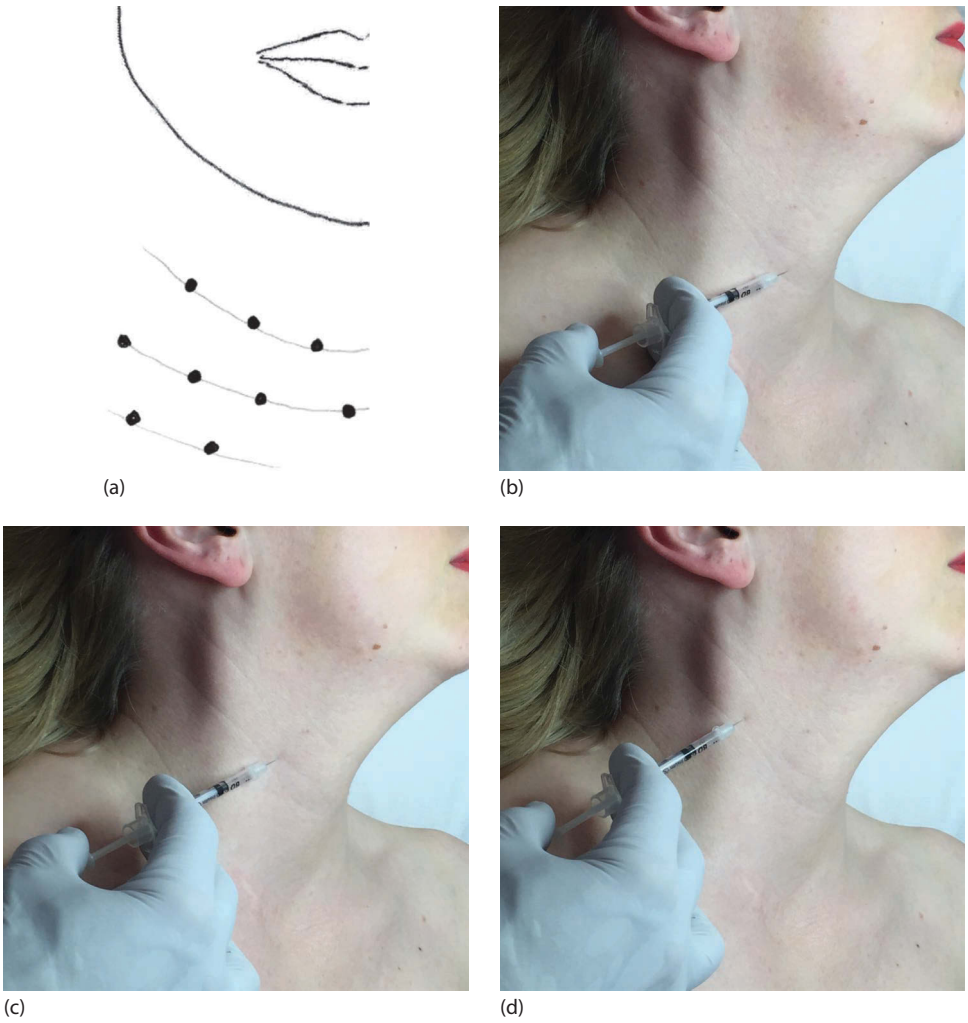


Figure 51.34 (a) Venus rings. Each injection is 1–2 Speywood units. (b–d) Inject along the Venus rings. Injections are made just superior to each ring.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

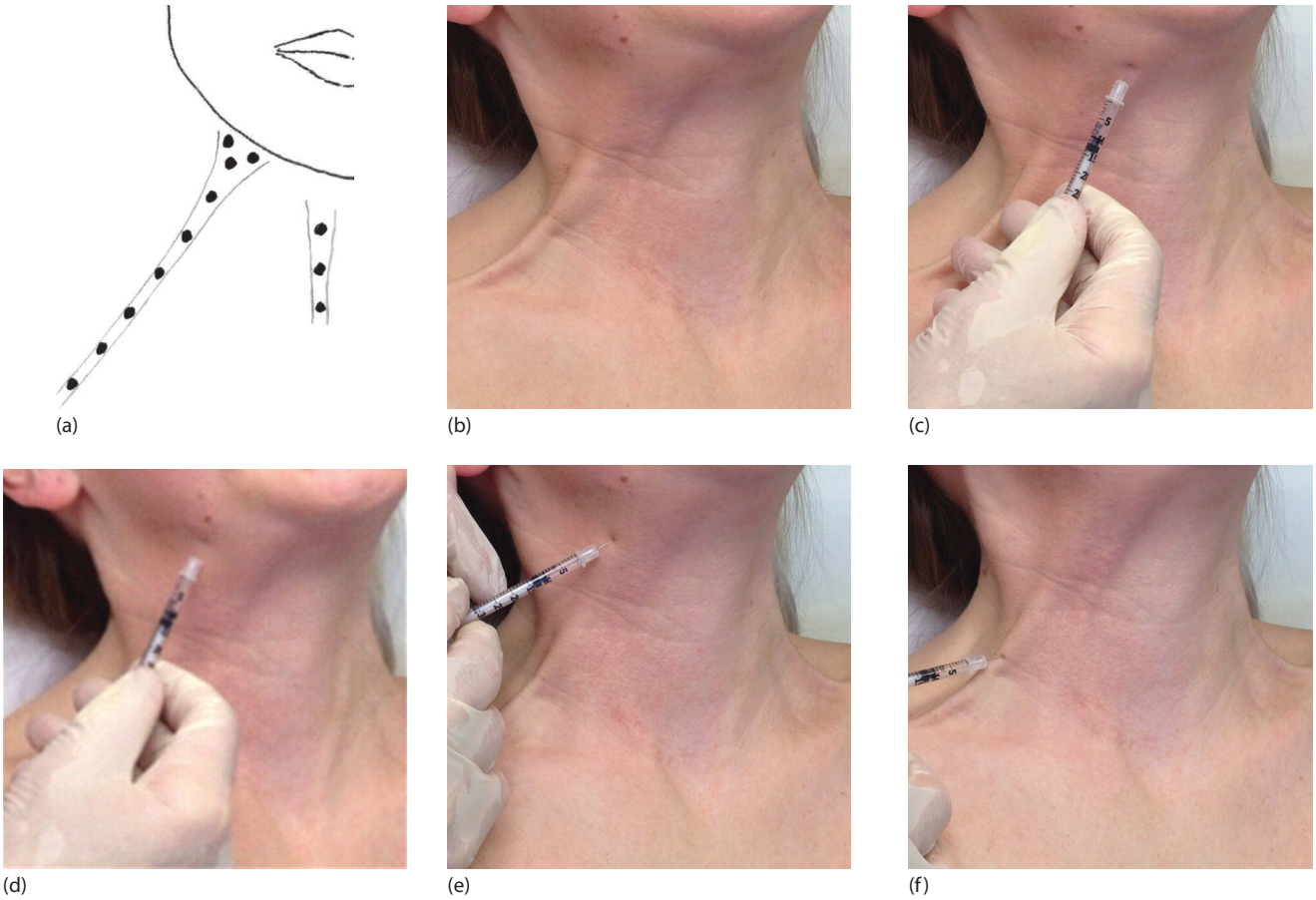


Figure 51.35 (a) Platysmal bands. Each injection is 2–4 Speywood units. (b) "Tense your neck muscles." (c and d) Inject platysma's attachment to the mandible. (e and f) Inject the platysmal bands at intervals along their length.

parts where they touch the mandible. Where the bands are thickest, injections of 4-6 Speywood units are used. Running inferiorly down the bands, intermediate depth injections of 2–4 Speywood units are made at 1–2 cm intervals along the full length of each band (Figure 51.35).

Migraine and Tension Headache

In some patients, unconscious resting tone is excessive in various muscles around the skull and this is aggravated by stress. This involuntary muscular contraction causes tension headaches and sometimes migraine. These disorders are beyond the scope of this chapter except in so far as when they coexist with dynamic rhytids or MMH. Tension headaches are very common and patients attending for BTX treatment for rhytids often also have concomitant headaches. Of 45 patients who were attending for BTX treatment of rhytids and who also happened to have concomitant headaches, 76% experienced improvement in their headaches [8].

AFTERCARE

After treatment, patients can immediately return to their normal lives. There are no restrictions on posture or flying or anything else.

The patient will begin to notice the BTX taking effect after 48 hours. Its full effect is apparent by 10 days. Patients having their first treatment with M-M BTX are routinely asked to return for a review 10–20 days after. Bespoke adjustments can be made at that point or noted for the next treatment.

After M-M BTX using Dysport/Azzalure, patients are routinely booked for their next treatment in exactly 5½ months time. (A few patients with the most hyperdynamic rhytids benefit from the next treatment at 3–4 months.)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

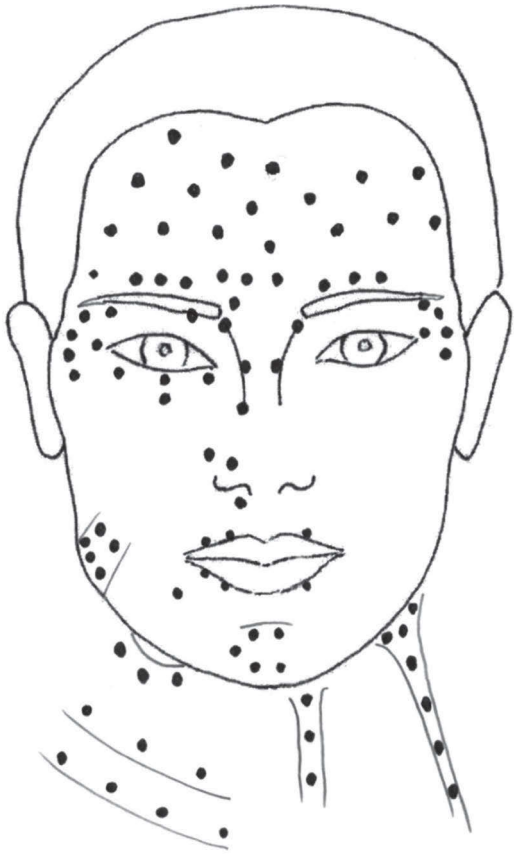


Figure 51.36 Multi-mini botulinum (M-M BTX).

CONCLUSIONS

M-M BTX allows personalized precision placement of multiple mini-dose injections of BTX. Best results are achieved by a bespoke approach that is determined by inspection and palpation.

A typical bilateral face (excluding masseter) treated by M-M BTX would receive approximately 50 injections, most of which would each be of 1 Speywood Dysport/Azzalure unit (a total of 50 Speywood units). A typical bilateral MMH treated by M-M BTX would receive approximately 10 injections, most of which would be 6 Speywood Dysport/Azzalure units (a total of 60 Speywood units). A typical bilateral neck treated by M-M BTX would receive approximately 30 injections, most of which would be of 2–4 Speywood Dysport/Azzalure units (a total of 80 Speywood units) (Figure 51.36).

If Allergan Botox/Vistabel or Merz Xeomin/Bocouture is used, a typical bilateral face would receive 50 injections, each of 0.4 Allergan/Merz units (a total of 20 Allergan/Merz units). A typical bilateral MMH would receive 10 injections, each of 2.4 Allergan Merz units (a total of 24 Allergan/Merz units). A typical bilateral neck would receive 30 injections, each of 0.8–1.6 Allergan/Merz units (a total of 32 Allergan/Merz units).

REFERENCES

1. Alavi M, Kalafi Y, Dehbozorgi GR, Javadpour A. Body dysmorphic disorder and other psychiatric morbidity in aesthetic rhinoplasty candidates. *J Plast Reconstr Aesthet Surg* 2011 June; 64(6):738–741.
2. Carruthers JD, Carruthers JA. Treatment of glabellar frown lines with *C. botulinum*-A exotoxin. *J Dermatol Surg Oncol* 1992 January; 18(1):17–21.
3. Crerand CE, Franklin ME, Sarwer DB. Body dysmorphic disorder and cosmetic surgery. *Plast Reconstr Surg* 2006 December; 118(7):767e–780e.
4. Dakanalis A, Di Mattei VE, Zanetti AM, Clerici M, Madeddu F, Riva G, Lanfranchi L, Baruffaldi Preis F. Personality and body image disorders in cosmetic surgery settings: Prevalence, comorbidity and evaluation of their impact on post-operative patients' satisfaction. *Eur Psychiatry* 2013; 28(Suppl 1):1.
5. De Maio M, Rzany B. *Botulinum Toxin in Aesthetic Medicine*. Vienna, Austria: Springer-Verlag, 2007.
6. De Maio M, Rzany B. *The Male Patient in Aesthetic Medicine*. Vienna, Austria: Springer-Verlag, 2009.
7. Finzi E, Rosenthal NE. Treatment of depression with onabotulinum toxin A: A randomized, double-blind, placebo controlled trial. *J Psychiatr Res* 2014 May; 52:1–6.
8. Goldman ND, Dorton LH, Marcum KK, Gilbert RM, Sandoval LF. Evaluation of headache relief with cosmetic onabotulinum toxin A injections. *J Cosmet Dermatol* 2014 September; 13(3):224–231.
9. Levy PM. The "Nefertiti lift": A new technique for specific recontouring of the jawline. *J Cosmet Laser Ther* 2007; 9:249–252.
10. Magid M, Reichenberg JS, Poth PE, Robertson HT, LaViolette AK, Kruger TH, Wollmer MA. Treatment of major depressive disorder using botulinum toxin A: A 24-week randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2014 August; 75(8):837–844.
11. Philipp-Dormston WG, Bergfeld D, Sommer B. Konsensusempfehlungen zur Behandlung mit Onabotulinumtoxin A in der ästhetischen Medizin. *J Deuts Dermatol Ges* 2012; 11(Suppl 1):1–42.
12. Rowland Payne CME. Multi-mini botulinum. In: Redaelli A, ed. *Botulinum Toxin A in Aesthetic Medicine*, 2nd ed. Florence, Italy: Officiana Editoriale Oltrarno, 2013, pp. 185–198.
13. Sarwer DB, Spitzer JC. Body image dysmorphic disorder in persons who undergo aesthetic medical treatments. *Aesthet Surg J* 2012; 32(8):999–1009.
14. Scott AB. Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. *Ophthalmology* 1980 October; 87(10):1044–1049.
15. Streker M, Luebberding S, Krueger N, Harrington L, Kerscher M. Patient-reported outcomes after incobotulinumtoxinA treatment for upper facial wrinkles. *Dermatol Surg* 2015 January; 41(Suppl 1):S29–S38.
16. Wollmer MA, de Boer C, Kalak N et al. Facing depression with botulinum toxin: A randomized controlled trial. *J Psychiatr Res* 2012; 46(5):574–581.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Complications and pitfalls of cosmetic botulinum toxin treatment

Christopher M.E. Rowland Payne

INTRODUCTION

Botulinum (BTX) has a narrow therapeutic ratio.

CLASSIFICATION OF COMPLICATIONS

Minor self-limiting unwanted effects, which cannot really be considered as complications, are common and include the mild pain of the injections, occasional ecchymoses, slight asymmetries, suboptimal effect on the target muscles, mild unwanted collateral effects on neighboring muscles, and occasional transient headache. They are all self-limiting.

True complications do also sometimes occur even in the most experienced and best of hands. Complications may result from

1. Imperfect placement
2. Imperfect dosage

Complications can be regarded as major or minor.

Major complications are very rare and include strabismus, ectropion, dysphagia, and dysphonia.

Minor complications comprise the BTX pitfalls.

PATHOGENESIS OF THE BTX PITFALLS

The BTX pitfalls are a number of characteristic clinical aspects that may occur after facial BTX treatment. They result from overrelaxation of muscle fibers. They fall into four groups:

1. *Overrelaxation of target muscles*
2. *Neighborhood effects* or collateral damage, that is, unintended relaxation of neighboring muscles
3. *Unopposed action of opposing muscles*
4. *Insufficient relaxation of target muscles*

Some pitfalls may cause distress to the patient. Others may pass unnoticed by the patient. Some are even welcomed by the patient. (1)–(3) are temporary and self-limiting. BTX pitfalls are logical. BTX pitfalls may be anatomically enlightening. Prevention of these pitfalls is the goal of ideal treatment. Each of the pitfalls is amenable to treatment.

METHODS OF CORRECTION OF THE BTX PITFALLS

Natural recovery: It is often sufficient to wait for natural recovery.

Strengthening exercises for overrelaxed target or neighborhood muscles: Residually active muscle fibers may be strengthened by exercise to compensate for the fibers that have been paralyzed. While standing in front of a mirror and covering the contralateral muscle, the patient is taught to contract the affected muscle. Each time the patient visits the lavatory, the patient is asked to do ten contractions (each sustained for 2–3 seconds). These "toilet training" muscle strengthening exercises result in a relatively rapid return of power in the affected muscle, as there are always some muscle fibers that have not been affected by BTX, which can, in a number of days, be trained to hypertrophy sufficiently to restore desired muscle function. Since multi-mini BTX (M-M BTX) uses very low doses of BTX, it lends itself especially well to this approach.

BTX treatment of opposing muscles: Following BTX treatment of a target muscle, it may happen that the opposing muscle is now insufficiently opposed and thereby causing rhytids of its own. In such a case, it may be desirable to treat the opposing muscle with a little BTX.

Additional BTX treatment of target muscles: If a target muscle has been insufficiently relaxed because an insufficient dose of BTX has been used, more may be added as a "top up" at 10–20 days.

Alternative methods of treatment: On occasion, to compensate for a particular unwanted BTX effect, other methods may be used, for example, filler.

COMMON BTX PITFALLS

Dosage Pitfalls and Antibody Considerations

The units of different brands of BTX are not the same. It is important to define the brand when considering dosage. The production of antibodies against BTX toxin may decrease the efficacy of the treatment in spasticity; in cosmetic practice, this problem is negligible, possibly because the cosmetic application of BTX uses only very low doses of BTX [2].

"Frozen" Face

In certain parts of the world, abolition of frontal and glabella movement is the aim of BTX treatment.

In other parts of the world, the aim is a more natural look with a reduction in resting rhytids without impairment of expressions of animation. This more natural result can be achieved by using lower doses of BTX applied in a more tailor-made fashion. This is the goal of M-M BTX.

Vacuous Expression

The corrugator muscle is not only the muscle of scolding and anxiety, but also the muscle of empathy, concern, and determination. Overtreatment of corrugator risks the look of

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

a dullard or one who is uncaring. Frowning exercises are all that are needed to restore sufficient function to the corrugator muscle.

Blepharoptosis

Lid ptosis, or "drooping eyelid," is rare (Figure 52.1a).

It results from relaxation of lavator palpebrae superioris (LPS) (Figure 52.1b). Since this is never an intended result of M-M BTX treatment, when it occurs, it is always a neighborhood effect. Typically, it occurs in two situations:

1. It is a risk of subdermal injection of BTX inferior to the eyebrow in the mid and/or medial pupillary line (which may have been performed with the aim of relaxing the superior part of orbicularis oculi (OO)).
2. More often, it is a consequence of preperiosteal injection of conventional BTX superior to the eyebrow in the mid and/or medial pupillary line (which may have been injected with the aim of relaxing either the tail of corrugator supercilii or the inferior part of frontalis). The BTX may track inferiorly, in the preperiosteal plane, until it reaches the tendon of LPS and then tracks anteriorly along the tendon until it reaches the muscle fibers of LPS. It is more likely with deeper injections of BTX and with more dilute BTX.

Blepharoptosis can be prevented by avoiding (1) and (2).

Blepharoptosis can be treated by

1. Strengthening exercises ("toilet training")
2. Simulation of Müller's muscle
3. Inhibition of the innermost fibers of OO in the upper eyelid

"Toilet training" strengthening exercises are recommended. Ten sustained stares should be performed, in the mirror, each time the patient visits the lavatory. Improvement is apparent in days.

Müller's muscle is a smooth muscle that assists LPS to raise the upper eyelid. Müller's muscle can be stimulated by using eyedrops of apraclonidine (Iopidine), an alpha-2 adrenergic agonist sympathomimetic usually used in the treatment of glaucoma. Given as 1–2 drops three times a day, it causes Müller's muscle to contract, thereby raising the upper eyelid margin by 0.5–1 mm.

The eyelids are brought together by the action of OO, which is a sphincter muscle. Its contraction closes the palpebral tissue by drawing the upper eyelid margin down and the lower up. The natural function of the innermost fibers of OO in the upper lid is to draw down the upper lid margin. To elevate the inferior margin of the upper eyelid by 1 mm, it is sufficient to relax the inferiormost fibers of OO of the upper eyelid. To achieve this, 1 Speywood unit is injected 1 mm superior to the upper eyelid margin in the mid pupillary line (Figure 52.2). This injection can be useful in helping compensate for blepharoptosis caused by Horner's syndrome or by Rowland-Payne's syndrome [3] or by unintended BTX-induced relaxation of LPS.

Brow Ptosis

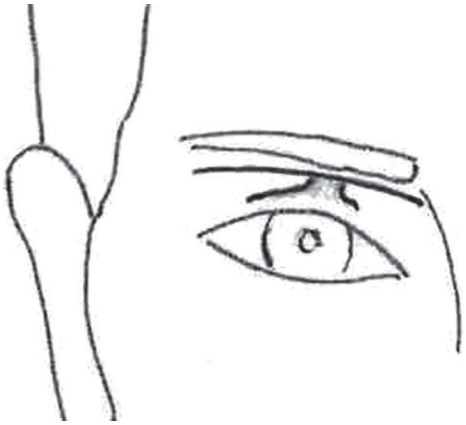
With brow ptosis, the patient may notice either a "droopy eyebrow" or a "puffy/waterlogged upper eyelid" or that it is more difficult to apply upper eyelid makeup. Brow ptosis is not as rare as lid ptosis. All those who inject BTX in the frontalis muscle will, sooner or later and from time to time, encounter a degree of post BTX eyebrow ptosis.

At particular risk of brow ptosis are

1. Patients with a short distance between eyebrow and superior eyelid margin
2. Older patients with "hooding" due to redundant eyelid skin, itself a result of involution of the subcutaneous fat of the superolateral part of the upper eyelids with consequent flaccidity of the overlying skin

Indeed, sooner or later and irrespective of BTX treatment, eyebrow ptosis is the destiny of almost every face. It results in a compensatory attempt to keep the eyebrows out of the eyes by contraction of frontalis, which eventuates in horizontal brow rhytids. Indeed, it may be these horizontal brow rhytids that initially prompted the patient to seek help. In such cases, inhibition of this compensatory contraction of frontalis inevitably risks eyebrow ptosis. This is especially likely when frontalis

(a)



(b)

Figure 52.1 (a) Blepharoptosis of left eye. (b) Levator palpebrae superioris runs from under the superior orbital rim over the top of the eyeball. If BTX affects this muscle, the consequence is blepharoptosis.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

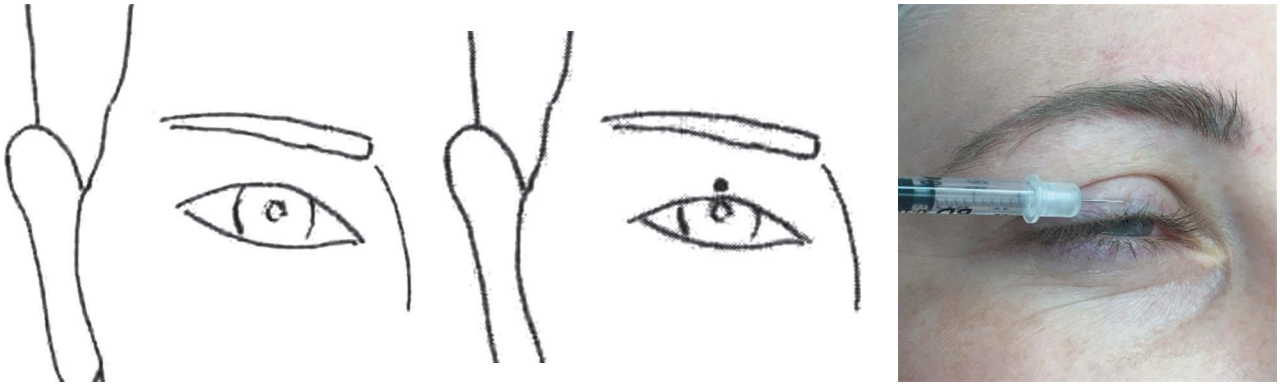


Figure 52.2 (a) Normal control. (b) Blepharoptosis correction. (c) To correct blepharoptosis, inject 1 Speywood unit in the mid pupillary line 1 mm from the eyelid margin.

is treated by BTX within 1.5 cm of the superior edge of the eyebrow.

The inevitable natural progression toward eyebrow ptosis occurs for five common reasons:

1. Facial expression muscles (repeated contraction of the four eyebrow depressors—procerus, corrugator supercilii, OO, and depressor supercilii)
2. Aging (involution of the subcutaneous eyebrow mound)
3. Sleep (in those who sleep on their sides, the eyebrow is often squashed by the weight of the head against the pillow)
4. Habits of eyelid rubbing or pulling (which stretches the skin and the loose advential tissue of the eyelids)
5. Gravity

To prevent eyebrow ptosis in such patients, it may be advisable to avoid BTX injections in the most inferior of their transverse brow rhytids and also to use only the smallest doses of BTX when treating the lateral insertions of corrugator. Before giving BTX treatment to the inferior part of frontalis, each of the relevant causes of brow ptosis needs consideration and perhaps treatment.

Facial expression muscles that depress the eyebrows (including corrugator and the fibers of OO that lie inferior to the lateral part of the eyebrow) are usually best treated using injections by 1 Speywood unit, a millimeter inferior to the eyebrows (Figure 52.3). (These injections are best omitted in the mid and medial pupillary lines in order to avoid the possibility of an unwanted relaxation of LPS that would result in blepharoptosis.)

Aging is characterized by involution of the eyebrow mound. The eyebrow mound is a composite subcutaneous structure comprising fat, fibrous septae, and some pilosebaceous glands. It provides anterior projection for the eyebrow. Like the female breast, the eyebrow mound involutes with the passage of time. With involution, anterior projection is lost from both breast and eyebrow and gravity determines that ptosis follows. Restoration of anterior projection corrects ptosis of this cause. Imagine a curtain hanging down a wall; if a cushion is put behind the curtain, the foot of the curtain will rise (Figure 52.4).

Subdermal hyaluronic acid (HA) filler, 0.1–0.2 mL, threaded subdermally along each eyebrow, will help restore

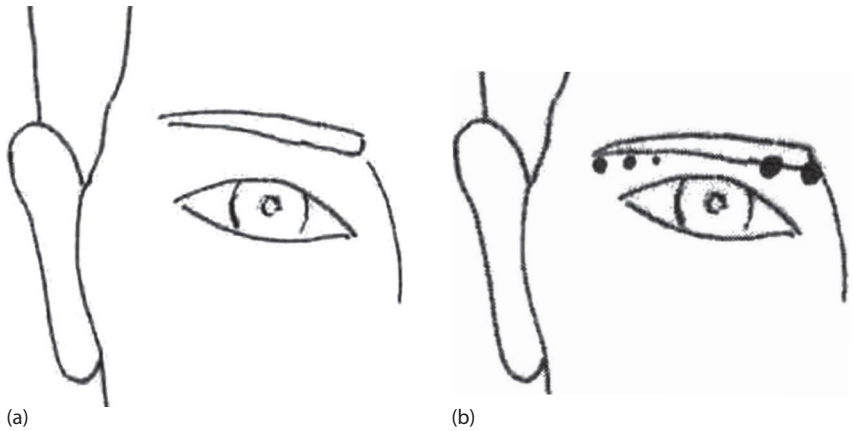


Figure 52.3 (a) Normal control. (b) Eyebrow ptosis correction. Each injection is 1 Speywood unit.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

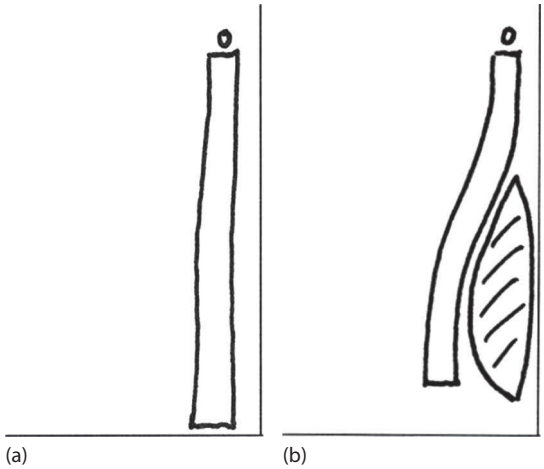


Figure 52.4 (a) The foot of the curtain touches the floor. (b) Put a cushion and the floor and the foot of the curtain rises.

the lost anterior projection of the eyebrow mound and thus improve brow ptosis.

Sleeping on the side of the face means that the eyebrow mound is squashed between the weight of the skull and the resistance of a compacted pillow or, worse still, the bones of the patient's hand. The eyebrow mound is thus compressed between "a rock and a hard place." This compression causes repeated and relatively prolonged microischemic episodes that accelerate involution of the eyebrow mound. Moreover, during sleep, many people lie on their face or side in such a way that their eyebrow is not only squashed but also either drawn inferiorly (so aggravating lateral descent of the eyebrows) or bunched medially (so causing vertical sleep rhytids in the middle part of the eyebrow). Those that sleep on their sides or prone are best advised to sleep on their backs.

Habits of eyelid touching or rubbing are best discontinued.

Gravity has no practical antidote.

Brow ptosis can be treated by

1. Strengthening exercises of the frontalis muscle ("toilet training")
2. BTX treatment of the brow depressor muscles (procerus, corrugator supercilii, OO, and depressor supercilii)
3. Injection of filler in the eyebrow mound
4. BTX treatment of corrugator and OO

Femme Fatale

The femme fatale look is common and to be expected if the conventional and product license–recommended glabella and crow's feet BTX injection sites and doses are used (Figure 52.5).

Some patients like and seek this look. It results in a linear eyebrow that combines descent of the medial eyebrow with elevation of the lateral eyebrow. The conventional pattern of injections, recommended in the product literature for use at the medial brow, inhibits frontalis more than corrugator and the net effect at the medial brow is a residual depressor action of corrugator, OO, and depressor supercilii that is largely unopposed by a now relaxed frontalis. At the lateral brow, conventional BTX injections inhibit the lateral part of OO and

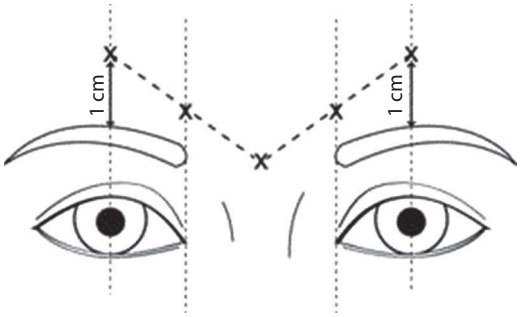


Figure 52.5 Conventional teaching: Azzalure injection sites.

leave untreated the lateral part of frontalis such that the net effect at the lateral brow is an action of frontalis that is largely unopposed by OO. The femme fatale look can be corrected by 1 Speywood unit in each of four points (Figure 52.6).

Mephisto Sign

The Mephisto–Ascher sign is a variant of the femme fatale pitfall. The devil in this can easily be put to flight by asking the patient to raise their eyebrows and then injecting 1–2 Speywood units into frontalis at the point or points of maximum contraction in the lateral brow. Sometimes, the medial eyebrow requires treatment as for femme fatale (Figure 52.7).

"Tell-Tail" Sign

To the eye of the experienced observer, the perfect BTX result may be slightly marred by one or two horizontal supraorbital rhytids running parallel and just superior to the outer tail of the eyebrow. This can be improved by one or more injections of 0.5 Speywood units (Figure 52.8).

Playground Sign

When the author collects his children from school, from time to time, he is struck by how well, beautiful, and wrinkle-free one of the mothers is looking. In a spirit of professional enquiry, he draws near, hoping to observe the said mother more closely, and then, in a moment of animation, her eyebrows rise a little beneath a wrinkleless brow… an almost wrinkleless brow—there are transverse wrinkles high in each temple—"the playground sign." This residual activity of the superior part of frontalis can be avoided or treated by taking the BTX treatment of the brow a rank higher in the lateral brows (Figure 52.9).

Clown Sign

Traditional clown's face paint includes a vertical line drawn through the middle of the eyebrow down across both eyelids and onto the infraorbital skin. If the orbit is considered as a clockface, the clown's line runs vertically from 12 to 6. A rhytid in the same place may be caused by habitually sleeping on that side. This can be potentiated by BTX treatment of crow's feet and bunny lines, which leaves the BTX-untreated superior and inferior parts of OO being relatively unopposed by the BTX-treated lateral and medial OO. Thus, the superior and inferior parts of OO contract upon themselves so causing or

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

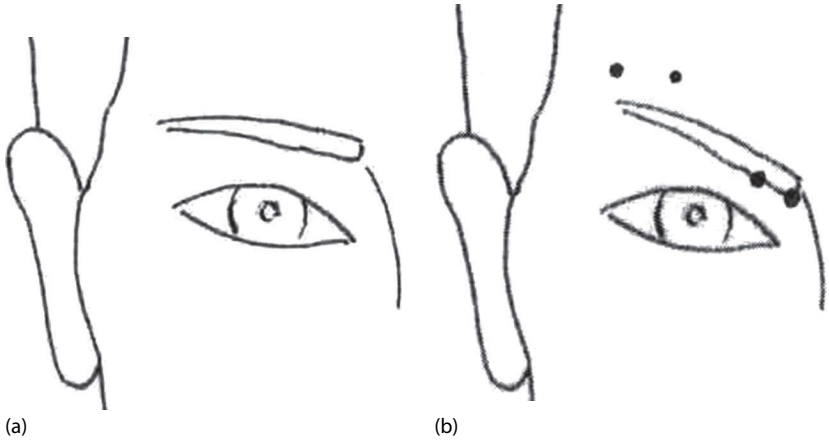


Figure 52.6 (a) Normal control. (b) Femme fatale and correction. Each injection is 1 Speywood unit.

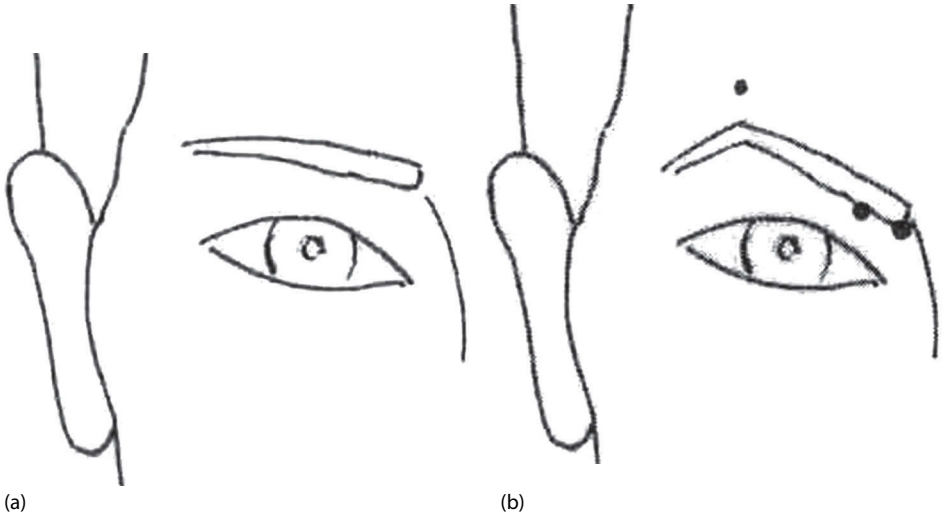


Figure 52.7 (a) Normal control. (b) Mephisto sign and correction. Each injection is 1 Speywood unit.

Figure 52.8 (a) "Tell-Tail" sign. (b) "Tell-Tail" sign correction. Each injection is 0.5 Speywood units.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 52.9 (a) Playground sign. (b) Playground sign correction. This injection is 1 Speywood unit.

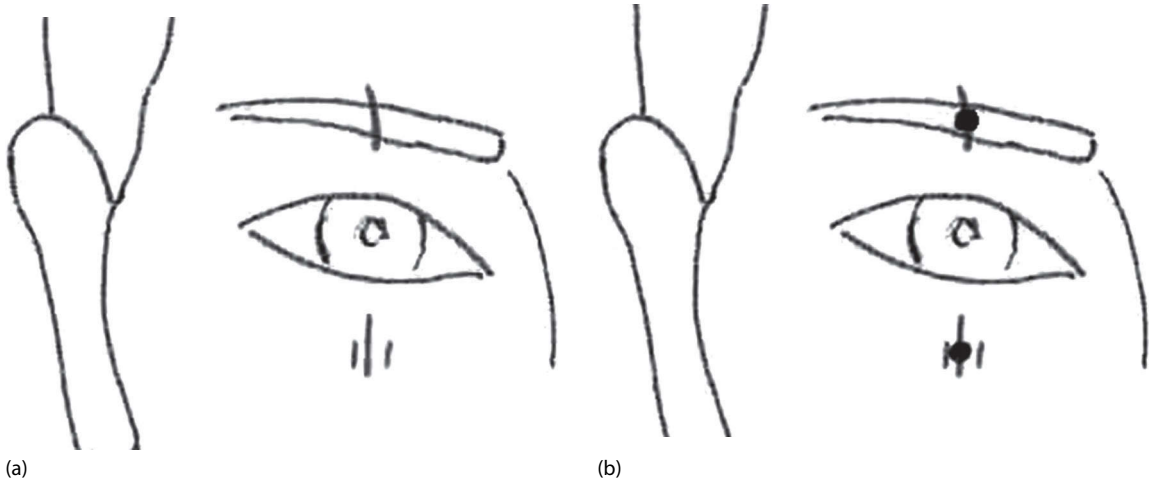


Figure 52.10 (a) The clown sign. (b) The clown sign correction. Each injection is 1 Speywood unit.

compounding the clown sign. The clown sign can be avoided by using low dose BTX laterally, superolaterally, inferolaterally, and inferomedially. The clown sign can be improved by 0.5 Speywood units in the vertical rhytids (Figure 52.10).

Residual Eyelid Wrinkles

If the outermost part of OO is treated generously with BTX at the crow's feet and bunny lines while the innermost part is left untreated, the innermost fibers will contract upon themselves leaving the eyelids a mass of wrinkles set in an otherwise wrinkle-free periocular skin. To avoid this or to correct it, BTX should be spread a little throughout OO not only in its outermost part but also in small doses in its innermost part (Figure 52.11).

Scleral Show

Scleral show occurs when the innermost fibers of OO of the lower eyelid are weakened (Figure 52.12). Strengthening exercises will hasten recovery.

"Puffy Lower Eyelids" and Intraorbital Fat Herniation of the Lower Eyelids

Intraorbital fat herniation of the lower eyelids results in "waterlogged or puffy lower eyelids" (Figure 52.13).

The orbit lies cushioned in its bony cone by fat pads. The intraorbital fat pads of the lower eyelid are held in place by the orbital septum which is a fibrous sheet running from orbital rim to tarsal plate. Anterior to the orbital septum lies the preseptal space then, in youth, the superior part of the suborbicularis

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

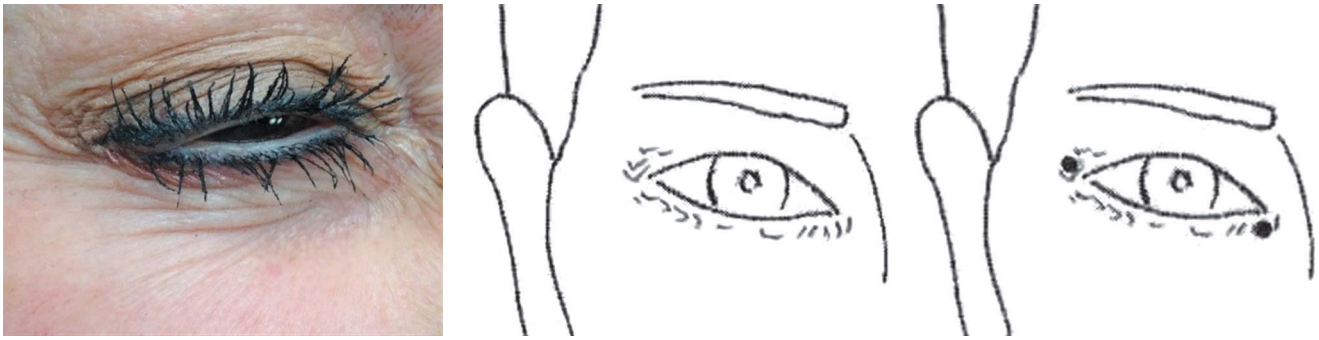


Figure 52.11 (a) Residual eyelid wrinkles. (b) Residual eyelid wrinkles. (c) Residual eyelid wrinkle correction. Each injection is 1 Speywood unit.

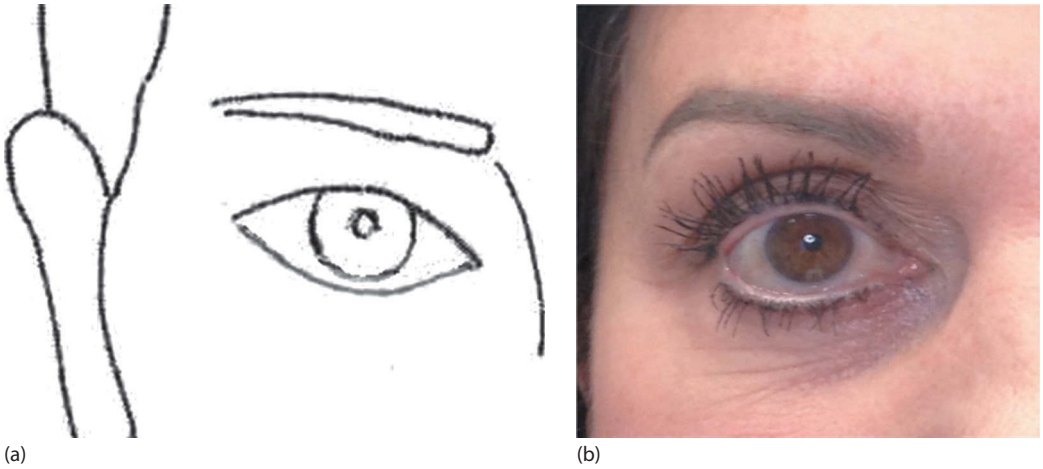


Figure 52.12 (a) Scleral show. (b) Scleral show.

Figure 52.13 Puffy lower eyelids.

oculi fat (SOOF), across which is slung, like a hammock, the OO muscle. Next is the loose advential subcutaneous tissue. Finally, there is the skin. All these structures lie within the intraorbital compartment of the lower eyelid. The preseptal space of the lower eyelid is delimited inferiorly by the orbital retaining ligament (ORL) (also known as the orbitomalar septum or malar septum), which is a fibrous sheet that runs from the orbital rim anteroinferiorly, between the fibers of OO, and to inserts into skin.

In youth, the skin surface of the intraorbital compartment of the lower eyelid is concave. With time, gravity, and weight gain, the intraorbital fat pads of the lower eyelids herniate anteriorly and prolapse inferiorly. Concavity becomes convexity, tending to give the lower eyelids a "waterlogged" or "puffy" or even "pouchy" appearance (the orbital septum and OO being insufficiently strong to hold them back). This puffy effect is always worse in the mornings, a few hours after alcohol, and with low atmospheric pressure (e.g., flying at high altitude or in the mountains). Any weakening of the OO muscle, especially inferolaterally where OO is weakest, risks aggravating this effect.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

This is a hazard of any BTX treatment of the inferior OO, for example, at the inferior crow's feet or the owwee point or the lower sand point or when BTX is given for OO bands. If there is a poor lower eyelid snap test or any tendency toward inferior eyelid fat pad herniation, BTX is best avoided at these sites.

Some recovery from "puffy lower eyelids" can be achieved by strengthening exercises of the lower OO. Lower blepharoliplasty is another possibility.

"Puffy Pommettes" and Malar Festoons

"Pommettes" or malar mounds are a normal anatomical finding, even in children. They are delineated inferiorly by the midjugal groove that runs from inner canthus, in a diagonal direction inferolaterally down and across the cheek.

With time and gravity, "pommettes" or malar mounds may progress to malar crescents and eventually malar festoons. The early phase of this process, "puffy pommettes," is often described by patients as a "puffiness" or a "waterlogged" appearance of the skin, situated 1–2 cm inferolateral to the inferolateral edge of the orbital rim (Figure 52.14).

Figure 52.14 Puffy pommette.

As the yolk of a fried egg sits upon its white, the malar fat pad (i.e., the malar mound) sits atop the OO.

At the level of the malar mound, a kebab skewer travelling perpendicularly through the skin to the zygomatic bone would have its tip in the periosteum, next on the stick would be the prezygomatic fat, then a glide plane called the prezygomatic space of Mendelson et al. [1] (which is itself lined by a fine membrane), then the SOOF which is adherent to the deep aspect of the fascia of OO, then the fenestrated part of the OO muscle, then the malar fat pad, and lastly there is the skin. The prezygomatic space is delimited superiorly by the ORL, a fibrous sheet that separates the prezygomatic space of the mid face from the preseptal space of the lower eyelid as explained above. The prezygomatic space is delimited inferiorly by a series of strong zygomatic ligaments (ZLs).

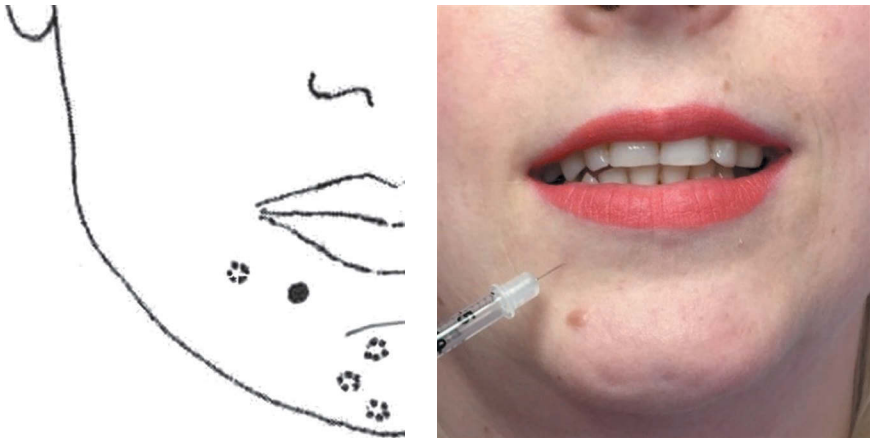
With time, the deeper fat (i.e., prezygomatic fat) involutes, leaving the once turgid prezygomatic compartment now flaccid. The same happens to the SOOF. Where fullness formerly provided anterior projection for the cheek, flaccidity now results in ptosis of the cheek. Moreover, the problem of collapse and descent of deep cheek fat and SOOF is compounded by involution of the overlying subcutaneous malar fat pad. Subcutaneous malar fat pad involution results in malar crescents, ultimately eventuating in malar festoons. Where in youth a full and turgid cheek was topped by a proud malar mound, in older years an involuted and fallen cheek is surmounted by a flaccid malar festoon. Any concomitant herniation and prolapse of the intraorbital fat of the lower eyelid further worsens the overall appearance of "pouchiness."

Any BTX-induced weakening of the OO in this zone will favor "puffy pommettes" first and later malar festoons.

Puffy pommettes can be improved by strengthening exercises of the lower OO and by filler treatment in each of the various fat layers (prezygomatic, SOOF, and malar fat pad) as well as by filler treatment supraperiosteally at the inferior border of the ORL.

Depressor Labii Inferioris Weakness

If a patient has a unilateral depressor labii inferioris palsy, a not infrequent complication of either depressor anguli oris BTX treatment or facelift or other trauma, the *contralateral*



(a) (b)

Figure 52.15 (a) Depressor labii inferioris. (b) Depressor labii inferioris is injected. This injection is 1 Speywood unit.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

depressor labii inferioris may be injected at its point of maximum movement with 0.5–1 Speywood unit to restore symmetry (Figure 52.15).

CONCLUSIONS

BTX has proven to be one of the safest and most exciting drugs in aesthetic medicine. BTX has a narrow therapeutic ratio. Complications do occur and are amenable to treatment.

REFERENCES

1. Mendelson BC, Muzaffar AR, Adams WP. Surgical anatomy of the midcheek and malar mounds. *Plast Reconstr Surg* 2002 September 1; 110(3):885–896.
2. Philipp-Dormston WG, Bergfeld D, Sommer B. Konsensus-empfehlungen zur Behandlung mit Onabotulinumtoxin A in der ästhetischen Medizin. *J Deuts Dermatol Ges* 2012; 11(Suppl 1): 1–42.
3. Rowland Payne CME. Newly recognised syndrome in the neck: Horner's syndrome with ipsilateral vocal cord and phreic nerve palsies. *J R Soc Med* 1981 November; 74(11):814–818.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

History of soft-tissue augmentation

Pierre André, Raphael André, and Eckart Haneke

For a long time, injections of foreign substances into the human body have been attempted to correct body defects or to enhance facial aspects.

Various products have been used over the years; many of them were poor and gave severe complications. In 1981, bovine collagen (Zyderm®) was U.S. Food and Drug Administration approved, and since then, filling agents have focused their attention on aesthetic physicians. Since then, many other fillers have been launched.

Among them, permanent agents produced severe complications and most of them were withdrawn from the market. Biodegradable agents are preferred as, in cases of complications, they are usually reversible.

This chapter will discuss the oldest agents that were used, until the appearance of hyaluronic acid, which is at the moment the safest exogenous agent available for injection (hyaluronic acid will be described in depth in the next chapter).

At the same time, "lipofilling" technique was described by Fournier [1] and then improved by Coleman [2], who termed it "lipostructure." Now, thanks to a better knowledge of fat tissue and to the discovery of stem cells, we can really dream to new techniques of rejuvenation.

PERMANENT PRODUCTS

Mineral Oil Injections

Since 1899, Gusuny, an Austrian surgeon, injected mineral oil (Vaseline) to substitute the absence of testicles. Since then, many injections with paraffin were performed either into the body (breast, penis, calves, buttocks, etc.) or into the face, mainly to correct wrinkles. The first reports of complications were published in 1906. They mostly appeared a few months or years after the initial treatment. Skin inflammation, skin necrosis, sterile abscesses, subcutaneous nodules, and diffuse lymphangitis appearing with lipogranuloma were the most important complication [3]. A case of disseminated lipogranulomas and sudden death from self-administered mineral oil injections has been reported [4].

Injections of paraffin or other oils (cottonseed oil, sesame oil, camphor oil, sheep lanolin, etc.) were performed essentially by nonphysicians, and more and more complications were reported. As mineral oils are permanent, so are their complications.

Penile paraffinoma [5] was frequent in the past, with all specific complications on erectile function and pain.

Today, injections of paraffin were illegally reintroduced by bodybuilders to increase muscles volume [6].

In some cases, lipogranulomas have been reported after hand injuries from high-pressure injection (specific to industrial oils). The clinical aspect is most often characteristic, but nonspecific, and sometimes it is a challenging diagnosis.

Histological examination is mandatory to demonstrate the granulomatous reaction. Foreign-body reactions often look like a "Swiss cheese" because of the presence of numerous ovoid or round cavities of varying size (spaces occupied by the oily substance). In a fibrotic connective tissue with macrophages, histiocytes and multinucleated foreign-body giant cells are present. If frozen sections are available, the mineral oils stain with Sudan, Nile blue, osmic acid, and oil-red-O. Spectrophotometry and chromatography may be used to identify the presence of paraffin in tissue specimens [7].

Treatment is very difficult apart from complete excision, which is not always possible.

Silicone Injections

Silicone has replaced paraffin both for body sculpting and wrinkle correction. It is a permanent product that does not require any skin test before being injected.

Silicone is a polymeric hydrophobic compound of dimethylsiloxanes. It can be fluid or solid depending on its molecular size.

Silicone injections were performed for many years [8] until severe complications were observed. These reports prompted the health authorities of many countries to interdict silicone injections. Nevertheless, many physicians are partisans of its use because medical grade silicone is an inert, well-tolerated, and permanent agent. Promoters of silicone believe that complications occur from impurities contained in the industrial grade products; however, this is rejected by other authors. The injection technique is also important; large volumes must be avoided and only microdroplet injections must be used. Unfortunately, even experts observed complications (due to the host-dependent response?) as well as overcorrection.

"Microdroplet silicone," well described by Orentreich [9] (polydimethylsiloxane fluid with a 360 centistokes viscosity), refers to the technique in which only amounts ranging from 0.005 to 0.01 mL are implanted into the deep dermis or hypodermis at 2–4 mm intervals. The silicone used must have been filtered and sterilized to eliminate heavy metals, low-chain-length polymers, and all impurities. The injection technique has been well described in many articles and books [10]. As a microcapsule of collagen forms around each silicone droplet, a second injection session is performed only 4 or 6 weeks after the first. Definitive results are observed after a few weeks, and

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

this is why undercorrection is mandatory. As each minidroplet is encapsulated by native collagen, it does not migrate.

Unfortunately, adverse events may occur, from minor to severe [8]. Minor events are common with all injections. Severe complications include granulomas, migration, cellulitis, ulcerations, embolism, blindness after injection in the glabella area, and pneumonia.

Inflammatory granulomatous reactions may appear months or years after the treatment.

Several reports of "human adjuvant disease" have been published in the literature after silicone breast augmentation [11–13], but nothing is evident after silicone injections.

Histopathological findings in local reactions reveal cystic spaces involving the dermis and the subcutaneous tissue. The vacuoles are round to oval, and the aspect is described as "Swiss cheese" like, with histiocytes, foamy macrophages, and multinucleated giant cells. The inflammatory reaction is variable with sometimes eosinophils [14]. Silicone can be detected by spectroscopy and scanning electron microscopy [7,14].

It has been used for correcting wrinkles, acne scars, small persistent defects after rhinoplasty, and lip augmentation and in podiatry to relieve pressure areas, corns, and painful plantar warts, as well as to correct facial lipoatrophy in HIV patients [15].

The use of large volumes (breast augmentation, buttock augmentation, etc.) caused severe complications.

Today, 360 centistokes medical grade silicone use is forbidden for cosmetic uses in most of the countries. In the United States, Silikon® 1000 and AdatoSil® 5000 have been approved by the FDA for retinal detachment only. These two silicones are sometimes used off label.

Bioplastique® (Bioplastique, Geleen, the Netherlands) was used (off label) for injections in the face and complications such as induration, swelling, and granulomas have been reported. It is a 38% biphasic polymer, made of textured polydimethylsiloxane particles of controlled size from 100 to 600 µcm suspended in a 62% biocompatible solution of water and organic polymer gel with lubricating properties [16].

Polymethyl-Methacrylate Microspheres in Collagen

As degradable products as bovine collagen were short-lived, some new inert and well-tolerated permanent agents were launched in the 1990s.

Arteplast® (polymethyl-methacrylate microspheres in collagen [PMMA] in gelatin) was introduced to the German market by Lemperle in 1991 and then Artecoll® (PMMA in bovine collagen). It is made of 20% microspheres of PMMA of 30–42 µm of diameter. This size avoids microspheres to be phagocytized by macrophages.

As Arteplast gave granulomas, its carrier gelatin was changed to collagen solution (3.5% atelocollagen) and named Artecoll [17,18] in 1996.

In the United States, Artefill® (Artes Medical, San Diego, CA), the latest refined version of PMMA, was approved in 2006; the PMMA microspheres have a smooth surface without electric charge and would be less reactive with a very low incidence of granulomatous reactions.

Artefill contains 0.3% of lidocaine to reduce the discomfort at injection. It must not be freezed, but kept at standard domestic refrigerator temperature. Like all products containing bovine collagen, it requires a skin test before injection.

Injections must be done into the deep dermis, not too deep and not too superficially to avoid a lumpy aspect. It is implanted through a 26 G needle. Successive implantations at 2 or more weeks may be necessary to achieve the best result.

Unfortunately, some rare complications [19–21] were reported, particularly permanent granulomatous reactions. These complications appear months or years later and are always a challenge for treatment.

Histological aspects reveal microspheres within spaces surrounded by fibroblasts and, in cases of granuloma, there is a diffuse and nodular inflammatory reaction intermingled with microspheres with epithelioid cells and multinucleate giant cells [7,14].

Polyethyl-Methacrylate Microparticles

These products named Dermalive® and Dermadeep® were first launched in France.

Dermalive is made of 40% acrylic hydrogel composed of ethylmethacrylate and hydroxyethylemethacrylate particles within nonanimal hyaluronic acid. The particle sizes range from 45 to 65 µm and have an irregular shape, but a smooth surface.

Dermadeep is similar except for the bigger particle size of 80–110 µm.

No skin test is required.

Injections must be done into the deep dermis as with Artefill.

Many complications have been reported [7,22]. Most severe are granulomatous reactions, which usually appear months or years later. As particles are permanent, complications too.

As after Artecoll/Artefill granulomas, treatment is long and always difficult.

Histological aspects of granuloma reveal particles of different sizes within a granulomatous reaction with numerous epithelioid cells and multinucleate giant cells [7,14].

Many patients had severe complications, and there are many current trials.

Polyacrylamide Gel

It was first used in 1980 for breast augmentation.

Aquamid® (Ferrosan, Soborg, Denmark) received the agreement (CE mark) of the European community in 2001. Many other polyacrylamide gels were launched during the same period (Argiform®, Bio-formacryl®, Outline®, etc.).

Acrylamide has neurological and carcinogenic effects, particularly its monomer. Polyacrylamide must be stable and resistant to degradation to avoid the threshold of toxicity, which is evaluated to 0.2 µg/kg/bw/day.

Aquamid contains 2.5% of polyacrylamide gel within 97.5% water. It is a permanent product. The concentration of monomer is 2 µg/syringe of 1 mL. As the product is very stable, there is no risk of toxicity.

No skin test is required.

Unfortunately, some complications are reported [23,24], overall after breast augmentation (infection, abscess, induration) but also after injection in the face (infection, migration, overcorrection, abscess, granuloma, etc.).

Treatment of complications is always difficult; this is why this product must be avoided.

Histological aspect looks like silicone. In case of granulomatous reaction, the examination reveals granulomas consisting of histiocytes, foreign-body giant cells, and fibroblasts and lymphocytes around amorphous material [14].

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Evolution® is a mixture of 6% polyvinyl hydroxide microspheres (5–80 µm) and 2.5% of polyacrylamide gel. It was injected to treat facial wrinkles. The same type of side effects was reported.

Polyalkylimide Gel

Bio-Alcamid® (Polymekon Labs, Milan, Italy) is a translucent gel made of a hydrophilic biopolymer with 96% water and 4% polyalkylimide [25]. It is nontoxic, nonallergenic, and permanent. It is considered as a real prosthesis, which is surrounded with a thin layer of fibrous tissue. For this reason, the product can be easily removed.

No skin test is required.

It was used for body and face, usually to create volume.

Infection is the main risk, requiring antibiotics and drainage [26].

COMPLICATIONS DUE TO PERMANENT PRODUCTS

Permanent products may give permanent complications, which is always a challenge for treatment.

Apart from common side effects, which may occur after all types of injections, many granulomatous reactions have been reported. They appear usually months or years later, and the treatment is always difficult; intralesional long-acting steroids, systemic steroids, minocycline, imiquimod cream, 5% fluorouracil, tacrolimus, and allopurinol have been tried with more or less success. New therapies with infliximab or etanercept may be proposed, but even if they can be effective, side effects have been reported, compelling to stop the treatment.

A new hypothesis would be in favor of a "biofilm," made of bacteria on the surface of the particles, which would be responsible for the formation of granulomas and "sterile infection" [27–30]. For this reason, high doses of combined antibiotics have been tried, but unfortunately without a constant success. Laser treatment (Nd:YAG laser 1064 nm) probably through thermal effect has been used with some success.

Complete surgical excision is the best way, but rarely possible.

Polytetrafluoroethylene Implant

It was first used in pulmonary and heart valve operations. In 1975, the FDA approved it also for plastic surgery [31].

Gore-Tex® (SoftForm R, Collagen Aesthetics, Palo Alto, CA) is a subcutaneous augmentation material made of biocompatible expanded polytetrafluoroethylene. It is for the repair or the enhancement of the soft tissues of facial area.

This implant is available in plaques, threads, and tubes.

It has been used for correction of facial atrophies; for augmentation of the chin, the nose, and the cheeks; and for filling the nasolabial folds [31,32].

Good results depend on the skill of the practitioner.

Most of the complications are due to the technique, but infection may occur and removal of the implant may be necessary.

BIODEGRADABLE PRODUCTS

Bovine Collagen

Zyderm I (Collagen Corporation, Palo Alto, CA) has been FDA approved in 981, Zyderm II in 1983, and Zyplast® in 1985.

It comes from a certified bovine spongiform encephalopathy–free herd.

Zyderm I contains 35 mg/mL of collagen and Zyderm II 65 mg/mL in phosphate-buffered saline. It is launched with or without lidocaine (0.4%) inside. To increase its lifetime, glutaraldehyde is added during processing, causing cross-linking: this is Zyplast.

Ninety-five percent is collagen type I, and the rest is type III.

As it is a bovine collagen, hypersensitivity reaction may occur.

Patients tested prior to any treatment have an 8.4% incidence of anticollagen antibodies as measured by ELISA. These individuals were probably sensitized by diet.

Skin test demonstrates hypersensitivity of 3.5%–4% in the literature [33–35].

The double skin test, well described by Klein [36], is more efficient to detect hypersensitivity.

But even after a negative double skin test, a small percentage of patients will develop allergic reactions (from 1% to 3%). IgG antibovine antibodies are predominant but IgA may be present too.

Zyderm I and II are indicated for treating superficial wrinkles. Zyplast is better for deep wrinkles and furrows. Injections must be placed in the dermis.

Longevity of the implant depends on the treated area and on the injection technique. It lasts between 5 and 10 months.

Complications [37–39] may be allergic, with a delayed reaction of a few days until a few weeks or months after implantation. Test site may react at the same time. Redness, swelling, and induration may be present. Most of the time, the reaction will gradually fade over months. Rare cases of cystic painful reactions have been reported, which need to be drained.

Histological examination of nodular reactions describes a foreign-body reaction with giant cells and lymphocytes infiltrate.

Human Collagen (Allograft)

AlloDerm® Regenerative Tissue Matrix (LifeCell Corporation, Palo Alto, CA) is a surgical implant. It is an acellular dermal matrix derived from donated human skin that undergoes a multistep proprietary process removing both the epidermis and the cells that can lead to tissue rejection.

It is available in two thickness ranges for use in different procedures.

It has been used in dental surgery [40] and in soft-tissue augmentation (lip augmentation, etc.).

Cymetra® Micronized AlloDerm Tissue (LifeCell, Palo Alto Corporation, Palo Alto, CA) is a minimally invasive FDA-approved, injectable form of AlloDerm Regenerative Tissue Matrix. It can be used for correcting small defects of the skin [41]. Before injection, the product must be rehydrated with lidocaine and saline.

With these two devices, no skin test is usually performed.

The longevity of the correction is currently not well known. After Alloderm lip augmentation, longevity would be of more than 2 years; after Cymetra, longevity is shorter, around 6–9 months.

Dermalogen® Human Tissue Matrix (Collagenesis, Beverly, MA) is derived from human cadaver (very similar to Cymetra) [42]. Longevity would be comparable. No skin test is required.

Fascian® (Fascia Biosystems, Los Angeles, CA) was launched in 1999. It derives from fascia of human cadaver [43].

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

It must be rehydrated with saline. It is not easy to inject and syringes are easily clogged. No skin test is required.

Its longevity would be around 3–6 months.

Cosmoderm® (McGhan Corporation, Santa Barbara, CA) is bioengineered human collagen that is obtained from fibroblasts grown from neonatal foreskin. No skin test is required.

Cosmoderm 1, Cosmoderm 2, and Cosmoplast are supplied in individual sterile syringes ready to use. They contain 0.3% lidocaine.

Cosmoderm 1 is injected into the papillary dermis, and Cosmoderm 2 contains twice the collagen concentration of Cosmoderm 1.

Cosmoplast is cross-linked. It is indicated for deeper lines.

Both are FDA approved [44,45].

Longevity would be 3–6 months.

Human Collagen (Autograft)

Autologous collagen: After harvesting fat cells from patients, the extracted tissue is mixed with sterile water and freezed. This process creates cell rupture, and after decanting, an oily fraction is separated from a solid fraction composed of lipocyte cell walls and connective tissue. This autologous collagen is ready to be injected.

Its longevity is close to bovine collagen's.

This technique is long and costly but is interesting for allergic patients to exogenous collagen.

Autologen® (Collagenesis Inc., Beverly, MA), FDA approved, is made of autologous collagen fibers derived from a skin sample removed by surgery from the same patient.

The sample is sent to the company to be processed. Syringes contain between 50 and 120 mg/mL of collagen and are ready for injection.

No skin test is required.

Its longevity would be greater than bovine collagen's [46,47].

Isolagen® (Isolagen Tech, Paramus, NJ) has been FDA approved since 1998 [48]. A 3 mm skin biopsy is taken from the patient's postauricular area and sent to the company for processing. The company cultures the fibroblasts and sends them back to the physician. Several treatments may be needed in a single site to get a good result. Injected fibroblasts are supposed to rejuvenate the treated area.

These techniques are costly, long, and results are not really superior to bovine collagen.

Porcine Collagen

Permacol® (Tissue Science Labs, Hants, United Kingdom) surgical implant is a porcine dermal collagen implant from which cells, cell debris, DNA, and RNA are removed in a gentle process that is not damaging the 3D collagen matrix. The resulting acellular collagen matrix is then cross-linked for enhanced durability.

Permacol surgical implant is ready to use when needed and is dimensionally stable. It is available in a wide variety of sizes, including larger sizes that eliminate the need for suturing multiple pieces together and provide the right size of implant regardless of the size of the defect [49].

Strattice® (LifeCell Corporation) is a sheet of sterile tissue derived from porcine (pig) skin that can be implanted to reinforce soft tissues, encourage cell regeneration, and support the development of new blood vessel networks [50]. It is non-cross-linked.

These two products are used essentially for corrective breast augmentation and hernia repair.

Surgisis® (Cook Biotech, West Lafayette, IN) Soft Tissue Graft and ES Soft Tissue Graft are derived from the submucosa of pigs. It is very similar to Alloderm® but with a greater longevity.

Evolence® and Evolence Breeze® (ColBar LifeScience, Herzliya, Israel) are supplied in syringes ready to use since 2004. It has been FDA approved in 2008 (J&J, New Brunswick, NJ) [51,52].

This is a porcine collagen that is treated by pepsin digestion to eliminate the immunogenic telopeptides. Monomeric telopeptide collagen is then cross-linked with D-ribose to increase the lifetime.

Evolence is injected into the deep dermis, and Evolence Breeze in the superficial dermis.

No skin test is required.

Its longevity is better than bovine collagen's.

As it is pig derived, according to religions, it may cause ethical problems.

NONCOLLAGENIC AGENTS

Lutrol F 127

This is a polymer of hydroxy-polypropylene and hydroxy-polyethylene.

It was launched in the French market in 1997 and named Profill® (OVI SA, France). This is a thermoelastic gel, which received the agreement of the European community (CE mark).

It is nonallergenic, biodegradable, and theoretically and immunologically inert.

Its indications are comparable to bovine collagen's.

Patients were injected in the nasolabial folds, with an immediate good correction, but at the follow-up, 6 months later or more, an amazing severe complication was reported [53]. Patients developed facial lipoatrophy, which is very similar to those of HIV patients under antiprotease treatment. These lipoatrophies evolve for years, sometimes with some improvement, but most often they are definitive. A few cases have been treated by fat grafting with success [54].

The pathogenesis is not well understood.

The histological examination is nonspecific; no foreign-body reaction, no particular inflammatory infiltration, but a severe fibrosis in the hypodermis.

Fibrel® (Mentor Corporation, Santa Barbara, CA) was FDA approved in 1988 for scars and in 1990 for wrinkles. It has been injected from the late 1970s until 1998, at which time the company ceased its manufacture.

A syringe contains 125 mg of ε-aminocaproic acid and 100 mg of gelatin powder. The content of the syringe is reconstituted with 0.5 mL of the patient's serum and 0.5 mL of saline. The content is ready to be injected, but, as it has a great viscosity, it is not suitable to fine lines. As gelatin is derived from pig, a skin test is required before injection. Incidence of allergy is not well known, but is less than 2% of tested patients.

Since Fibrel injections are painful, local anesthesia is suitable.

The best results were obtained for scars, with a greater longevity than with bovine collagen [55].

As usually a markedly red/blue area with swelling that develops around the implant and may last a few weeks, this product is not comfortable for aesthetic indications.

Novabel® (Merz Pharma, Germany) was launched in 2010.

It represents a new class of fillers made of alginate, which is a biodegradable product. It comes from sea algae; it is a

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

polysaccharide (alginate) that consists of microscopic spheres, called geleons (diameter around 150 µm). These geleons are saturated with Ringer's solution (<5% of product). Viscosity is very low (water-like), which enables us to inject it easily through a very fine needle, or a fine flexible cannula.

According to Merz Company, this alginate is extremely pure and the endotoxin content would be of less than 0.1 IE/mL. This product would be inert and would not require any skin testing. Alginate is a biodegradable product, which is degraded by nonenzymatic hydrolysis. Longevity of Novabel would be around a year.

Injections may be done into the dermis or deeper and the company has emphasized the benefit over other fillers in infraorbital hollows.

This new class of fillers seemed particularly interesting for filling hollows around the eyes. In this area, the skin is thin and hyaluronic acid (which is the "gold standard" for the moment) may sometimes give a bluish aspect due to the Tyndall effect. In other cases, hyaluronic acid may swell and give bags.

Advertising for treating patients around the eyes without risk, as mentioned by Merz Company, resulted in infatuation for Novabel.

Unfortunately, after a few months, many side effects were reported, particularly nodules under the eyes.

The histological examination reveals a granulomatous reaction made of foreign-body giant cells around spheroidal particles in the deep dermis or deeper [56,57].

Without treatment, these complications last for a long time. Intralesional injections of corticosteroid may help.

As the number of granulomatous reactions was too frequent, the company decided to withdraw Novabel from the market.

Poly-L-Lactic Acid

Poly-L-lactic acid has been used for a long time in many surgical and medical indications (suture threads, ligaments, restoration in orthopedics, etc.).

Its use as a filler for aesthetic indications started in France in the 1990s under the name New-fill® (Biotech Industry, France). Some years later, the same product was renamed Sculptra® (Sanofi Aventis, France). In 2004, it was FDA approved for facial lipoatrophy in HIV patients [58,59].

It is a synthetic molecule discovered in 1954 in France. It comes from lactic acid, which belongs to the family of fruit acids. It is a biodegradable product and immunologically inert and does not require skin test before using it.

It is a filler that will induce a "fibrosing" reaction, and this is why it needs to be injected into the hypodermis or into the deep dermis, but never too superficially. In this case, nodules may appear. The degree of volume produced by any given individuals is difficult to predict. It needs two or three sessions, each spaced 4–6 weeks to obtain the best result, but the result depends on the ability of each patient to produce new collagen.

Technical Aspects

New-fill/Sculptra is supplied as a lyophilized powder. Each vial contains a mixture of poly-lactic acid microspheres, sodium carmellose, and mannitol. Poly-L-lactic microsphere diameter ranges from 2 to 50 µm.

At the beginning, the company claimed to dilute the powder with 3 mL of sterile water, but many subcutaneous nodules were reported and at present most of the injectors prefer to reconstitute it with 5–10 mL of water and 1 mL of lidocaine with epinephrine to decrease the incidence of bruising.

The reconstitution should be done at least 30 minutes before injection.

Once the material is mixed, it seems possible to keep it refrigerated up to 3 weeks.

Before injections, the product must be agitated permanently to keep it homogeneous. Ultracentrifugation is suitable.

The needle diameter must be large enough to avoid clogging (25–26 G).

After the injections, a massage for a few minutes is important to well distribute the product.

Indications

The best indication is correction of HIV facial lipoatrophy.

It is a "volumizer" and must be injected deep. Cheekbones, cheeks, and deep nasolabial creases may be treated [60–63].

It is not suitable to treat fine lines.

Hand remodeling was performed with success, but dilution must be with 10 mL of water to avoid any lumpy aspects.

Complications

Most of the side effects [64] are due to the injection technique or to an insufficient dilution.

Sometimes, nodules are only palpable, but they may also be visible. As the result depends on host response (production of new collagen), it is not really predictable.

The histological examination is quite characteristic: multiple translucent particles of different sizes with giant cells and lymphocytic infiltrate. The particles are birefringent in polarized light examination [14].

Treatment is difficult, but long-acting corticosteroid injections may give a good outcome.

Calcium Hydroxyapatite

It has been used for a long time in orthopedics, dentistry, or plastic surgery. It is biodegradable and well tolerated.

Radiesse® (Merz Pharma, Frankfurt, Germany) has been FDA approved for use in craniofacial defects and for laryngoplasty and then in 2006 for HIV lipoatrophy and moderate-to-deep wrinkles. It is composed of synthetically produced smooth calcium hydroxyapatite (CaHA) microspheres of 25–45 µm suspended in a sodium carboxymethylcellulose gel carrier. Radiesse wrinkle filler is approximately 30% CaHA and 70% gel carrier by volume.

Over time, the gel is absorbed, and fibroblasts appear. The process of neocollagenesis begins, stimulating the gradual growth of the patient's own collagen. The CaHA microspheres naturally degrade to calcium and phosphate ions, which are metabolized by the body's normal processes. Results last up to a year or more for many patients. Virtually no risk of allergic reaction exists.

It does not require sensitivity testing prior to treatment.

The product is presented in 1.5 mL syringes (0.3 mL for touch up).

The injection is unpleasant for a few minutes. Some physicians prefer to mix the product with lidocaine to make it more tolerable.

Injections must be into the deep dermis or deeper to avoid lumpiness, but injections may be more superficial if the product is diluted.

It is indicated for filling wrinkles [65–67], particularly in thick skin (male skin), and for remodeling hands [68].

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Complications are very rare, and most often they are due to a poor technique or a wrong indication [69,70].

A new presentation with larger particles would have a greater longevity [71].

AUTOLOGOUS FAT TRANSPLANTATION

The first published reports of autologous fat transfer appeared in the medical literature in the late 1800s. Neuber [72] and then Bruning [73] described their techniques. In 1950, Peer [74] published his cases of autologous fat grafting; 50% of the injected volume of fat persisted at 1 year.

In 1974, Fischer [75] described the first liposuction technique, and then Illouz [76] and Fournier improved the technique. In 1985, Fournier described his technique of lipofilling [1], which was refined by Coleman in 1994 [2,77] and named lipostructure.

Since then, the reports are amazing and lipostructure realizes a real fat grafting.

The indications are numerous, essentially to create volumes, in the face and in the breast, or to correct body's defects.

Lipostructure gives marvelous results, but must be performed in a surgical environment to avoid any risk of infection.

REFERENCES

1. Fournier PF. Facial recontouring with fat grafting. *Dermatol Clin* 1990; 8(3):523–537.
2. Coleman SR. Structural fat grafting: More than a permanent filler. *Plast Reconstr Surg* 2006; 118(Suppl):108S–120S.
3. Urbach F, Wine SS, Johnson WC et al. Generalized paraffinoma (sclerosing lipogranuloma). *Arch Dermatol* 1971; 103:277–285.
4. Rollins CE, Reiber G, Guinee DG et al. Disseminated lipogranulomas and sudden death from self-administered mineral oil injection. *Am J Forensic Med Pathol* 1997; 18:100–103.
5. Cohen JL, Keolieian CM, Krull EA. Penile paraffinoma: Self-injection with mineral oil. *J Am Acad Dermatol* 2001; 45:S222–S224.
6. Georgieva J, Assaf C, Steinhoff M et al. Bodybuilder oleoma. *Br J Dermatol* 2003; 149(6):1289–1290.
7. Requena L, Requena C, Christensen L et al. Adverse reactions to injectable soft tissue fillers. *J Am Acad Dermatol* 2011; 64:1–34.
8. Hexsel D, Hexsel C, Lyengar V. Liquid injectable silicone. History, mechanism of action, indications, technique and complication. *Semin Cutan Med Surg* 2003; 22:107–114.
9. Orentreich D. Liquid injectable silicone: Techniques for soft tissue augmentation. *Clin Plast Surg* 2000; 27:595–612.
10. Duffy D. Liquid silicone for soft tissue augmentation. *Dermatol Surg* 2005; 31:1530–1541.
11. Varga J, Schumacher R, Jimenez SA. Systemic sclerosis after augmentation mammoplasty with silicone implants. *Ann Intern Med* 1989; 111:377–387.
12. Fenske N, Vasey F. Silicone-associated connective-tissue disease. The debate rages. *Arch Dermatol* 1993; 129:97–98.
13. Granel B, Serratrice B, Gaudy C et al. Localized morphea after silicone gel filled breast implant. *Dermatology* 2001; 202:143–144.
14. Zimmermann US, Clerici ThJ. The histological aspects of fillers complications. *Semin Cutan Med Surg* 2004; 23:241–250.
15. Jons DH, Carruthers A, Orentreich D et al. Highly purified 1000 cs silicone oil for treatment of human immunodeficiency virus-associated facial lipoatrophy: An open pilot trial. *Dermatol Surg* 2004; 30:1279–1286.
16. Ersek R, Beisang A. Bioplastique: A new texture copolymer particle promises permanence in soft tissue augmentation. *Plast Reconstr Surg* 1991; 33:693–702.
17. Lemperle G, Romano J, Busso M. Soft tissue augmentation with Artecoll®: 10 year history, indications, techniques and complications. *Dermatol Surg* 2003; 29:573–587.
18. Haneke E. Polymethyl methacrylate microspheres in collagen. *Semin Cutan Med Surg* 2004; 23:227–232.
19. Alcalay J, Alcalay R, Gat A et al. Late-onset granulomatous reaction to Artecoll. *Dermatol Surg* 2003; 29:859–862.
20. Kim K, Lee M, Choi J et al. Artecoll granuloma: A rare adverse reaction induced by microimplant in the treatment of neck wrinkles. *Dermatol Surg* 2004; 30:545–547.
21. Al Qattan M. Late Artecoll granuloma aggravated by pregnancy. *Ann Plast Surg* 2007; 58:592.
22. Andre P, Lowe N, Parc A et al. Adverse reactions to dermal fillers: A review of European experiences. *J Cosmet Laser Ther* 2005; 7:171–176.
23. Trevidic P. Polyacrylamide gel in cosmetic procedures: Experience with Aquamid. *Semin Cutan Med Surg* 2004; 23:233–235.
24. Liu H, Cheung W. Complications of polyacrylamide hydrogel (PAAG) injection in facial augmentation. *J Plast Reconstr Aesthet Surg* 2010; 63:e9–e12.
25. Lafarge Claoue B, Rabineau P. The polyalkylamide gel: Experience with bio-alcamid. *Semin Cutan Med Surg* 2004; 23:236–240.
26. Jones D, Carruthers A, Fitzgerald R et al. Late-appearing abscesses after injections of non absorbable hydrogel polymer for HIV associated facial lipoatrophy. *Dermatol Surg* 2007; 33:s193–s198.
27. Bjarnsholt T, Tolker-Nielsen T, Givskov M et al. Detection of bacteria by fluorescence in situ hybridization in culture-negative soft tissue filler lesions. *Dermatol Surg* 2009; 35(Suppl 2): 1620–1624.
28. Hassid VJ. Soft-tissue filler complications: The important role of biofilms. *Plast Reconstr Surg* 2010; 126(5):1801–1802.
29. Yoneda M, Suzuki N, Masuo Y et al. Effect of S-PRG eluate on biofilm formation and enzyme activity of oral bacteria. *Int J Dent* 2012; 2012:814–913.
30. Ionescu A, Wutscher E, Brambilla E et al. Influence of surface properties of resin-based composites on in vitro *Streptococcus mutans* biofilm development. *Eur J Oral Sci* 2012; 120(5):458–465.
31. Mole B. The use of GoreTex in aesthetic surgery of the face. *Plast Reconst Surg* 1992; 90:200–206.
32. Conrad K, Torgerson CS, Gillman GS. Applications of Gore-Tex implants in rhinoplasty reexamined after 17 years. *Arch Facial Plast Surg* 2008; 10(4):224–231.
33. Klein A. Implantation techniques for injectable collagen: Two-and-one-half years of personal clinical experience. *J Am Acad Dermatol* 1983; 9:224–228.
34. Castrow F, Krull E. Injectable collagen implant-updated. *J Am Acad Dermatol* 1983; 9:889–893.
35. Klein A, Risch D. Injectable collagen update. *J Dermatol Surg Oncol* 1984; 10:519–522.
36. Klein A. In favour of double testing. *J Dermatol Surg Oncol* 1989; 15:263.
37. Rapaport M. Granuloma annulare caused by injectable collagen. *Arch Dermatol* 1984; 120:837–838.
38. Hanke C, Hingley H, Jolivette D et al. Abscess formation and local necrosis after treatment with Zyderm or Zyplast collagen implant. *J Am Acad Dermatol* 1991; 25:319–326.
39. Rosemberg M, Reiclin M. Is there an association between injectable collagen and polymyositis/dermatomyositis? *Arthrit Rheum* 1994; 37:747–753.
40. Woodyard JG, Greenwell H, Hill M et al. The clinical effect of acellular dermal matrix on gingival thickness and root_coverage compared to coronally positioned flap alone. *J Periodontol* 2004; 75:44–56.
41. Hirsch RJ, Cohen JL. Soft tissue augmentation. *Cutis* 2006; 78(3):165–172.
42. Fagien S, Elson ML. Facial soft-tissue augmentation with allogeneic human tissue collagen matrix (Dermalogen and Dermaplant). *Clin Plast Surg* 2001; 28(1):63–81.
43. Burres S. Soft-tissue augmentation with Fascian. *Clin Plast Surg* 2001; 28(1):101–110.
44. Bauman L. CosmoDerm/CosmoPlast (human bioengineered collagen) for the aging face. *Facial Plast Surg* 2004; 20(2):125–128.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

45. Matarasso SL. Injectable collagens: Lost but not forgotten: A review of products, indications, and injection techniques. *Plast Reconstr Surg* 2007; 120(Suppl 6):17S–26S.
46. Apesos J, Muntzing MG 2nd. Autologen. *Clin Plast Surg* 2000; 27(4):507–513.
47. Sclafani AP, Romo T 3rd, Parker A et al. Autologous collagen dispersion (Autologen) as a dermal filler: Clinical observations and histologic findings. *Arch Facial Plast Surg* 2000; 2(1):48–52.
48. Alkek DS. Isolagen, a new autologous collagen. *Cosmet Dermatol* 1998; 11:30.
49. Broderick G, McIntyre J, Noury M et al. Dermal collagen matrices forventral hernia repair: Comparative analysis in a rat model. *Hernia* 2012; 16(3):333–343.
50. Hirsch EM, Dumanian GA. Discussion: AlloDerm and strattice in breast reconstruction: A comparison and techniques for optimizing outcomes. *Plast Reconstr Surg* 2012; 129(6):1234–1235.
51. Carruthers J, Carruthers A. Two-center Canadian report on the safety and effectiveness of Evolence Breeze. *J Drugs Dermatol* 2009; 8(9):830–834.
52. Narins RS, Brandt FS, Lorenc ZP et al. Twelve-month persistency of a novel ribose-cross-linked collagen dermal filler. *Dermatol Surg* 2008; 34(Suppl 1):S31–S39.
53. Andre P, Wechsler J, Revuz J. Facial lipoatrophy: Report of five cases after injection of synthetic filler into naso-labial folds. *J Cosmet Dermatol* 2002; 1:120–123.
54. Andre P. Facial lipo-atrophy secondary to a new synthetic filler device (Profill) treated by lipofilling. *J Cosmet Dermatol* 2002; 1:59–61.
55. Millikan L, Banks K, Purkait B et al. A five-year safety and efficacy evaluation with Fibrel in the correction of cutaneous scars following one or two treatments. *J Dermatol Surg Oncol* 1991; 17:223.
56. Moulonguet I, de Goursac C, Plantier F. Granulomatous reaction after injection of a new resorbable filler Novabel. *Am J Dermatopathol* 2011; 33(7):710–711.
57. Schuller-Petrović S, Pavlović MD, Schuller SS et al. Early granulomatous foreign body reactions to a novel alginate dermal filler: The system's failure? *J Eur Acad Dermatol Venereol* 2013; 27(1):121–123.
58. Burgess C, Quiroga R. Assessment of the safety and efficacy of poly-L-lactic acid for treatment of HIV-associated facial lipoatrophy. *J Am Acad Dermatol* 2005; 52:233–239.
59. Levy R, Redbord K, Hanke C. Treatment of HIV lipoatrophy and lipoatrophy of aging with poly-L-lactic acid: A 3-year follow-up study. *J Am Acad Dermatol* 2008; 59:923–933.
60. Vochelle D. The use of poly-L-lactic acid in the management of soft tissue augmentation: A five year experience. *Semin Cutan Med Surg* 2004; 23:223–226.
61. Moy R, Fincher E. Poly-L-lactic acid for the aesthetic correction of facial volume loss. *Aesthet Surg J* 2005; 25:647–648.
62. Lam S, Azizzadeh B, Graivier M. Injectable poly-L-lactic acid (Sculptra): Technical considerations in soft tissue contouring. *Plast Reconstr Surg* 2006; 118:s55–s63.
63. Vleggaar D. Soft tissue augmentation and the role of poly-L-lactic acid. *Plast Reconstr Surg* 2006; 118:s46–s54.
64. Goldan O, Garbov-nardini G, Regev E et al. Late-onset infections and granuloma formation after facial polylactic acid (new-fill) injections in women who are heavy smokers. *Plast Reconstr Surg* 2008; 121:336–338.
65. Fakhre GP, Perdikis G, Shaddix KK, Terkonda SP, Waldorf JC. An evaluation of calcium hydroxylapatite (Radiesse) for cosmetic nasolabial fold correction: A meta-analysis and patient centric outcomes study. *Ann Plast Surg* 2009; 63(5):486–489.
66. Lizzul PF, Narurkar VA. The role of calcium hydroxylapatite (Radiesse) in nonsurgical aesthetic rejuvenation. *J Drugs Dermatol* 2010; 9(5):446–450.
67. Bass LS, Smith S, Busso M et al. Calcium hydroxylapatite (Radiesse) for treatment of nasolabial folds: Long-term safety and efficacy results. *Aesthet Surg J* 2010; 30(2):235–238.
68. Gargasz SS, Carbone MC. Hand rejuvenation using Radiesse. *Plast Reconstr Surg* 2010; 125(6):259e–260e.
69. Buchanan AG, Holds JB, Vagefi MR et al. Anterior filler displacement following injection of calcium hydroxylapatite gel (Radiesse) for anophthalmic orbital volume augmentation. *Ophthal Plast Reconstr Surg* 2012; 28(5):335–337.
70. Daley T, Damm DD, Haden JA et al. Oral lesions associated with injected hydroxyapatite cosmetic filler. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012; 114(1):107–111.
71. Alam M, Havey J, Pace N et al. Large-particle calcium hydroxylapatite injection for correction of facial wrinkles and depressions. *J Am Acad Dermatol* 2011; 65(1):92–96.
72. Neuber F. Fetta transplantation. *Chir Kongr Verhandl Dtsch Gessellsch Chir* 1893; 22:66.
73. Bruning P. Contribution à l'étude des greffes adipeuses. *Bull Acad R Med Belgique* 1919; 28:66.
74. Peer LA. Loss of weight and volume in human fat grafts. *Plast Reconstr Surg* 1950; 5:217.
75. Fischer A, Fischer GM. Revised technique for cellulitis fat. *Bull Int Acad Cosmet Surg* 1977; 2:40.
76. Illouz YG. Body contouring by lipolysis: A 5-year experience with over 3000 cases. *Plast Reconstr Surg* 1983; 72(5):591–597.
77. Coleman SR, Saboeiro AP. Fat grafting to the breast revisited: Safety and efficacy. *Plast Reconstr Surg* 2007; 119(3):775–785; discussion 786–787.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Mesotherapy

Philippe Petit and Philippe Hamida-Pisal

HISTORY OF MESOTHERAPY

> … But the action on the tissues of mesodermal origin is so important that these treatments deserve the overall name MESOTHERAPY…

As a consequence, Dr. Michel Pistor (1925–2003) coined the term "mesotherapy" in an article entitled "Summary of the new properties of the local procaine in human pathology," published on June 4, 1958, in *Medical News*.

The Word "Mesotherapy"

Without mistake, the word "mesotherapy" is derived from the words "mesoderm" and "therapy."

Mesoderm or mesoblast, as opposed to endoderm and ectoderm, refers to the middle of the metazoan embryo at the time of gastrulation. They are cells derived from all or part of the internal organs, with the exception of the nervous system (derived from the ectoderm), and organs of the digestive system (derived from the endoderm). Therefore, in mammals, the mesoderm gives rise to the lungs, vertebrae, a part of the brain, skeletal blood vessels, blood cells, kidneys, bones, and muscles. It also limits serous cavities (or coelomic cavities), which are of a mesoblastic origin.

Dr. Pistor, as indicated in his early work, concludes that his new technique and its effects are particularly sensitive to the tissue that is of mesodermal origin, that is, supporting tissues, the bones, muscles, ligaments, tendons, and blood vessels.

Today, this term could be questioned because it is imperfect. All mesodermal tissues are not sensitive to mesotherapy, including the brain and blood cells. Also, some use the word "intradermotherapy." But continued use of the word mesotherapy today has led to it being widely recognized around the world.

Later, some saw this term in a therapeutic environment, between classical medicine and "soft" medicine. According to Dr. Pistor, mesotherapy was a green medicine, and indeed it is true that the simplicity and safety of mesotherapy allow such comparisons.

History of Mesotherapy

This discovery was not accidental, but as is always the case of great discoveries, it is the result of a long history that can be traced back to the roots of medicine.

Around 3000 BC, whether in China, Brazil, India, or Upper Egypt, doctors used to practice puncturing the mesoderm, which was preceded or followed by the application of an ointment [3].

Some even claim that Hippocrates healed a shepherd with shoulder pain using the thorns of a prickly pear leaf (cactus found in the Mediterranean Basin: Opuntia) and interposing a fig leaf (*Ficus carica*), whose sap possesses anti-inflammatory properties. This took place in 460 BC, and a fresco located on the island of Kos attests these words, but I have personally not yet had the opportunity to verify this claim.

The ancient history of acupuncture shows that the *prick* (*injection*) is part of our world heritage, and in 460 BC, a Chinese doctor (Huang Fu Mi) wrote a thesis on acupuncture and *moxa treatment*.

The history of mesotherapy can now be linked to the discovery of injectable technology in 1668, with the first intravenous injection in humans reportedly undertaken by JD Major.

In 1728, Fauchard, a French dentist, recommends gingival scarification around periodontal areas. In 1844, Rynd, an Irish physician, practiced the first subcutaneous injections, and Pravaz, a French orthopedist, made a breakthrough discovery developing his famous syringe with a hollow needle, followed by the first all-glass syringe introduced by Fergusson in 1869.

The twentieth century began with a very important discovery in 1905 the synthesis of novocaine by the German pharmacologist Einhorn; novocaine which was made famous by *loco-dolenti usage* by Lemaire (Belgian physician), was used to relieve rheumatic pains (1924), and especially Leriche, a French surgeon, used procaine via deep intradermal injections for the relief of joint diseases (1928). No doubt that Dr. Pistor's studies would have been influenced by these findings.

Furthermore, in 1908, Mantoux, a French physiologist, introduces intradermal tuberculin reaction, a technique that became widely adopted later in mesotherapy.

The story would not be complete without mentioning the thesis published in 1932 by Jarricot on the historical methods of local injections and the discovery of neural therapy by Huneke in 1938.

To complete this "pre-history" of mesotherapy, we must also mention the work of Dr. Aslan, a Romanian pharmacologist and gerontologist, who, in the 1950s–1970s, dealt with the Soviet *nomenclature* and wealthy Westerners in a luxurious fitness spa located on the edge of the Black Sea, using Gerovital, a mixture composed by Dr. Aslan, whose essential element was procaine.

Now we are in 1952, in Bray-et-Lu, a small town in Vexin, northwestern France, just 75 km from Paris, close to Normandy, where a young Michel Pistor settled.

It is worth mentioning again that Dr. Pistor was instilled with all this new culture of intradermal injection and the frequent use of procaine.

It is worth quoting a wonderful story of Dr. Pistor's (University Victor Segalen Bordeaux, Inter University Diploma

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

of Mesotherapy, January 28, 2000) about a Bray-et-Lu cobbler, a moment in history that confirmed the birth of mesotherapy:

> Now I'll tell you a story that reads somewhat as a short novel. I was confronted with some totally unexpected therapeutic results that have been the basis of mesotherapy.
>
> We are in 1952, I am a young doctor from the rural countryside of Bray-et-Lu, a small town in Vexin, 60 km from Paris.
>
> One evening, I received a visit from an elderly gentleman aged 84, a cobbler, called Jules Paré, not Ambroise but Jules, and he said, "Doctor, I have not come to see you for my deafness, which you are familiar with, but because I find it hard to breathe," As he spoke he was coughing. "I come to ask you if you can help me breathe better?" I perform a lung examination to discover wheezing in both lungs that are a principle characteristic of chronic bronchitis, and I did as a therapeutic thing that was very fashionable at the time, and sometimes gave spectacular, but short-term results. There was an intravenous injection of procaine such as prescribed at the time by Professor Leriche (who invented the surgical treatment of the sympathetic system), and he described the treatment of dyspnea with wheezing by slow intravenous injection of 1% procaine.
>
> I then gave the cobbler, Jules Pare, this injection, admitting that I was not sure of the result. "This will probably provide some relief but it may not last long." "What?" he asked me because he was deaf so I repeated the same and added, "Come and see me tomorrow morning to tell me how you spent the night." I then continued with my other consultations.
>
> The following morning I see this man who was normally slow, as people often are at this age. He returned completely excited saying, "Doctor, it happened, something extraordinary. I was not really relieved a short hour but the whole night. I did not sleep, but I heard my clock ringing every hour. But you know, I'm deaf, completely deaf and have been for many years and do not remember hearing my alarm clock ringing, and since you made *this injection,* I have heard my clock every fifteen minutes. Unfortunately, since this morning I cannot hear any more. So, please perform *the injection* again so I can hear once more."
>
> Unquestionably something amazing had happened.
>
> The enthusiasm of this man, usually biased, or far-fetched proved the existence of a phenomenon. I then repeated the same 100 ml intravenous injection of procaine. Today, this practice seems inconceivable and even dangerous, but at the time, it was commonly accepted while taking necessary precautions related to the risk of sudden hypertension with fainting. *In this instance, there were no further complications.*
>
> But I figured there was significant potential in the results because not only the old cobbler, but also his wife and his children had been telling everyone of their enthusiasm, and news began to spread rapidly that the doctor of *Bray-et-Lu* could cure deafness. This news spread like wildfire, and in the following days and weeks, dozens of deaf people from all the region came and say, "*Can you give me THE injection to cure my deafness*." Despite my explanation that the phenomenon was short-lived, all wanted *the injection*.
>
> So for a week, I repeated the same treatment to dozens of deaf people, but I was very disappointed with myself that there might be a phenomenon of stimulation of the hearing related to procaine. So after ten days, I decided to stop.
>
> And then one night, I thought that for auditory stimulation it was not logical to make an intravenous injection and that it would be more appropriate to administer a local injection around the ear subcutaneously, and that is when I started getting results. Results that surpassed anything I could anticipate.
>
> Some deaf patients who had tinnitus told me a few days after their treatment that their buzzing had significantly decreased or even, in some cases, disappeared. And then one day in came deaf man who had an ear discharge and eczema within the external auditory canal. After I injected procaine around the ear, the discharge and eczema decreased significantly.
>
> From this I concluded that a local condition could be improved by local treatment.
>
> A few days later I see a patient with eczema of the scalp. I injected the scalp with 1% of procaine and the next week the patient told me that although his eczema improved and also that he slept much better at night following treatment and no longer required sleeping pills.
>
> I was comforted with the idea that the local treatment could treat local pathology and it was unnecessary to prescribe a concoction of drugs if other means could be just as effective.
>
> Therefore, the treatment I referred to as "mesotherapy" was conceived in 1958 during my first publication.
>
> I then adapted this technique for the treatment of migraine, a condition that most often is related to a vascular problem, and I performed the localized injection of procaine around the area of pain based on the treatment of a deaf patient who said he was also relieved of headache.
>
> Since, mesotherapy was gradually developed from observations that were neither rigorous nor scientific but were clinical and generated real results like the old clinicians did who did not have the means available today.
>
> So I dealt with knee osteoarthritis using drugs such as Iodogluthional® which consisted of vitamin B1, sulphur and iodine, because non-steroidal anti-inflammatory drugs (NSAIDs) did not exist at that time. The results were outstanding especially around the knees, shoulders, and surface joints.
>
> Intradermal injections were common practice, including Algipan®, administered adjacent to the

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

local area of pain, which explains my technique, but this was limited to these domains.

So what has mesotherapy introduced that is new in this field? This discovery was significant, because beyond the rheumatic pain, mesotherapy can also relieve migraines and painful menstrual cramps. Within the field of sports medicine, mesotherapy can often replace the local infiltration of cortisone with just a few drops introduced intradermally. In rheumatology, mesotherapy often replaces large doses of NSAIDs, which are absorbed orally, providing relief and protecting the gastric mucosa, which is particularly sensitive in the elderly and those prone to degenerative pains.

But now I had to promote the benefits of mesotherapy that I had discovered.

Fortunately, a distinguished professor of medicine, Professor Ravinat, whose home was a country house in Bray-et-Lu. Professor Ravinat was head of the department of dermatology at the Beaujon hospital in Paris and a member of the editorial board of *Medical News*, a monthly medical journal well known in its time. Informed by the results of "small injections" made by the local doctor, he asked me to meet him to explain the process. Convinced of the merits of my technique and the results he had suggested a publication reported in the "Medical Press." It is in this article that the word "mesotherapy" appeared for the first time. This was based on my finding that the most important results were in diseases whose tissues were mesodermal in origin, i.e., muscles, bones, tendons, connective tissue, blood vessels, and the dermis.

At this time, two of my veterinary friends asked me if this technique could deliver the same effects in the treatment of animals. Good results were delivered when the practice was used on tendonitis in both horses and dogs.

These outcomes had two important consequences. The first was to prove to my detractors that the placebo effect was negated in the treatment of the horse and that the observed improvement was evidence of the effectiveness of mesotherapy. In addition, through the networking of veterinary colleagues I introduced mesotherapy into the Veterinary School of Maisons-Alfort, the most prestigious veterinary school in France. Thus, the first lesson and the first consultation on mesotherapy occurred not at a hospital or university but in the services of Professor Bordet, chair of general surgery at the Veterinary School of Maisons-Alfort.

Therefore, through time, mesotherapy become recognized for its results, and in 1976, the first international conference on mesotherapy was held in Bray-et-Lu, which brought together hundreds of French doctors, but also Swiss and Italian doctors. In the early 1980s, mesotherapy became a popular treatment in France and then the practice became highly regarded around the world.

Meanwhile, Dr. Lebel, a surgeon, was developing the famed needle that was 4 mm long and 4/10 in. in diameter, allowing the controlled injection of the intradermal.

In 1957, Bold and Gerard reported intradermal injections of Peridil Heparine® in patients with periarthritis of the shoulder.

"Mesotherapy," published in 1961 by Editions Maloine, is the work of Dr. Pistor who in 1964 founded the French Society of Mesotherapy (SFM), chaired by Dr. Lebel, and on April 21, 2015, of this year, the first general assembly was launched, which was attended by 16 doctors.

In 1966, Dr. Bicheron joined the SFM. For over 30 years, Dr. Bicheron led the training, in the CIDET medical centre *Rue de Miromesnil*, Paris, where hundreds of doctors came from around the world, and in 1979 I was introduced to mesotherapy.

Mesotherapy was introduced in the field of dentistry by Podguszer in 1967, and in the same year, Dr. Pistor invented the first circular, multiinjector, and in 1968, he published his paper entitled "Mesotherapy versatile technique" and presented it to the Academy of Medicine.

The first thesis on the topic in 1969 focused not on human but on veterinary medicine and it was supported by Richard Lecomte.

The following year saw the introduction of another teaching, from Dalloz Bourguignon, published in 1972, and this was the first thesis in human medicine and was supported by Delahaye. In the same year, mesotherapy began to advance in Italy (Bartoletti), Spain (Lopez-Barri), and then Switzerland.

Dr. Pistor published "Mesotherapy: A Therapeutic Challenge" in 1974.

In 1976, Dr. Dalloz Bourguignon inaugurated the first hospital consultation in the radiology department of Professor Azat Thierre at Necker Hospital.

The "international" congress also emerged: 1976 in Bray and Lu, 1979 in Chantilly, and 1982 in Rome.

The first electronic injection termed "the Pistormatic" was designed by Dr. Pistor and directed by his son-in-law, the engineer, Muy.

From the 1980s, the story fast-tracks and mesotherapy begins to experience a real growth in France. In 1984, with the creation of Circles of Study and Research in Mesotherapy (CERM), whose role was crucial for the dissemination of this technique. The first CERM was created in Alsace Lorraine (Michel Retzmanick) and the second CERM was created in Southwest France (Philippe PETIT). Sixteen CERMs were created, thus enabling decentralization of education and improved dissemination and communication of mesotherapy techniques and outcomes, aimed at both physicians and the general public.

In 1981, Italy published the first scientific study by Professor Pitzurra, demonstrating better dissemination of an injectable mixture intradermally versus intramuscularly.

This was the same year that Le Coz opened consultation conference on mesotherapy at the National Institute of Sport and Physical Education (INSEP) in Paris, and this discussion has played and continues to play an important role in the knowledge of mesotherapy in sport. This conference was created with the assistance of Dr. Demarais, medical director of INSEP.

Dr. Bicheron, in 1982, included mesotherapy under DUMENAT (University Diploma of Natural Medicines) at the Faculty of Paris XIII (Bobigny). This education will always be challenged by the majority of mesotherapists who do not want the label natural medicine, but instead contest that mesotherapy be an integral part of general medicine.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

In that same year, Ballesteros (Tours) created the concept of energy mesotherapy, which remained a marginal technique throughout mesotherapy, and Dr. Pistor found the International Society of Mesotherapy (SIM).

Dentists with Medioni in 1983 founded their society: the National Circle for the Study and Research Mesotherapy in Odonto-Stomatology (CNERMOS).

In 1984, the word "mesotherapy" made its first entry into the Larousse dictionary and the *Quid*. Paris hosted the *Fourth* and *Fifth International Congress of Mesotherapy* held in 1985 and 1988, respectively.

The year 1987 marked a major turning point in the history of mesotherapy: after an audit commissioned by the Ministry of Health on all medical practices, the French Academy of Medicine finally classified mesotherapy as a technical and integral part of general medicine.

In the same year, a diploma course in mesotherapy was introduced at the Marseille University by Dr. Mrejen, who developed the concept of spot systematized mesotherapy in 1975.

In 1991, Dr. Pistor, who succeeded Lebel, relinquished the chair of the SFM Le Coz and Petit became vice president. The *Sixth and Seventh International Congresses of Mesotherapy* were held in Brussels (Belgium) in 1992 and in Bordeaux in 1995, respectively.

In 1996, Dr. Lavignolle and Dr. Petit introduced a university diploma in mesotherapy at the University Victor Segalen Bordeaux II with the support of Dean Reiffers. This diploma was the first to have a comprehensive education of mesotherapy and was prepared with the collaboration of 10 university professors. This diploma became recognized as an interuniversity diploma.

In 1998, Le Coz relinquished the chair of the SFM to Dr. Petit and in the same year the *Eighth International Congress of Mesotherapy* took place in Sao Paulo (Brazil).

The following year, Dr. Petit developed the international course in mesotherapy at the University Victor Segalen Bordeaux II for overseas doctors and then he succeeded Dr. Pistor as president of the International Society of Mesotherapy.

In 2000, the *Ninth International Congress of Mesotherapy* was held in Paris.

The year 2001 was an important year for ANAES (certification body) as it recognized the use of mesotherapy in pain management and thus allowed the entry of the performance of mesotherapy in new medical nomenclature (CCAM).

In 2002, University of Bordeaux II, Marseille Mediterranean, and Paris VI created an interuniversity diploma of mesotherapy. The universities of Dijon, Clermont-Ferrand, and Lyon joined the first group. This concludes the effort of 50 years of work within the field of mesotherapy. Dr. Laurens succeeded Dr. Petit as president of SFM.

Before his death on August 3, 2003, Dr. Pistor has seen mesotherapy practised *urbi et orbi*. He now rests in the cemetery in Bray-et-Lu, where some 50 years earlier he had treated Jules Paré, a cobbler, in his early practice.

In October 2003, the *Tenth International Algiers* (*Algeria*) *Congress* was held.

The following year, the Council of the College of Physicians recognized mesotherapy as a valid technique. An interuniversity diploma was essential to be able to practice the technique. In France, doctors can now use "mesotherapy" on their plates and prescriptions and have a special section reserved for them in the phone book.

Therefore, we can conclude that mesotherapy is taught in the university, practiced in the hospital, and recognized by all the administrative, ministerial, and professional bodies. It has definitely become an integral part of the health-care system.

Alongside the French establishment, mesotherapy treatment is recognized in almost all countries and regions throughout the world. In 2006, as the president of the SIM, I visited more than 18 countries to educate and/or to participate in global, national, or regional conferences on the topic, including a number of countries where mesotherapy is particularly established (the United States, Brazil, Argentina, Algeria, Tunisia, Spain, Belgium, Russia, Kazakhstan, Korea, Japan, Thailand, and Australia).

However, this rapid development unfortunately resulted in the training of inappropriate practitioners who are not limited to the medical field. It is not uncommon to find in some countries the practice of mesotherapy undertaken by beauticians and even hairdressers. Therefore, greater regulation and control is necessary to ensure the safe and controlled application of this technique.

The second part of the twentieth century saw the installation of mesotherapy as a technique in medicine, in both the field of pain management and that of aesthetic medicine, combining the benefits of efficiency, safety, simplicity, and low cost.

INDICATIONS FOR MESOTHERAPY

Indications of mesotherapy are numerous, but that of principal importance is pain management, especially proprioceptive pain, mainly observed in the following diseases:

- *Rheumatology*: Arthritis especially, but also inflammatory pathology
- *Sports medicine*: Simple and complex tendonitis, muscle trauma injuries, ligament pathologies, and splints
- Physical medicine and neurology

Other diseases with proprioceptive pain:

- *Vascular disease*: Lympholymphatic insufficiency, venous and arterial ulcers, and migraines
- Digestive diseases that are essentially functional
- *Functional pathologies*: Anxiety or mild depression and sleeping disorders
- Dermatological diseases
- Chronic infectious diseases in accordance with very specific rules

Mesotherapy is often the first-line treatment, but can be complementary as well with sports medicine treatment.

In aesthetic medicine, the focus of this section, the results of mesotherapy are many, and outside the three essentials that we have developed, mesotherapy can prove to be effective in the treatment of stretch marks, small keloids, senile skin pigmentation, and small tissue ptosis and in reducing the appearance of localized excess fat deposits.

The three major indications are

1. The prevention and treatment of skin aging and wrinkles
2. The hydrolipodystrophies known more commonly as cellulite
3. Androgenic alopecia

Let us explore in more detail the importance of mesotherapy in these three major indications.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

PREVENTION AND TREATMENT OF SKIN AGING AND WRINKLES

Also called MesoLift or MesoGlow (USA).

Introduction

In recent years, the facials, the "antiaging medicine," have become extremely fashionable. The reasons are simple. Primarily, the techniques are easily accessible to any doctor; the products are deemed to be very effective with only moderate risk. Mesotherapy is no exception to this phenomenon.

Efficacy, safety, low cost, and lack of social restraint are the elements of these success factors.

The field of action of mesotherapy is the skin, but in this chapter, we will not discuss the embryological or histological basis, which is indispensable for knowledge of mesotherapy.

It is obvious that mesotherapy is not intended to slow the aging process but simply to act on certain components and thus reduce and slow the effects of aging through its results.

The Mesolift

Definition

The "mesolift" is a recent medical mesotherapy technique performed as part of aesthetic treatment of the facial area.

It is a progressive technique, being both gentle and without side effects. It produces quick results but transient effects, which is ideal for the target audience. Mesotherapy encompasses an approach that is both a prevention and a treatment.

What elements are essential for the proper practice of mesotherapy on the face for prevention and treatment of skin aging?

Equipment

Needles of 4 mm and 13 mm in length, 30 G (Figures 54.1 and 54.2)

Syringes of 3 or 5 mL capacity.

Techniques and Depths of Injection

Compliance with a specific protocol provides a good result. Mesotherapy has three phases using three technical depths (Figure 54.3):

- *The epidermal technique*: The intraepidermal (IED) layer
- *The papula*: The dermoepidermal junction
- *Intradermal technique* that can also be conducted with a cannula

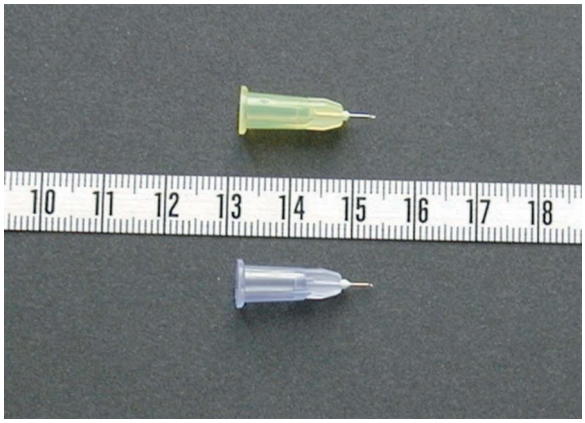


Figure 54.1 A 4 mm × 30 G needle.

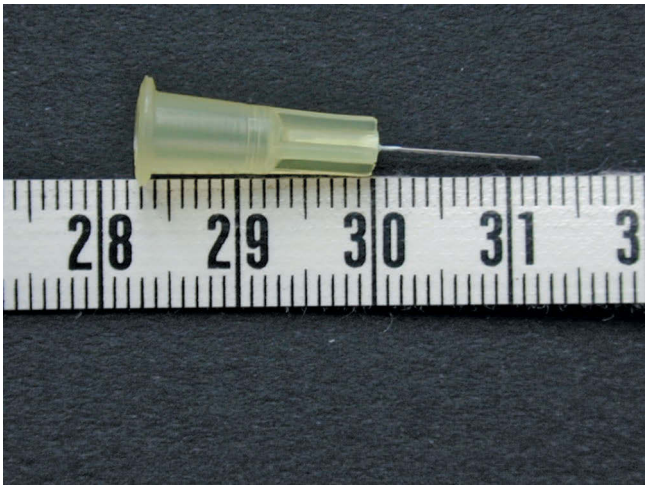


Figure 54.2 A 13 mm × 30 G needle.

Phase One: Epidermal Mesotherapy, IED 13 mm needle length, 30 G

Technique (Figure 54.4)
Needle used parallel to the skin
Bevel facing upward

The flexibility of the needle allows for support to the tip of the needle, which can reciprocate a discrete entry point and

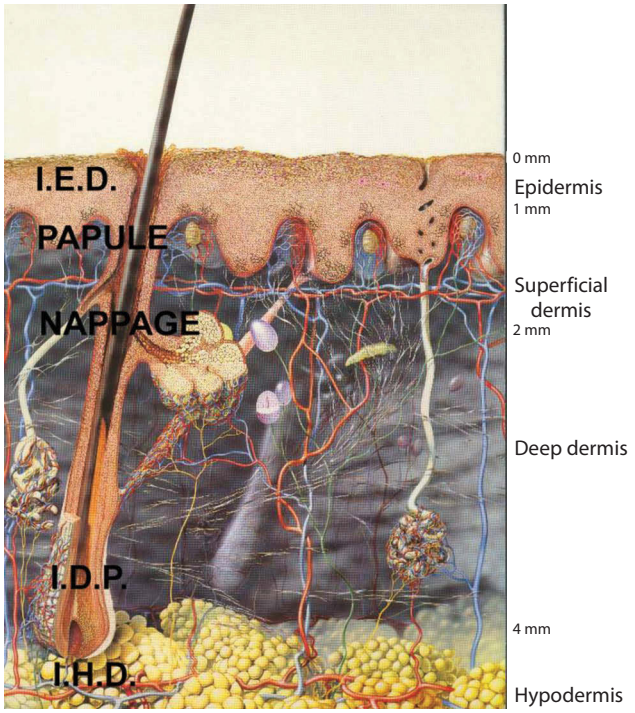


Figure 54.3 Layers of the skin: IED, epidermal layer; Papula, papula level; ID, intradermal layer; IHD, intrahypodermic level. (From Draelos Z, *Cosmetics and Dermatological Problems and Solutions*, Informa Healthcare, New York, 2011, p. 4.)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

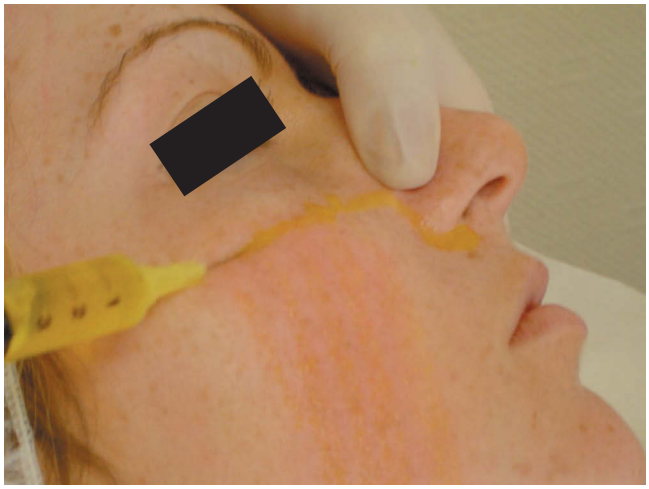


Figure 54.4 Epidermal technique.

Figure 54.6 Papula fine lines (neck).

become slightly beveled for admission of the drug mixture, done by exerting a constant and sustained pressure on the piston of the syringe throughout the technique.

This technique causes intense stimulation of the immune system and an important underlying microcirculation.

It is very effective for epidermal treatment on the face without scarring.

Phase Two: Papula Technique This technique involves separating the epidermis from the dermis by injecting a small amount of product, 0.1 mL (Figures 54.5 and 54.6).

Depth: Dermoepidermal junction

Needle: 13 mm in length, 30 G

Technique: The bevel directed upward is introduced parallel to the skin to reach the dermoepidermal junction, which is injected generally less than 1 mm in depth into the face.

This stimulates the immune components located on either side of the basal.

Injection into small wrinkles of the face and neck and the neck area with small papules replicates the effect, not unlike a pearl necklace.

Phase Three: The Intradermal Technique This technique, as its name indicates, is strictly intradermal (Figure 54.7).

Needle: 4 mm in length

Technique: This technique is intradermal only and similar to that of "filler": hyaluronic acid and nutrients.

The diffusion of the product by intradermal injection and due to the molecular weight is slow due to the technique. However, it allows travel of the product to the blood faster than the epidermal technique.

Figure 54.5 Papula (eye).

Figure 54.7 Intradermal mesotherapy (cheek).

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

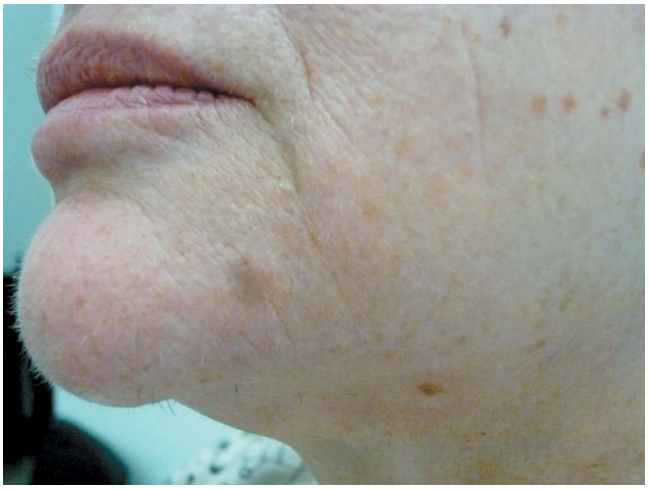


Figure 54.8 Areas to be treated and injection site.

Figure 54.9 Introduction of the cannula.

Meso-Canulla This technique is increasingly replacing the nappage technique because it is less traumatic on the skin as it involves fewer entry points.

This is introduced in areas that are rich in fine lines (Figure 54.8): usually around the eyes, chin, and cheeks, and the mixture is placed deep in the dermis by the fanning technique (Figures 54.8 and 54.9).

Compared to nappage, this technique has three important advantages:

- There is no loss of product.
- There is no bruising and pain is much less.
- The distribution in the deep dermis is smooth and regular, and the results are almost instantaneous.

Medicines

In aesthetic medicine, we must be especially vigilant in the exclusive use of products authorized by health authorities, as they are legal and pose no risk to patients.

Medicines with Microcirculation Action

Pentoxifylline

Torental Trental®
Peripheral vasodilator
It restores red blood cell deformability, facilitates their passage through small capillaries, and increases irrigation of ischemic tissue (smokers); it is an excellent addition to Papaverine®.

Papaverine

This is a vasodilator that acts on the expanding vessel wall.

Antioxidant

Silicon or Conjonctyl®

Conjonctyl is dispensed and CE approved.

Conjonctyl is preferred due to the close interaction between silicon and aging.

The pathology to be treated is silica deficit, which worsens with age as 80% of the silica decreases between the period of sexual maturity and the end of life, especially within the richest tissues (the skin, arteries, and thymus).

Vitamins

mainly used in a mixture as the NCTF (an aesthetic product from FILORGA Laboratories): This is the ideal product containing all the elements necessary for the nutrition of the dermis.

Non-Cross-Linked Hyaluronic Acid

Hyaluronic acid is a polysaccharide comprising of around 50,000 disaccharides linked by glycosidic liaison. It is an essential component of the extracellular matrix and is widespread in the body. It is mainly synthesized in the membrane of a number of cells, particularly fibroblasts and keratinocytes.

It has hydrophilic properties and decreases with age, resulting in decreased uptake of water in the tissues, and therefore resulting, over time, in a reduction in the quality of the skin tone.

The flexibility of the skin is closely related to the viscoelastic properties of the hyaluronic acid.

Renewal and cell migration are facilitated by its action on cell receptors and its rheological properties.

It is only used in mesotherapy in its non-cross-linked form; therefore, we do not use its filling properties in this instance.

We usually use the NCTF HA, which combines both vitamin and nutrient intake, general actions of non-cross-linked hyaluronic acid.

Indications

Stimulation of cell growth
Active improvement of the quality of the dermis
Cell protection
Improvement of the tonicity of the skin

Composition

Highly concentrated hyaluronic acid + poly-revitalizing solution

- Non-cross-linked hyaluronic acid
- 13 vitamins

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

- 6 minerals
- 5 nucleic acid
- 2 antioxidants
- 23 amino acids
- 6 coenzymes

Therefore, there are 55 + 1 ingredients in total.

Mixture and Techniques

Epidermal technique: Papula where there are wrinkles; crow's feet, cheeks, neck, and decolletage.

Nappage: On the face (the forehead, cheeks). Or, for an improved result, use a cannula that allows more even distribution of the mixture within the facial area and greatly reduces the likelihood of bruising.

For the three techniques, the mixture used is always

1. Non-cross-linked hyaluronic acid
2. Silica
3. Vasodilator

Typical example:

- NCTF HA 3 mL
- Conjonctyl 2.5 mL
- ± Vasodilator

Frequency of Session

The best results are achieved in five sessions, typically 2 weeks apart, repeated in one to two groups per annum.

The Frequency Depends on the Regeneration Rate of Skin

The more evidence of skin damage, the longer it takes for skin to renew and achieve the desired results.

In the Case of a Combined Treatment

The combination of mesotherapy with other treatments provides an opportunity for the best possible result as opposed to a stand-alone treatment.

It is possible to alternate or combine mesotherapy with a chemical peel, laser treatments, botulinum toxin, and/or dermal fillers to maximize the result.

Results

In Figures 54.10 and 54.11, the main lines of the cheeks achieve excellent results with mesotherapy. At this level, it is difficult to use fillers because often the grooves are too shallow and the elevation of the skin in this area would cause the appearance of lumps below the dermis, leading to an undesirable result.

In Figure 54.12, the tightening effect of mesotherapy improves the oval shape of the face.

In Figure 54.13, the fine lines on the cheeks and the wrinkles around the eyes have considerably reduced or have even disappeared.

In Figure 54.14, there is considerable improvement to the lower face at both the oval and the nasolabial fold (using only mesotherapy).

In Figure 54.15, also a dramatic improvement in the appearance of an elderly female patient has been achieved.

Figure 54.10 Fine lines before treatment.

Figure 54.11 Fine lines after treatment.

Conclusion

New protocols in the use of mesotherapy for facial treatment have produced varied results.

The aim of the first syringe is always to improve microcirculation. The epidermal injection treats the skin from the epidermis, going through the dermoepidermal junction to diffuse more deeply within the dermis.

The contents of the second syringe are always injected between 2 and 3 mm depth nappage or cannula.

Intrahypodermic injection is targeted by the third syringe to act toward the hypodermis, adipocytes, and lipolysis.

Mesotherapy plays an important role in the management, prevention, and treatment of skin aging.

Mesotherapy is an effective treatment, and it now has cemented its place in the overall therapeutic strategy, which

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 54.12 Oval face (a) before and (b) after treatment.

(a) (b)

Figure 54.13 Fine lines around the eyes (a) before and (b) after treatment.

(a) (b)

Figure 54.14 Oval and nasolabial fold (a) before and (b) after treatment.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 54.15 Elderly person (75 years) (a) before and (b) after treatment of 10 sessions.

includes all the treatments available at our disposal: peels, fillers, lasers, and botulinum toxin, among others.

The practice of mesotherapy will soon be 60 years old; therefore, it is still a relatively new treatment and its full benefits have yet to be fully realized.

Increase in size of adipocytes and water retention within the tissue are the major causes for the increase in the size of the hypoderm. This is due to poor venolymphatic flow and hormonal imbalance.

LIPODYSTROPHY OR CELLULITE

Cellulite! What woman in the world is not familiar with this word? Before exploring this further, it is essential to understand what we mean by the term cellulite.

Cellulite or superficial lipodystrophy is a cluster of hypodermic fat. Its scientific name is PEFS for edematofibrosclerotic panniculopathy, corresponding to different states of advancement of cellulite.

It is related to "estrogen–progesterone" acting on capillary permeability.

The greater the excess fat stored as triglycerides, the greater the swelling of adipocytes, which fill with fat, and they can grow up to 50 times compared to the original volume.

The term cellulite is incorrect because its literal translation means "inflammation of the cells," but as the terminology is now widely established around the globe, it is here to stay.

Three phenomena characterize cellulite: adiposity, water retention, and fibrosis. It is on this basis that we choose the appropriate mesotherapy treatment.

Physiopathology

We must distinguish three different entities.

Cellulite is an increase in the number and volume of adipocytes. Cellulite accumulates in the superficial hypoderm.

The fat overload sits deep within the hypodermis and the subcutaneous tissue. These are steatomeries. A steatomery is a deep lipodystrophy that characterizes obesity.

Since the early 1980s, researchers and physicians jointly agree on the multifactorial origin and pathophysiological mechanisms of cellulite:

- Hypertrophy of fat lobes of the hypodermis slows down the microcirculatory function.
- Dilated capillaries cause interstitial fluid infiltration.
- A slowdown in the lymphatic circulation prevents the removal of tissue edema.
- The fatty lobes are grouped into nodules encapsulated in a fibrous shell causing a pronounced disturbance of the adipocyte metabolisms.
- The connective tissue between the fat lobes thickens, hardens, and shrinks, resulting in a dimpled appearance of the skin (orange peel effect), accompanied by disruption of tissue metabolism and circulatory exchanges.

Classification

Cellulite dates back to the work of Lageze and Allen in the early twentieth century.

In 1978, Nurnberger and Muller proposed a classification based on the appearance of the skin. They demonstrated through biopsies particular organization of cellulite adipose lobules. In females, the adipose tissue is contained in chamber-like structures that favor its expansion into the dermis. Conversely, men have a network of criss-crossing, connective tissue architecture, forming smaller polygonal units that allow subcutaneous fat deposits to expand laterally and internally but with little protrusion into the dermis. This explains the orange peel effect in women.

Stage 0: Smooth appearance of the skin when prone, standing, and pinched
Stage 1: Smooth appearance of the skin, but when standing and lying, orange skin effect is evident
Stage 2: Smooth appearance of the skin when lying but padded when standing
Stage 3: Padded appearance in all positions

In 1979, Curri and Merlen were the first to explain and prove the physiopathology of cellulite using video capillaroscopy, allowing direct observation of the blood flow between the adipocytes, highlighting the essential role of microcirculatory failure.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

They proposed a classification split into four phases:

1. *Phase 1*: Decreased loss of mucopolysaccharides with increased permeability and plasma exudation, which leads to water retention.
2. *Phase 2*: Increased size of adipocytes; lipodystrophy phenomenon with microlipogranulomas
3. *Phase 3*: Formation of a capsule of connective fibers enclosing adipocytes
4. *Phase 4*: Formation of microcellulite nodules (30–50 adipocytes) surrounded by collagen fibers evolving into macronodules, causing microdiffuse sclerosis

In 2000, Blanchemaison, on repeating this classification, provides a new r-fat called cellulite: water retention, fibrosis, and adiposity. This classification is based on the development of an index of water retention (IWR) quantified by the use of high-frequency ultrasound.

Each of the three factors of cellulite, adiposity, water retention, and fibrosis can then be defined in terms of the physiopathology (Blanchemaison).

1. *Adipose cellulite*: Lipodystrophy
2. *Cellulite water retention*: Hydrolipodystrophy
3. *Fibrous cellulite*: Fibrolipodystrophy

In mesotherapy, the treatment is based on this triple notion.

Local Injection Treatment

The variety of treatments for cellulite indicates that there is no one treatment that can eradicate the effect. Treatments vary from

- Cosmetic treatments usually of a herbal origin
- Local surface drainage treatment type Cellu-M6, electrotherapy
- Lymphatic drainage
- Injection lipolysis, either by laser or other LEDs
- Mesotherapy
- Surgery

Let us focus on mesotherapy as a treatment.

Treatment with Mesotherapy

Before treating with mesotherapy, ask these seven questions:

1. What drugs?
2. How much?
3. What percentage?
4. Where to inject?
5. Which technique?
6. How deep?
7. How often?

One more question: What additional resources?

1. What drugs? This is obviously the most important question to answer and we will recall the previous notions of physiopathology. We distinguish
   a. The medicines for the circulation:
      i. *Pentoxifylline*: Trental peripheral vasodilator with arterial vasodilator effect demonstrated. Greater use of pentoxifylline causes a slight decrease in fibrinogen and changes in erythrocyte deformability.
      ii. *Papaverine*: is a musculotropic spasmolytic. In mesotherapy, it acts on microcirculation by promoting capillary vasodilation.
      iii. *Ethamsylate*: Dicynone® is used in functional manifestations of venolymphatic insufficiency and impaired capillary fragility. Mesotherapy using ethamsylate promotes drainage of the connective tissues and improves the state of the capillaries.
      iv. Rutin and melilot used as ethamsylate, important action of venolymphatic drainage
   b. Medicines of the connective tissue:
      i. *Organic silica*: Conjonctyl is a 1% solution of sodium monomethyltrisilanol orthohydroxybenzoate. The active ingredient of Conjonctyl is monomethyl trisilanol salicylate, a digestible and bioavailable organic silica. This rebuilds the inner lining of the blood vessels and improves blood circulation. Silica is used in mesotherapy for the reorganization of the architecture of the dermis. Conjonctyl boosts the synthesis of elastic tissue and thereby improves circulation.
      ii. *Synthetic salmon calcitonin*: Miacalcin® is generally widely used in mesotherapy. It has a stimulating effect on microcirculation within the cellulite. However, practitioners need to be aware of potential side effects if the dosage is too high or if the vascular passage is fast.
      iii. *Nutritional cocktail*: NCTF® 135 is a part of general nutrition made up of vitamins, minerals, amino acids, and nucleic acids.
      iv. *Magnesium*: Nutrient and antioxidant.
   c. Medicines for the lipolysis
      i. *Xanthine bases*: Theophylline® are inhibitors of phosphodiesterase and thus act on lipolysis.
      ii. *Caffeine*: The use of caffeine is generally frowned upon because the effective dose and the toxic dose are very similar and dependent on the individual.
2. How much and what percentage?
   a. In most cases, the same quantity when the rules of pharmacology permit. Calcitonin is used with caution (50 I.U. in general) so as to not cause side effects associated with the molecule.
   b. The amount must be carefully calculated according to the surface area to be treated, usually 10 mL.
3. Where to inject?
   a. In relation to cellulite areas, the stomach, upper thighs, inner areas of the upper thighs, inner knees, or buttocks
4. What technique and how deep?
   a. The injection is always intradermal and hypodermal, i.e., between 3 and 6 mm.
   b. The intradermal technique (see the section "The Mesolift") is most often used. In case of severe pain at the point of injection, "point by point" technique may be an alternative.
   c. The use of an electron injector (mesogun) aids the technique.
5. How often?
   a. Weekly for 10–12 weeks. The results are slow but they are long-lasting. Mesotherapy is not only a therapeutic treatment but also a preventative technique.
6. And, of course, do not hesitate to involve other means of mesotherapy because, as we said earlier, there is no effective technique used in isolation. 1 + 1 in medicine often equals three or four which will help to achieve the best results.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Therapeutic Protocols

First, it is important to remember that any treatment of cellulite must include a treatment for general circulation, which needs to be performed every 2 weeks.

On some occasions, it is also useful to treat stress because without an aggravating factor, it often prevents them from having a good result. It is now accepted that stress can be a cause of cellulite and can inhibit a good response to treatment.

- Adipose treatment
  - *Primary medicine*: Base xanthan, theophylline aminophylline® and Euphylline®
  - *Secondary medicines*: Vasodilator, Papaverine
  - *Silica*: Conjonctyl, magnesium
  - Mixture:
    - Lidocaine® 2 mL
    - Euphylline 2 mL
    - Papaverine 2 mL
    - Conjonctyl 2 mL
- Treatment for water retention
  - *Main medicine*: Ethamsylate (Dicynone)
  - *Secondary medicine*: Papaverine
  - Vitamin C, Conjonctyl, magnesium
  - Mixture:
    - Lidocaine 2 mL
    - Dicynone 2 mL
    - Papaverine 2 mL
    - Conjonctyl 1 mL
    - NCTF 135 1 mL
- Fibrosis treatment
  - *Main medicine*: Calcitonin
  - *Secondary medicine*: Vasodilator, Papaverine
  - Silica, vitamin C
  - Mixture:
    - Lidocaine 2 mL
    - Calcitonin® 50 U.I.
    - Papaverine 2 mL
    - Conjonctyl 1 mL
    - NCTF 135 1 mL

In this chapter, we do not address the treatment of deep lipodystrophy (steatomery). This is a particular entity very different from cellulite. The prime treatment is phosphatidylcholine, a drug used worldwide but has no official authorization in the marketplace. The use of mesodissolution is a good alternative.

Figures 54.16 through 54.19 show patients before and after treatment.

(a)

(b)

Figure 54.16 (a) Before and (b) after treatment.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

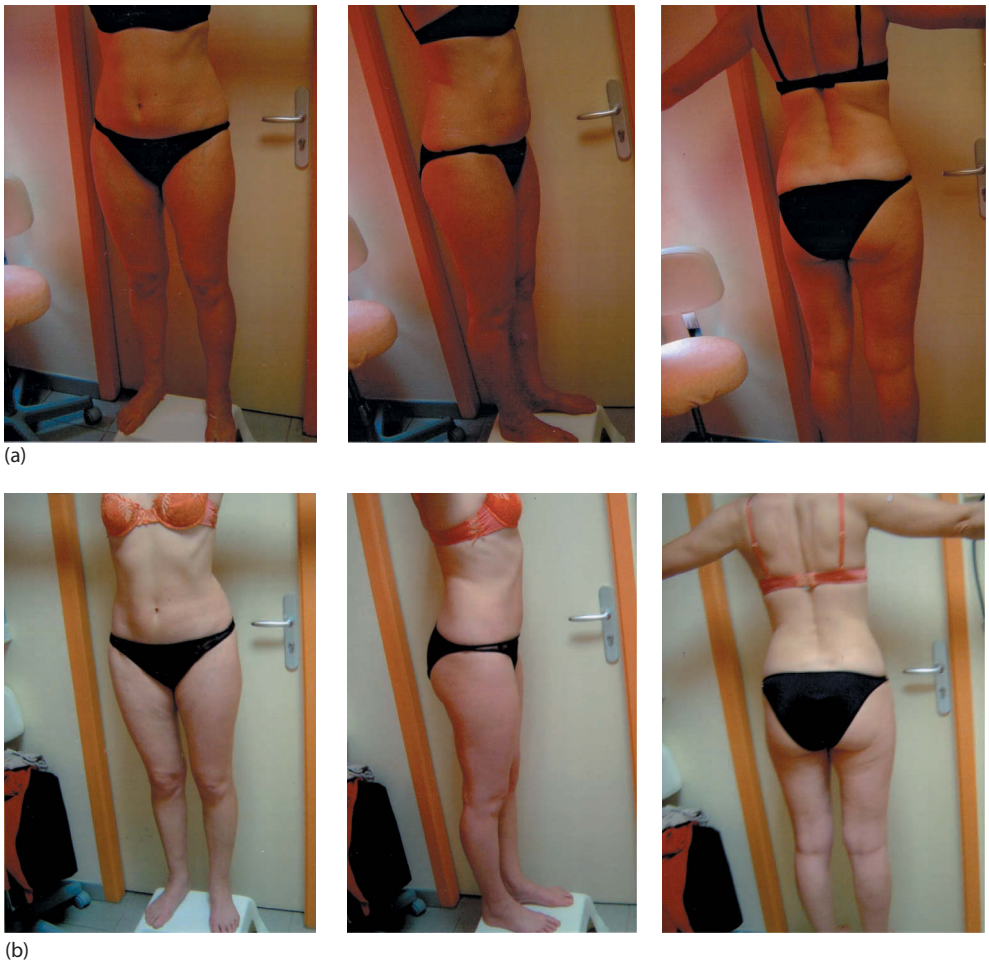


Figure 54.17 (a) Before and (b) after treatment.

Video 54.1 demonstrates treatment of the thigh. The syringe is held at an angle; the sites of injection are close together and regularly spaced; small punctures appear on the skin after 24 hours.

Video 54.2 demonstrates treatment using phosphatidylcholine. This consists of four phases: inspection, marking the zone for treatment, a precise grid inside the zone, and systematic injection using a 13 mm needle.

Conclusion

Cellulite is not a disease but a chronic dysfunction, and the reasons for its existence are multifactorial.

Mesotherapy is an effective treatment and has been used for well over 50 years. The results are favorable, but better results can be achieved in combination with other treatments. These are selected based on the specific case of cellulite in each patient and the doctor's knowledge and resources at their disposal. Mesotherapy requires precise technique and the doctor needs to know the procedure. All accidents referenced to date (including infection) can be partly due to negligence or malpractice on behalf of the practitioner and the methods they adopt.

Finally, we never insist enough on the lifestyle and diet of the patient, and regular physical activity coupled with a healthy, balanced diet will deliver optimal results every time.

ANDROGENIC ALOPECIA

Alopecia can be defined as partial or total hair loss.

Since ancient times, hair has always had a strong symbolic value associated with physical strength and religious, sexual, and seductive properties.

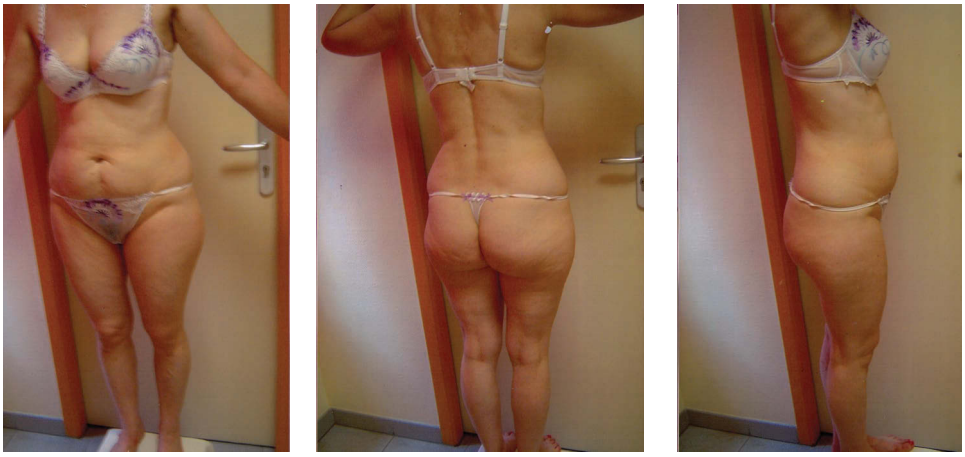
Each person has between 100,000 and 150,000 hair follicles with a coverage of around 200 hair follicles/cm^2.

Each hair can grow from 1 to 1.5 cm/month, and each hair has a life cycle between 2 and 7 years; this explains why we can become bald by 35 years of age.

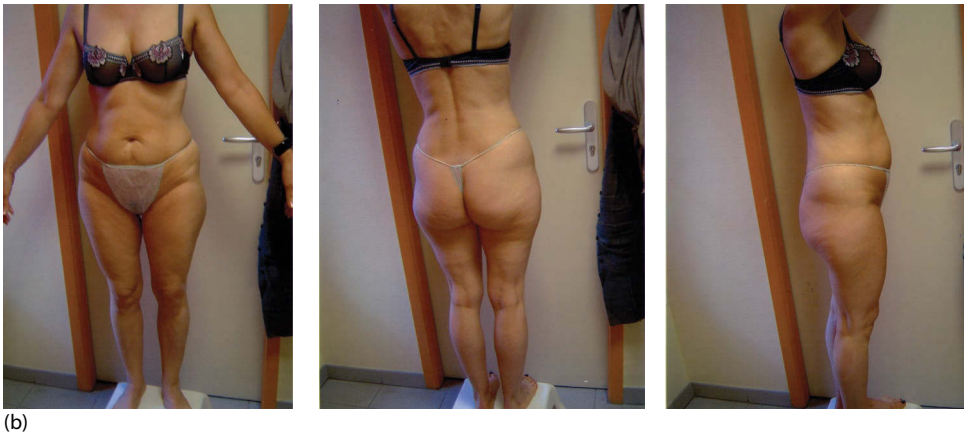
The number of hair cycles is thought to be between 15 and 20 in number and this is applicable to all of us.

The mechanism of androgenic alopecia is well known, besides the obvious genetic element passed on from each generation. The other main factors are sex and age. Alopecia

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a)



(b)

Figure 54.18 (a) Before and (b) after treatment.

most often affects young males between the ages of 16 and 18 years with potential for total alopecia by the age of 35 years.

So Why Mesotherapy?

We have already stated that the life of a human hair can vary from 2 to 7 years, but the number of cycles remains fairly constant, between 15 and 20.

- If a person has hair with a life-span of 7 years and the number of cycles is 15, then that person will never become bald: 15 × 7 = 105 years.
- However, if a person has hair with the life-span of just 2 years and the number of cycles is 15, the person may become bald by the time he/she reaches 30 years of age: 2 × 15 = 30.

Mesotherapy treatment aims to extend (albeit very slightly) the anagen phase of each hair, thereby delaying total alopecia, which we will discuss later.

Androgenic alopecia is diffuse, noninflammatory, and chronic.

Hair life cycle is divided into three phases:

1. *Anagen phase*: This is the growth phase and lasts 2–5 years.
2. *Catagen phase*: Involution lasts 2–3 weeks.
3. *Telogen phase*: Shedding lasts around 3 months.

The trichogramma or tensile test is a simple and yet reliable test that eliminates false falls to confirm the diagnosis, especially when used to assess the prognosis and monitor progress.

This is a test that we often use to remedy the case (Figures 54.20 and 54.21).

In males, the most common classification of androgenic alopecia is that accredited to Norwood and Hamilton and has seven stages. Mesotherapy is valid up to stage 4, i.e., when there are still active follicles.

In women, the classification of Ludwig is used and has three stages; mesotherapy is only effective in the first two stages.

Mesotherapy is an excellent technique that complements the treatment of androgenic alopecia.

It improves and accelerates local circulation within the scalp and causes better nourishment of hair bulbs.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a)

(b)

Figure 54.19 (a) Before and (b) after treatment.

J.F.D. 02/10/06

Trichogram

	Frontal %		Occipital %		Temporal %	
Taken hair	51		37		40	
Broken hair	2		0		0	
Hair with bulb	49		37		40	
Total anagens A	36	73	22	59	32	80
Other anagens	1		0		0	
Dystrophic An	3		3		1	
Telogens T	13	27	15	41	8	20
Ratio A/T	2.8		1.5		4.0	1

Figure 54.20 Trichogram before.

J.F.D. 12/09/07

Trichogram

	Frontal %		Occipital %		Temporal %	
Taken hair	44		42		49	
Broken hair	3		1		0	
Hair with bulb	41		41		49	
Total anagens A	34	82	32	78	41	84
Other anagens	0		0		0	
Dystrophic An.	2		1		0	
Telogens T	7	18	9	22	8	16
Ratio A/T	4.8		3.6		5.1	1

Figure 54.21 Trichogram after 1 year.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Obviously, the results depend on the factors mentioned earlier, the evolutionary stage, sex, and age of each patient.

Material

- 5 mL syringe
- Needle 4 mm

Medicines

The medicines used aim to improve local microcirculation and make a nutritional contribution to slow down the development process within the follicles.

- *Vasodilators*: In each country, there is at least one vasodilator referenced:
  - Buflomedil
  - Pentoxifylline
  - Papaverine
- *Specific vitamins for the hair*:
  - Vitamin H or Biotin: Facilitates healthy growth of hair and can prevent hair loss.
  - Vitamin B5 or bepanthene: This is a metabolic precursor of coenzyme A and is necessary for the metabolism of carbohydrates, lipids, and proteins. This is a typical treatment for androgenic alopecia.
- *Organic silica*: It participates in the formation of collagen fiber, providing mobility and elasticity. It is well known that silica is a bridge element of the four constituent macromolecules of the connective tissues of the skin. It is therefore a particularly important element of the three-dimensional spatial structure of the skin, which provides its mechanical properties. Over time, silica volume slowly decreases by around 1% per annum.
- *Procaine*: This is used as a diluent as well as a vasodilator. If this is not available, we can use lidocaine, but this does not possess a vasodilatory effect.

For example, a concoction can include the following:

- 1 mL procaine
- 2 mL vasodilator
- Complex vitamin 2 mL
- 2 mL organic silica
- 1 mL procaine
- 2 mL vasodilator
- Biotin 2 mL
- 2 mL bepanthene
- 2 mL organic silica

This concoction was deemed to be our favorite.

Technique

- Known as superficial intradermal, this is called nappage (Figures 54.22 through 54.25).

Frequency

- Every 2 weeks for the first 2 months.
- Then, every 2 months for the next 6 months.
- Every 2 months for a period of 4 months.
- And after a year, perform a trichogramma test to compare with the position at the start of treatment.
- If the results are satisfactory, continue then at a rate of one session every 3 or 4 months.

Figure 54.22 Areas to be treated.

Figure 54.23 Areas to be treated.

Results

- The fall is usually improved from around the third month.
- If the patient suffered from seborrhea alopecia, then this should show signs of improvement also.
- Regrowth is usually observed after the fourth month of treatment, and the younger the patient, the better the result.

And as with every treatment regime, it can be combined with other treatments, as mesotherapy is a complementary treatment.

Conclusion

- Mesotherapy is one of the better treatments for androgenic alopecia when combined with other techniques.
- It helps to slow down the process and the impact of androgenic events.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 54.24 Technique of nappage.

Figure 54.25 Technique of nappage.

- It is also an excellent accelerator promoting regrowth after postpartum (postnatal) effluvium.
- Finally, the information must be honest, realistic, and fair.

OTHER INDICATIONS OF MESOTHERAPY IN AESTHETIC DERMATOLOGY AND AESTHETIC MEDICINES

There are many other indications in dermatology and aesthetic medicine, sometimes unbelievable!

We generally refer to the most common.

Acne is not a good indication of mesotherapy as local treatments are simpler and more effective.

Non-androgenic alopecia: Psychogenic alopecia treatment varies in its success.

Hypertrophic Scars and Keloids

- Good results are achieved when the lesion is limited. The treatment is often performed in two stages:
  - Dry injection directly into the scar or keloid
  - Injection of products with vascular and nutritional properties

Stretch Marks

- Very good indication when the stretch mark is recent and purple.
- Less effective after this stage.
- The same protocol as for keloid.
- Tissue destruction associated with stretch marks exists but is no longer visible.

Psoriasis

- Those who claim to achieve good results are fortunate.

Viral Warts

- It would be as effective as those who claim to have healing hands!

Vitiligo

- It is the same as for psoriasis.

CONCLUSION

In conclusion, it is clear that mesotherapy can deliver good results in a number of conditions. However, we must be mindful of being honest with the patient when proposing the results of treatments and not promise the impossible and raise their hopes for a cure. In general, this statement is correct for mesotherapy but should also be applied if all of aesthetic medicine.

VIDEOS

Video 54.1. Demonstration of mesotherapy treatment of cellulite of the thigh: http://goo.gl/FCZDjZ

Video 54.2. Demonstration of treatment using phosphatidylcholine: http://goo.gl/1aQ3Eh

REFERENCES

1. Pistor M. Personal discussions.
2. Pistor M. Exposé sommaire des propriétés nouvelles de la procaïne locale en pathologie humaine. *Presse Médicale* 1958; 66(44):999–1000.
3. Pascal H. History of mesotherapy, PhD, Faculty of Medicine of Strasbourg, Louis Pasteur University, Strasbourg, France, 1994, p. 189.
4. Petit P. *Cours de Mésothérapie*. Diplôme Inter Universitaire de Mésothérapie. Université Victor Ségalen, Bordeaux II, 2006–2007.
5. Draelos Z. *Cosmetics and Dermatological Problems and Solutions*. New York: Informa Healthcare, 2011, p. 4.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Hyaluronic acid: Science, indications, and results

Pierre André and Gürkan Kaya

In cosmetic dermatology, many different filling agents have been used (see Chapter 53). A lot of them gave poor results or severe complications until the appearance of injectable hyaluronic acid (HA), which is for the moment the safest filler and the only one that can be dissolved by a specific enzyme, which is particularly useful in the case of adverse events.

HA was discovered by Karl Meyer, a German biochemist immigrant in the United States, in the 1930s. He was working on the vitreous humor of bovine eyes (hyalos = vitreous) and discovered that a new aminoglycan is a disaccharide without sulfate group, whereas the other glycosaminoglycans, already discovered, were sulfated. HA is bound to specific proteins, which may still be present in the filler and cause allergic reactions. HA is a polysaccharide that is present in all tissue vertebrates; there is no species specificity. It is also present in nematodes and some bacteria. It is essentially present in the skin (>50% of total HA), the vitreous corpus, the synovial fluid, and the cartilage. The first HA, used as a filler, came from rooster's comb; now it comes from bacterial fermentation (streptococcus).

In the human body, HA lifetime is very short, around 24–48 hours, which is why the polysaccharide chains of HA must be cross-linked before being injected. The degree to which the molecules are cross-linked greatly affects the stability of the HA *in vitro* and *in vivo*. Moreover, HA is not only a filling agent, but it has also a lot of biological functions, which will be explained later.

Thanks to a large range of HAs, soft-tissue augmentation has evolved and affords us to obtain amazing results to rejuvenate the face [1,2] and the body.

In this chapter, the scientific aspects of HA are explored with different procedures of injections according to the indications. Side effects and complications are described in the next chapter on filler complications.

SCIENCE OF HA

HA is a high-molecular-weight nonsulfated glycosaminoglycan formed by repeating units of D-glucuronic acid and *N*-acetyl-D-glucosamine [3]. An average HA chain contains up to 10,000 disaccharide repeats with molecular weight ranging from 2×10^5 to 10^7 Da.

HA is synthesized by HA synthases (HASs) at the inner surface of the plasma membrane as long chains by adding sugar residues at the reducing end and then extruded to the extracellular space where it is bound by proteoglycans [4]. In vertebrates, three HASs have been characterized (HAS1, HAS2, and HAS3), which synthesize HA chains of different average length and function [5].

In the vertebrate body, there is around 15 g of HA, of which 5 g is turned over daily. The half-time ($t_{1/2}$) of HA in the circulation is around 2–5 minutes. In the skin, where half of the total body HA is found (epidermis 90 µg/g, dermis 440–520 µg/g), the $t_{1/2}$ is around 1–2 days. $t_{1/2}$ of exogenous HA is around 0.5–1 day. Local degradation is followed by degradation in the lymph nodes and liver [6].

The degradation of HA is a two-step process: (1) rapid degradation into medium-sized with diffusion out of the dermis (about ½ of the HA during the first day) and (2) slower degradation during the subsequent days (10%–20% after 5 days) [6]. Rapid breakdown is probably due to nonenzymatic factors such as oxygen-free radicals released by polymorphonuclear leukocytes and endothelial cells or induced by UV irradiation [7]. Slower breakdown is realized by fibroblast hyaluronidases or endocytosis mediated by CD44, the principal cell surface receptor of HA, localized on keratinocytes.

Hyaluronidases are endo-β-*N*-acetyl-hexosaminidases. At least two acid-active hyaluronidases, *Hyal1* and *Hyal2*, have been recognized; the identification of *Hyal3*, *Hyal4*, and *Hyal5* is based on homology. Hyal2 is the major tissue HA-degrading enzyme; it is believed to be a lysosomal enzyme, but is also found in the membrane. Hyal2 cleaves HA to 50 disaccharides (20 kDa); Hyal1 rapidly cleaves HA into small fragments (0.8 kDa) [7].

High-molecular-weight HA polymer (around 10^6 Da) has structural and mechanical functions such as filling, hydration, and viscoelasticity. However, HA fragments (HAFs) (>8×10^2 to <10^6 Da) are generated in case of stress and injury and implicated in cell signaling in different physiological processes such as cell renewal, cell activation, and angiogenesis. Small molecular weight HAFs (0.8–2.8 kDa) have been shown to have proinflammatory properties by activation of dendritic cells via TLR4 [8]. Intermediate-sized HAFs (>50 kDa) induce in vitro mouse keratinocyte proliferation [9], increase the number and size of filopodia in cultured human keratinocytes [10], and correct dermatoporosis, a chronic skin fragility syndrome characterized by epidermal and dermal HA deficiency [11], by activating keratinocyte CD44 platform, hyalurosome [9,12].

CONTRAINDICATIONS

Natural HA is nonallergenic and does not usually require a skin testing before injection.

However, as the final product may be mixed to other ingredients and be more or less cross-linked (usually after BBDE cross-linkage), there is always a risk of hypersensitivity. With new HAs mixed to lidocaine, questioning patients on a possible allergy is mandatory.

In the case of animal-derived HA, risk is higher (possibility of allergy to chicken proteins). Even if HA produced by bacterial fermentation may still contain some residues of bacterial

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

proteins, it is safer for allergic patients to avoid it due to possible occurrence of "Gram-positive bacterial proteins."

High-risk allergic patients should get a skin test. As all injection techniques, they must not be done in case of infection of the skin and must be used cautiously in patients taking medications interfering with coagulation.

Permanent implanted devices in the site where new HA injections are needed may be the cause of adverse events, and, in this case, the benefit–risk ratio has to be discussed.

No "human adjuvant disease" has been reported with HA injections, compared to collagen injections.

Pregnancy and lactation are not contraindications.

INDICATIONS

Looking young and feeling fit are considered the norm in all industrialized countries.

As the world's population is aging, aesthetic demands from patients are increasing.

Surgical techniques were the first ones considered in the past for rejuvenation, but now, thanks to all the new noninvasive techniques, demands from patients have evolved.

Although wrinkle filling remains one of the main indications, the restoration of volumes and contours [13,14] and the creation of a balanced, natural look must also be taken into account when treating the aging face today.

Hydrating the skin with the mesotherapy technique injecting non–cross-linked HAs enhances the structure of the superficial dermis and epidermis [15]. Moreover, biological effects of HA of different molecular weight (due to HA degradation) act on the structures and functions of the skin (see earlier text).

PRETREATMENT CONSIDERATIONS

Ask the patient what he/she wants as correction and explain to him/her what you can obtain according to the volume of injected HA and to the indication. Avoid patients with unrealistic expectations.

Overall, detect and eliminate dysmorphophobic patients.

After listening to the patient, examine him or her to propose the best procedure.

Explain the duration of the correction to the patient, knowing that HA is a biodegradable product and not a permanent product.

Explain to him or her that some swelling and bruising are always possible, depending on the injected volume and on the number of injections (all medications interfering with coagulation must be stopped if possible).

If a lip correction is being considered, the trauma to the skin may induce an outbreak of herpes in patients that are so predisposed. In this case, an antiherpes treatment must be done—acyclovir or valacyclovir—initiated on the day of procedure.

Inform patients of any adverse events, and, in some countries, a signed informed consent is mandatory.

As HA is the injected product, tell patients that in case of overcorrection or very rare granulomatous reaction, it is always possible to dissolve the product with hyaluronidase, which is the specific degradation enzyme of HA (see later text).

At last, taking pictures before the injections is useful in case of conflict with the patient.

ART OF INJECTIONS

How to Minimize the Pain?

Injecting the face is usually not really painful, except for the lips.

The pain depends on the diameter of the needle or of the cannula, the speed of injection, the technique of injection (serial puncture and threading technique), the operator, the site of injection, and the product itself, which is more or less viscous and may change the tissue pressure.

Overall, the pain is variable according to the patient's sensibility!

Avoiding patients' suffering is important; otherwise, he/she will be unlikely to return for additional treatments.

The lips are more heavily innervated, and injecting into this area is very painful. The best anesthesia is a nerve block (infraorbital nerve and dental nerve). It can be performed either by intraoral injection or through the skin (see Chapter 24). Several anesthetic agents may be used; some act faster than others and some are mixed with epinephrine. The most commonly used agent is 1% lidocaine mixed with epinephrine (1:100,000).

In the other areas of the face, a topical anesthesia may be proposed to feared patients. Prepared products such as Emla® cream must be applied 1 or 2 hours before injections.

Finally, remember that the best anesthesia is talk anesthesia! The patients must trust you.

How to Inject?

First of all, do not forget to clean the skin and to apply an antiseptic solution.

The choice of the needle is important and will depend on the viscosity of the HA and the site where you want to place the product. For treating fine lines, small diameter needles are suitable (30 or 32 G); for deep lines or for volumizing, it is usual to use thicker HAs through a bigger diameter needle (27 or 24 G). The right length of the needle enables us to decrease the number of entry points (which is less unpleasant and creates less bruise).

In some areas and particularly for remodeling the face, the use of a flexible cannula with a suitable length may be a great choice [16]. Most commonly, a 27 G cannula with an "ultra thin wall" is used. These cannulas slide into the cutaneous tissues, and as the tip is blunt, it hurts neither the vessels nor the nerves.

After the needle choice is made, several injection techniques may be used: serial puncture, linear threading, fanning, and bolus technique. Best injectors often combine different techniques according to their own expertise. In all cases, check that you are not injecting into a vessel; the worst complication is blindness, which is never reversible [17].

Recently, electric injectors (Artiste®, Nordson, Westlake, OH; Anteis Injection System®, Anteis, Geneva, Switzerland; JuvaPen®, Juva, Geneva, Switzerland) have been launched into the market. It enables us to inject HAs with different speed and without effort (it is useful if you use high-viscosity HAs).

After the completion of the procedure, the pressure on the entry point is important to avoid bleeding and bruising. A light massage of the treated areas is useful to avoid lumpiness, and application of a frozen gel pack may be quite helpful to avoid swelling.

Usually, there is no pain, but postoperative analgesia may consist of acetaminophen or paracetamol. Tell the patients that aspirin may increase ecchymosis.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Why Filling the Face?

Although wrinkle filling remains one of the main indications, the restoration of volumes and contours and the creation of a balanced, natural look must also be taken into account when treating the aging face today. Thanks to HA, which is at the moment the "gold standard" of fillers, a lot of new techniques of correction may be proposed to the patients [1].

SOME CONSIDERATIONS ON SPECIFIC AREAS

Forehead

Horizontal lines may be filled by a thin HA, but anyway, the best treatment is botulinum toxin injections.

Glabellar Area

A deep crease may be corrected by HA injection, but the best result will be obtained in combination with botulinum toxin. HA injections in the best scenario will be performed 1–2 weeks after botulinum toxin injections (Figure 55.1).

This area is risky; if the injection is too deep, there is a risk of intravascular injection, or if it is too "thick," there is a risk of vascular compression. As with other filling agents, necrosis has been described [18], and even in rare cases, blindness has been reported. Injections must be done slowly, and in case of blanching, it is safer to stop. Not too viscous HAs are safer.

Eyebrows

While aging, the shape of the eyebrows changes and it falls (due to the decrease of fat tissue). Reshaping them is possible with HA, giving a more pleasant look (Figure 55.2).

As there are a lot of vessels and nerves, it is safer to use a flexible cannula with a blunt tip and a suitable length. An intermediate or a high-viscosity HA is suitable. Procedure is best done under local anesthesia (supratrochlear/supraorbital nerve block). Massage is important to well place the product.

Crow's Feet

Dynamic rhytides of the orbicularis are best treated by botulinum toxin (Botox® 15 U, Xeomin® 15 U, Dysport® 45 U), but sometimes HA injections in combination may improve the rest lines. A very thin HA is suitable.

Temples

With aging, the temples become hollow [19]; a fanning technique of injection with an entry point in the scalp and the use of a cannula may be performed, but a bolus technique done with a needle and a perpendicular injection to the skin is easier and gives, in our hands, the best results (Valsalva's maneuver is useful to visualize temporal vessels and to avoid them during the injection). With the bolus technique, the HA must be placed just above the periosteum (the needle must be long enough) and a light massage may be useful. A high-viscosity HA is usually used.

Sunken Eyes

This is the most risky area (protect the globe) and great expertise is needed before injecting it.

A good knowledge of the anatomy is fundamental.

Circles of the lower eyelids and deep orbital rims of the upper eyelids may be corrected (Figure 55.3).

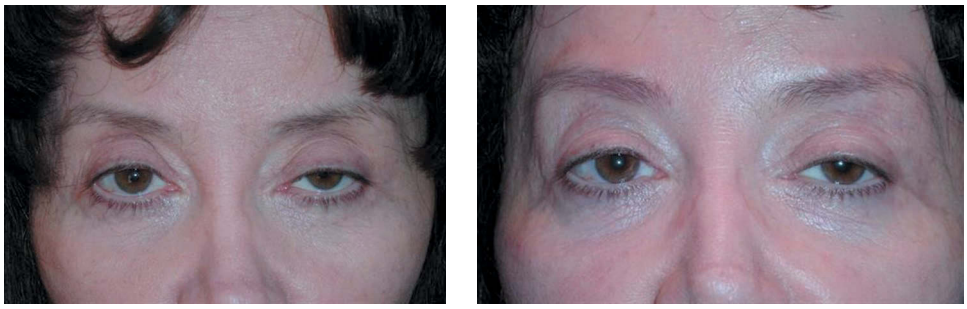
(a) (b)

Figure 55.1 Glabellar area: (a) before and (b) after botulinum toxin and HA.

(a) (b)

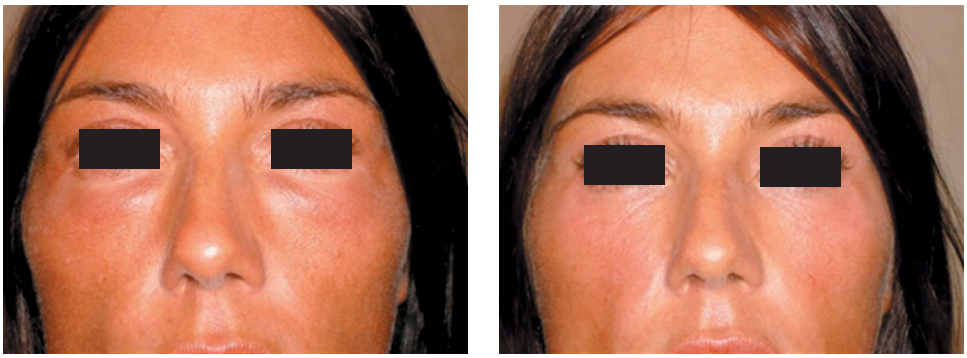
Figure 55.2 (a) Before and (b) after eyebrow remodeling.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b)

Figure 55.3 Periorbital area (a) before and (b) after HA.



(a) (b)

Figure 55.4 (a) Before and (b) after HA and hyaluronidase.

As the skin is very thin [20,21], only a thin HA must be used. The injections must be injected through a small diameter needle (30, 32 G) or a thin flexible cannula (27–30 G).

If HA is placed too superficially, a bluish aspect may result (Tyndall's effect). The HA must be placed deep into the submuscular plane just above the periosteum. The injected volume must be adapted to this area, knowing that it is better to undercorrect to avoid the appearance of "pseudo-bags." A gentle massage enables a homogeneous correction.

"Pseudobags" may appear months later, really unsightly, and can be dissolved by hyaluronidase (Figure 55.4).

Tear Trough

It is a not well-defined popular name. It is delineated from the inner part of the circle to the palpebrojugal groove or to the mediojugal groove. It gives a tired look and is a real part of aging. Correcting this area is very important to rejuvenate the face [20] (Figure 55.5).

When injecting it, assess the extent of the trough and use the right viscosity of HA. Injections must be deep into the hypodermis, the muscle, or just above the periosteum. In the lower part, it is better to use a high-viscosity HA, which has a greater longevity.

Zygomatic Arch

While aging, cheekbones become less well defined and the "V shape" of the young face turns into a "U shape." Injections must be deep into the subcutaneous plane to reposition the midface in a more youthful position. A high-viscosity HA is useful in the deep plane, and a thinner HA may be useful to correct the fine lines of the superficial dermis.

Nose

HA is easily injected into the nasal ridge to correct small defects (Figures 55.6 and 55.7). Choose an intermediate viscosity HA with lidocaine inside and use a fine needle (30 G) to avoid pain. The tip of the nose is not well vascularized, and there is a risk of necrosis (particularly after rhinoplasty) in case of injection of too much volume [18,22].

Botulinum toxin into the depressor septi nasi (Botox 5 U, Xeomin 5 U, Dysport 15 U) may be combined to raise the tip of the nose.

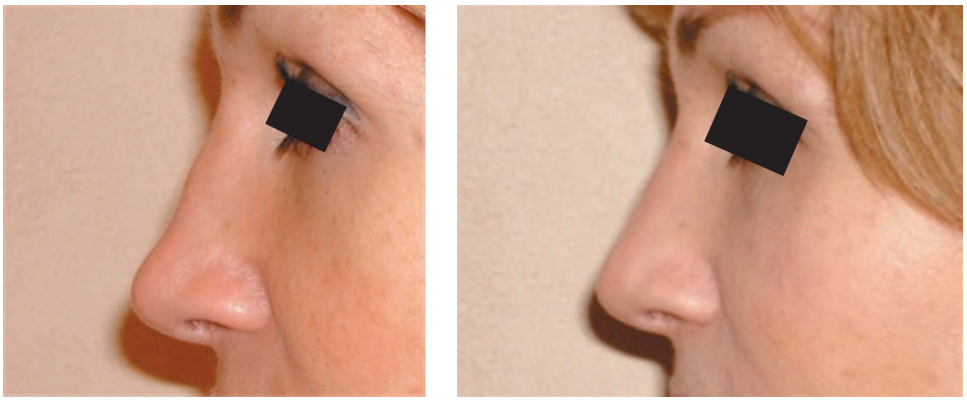
Lower Face

Nasolabial crease filling procedure is well known and has no particularity, but the risk of intravascular injection (angular artery) in the superior inner part is there if injections are too deep.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 55.5 Tear trough (a) before and (b) after treatment.



(a) (b)

Figure 55.6 Nose (a) before and (b) after treatment.

(a) (b)

Figure 55.7 Nose (a) before and (b) after treatment.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 55.8 Lip augmentation: (a) before injection and (b) after injection. (Courtesy of Ines Verner.)

The first study of HA (Restylane) versus collagen (Zyplast®) has demonstrated its efficacy and tolerability [23].

High-viscosity HAs are placed deeply, with, in some cases, a softer HA more superficially.

Filling *fine lines of the upper lip* is not the best technique for this area, but it may bring some improvement [24] for patients who do not want to undergo resurfacing. A very thin HA is suitable to avoid lumpiness.

Marionette lines are easily filled, but the best correction may be achieved in association with botulinum toxin injections into the depressor anguli oris muscle (Botox 5 U, Xeomin 5 U, Dysport 15 U), which raise the corners of the mouth. As often the corner of the mouth turns down, injections of a small quantity of HA in this area will improve it also.

The *lips augmentation* is also a classical indication and gives marvelous results [24] (Figure 55.8a and b). In this area, swelling and bruising are more frequent than elsewhere, and the procedure is painful without anesthesia. Nerve block anesthesia is the best for sensitive and feared patients, but the use of HA mixed with lidocaine is usually adequate.

Aesthetic proportions of the lips depend on race and fashion. In African types, volume of the upper and lower lips is generally equal; in Caucasian type, the volume of the lower lip is greater than the upper lip (ratio 2/3, 1/3). The vermilion border is also more pronounced in the African type.

To date, fashion is rather to the African type, and this is why most of the female patients want to have full in volume, sharply defined, and glossy lips. This is also why to inject lips requires a minimum artistic talent to avoid duckbill lips!

Several techniques may be performed according to what you want to enhance. Injections may be done into the body (red part) of the lips to increase the volume, whereas those designed to shape them are placed into the vermilion border (virtual space). Many aged female patients complain about the "bleeding" of lipstick; this can be corrected by vermilion border injection.

Some patients have a flat *philtrum*, which can be reshaped with HA injections.

Remodeling of *the chin* and particularly the lateral parts, which become hollow with aging, is of great importance. The only drawback is swelling if too much HA is injected. Many patients, who have a long nose, have also a retrogenia; it is easy to enhance the chin profile with a high-viscosity HA (Figure 55.9). Injection must be deep into the muscles or just above the periosteum.

Reshaping *the jawline* is also a new trend, sometimes in combination with botulinum toxin injections.

Low cross-linked HA or non–cross-linked glycerol added HA [21] may be injected into the superficial dermis just to change the texture and the reflectance of the skin.

Non–Cross-Linked HAs for Mesotherapy

As HA has great properties for hydrating the skin and others as biostimulator, it is used with the mesotherapy technique.

(a) (b)

Figure 55.9 The profile (a) before and (b) after treatment.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

In this indication, HA must be thin and non–cross-linked (sometimes glycerol added) to be very fluid and to avoid superficial nodular aspects. Longevity of the product is short, and several sessions at a short interval (2–4 weeks) must be performed if good results are to be expected.

Hand rejuvenation is another important field in cosmetic dermatology [25–27]. The surface of the hands with solar lentigines and actinic keratosis may be considerably improved by a variety of techniques such as lasers, intense pulsed light, and peels, but the osseous aspect due to the loss of fat tissue requires "liposculpture" or filler injections.

HA injections give good results (Figure 55.10). Anesthesia of the entry point at the proximal aspect of the hands is enough. A small diameter cannula of suitable length (18 G, 100 mm) is introduced into the skin and pushed between all interosseous spaces. Injections are slowly done backward, and, after asking the patients to make fists, a light massage forward obtains an even plane of correction.

HA FOR THE BODY: MACROLANE® (GALDERMA)

First launched by Q-Med Co (Sweden) for body's augmentation particularly the breast [28] (Figure 55.11), it is now reserved for the body, but not for the breast. Clinical studies after breast augmentations reported too many capsule formations [29] and too short longevity of the product for a good correction. Overall, the problem is with the analysis of mammograms and ultrasound after injections and the risk of poor detection of breast cancer. For these reasons, Galderma Company has preferred to withdraw the indication for breast augmentation [30].

Nowadays, it is used for buttocks augmentation (Figure 55.12) or for correction of defects after liposuction

Figure 55.10 Hand (a) before and (b) after remodeling.

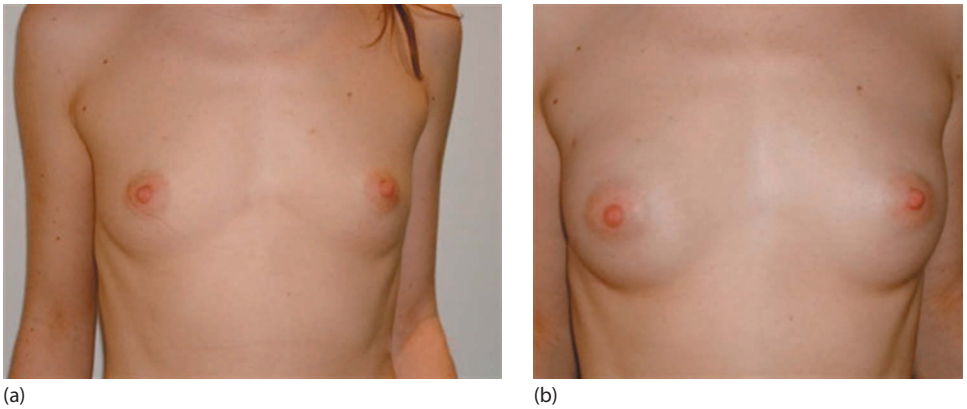
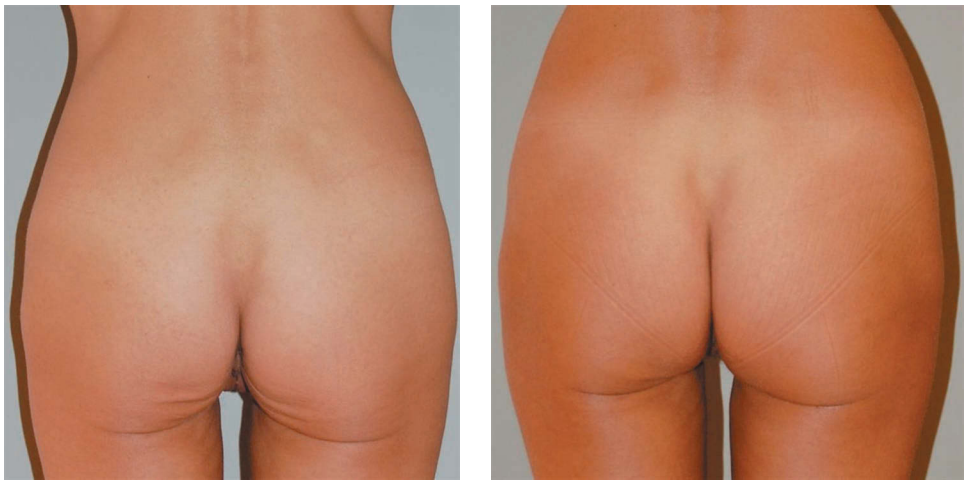


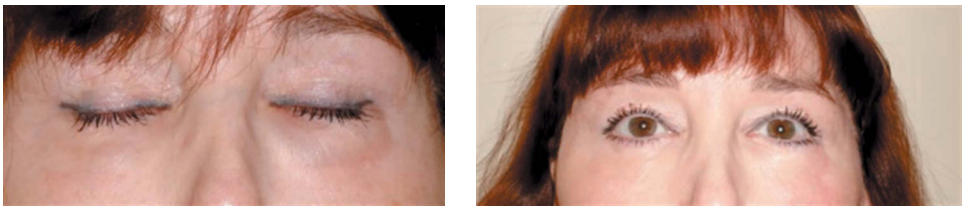
Figure 55.11 Breast (a) and (b) after augmentation (Macrolane).

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b)

Figure 55.12 Buttocks (a) before and (b) after augmentation. (Courtesy of Dr. O. Claude.)



(a) (b)

Figure 55.13 (a) Before and (b) after hyaluronidase treatment.

[31] or surgery. As Macrolane® is very viscous, it is injected through suitable disposable cannulas.

HYALURONIDASE

As mentioned earlier, it is a soluble protein, which hydrolyzes complex hyaluronan HA glycosaminoglycan polysaccharides by splitting the glucosaminidic bond between C1 of the glucosamine moiety and C4 of glucuronic acid. Most products available are bovine, ovine, or cobra venom derived, except the newest recombinant human hyaluronidase named Hylenex® (Halozyme, San Diego, CA). Animal-derived hyaluronidases (Wydase®, Vitrase®, Spreadase®, Amphadase®) are extremely well tolerated with only very rare allergic events reported. Hylenex has a purity up to 100-fold higher than currently used bovine preparations, and hypersensitivity risk is quasizero. As HA injections are emerging, adverse events as overcorrection will increase, hence, the importance for injectors to use it in case of necessity [22,32–34] (Figure 55.13).

Before testing/treating the patient, inquiry for allergic background and hypersensitivity to insect bites is suitable.

It is important to not inject hyaluronidase in an infected tissue, to avoid spreading of the infection.

Every company recommends to perform a skin test before use, unless in an emergent situation (e.g., impeding necrosis from an HA thrombus).

Skin testing is performed to detect an eventual immediate hypersensitivity reaction [35]. A prick test is recommended and reaction is read until 6 hours after. It is safer to keep the tested patient for 30 minutes in the office to detect any signs of Quincke's edema or anaphylactic reaction.

Hyaluronidase acts quickly, in a few hours in case of overcorrection. In case of HA granulomatous reaction, hyaluronidase may act more slowly and several injections may be necessary.

CONCLUSION

At present, there is a large range of HAs on the market, which enables cosmetic dermatologists to treat many defects. The addition of lidocaine in all new products enhances patient comfort, especially in the perioral area. A better cross-linkage and may be the addition of other molecules are likely to provide a longer longevity and a better tolerance.

Side effects may occur [17,22,36,37] either due to the technique of injection or to the product itself; this will be described in depth in the next chapter on filler complications.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

REFERENCES

1. Andre P. New trends in face rejuvenation by hyaluronic acid injections. *J Cosmet Dermatol* 2008; 7:251–258.
2. Andre P. Hyaluronic acid and its use as a "rejuvenation" agent in cosmetic dermatology. *Semin Cutan Med Surg* 2004; 23:218–222.
3. Laurent TC, Fraser JR. Hyaluronan. *FASEB J* 1992; 6:2397–2404.
4. Prehm, P. Hyaluronate is synthesized at plasma membranes. *Biochem J* 1984; 220:597–600.
5. Hascall V, Esko JD. Hyaluronan. In: Varki A, Cummings RD, Esko JD, et al., eds. *Essentials of Glycobiology*, 2nd ed. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, 2009, Chapter 15.
6. Tammi R, Agren UM, Tuhkanen AL et al. Hyaluronan metabolism in skin. *Prog Histochem Cytochem* 1994; 29(2):1–81.
7. Stern R, Kogan G, Jedrzejas MJ et al. The many ways to cleave hyaluronan. *Biotechnol Adv* 2007; 25:537–557.
8. Termeer C, Benedix F, Sleeman J et al. Oligosaccharides of hyaluronan activate dendritic cells via toll-like receptor 4. *J Exp Med* 2002; 195:99–111.
9. Kaya G, Tran C, Sorg O et al. Hyaluronate fragments reverse skin atrophy by a CD44-dependent mechanism. *PLoS Med* 2006; 3:e493.
10. Barnes L, Ino F, Jaunin F et al. Inhibition of putative hyalurosome platform in keratinocytes as a mechanism for corticosteroid-induced epidermal atrophy. *J Invest Dermatol* 2013; 133:1017–1026.
11. Kaya G, Saurat JH. Dermatoporosis: A chronic cutaneous insufficiency/fragility syndrome. Clinicopathological features, mechanisms, prevention and potential treatments. *Dermatology* 2007; 215:284–294.
12. Barnes L, Tran C, Sorg O et al. Synergistic effect of hyaluronate fragments in retinaldehyde-induced skin hyperplasia which is a CD44-dependent phenomenon. *PLOS ONE* 2010; 5:e14372.
13. Lowe NJ, Grover R. Injectable hyaluronic acid implant for malar and mental enhancement. *Dermatol Surg* 2006; 32:881–885.
14. Kestemont P, Cartier H, Trevidic P et al. Sustained efficacy and high patient satisfaction after cheek enhancement with a new hyaluronic acid dermal filler. *J Drugs Dermatol* 2012; 11(Suppl 1): 9–16.
15. Taieb M, Gay C, Sebban S et al. Hyaluronic acid plus mannitol treatment for improved skin hydration and elasticity. *J Cosmet Dermatol* 2012; 11:87–92.
16. Hertzog B, Andre P. The flexible needle, a safe and easy new technique to inject the face. *J Cosmet Dermatol* 2010; 9:251–252.
17. Kim YJ, Kim SS, Song WK, Lee SY, Yoon JS. Ocular ischemia with hypotony after injection of hyaluronic acid gel. *Ophthal Plast Reconstr Surg* 2011; 27:152–155.
18. Hirsch JR, Cohen JL, Carruthers JD. A Successful management of an unusual presentation of impending necrosis following a hyaluronic acid embolus and a proposed algorithm for management with hyaluronidase. *Dermatol Surg* 2007; 33:357–360.
19. Raspaldo H. Temporal rejuvenation with fillers: Global face sculpture approach. *Dermatol Surg* 2012; 38:261–265.
20. Rzany B, Cartier H, Kestemont P et al. Correction of tear troughs and periorbital lines with a range of customized hyaluronic acid fillers. *J Drugs Dermatol* 2012; 11(Suppl 1):27–34.
21. Succi IB, da Silva RT, Orofino-Costa R. Rejuvenation of periorbital area: Treatment with an injectable non animal non-cross-linked glycerol added hyaluronic acid preparation. *Dermatol Surg* 2012; 38:192–198.
22. Kim DW, Yoon ES, Ji YH et al. Vascular complications of hyaluronic acid fillers and the role of hyaluronidase in management. *J Plast Reconstr Aesthet Surg* 2011; 64:1590–1595.
23. Narins RS, Brandt F, Leyden J et al. A randomized, double blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. *Dermatol Surg* 2003; 29:588–595.
24. Cartier H, Trevidic P, Rzany B et al. Perioral rejuvenation with a range of customized hyaluronic acid fillers: Efficacy and safety over six months with a specific focus on the lips. *J Drugs Dermatol* 2012; 11(Suppl 1):17–26.
25. Fabi SG, Goldman MP. Hand rejuvenation: A review and our experience. *Dermatol Surg* 2012; 38:1112–1127.
26. Dallara JM. A prospective, non interventional study of the treatment of the aging hand with Juvéderm Ultra® 3 and Juvéderm® Hydrate. *Aesthetic Plast Surg* 2012 August; 36:949–954.
27. Leclère FM, Vögelin E, Mordon S et al. Non animal stabilized hyaluronic acid for tissue augmentation of the dorsal hands: A prospective study on 38 patients. *Aesthet Plast Surg* 2012; 36:1367–1375.
28. Goisis M, Yoshimura K, Heden P. Breast augmentation after Macrolane filler injections. *Aesthet Plast Surg* 2011; 35(4):684–686.
29. Becchere MP, Farace F, Dessena L et al. A case series study on complications after breast augmentation with Macrolane. *Aesthet Plast Surg* 2013; 37(2):332–335.
30. Chaput B, De Bonnecaze G, Chavoin JP et al. France prohibits the use of macrolane in aesthetic breast augmentation for reasons similar to criticisms of autologous fat grafting to the breast. *Aesthet Plast Surg* 2012; 36(4):1000–1001.
31. Cerqua S, Angelucci F. Macrolane (large particle biphasic hyaluronic acid) filler injection for correction of defect contours after liposuction. *J Cosmet Laser Ther* 2013; 15(4):228–230.
32. Lambros V. The use of hyaluronidase to reverse the effects of hyaluronic acid filler. *Plast Reconstr Surg* 2004; 114:114.
33. Brody HJ. Use of hyaluronidase in the treatment of granulomatous hyaluronic acid reactions or unwanted hyaluronic acid misplacement. *Dermatol Surg* 2005; 31:893–897.
34. Andre P, Levy P. Hyaluronidase offers an efficacious treatment for inaesthetic hyaluronic acid overcorrection. *J Cosmet Dermatol* 2007; 6:159–162.
35. Andre P, Flechet ML. Angioedema after ovine hyaluronidase injection for treating hyaluronic acid overcorrection. *J Cosmet Dermatol* 2008; 7(2):136–138.
36. Andre P. Evaluation of the safety of a non animal stabilized hyaluronic acid (NASHA—Q-med, Sweden) in European countries: A retrospective study from 1997 to 2001. *J Eur Acad Dermatol Venereol* 2004; 18:422–425.
37. Andre P, Lowe NJ, Parc A et al. Adverse reactions to dermal fillers: A review of European experiences. *J Cosmet Laser Ther* 2005; 7:171–176.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Complications of fillers

Eckart Haneke

Filler injections belong to the most frequently performed beautifying procedures in cosmetic medicine. Untoward side effects are a catastrophe for the affected person, and everything possible must be done to avoid them. This starts with a careful and thorough patient history concerning previous injections; allergies; immune reactions and diseases; drug treatments, particularly those with an immunomodulatory potential; and chronic infections, as well as a family history as to serious diseases, so-called collagenoses, immune defects, genetic disorders, etc. It is well known that some fillers are not well tolerated when injected next to another one.

Filler adverse effects can be classified according to their time course and due to user-dependent, filler, and host factors [1,2]. Technical errors concern too much or too little volume, incorrect depth of filler placement, wrong location, and inappropriate product choice [3].

The physician injecting the filler must, of course, be experienced to avoid gross mistakes concerning the site of injection, the volume, the speed, the depth, etc., as well as the postinjection treatment. The physician should be available after the injection and never dismiss a patient's concerns. The nature of complication is checked and can be classified into light and disappearing by itself, moderate and requiring treatment, or severe and necessitating immediate intervention. Treating a patient with empathy has avoided many law suits.

Concerning the fillers themselves, it is the substance on one hand and its chemistry, purity, homogeneity, particle size, shape, and roughness [4], electrical charge, ability to biointegrate, and to react with other substances that matter. It has also to be kept in mind that a filler result that is desirable at the age of 20 might look odd at age 50 or 60. Finally, the host and his or her immune system are of paramount importance. This can change during the life of a filler and have a great impact on its tolerability.

TIME COURSE OF FILLER EFFECTS

Fillers are divided into reversible (early or temporary, collagens and hyaluronic acid [HA], late or long term, HA with dextranomer beads, poly-L-lactic acid [PLL], and calcium hydroxylapatite), and irreversible (delayed or permanent ones: paraffin, silicon preparations, polymethylmethacrylate [PMMA] microspheres, hydroxyethylmethacrylate fragments, polyacrylamide hydrogel, polyalkylimide gel, polyvinylhydroxide microspheres in polyacrylamide gel [PAAG], and many more). In general, their adverse effects last as long as their intended ones [5]. Although it is often thought that temporary fillers are better tolerated than permanent ones, this is apparently not true as the frequency of short-term adverse reactions is very similar. In fact, whatever substance is injected into the tissue, it is perceived as a foreign substance with an initial challenge to the host's immune system. The famous injections of the patients' own blood had a nonspecific immunostimulatory effect as even this was a short-term challenge to the immune system.

Early complications develop within less than 2 weeks and include erythema, edema, and allergy. Bumps and lumps following superficial injection are usually visible immediately after the injection or shortly thereafter. Necrosis due to intraarterial injection becomes obvious within a day.

Late complications are chronic inflammation, late allergic reactions, nodules (granulomas) and filler migration, hypertrophic scar, and telangiectasia [6].

Delayed complications are considered to be largely due to biofilm formation [7].

Often, adverse effects develop weeks, months, or even years after the injection, and the patients frequently do not remember which filler they had gotten. The problem may even be confounded by the fact that different fillers may have been injected at various times by different physicians and even sometimes by nonphysicians.

Immediate reactions such as adequate pain after procedure, mild bruising, redness, and some edema are normal and are not complications. They can often be avoided by cooling the injected area, and this is also the most common treatment. Pain can be reduced by local anesthesia, slow injection, and low volume. Aloe vera, arnica, or vitamin K creams are recommended to reduce or avoid bruising. Bleeding and ecchymoses are rare when blunt cannulas are used. Swelling depends on the substance used, the localization of the injection, the amount, and the individual tolerance. Again, cooling usually reduces the swelling.

Vascular compromise may be the consequence of arterial or venous obstruction, which in turn may be due to intravascular injection of the filler, direct pressure of the filler on the vessel wall, or indirect trauma to the vessel wall. Particular attention has to be paid during glabella and nasal ala injections where inadvertent intravascular filler injection may result in necrosis and even blindness when the retinal artery is occluded [8,9]. Whenever blanching is seen during the injection, this must immediately be stopped [10]. In case of HA, hyaluronidase is injected as close to the site of intravascular injection as possible. Whether aggressive massage, warm compresses, and nitroglycerin application are really helpful for other fillers remains to be seen [11–13]. Intravascular injection is virtually impossible when using a blunt cannula [14].

Late complications are infection, granuloma formation, scarring, and loss of function. Infection may be due to

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

insufficient disinfection of the treatment area, injection into or through an oily skin, or application of makeup into an infected region [15]. Infection can develop into a major problem when particulate permanent fillers are used that may develop a bacterial biofilm on the surface of the particles. Whereas cellulitis promptly responds to systemic antibiotics, biofilms are usually resistant to antibiotics and require complete removal of the filler [16]. Granulomas are another serious problem. There are some general rules as to their development; nonparticulate substances rarely produce granulomas with the exception of silicon, but all particles may induce granulomas. The frequency of granulomas is higher the bigger the surface is in relation to the volume and the sharper the edges of the particles are, i.e., crystalloid particles are much more likely to induce granulomas independent of the longevity of the particles. PLL is a slowly dissolving crystalloid compound that caused a number of granulomas, particularly at the time when the recommendation to reconstitute it with a small volume of saline was followed by the users [17]. Even though some permanent fillers are advertised as being gels, they may consist of small polygonal particles, such as PAAG or HEMA (DermaLive®, DermaDeep®).

Delayed reactions are thought to be due to bacterial biofilms [18]. They may induce granulomas as well as so-called cold abscesses. This is the reason why granulomas should not be injected with corticosteroids as the first therapy but rather be treated with antibiotics for at least 14 days.

CLASSES OF SOFT-TISSUE FILLERS

General Remarks

Many different agents are available. Some have the same or very similar names and are chemically different, whereas some popular substances are sold under many different brand names.

The same agents may display different behavior due to variations in the production process, different molecular size, and variable protein moieties. This is particularly the case for the innumerable HA products.

The clinical appearance of adverse side effects of the various does not usually allow to make the diagnosis of the filler used as they are, in most cases, not filler specific.

Soft-tissue fillers are subdivided into

- Human substances
- Biological agents
- Synthetic products

Be aware that "biological" does not automatically mean degradable and that "biodegradable" is not a guarantee that the human body has the necessary enzymes to digest this filler.

Autologous Fat

Autologous fat is the prototype of a human substance and often thought of as being without side effects. However, fat injections also have potential adverse effects. They are due to collect the fat, fat storage, or injection and reach from rapid disappearance to infection and even death due to inappropriate injection technique [19].

Collagen

A great number of biological substances are on collagen basis: human collagen, bovine collagen, and porcine collagen with bovine collagen being the first commercially available product, e.g., Zyderm®. The degree of cross-linking and the chemical used for it also influence the tolerability of collagen fillers [20].

It was thought that human collagen would have an advantage as it does not require preinjection tests as bovine collagen. However, it turned out that apart from the allergic reactions, the human collagen has virtually the same life-span and may be associated with as strong inflammatory reactions as bovine collagen [21]. In contrast, morselled autologous dermis appeared to be very well tolerated with only transient inflammatory reaction during the wound-healing phase and effective revascularization [22]. Collagen is also synthesized by cultured fibroblasts (Cosmoderm I with 35 mg/mL, Cosmoderm II with 65 mg/mL, and Cosmoplast with 35 mg of glutaraldehyde-stabilized human collagen/mL). Human collagen from cadaveric dermis (Dermalogen®, Cymetra®) is available, too. Human collagen is also produced by injected fibroblasts (Isolagen®). They are cultured and expanded from a small biopsy of the patient and reinjected. Although they are said to give good results, the procedure of taking a biopsy, sending it to a specialized laboratory, and waiting 6–8 weeks until getting the expanded cells and the high cost have prevented it from becoming a popular method.

Porcine collagen was found to last longer and be tolerated better than bovine collagen and not require pretesting [23,24]. However, lip injection is discouraged [25].

Hyaluronic Acid

HA is a linear, unbranched, high-molecular-weight glycosaminoglycan, consisting of alternating D-glucuronic acid and *N*-acetyl-D-glucosamine. As a biological substance without species specificity, it should, in principle, be tolerated by all living organisms. However, the natural glycosaminoglycan moiety is linked to species-specific proteins and also the production process is critical. HA is not only a biological and naturally occurring filler, it also has a variety of different biological effects that depend on its molecular size [26]. Small fragments are proinflammatory, whereas long chains inhibit inflammation [27–29]. For its use as a filler, it has to be stabilized and the way and degree of stabilization are also important for the tolerability of HA [30]. The more HA is cross-linked and thus stabled, the more its tolerability is reduced.

Perhydrosqualene and Collagen Polyvinylpyrrolidone

This has recently been proposed as a filler for deep nasolabial folds with a lifetime of 12–18 months. It was claimed that no significant side effects were seen [31,32].

Polycaprolactone

Polycaprolactone (PCL)-1 dermal filler (Ellansé™, AQTIS Medical, Utrecht, the Netherlands) is a soft-tissue dermal filler based on PCL microspheres. The totally smooth spherical-shaped PCL microspheres (25–50 μm) are homogenously suspended in a tailor-made aqueous carboxymethylcellulose (CMC) gel carrier. PCL in CMC has been widely used in many medical devices. It is totally biodegradable, nontoxic, and completely excreted BY the human organism. The CMC gel carrier is gradually resorbed by macrophages over a period of several weeks, during which the PCL microspheres trigger a natural response of the skin and stimulate a natural wound-healing process with neocollagenesis. The new collagen replaces the volume of the resorbed carrier. The microspheres are not

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

phagocytosed because of their size and surface characteristics. The PCL dermal filler is indicated for deep dermal and subdermal implantation including hand rejuvenation. Adverse effects were not (yet) reported [33,34].

Biologic, but Not Degradable by Humans

Alginate-derived mannans were thought to offer advantages over other short-lived biological fillers, but they soon turned out to have a high rate of side effects, particularly granuloma formation [35].

LONG-LASTING FILLERS

The currently used fillers with a long-lasting effect are PLL and calcium hydroxyl apatite (CHA). The former has been used for more than half a century as suture and other materials in surgery and proven to be well tolerated. CHA has been used as bone cement with good effect. However, both substances are different in particle size and shape when injected as filler for soft-tissue augmentation. Granulomas were observed after PLL injections and rarely after CHA.

PERMANENT (IRREVERSIBLE) FILLERS

There are a huge number of different substances that had been or are still in use for soft-tissue augmentation. The main classes comprise PMMA (Arteplast, Artecoll®, Artefill®, Metacrill, Metrex), methacrylate fibers (Procell), acrylic hydrogel (DermaLive, DermaDeep), PAAG (Amazing gel, Aquamide, Argiform, Bioformacryl, Evolution®, Formacryl, Outline), polyethylene beads (Profill) (Figure 56.13), polyalkylamide (Bio-Alcamid), solid silicone particles in polyvinylpyrrolidone (Bioplastique®), polydimethylsiloxane (Biopolimero, Biopolymere), silicone oil (medical grade silicone oil), polymeric compound of natural silica and oxygen (Dermagen), polyoxyethylene fatty acid and elastin copolymer gel (Kopolymer 4E), and methacrylate and copolymer 4-G (Rhegecoll). Some are illegal in the United States and the European Union; others have been withdrawn from the market since several years but continue to induce granulomas and other severe side effects. Chemically similar or even identical substances are marketed as different particle sizes and shapes and exhibit very different side effect profiles.

ADVERSE SIDE EFFECTS

Many adverse effects are not specific for a particular filler but may be ascribed to the volume augmentation or to technical faults such as wrong indication, placement site, wrong injection needle [36], and infection due to contaminated ice or water [37]. Infections can best be differentiated from other nodules and granulomas by radiolabeled leukocyte scintigraphy [38]. Late-onset adverse effects are often inflammatory and immune mediated. Edema, granulomas [39], sarcoid-like reactions, and panniculitis are the findings most commonly seen. Systemic granulomatous and autoimmune diseases and, even less frequently, acute hypersensitivity reactions are rarely seen [40].

Autologous Fat

Adherence to key principles, including sterile technique and low-volume injection throughout layers of tissue, is critical to obtaining excellent results. Adverse outcomes are infrequent. However, early adoption of surgical procedures by those without a sound understanding of the underlying principles and techniques can have disastrous consequences. Furthermore, physicians operating on any patient must understand the potential for complications and be able to manage these appropriately when they occur [41]. Fat longevity is dependent upon handling and preparation of the fat. Poor fat viability produces an inadequate result and thus has to be considered as a complication [42]. On the other hand, deterioration of the aesthetic results after a significant weight gain due to corticosteroids, oral contraception, and a change of lifestyle was seen in a patient with Romberg's syndrome [43]. Lipomodeling of the breast was performed in 880 cases; approximately 140 mL had to be injected for a desired volume of 100 mL, which remained stable for 3–4 months. No radiological problems were found in mammography after procedure. Fat necrosis occurred in only 3%, but serious complications included one case of infection at the harvest site, six cases of infection at the injection site, and one case of intraoperative pneumothorax [44]. Further, there are case reports on abscess formation, life-threatening sepsis, and residual deformity [41]. Neurological complications were repeatedly reported with two patients developing unilateral loss of vision after fat injection in glabella; two patients with loss of vision, aphasia, and hemiparesis; and one patient developing sensorimotor hemiparesis after infarction of the middle cerebral artery [45–48]. Death after autologous fat grafting occurred in a 20-year-old woman with a 20-year history of lupus profundus and hereditary C4 complement deficiency who had already got three fat injections from 1997 to 1999 with ~50% resorption. A flare of her lupus profundus in 2007 resulted in the loss of most of the injected fat despite treatment with thalidomide 25 mg and prednisolone 7.5 mg daily. After donor site tumescent anesthesia and bilateral infraorbital blocks for recipient sites, 35 mL fat was injected with minimal pressure using an 18-gauge sharp needle because of scarring of the recipient site. There was dizziness immediately after injection of the left cheek and a vasovagal syncope suspected and the patient was placed in supine position. Another 35 mL of fat was subsequently injected. The patient became increasingly unwell over the next 2 hours, eventually developed progressive refractory hypoxic respiratory failure and cardiovascular decompensation. Despite emergency treatment in a critical care unit, she developed fulminant pulmonary edema and right ventricle dilatation and died due to cardiac arrest 4 hours after fat transfer [19]. Whether or not using a blunt cannula would have prevented the death of this patient is not clear. Apparently, these side effects were technique dependent and not due to the substance.

Liposuction is often used to collect fat and is a very safe procedure when performed under tumescent anesthesia and infection, bruising, hematoma, and seroma are rare. Fat embolism is very rare when not too much is aspirated and liposuction is not associated with other cosmetic procedures. Most of the serious complications were associated with general anesthesia.

Human Collagen

Autologous human collagen is well tolerated, when derived from both cultured fibroblasts and autologous injectable dermis [22]. Human allogenic collagen was observed to elicit acute to subacute inflammatory reactions [49], but no serious long-term side effects were reported. The cosmetic effect lasts between 4 and 7 months.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Nonhuman Collagens

They are foreign proteins with a propensity to induce allergies and granulomas, particularly bovine collagen, whereas human and porcine collagens are better tolerated. The side effects are usually temporary until all collagen has been resorbed, but one case was observed with stone-hard granulomas not disappearing with any treatment over more than a decade [50]. Usually, the granulomas are palisaded around amorphous eosinophilic material representing bovine collagen (Figure 56.1). This is characterized by very thick bundles, pale gray-violet staining with Masson's trichrome stain, and a lack of birefringence [51]. Whether the injection of collagenase [52] would be successful has not yet been tried. The most common side effects were temporary granulomas at the site of injection in about 4% of the patients. Testing and double testing before treatment were recommended, but nevertheless, granulomas did occur.

Collagen fillers are now used less and less frequently and adverse effects are expected to be seen rarely.

Hyaluronic Acid

HA is universally present in all animal species. It is said to be nonspecies specific; however, hyaluronans are linked to proteins that are species specific. Good preparations are (almost) free from foreign proteins. They have a low propensity to induce granulomas, but show a variety of transitory side effects, including rare granulomas and infection [53,54] At present, there are probably almost 200 preparations on the market. In order to prevent untoward adverse effects, well-known brands with high quality should be preferred as their complication rate has been shown to be much lower.

Untested cheap products should never be used.

HA preparations are currently the most widely used fillers with a longevity of approximately 6 months, but this is highly variable depending on molecular size and cross-linking. There are differences among them concerning the size of the molecule, protein content, chemical bonding, fluidity, injection pain, and longevity and whether they are monophasic or biphasic [55]. A good preparation must not clump as this may give rise to granulomas. Whereas granulomas were not rare in the beginning of the non–animal-derived synthetic HAs, they are now exceptional, except for a new product marketed roughly 3 years ago. This induces foreign body giant cell granulomas with a high content of eosinophils, and HA can be seen in giant cells.

Also in the early period of HA fillers, reactions interpreted to be hypersensitivity were observed [55–57]. Very rare side effects are a multiform rash and systemic anaphylactoid reactions [58] after intraarticular injection of HA [59] with native HA having a lower sensitizing potential [30].

Side effects due to the substance are usually short-lived and can be repaired by injecting hyaluronidase. The dose depends on the specific drug and may also vary according to the HA used and its degree of cross-linking. This enzyme cleaves both natural and cross-linked HAs. Three sources are available: bovine, ovine, and recombinant. As they are proteins, they have the potential of causing an anaphylactic shock in sensitized individuals. It is, therefore, necessary to question the patient about possible allergies. Hyaluronidase has also been used to treat HA granulomas [60].

Technique-dependent side effects may occur as with other fillers. When HA is injected too superficially, it may shine through with a bluish-grayish color, giving rise to the so-called Tyndall effect. It has to be used with care in the eyelids as it may cause swelling due to its ability to attract water. Accidental intracapillary injection may cause livedo reticularis [53,61].

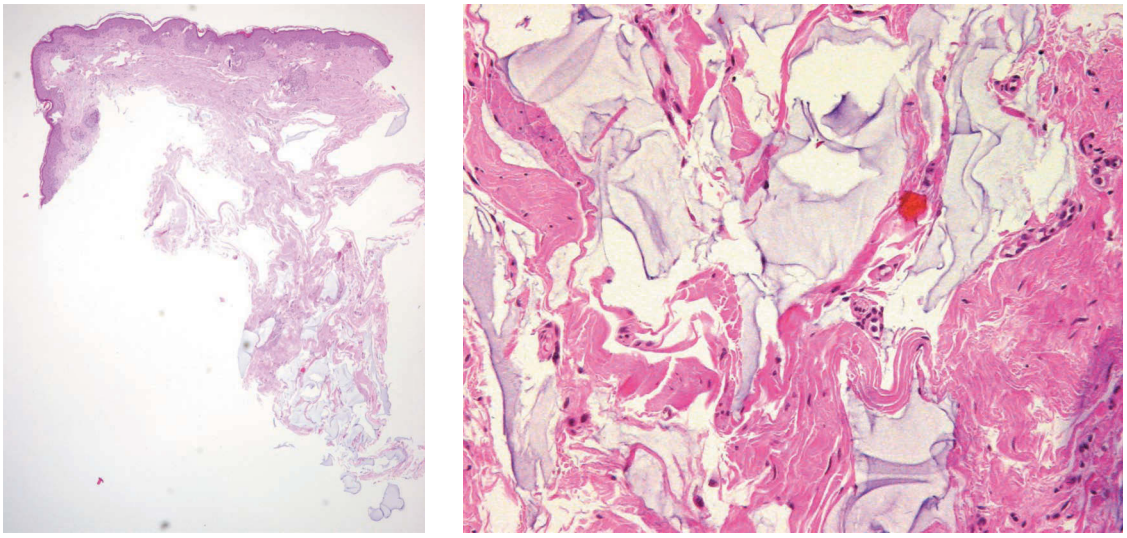
Histopathology of grayish-glassy nodules after superficial injection just shows HA deposits without any further tissue changes (Figure 56.2). Granulomas may show a very dense lymphocytic infiltrate with abundant eosinophils and many foreign body giant cells often containing basophilic amorphous material that corresponds to HA (Figure 56.3).

A middle-aged woman was seen with widespread swelling in the glabella, central ocular, and nasal regions after she had injected herself with a diluted HA-containing cream for topical use; histopathology showed a "Swiss cheese–like" picture similar to that after vaseline injection; this side effect was most probably not due to the HA component in the abused topical preparation (unpublished observation).

(a) (b)

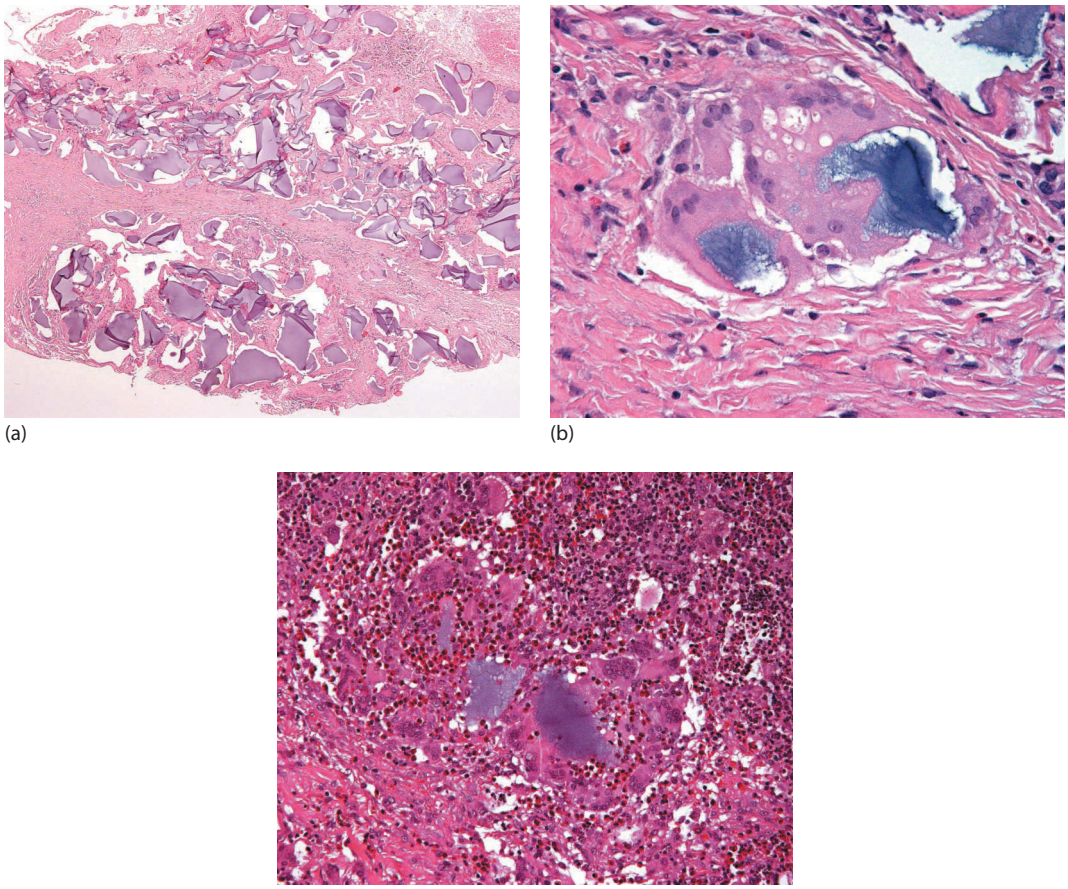
Figure 56.1 Long-lasting, virtually persistent granuloma formation due to collagen (Zyderm); (a) clinical picture and (b) histopathology of a granuloma. (Courtesy of A. Coninckx, Brussels, Belgium.)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b)

Figure 56.2 (a) Hyaluronic acid (HA) in the dermis: there was a slightly bluish color to skin colored nodule (Tyndall effect) that had been biopsied under the suspected diagnosis of a basal cell carcinoma. A filler had been injected 5 years prior to the biopsy. There is no inflammatory infiltrate. Scanning magnification, hematoxylin–eosin stain. (b) A close-up shows HA in the dermis without any inflammatory reaction. HE, ×200.



(a) (b)

(c)

Figure 56.3 (a) Inflammatory and granulomatous reaction to hyaluronic acid (HA) (Hylacorp®). HE, ×100. (b) Foreign body giant cells engulfing clumped HA (Hylacorp). (c) Epithelioid cells, foreign body giant cells with ingested HA (Hylacorp), and a very dense eosinophilic infiltrate.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Alginate

An alginate-derived filler (Novabel®) was marketed as a new biological filler with prolonged augmentation effect; however, very shortly after its marketing, granulomas were observed [62] and it was withdrawn from the market. The granulomas start with erythema and swelling until hard nodules form 2–5 months after injection (Figure 56.4). Ultrasound shows hypoechoic structures surrounded by a hyperechoic rim. Histopathology demonstrates spherical basophil structures of 100–120 μm in diameter enveloped by a prominent rim of giant cells. The granulomas are surrounded by a distinct hyaline collagen capsule [62].

HA Plus Dextranomer Microspheres

The dextranomer beads are added to the HA to improve the longevity of the filler. They consist of cross-linked dextran molecules with a positive surface charge and a diameter of 80–120 μm. They attract macrophages releasing tumor growth factor-β and interleukins, which stimulate collagenesis around the detranomer beads, maintaining the volume correction effect after the resorption of HA [63]. The material is apparently well tolerated with three reports of a granulomas; one of which was suppurative [64] and the other ones are with foreign body giant cell-rich granulomas [65,66]. The dextranomer beads stain dark bluish or purplish, or may even look like empty spaces giving a "Swiss cheese" aspect. Incision of the nodules and treatment with cephalexin and methylprednisolone aceponate leads to complete resolution in one case [64].

Poly-L-Lactic Acid

This substance has been used for decades in medicine and surgery and was well tolerated. In contrast, PLL as a filler comes as a powder of crystalloid particles that has to be reconstituted before injection. Subcutaneous nodules are either fibrotic or granulomas. They can form because of insufficient time during reconstitution of the material, inadequate dilution, overcorrection, superficial injection techniques, or inappropriate concentration of PLLA molecules secondary to muscle movement, and granulomas are thought to be due to allergic or inflammatory host responses [67]. In the early years, the recommendation was to use 3 mL; this turned out to cause granulomas and also often clogged the injection needle. Now, most physicians use 10 mL or more of physiological saline, often with some lidocaine added. After injection, the water is resorbed and the PLL particles induce a fibroblastic reaction lasting for 24 months or longer. This may cause fibrotic nodules, which may be visible in thin skin like around the eyes and in the hands [68], and the substance may clump in the lips; these are adverse effects of faulty technique (Figures 56.5 and 56.6). PLL granulomas are classical giant cell granulomas with many epithelioid cells and relatively few lymphocytes. The PLL particles are oval, fusiform, or spiky and seen in epithelioid and giant cells as well as in between (Figure 56.7). They are birefringent in polarized light [17]. The granulomas last at least 18 months [69].

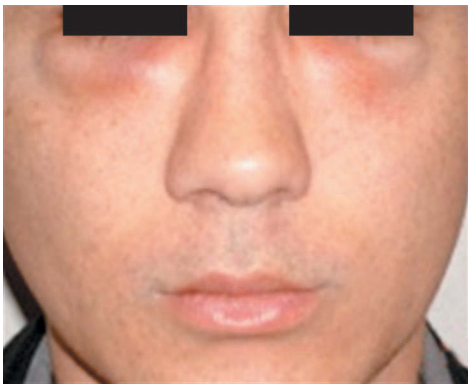


Figure 56.4 Granulomatous swelling under both eyes due to alginate filler (Novabel). (Courtesy of P. André, Paris, France.)

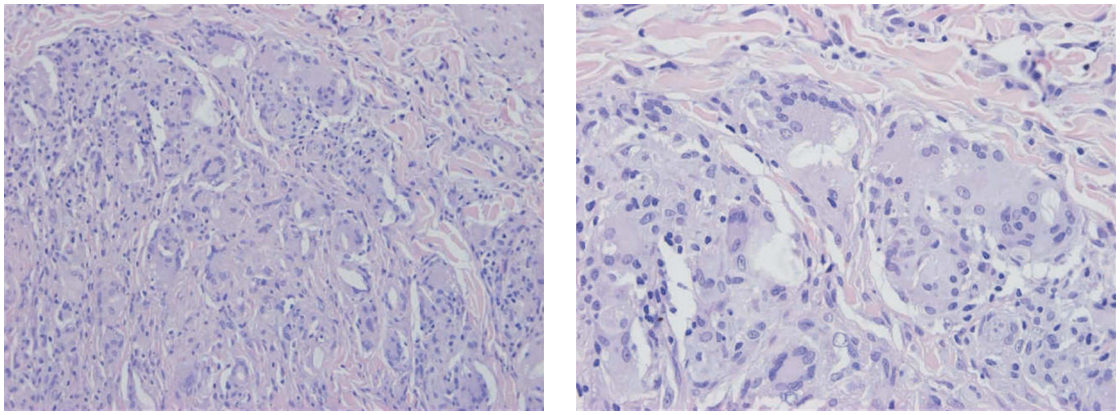
Figure 56.5 Poly-L-lactic acid (NewFill®) was injected superficially in a very thin skin giving rise to a palpable and visible nodule. (Courtesy of P. André, Paris, France.)

Figure 56.6 Granulomas and nodules due to poly-L-lactic acid (NewFill). (Courtesy of F. Bruins, Haarlem, the Netherlands.)

Calcium Hydroxyl Apatite

CHA is an inorganic material and has long been used successfully as bone cement. The currently available preparation is Radiesse®, which consists of microspheres (30%) of 25–45 μm suspended in a gel made of water, glycerol, and sodium CMC (70%). It is inert and nonantigenic, but stimulates collagen production. It is very well tolerated when injected as a suspension for soft-tissue augmentation. The duration of correction is between 9 and 12 months [70], but may also be longer. Most

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b)

Figure 56.7 (a) Granuloma formation due to poly-L-lactic acid (NewFill). There are mainly epithelioid and foreign body giant cells. The latter often engulfed crystalloid PLL particles. HE, ×200. (b) High magnification of a PLL granuloma. HE, ×400. (Courtesy of F. Bruins, Haarlem, the Netherlands.)

adverse effects are due to technical faults. In particular when injected into the lips, it tends to clump and produces palpable nodules. In one study, postinjection cellulitis was observed at a frequency of 1.7% [71]. However, granulomas also occur with a higher frequency in elderly women [72]. They consist of tightly packed, dark bluish microspheres with a diameter of 25–40 µm and giant cells [73]. The nodules were shown to rapidly decrease after fractional CO_2 laser treatment [74]. Recently, a grade 3 systemic reaction was observed 30 minutes after injection of CHA vocal cord filler prompting the authors to recommend a 30 minute postprocedure observation period [75].

Polyacrylamide Gel

PAAG is a suspension of 2.5%–5% PAAG in sterile water. It is marketed under many different names: PAAG (Sinocos Eastcos, Hong Kong, China), Amazing gel, Aqualift, Aquamid, (Contura International, Söborg, Denmark), Argiform, Bioformacryl, Formacryl, and Outline, which are slightly different in minute additional components [1]. The material is widely resistant to enzymatic degradation and phagocytosis. The particles can harbor bacteria on their surface and give rise to late infections, biofilms, and abscesses [76]. It is claimed not to induce allergic reactions or to interfere with the hemodynamic system. It can hold 300–400 times its weight in water. It was widely used for breast augmentation in Eastern countries. The results are immediate and overcorrection is necessary. Its major advantage is that it remains soft and pliable after injection [77]. However, the products should not be injected over other ones. PAAG is generally well tolerated, but severe adverse effects have also been described, e.g., swelling, lumps, abscesses, facial disfigurement, gel dislocation, and respiratory distress [78]. Breast deformity, lumpiness, intermittent swelling, pain, and gel extrusion were observed in other series [79–81]. The gel is exceedingly biocompatible and thus an excellent medium for bacteria [82]. The main risk is infection often developing after 8–12 months or even later, but cultures often remain negative and only PCR could identify bacteria that are normally not pathogenic, such as *Propionibacterium acnes*, *Streptococcus oralis* and *mirabilis*, *Staphylococcus aureus*, and some atypical mycobacteria. Histopathology shows foci of neutrophils and karyorrhectic material, numerous macrophages, and foreign body giant cells around a gel that appear somewhat similar to HA. Often, giant cells contain vesicles full of PAAG and the material frequently shows small empty blebs both in the giant cells and when present in large lakes (Figure 56.8). PAAG is positive with Alcian blue and not birefringent.

Polyalkylimide Gel

Polyalkylimide gel 4% in water (Bio-Alcamid, Polymekon, Milan, Italy) is another large volume filler to be injected into the deep dermis or under the dermis. A thin collagen capsule forms after injection preventing migration and keeping it apart from the surrounding tissue. Aspiration or punching a small hole over it permits its removal. Side effects were edema, bruising, nodules, infections, severe inflammatory reactions, migration despite the capsule-like fibrosis around it, unsatisfactory appearance, and late-appearing abscesses. Migration is a rare event [83]. Histopathology shows basophilic amorphous material surrounded by neutrophils and erythrocytes. Gram stain may reveal bacteria. The infections are very difficult to treat and require high-dose long-term antibiosis, incision, drainage, and irrigation [84,85].

Polyvinylhydroxide Microspheres in Polyacrylamide Gel

This filler is a suspension of 6% polyvinylhydroxide microspheres in 25% PAAG hydrogel (Evolution, ProCytech SA). It is apparently well tolerated though it is not often used [51,86].

Acrylic Hydrogel

A suspension of ethylmethacrylate and hydroxyethylmethacrylate particles in HA was marketed under the brand names of DermaLive and DermaDeep. Initially reported as being well tolerated [87], it soon turned out that this biphasic filler caused late granulomas in a very high percentage of cases [88–90] so that it had to be withdrawn from the market.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

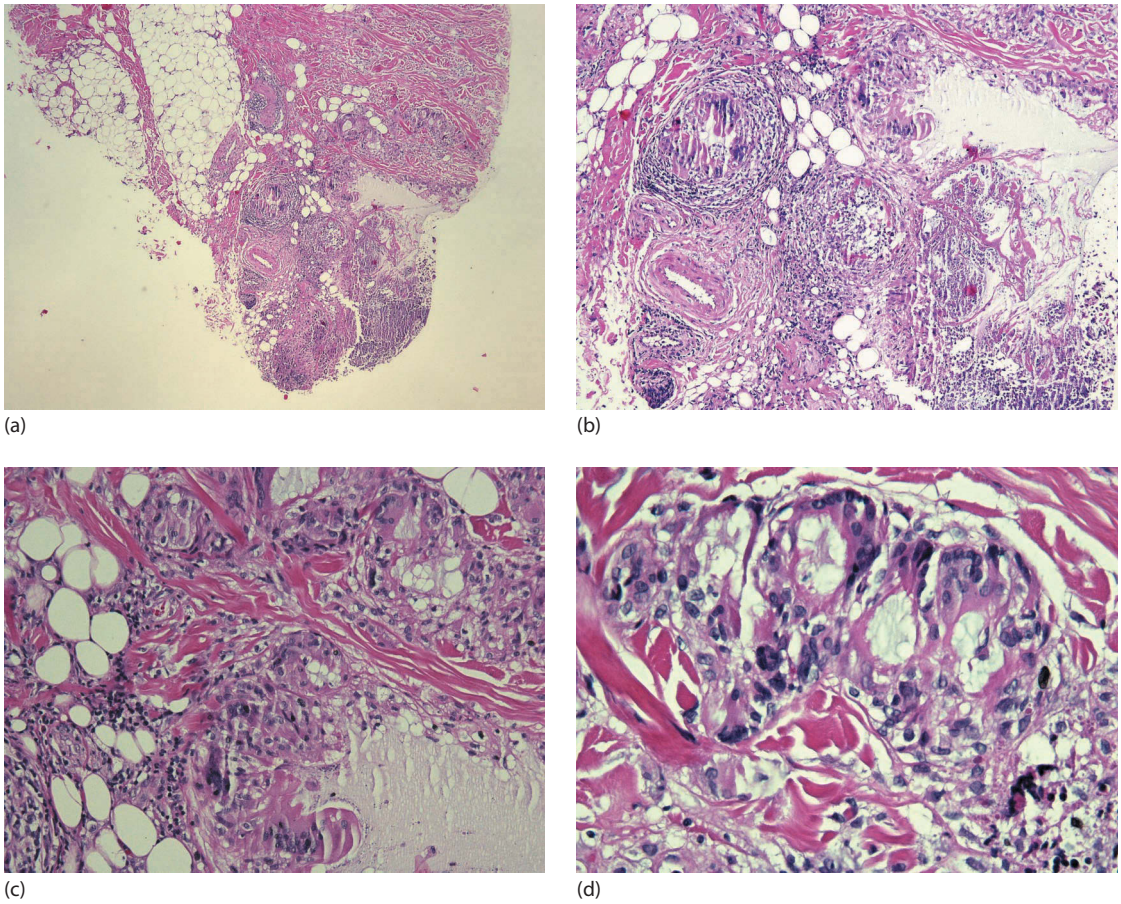


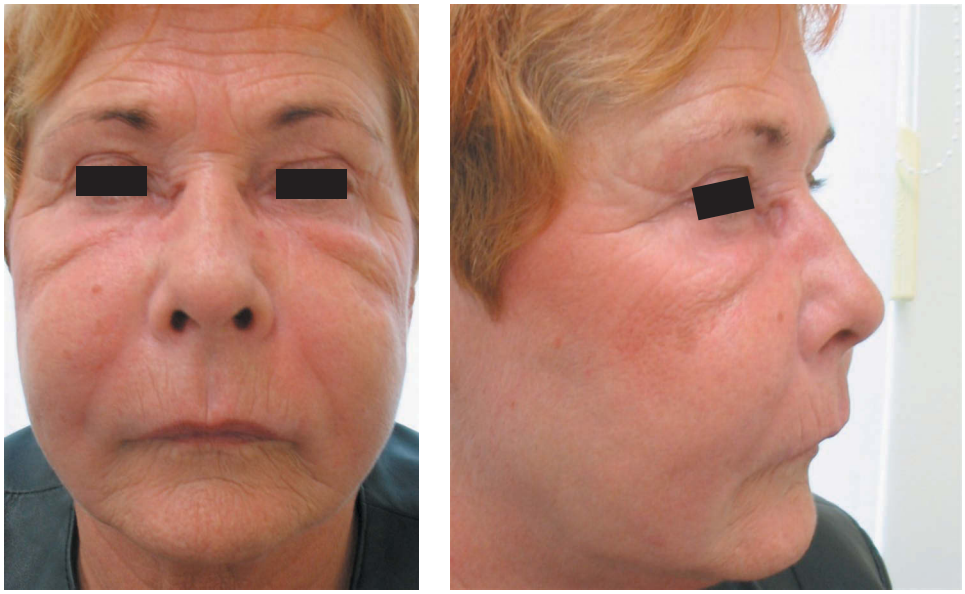
Figure 56.8 Granulomatous reaction to polyacrylamide gel (PAAG) in the deep dermis and adjacent cutaneous fat. (a) HE, original magnification 4×. (b) Granulomatous reaction to PAAG. HE, original magnification 10×. (c) The PAAG is seen as a faintly basophilic amorphous substance, but there are also empty spaces resembling fat cells. HE, original magnification 20×. (d) The giant cells contain PAAG with small blebs in it. HE, original magnification 40×.

However, granulomas still occur [91]. They usually present as nodules that are first palpable and then often become visible (Figure 56.9). Fistulation may develop, and even a keratoacanthoma-like appearance was seen [92]. The granulomas are well delimited and relatively easy to remove surgically; however, new granulomas often develop. Other treatments are intralesional corticosteroids, allopurinol, and 5-fluorouracil. Antibiotics have to be given before if an infection is suspected [93]. Histopathology shows a dense granuloma with a fibrous pseudocapsule containing masses of crystalloid acrylate particles. The granulomas are made up of epithelioid and foreign body giant cells that try to engulf the particles. Some areas become necrotic and contain cholesterol clefts. Epidermal ridges may grow down and try to surround the foreign material giving rise to fistule formation. Some granulomas may become sclerotic with time (Figures 56.10 and 56.11).

Polymethylmethacrylate

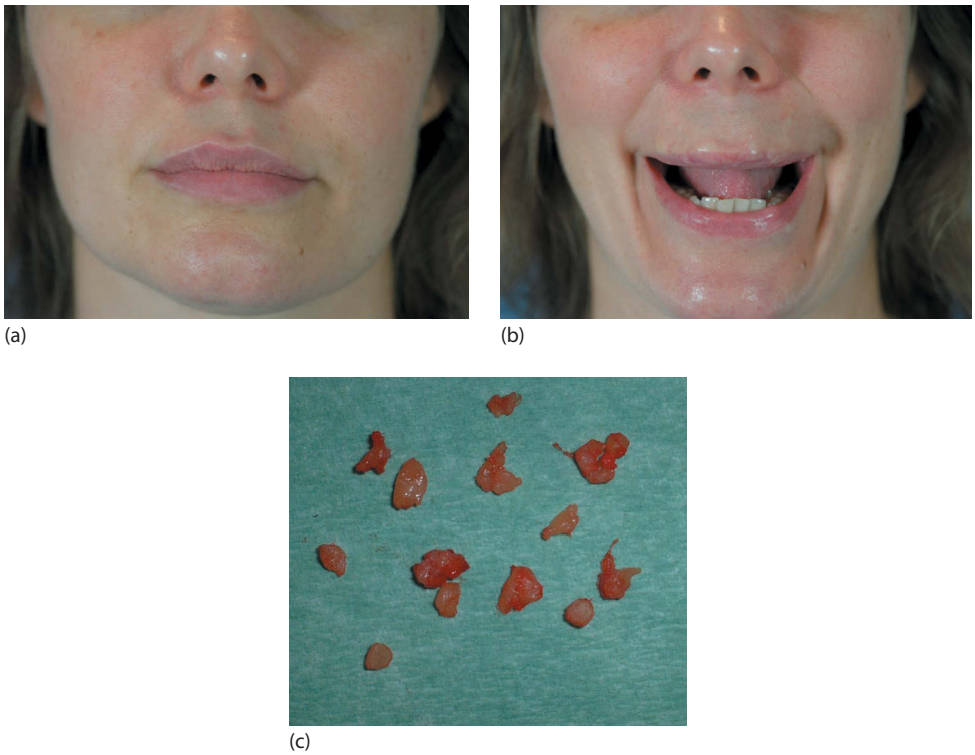
Artecoll, Artefill, and Artesense® are PMMA beads suspended in bovine collagen. Testing of bovine collagen is necessary before use to avoid an immune reaction. Individuals with a history of keloids should not be treated [94]. Approximately 3 weeks after injection, the body starts depositing own collagen around the microspheres, which get virtually encapsulated by own collagen. Overcorrection is not performed. Artefill has polished microbeads being thought to attract fewer impurities and thus being less prone to induce granuloma formation [95]. Methacrill and Metrex are also PMMA particles though not round and polished. Although granulomas are rare with 0.01% reported [96,97], they do occur and are difficult to treat [98]. Lumps often form, particularly in the lips, but most are just palpable and not visible. Granulomas may develop several years after the injection [99]. Granuloma precipitation many years after injection when a patient was treated with interferon because of hepatitis C [100] or laser skin resurfacing was performed over the area of injection (Vochelle D, personal communication) is possible. The granulomas appear suddenly with induration, swelling, tenderness, and erythema (Figure 56.12). Histopathology shows a typical granuloma with round empty-appearing clear spaces in a fibrotic tissue. Treatment was performed with intralesional corticosteroids and 5-fluorouracil [101] as well as allopurinol and surgery. Methacrill granulomas were melted with high-frequency *endocoagulation* leaving a residue of burnt plastic with a characteristic smell [102]. Intralesional laser treatment is another option.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b)

Figure 56.9 (a and b) Bio-Alcamid (polyalkylimide hydrogel) allergic reaction: massive edema. (Courtesy of F. Bruins, Haarlem, the Netherlands.)



(a) (b) (c)

Figure 56.10 (a) Small palpable nodules in the lip after HEMA injection (DermaLive). (b) Stretching the lips makes the nodules visible. (c) Many of the nodules could easily be extirpated from the mucosal side of the lip. (a and b: Courtesy of Klinikk Bunæs, Sandvika, Norway; c: Courtesy of J. Bunæs, Sandvika, Norway.)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

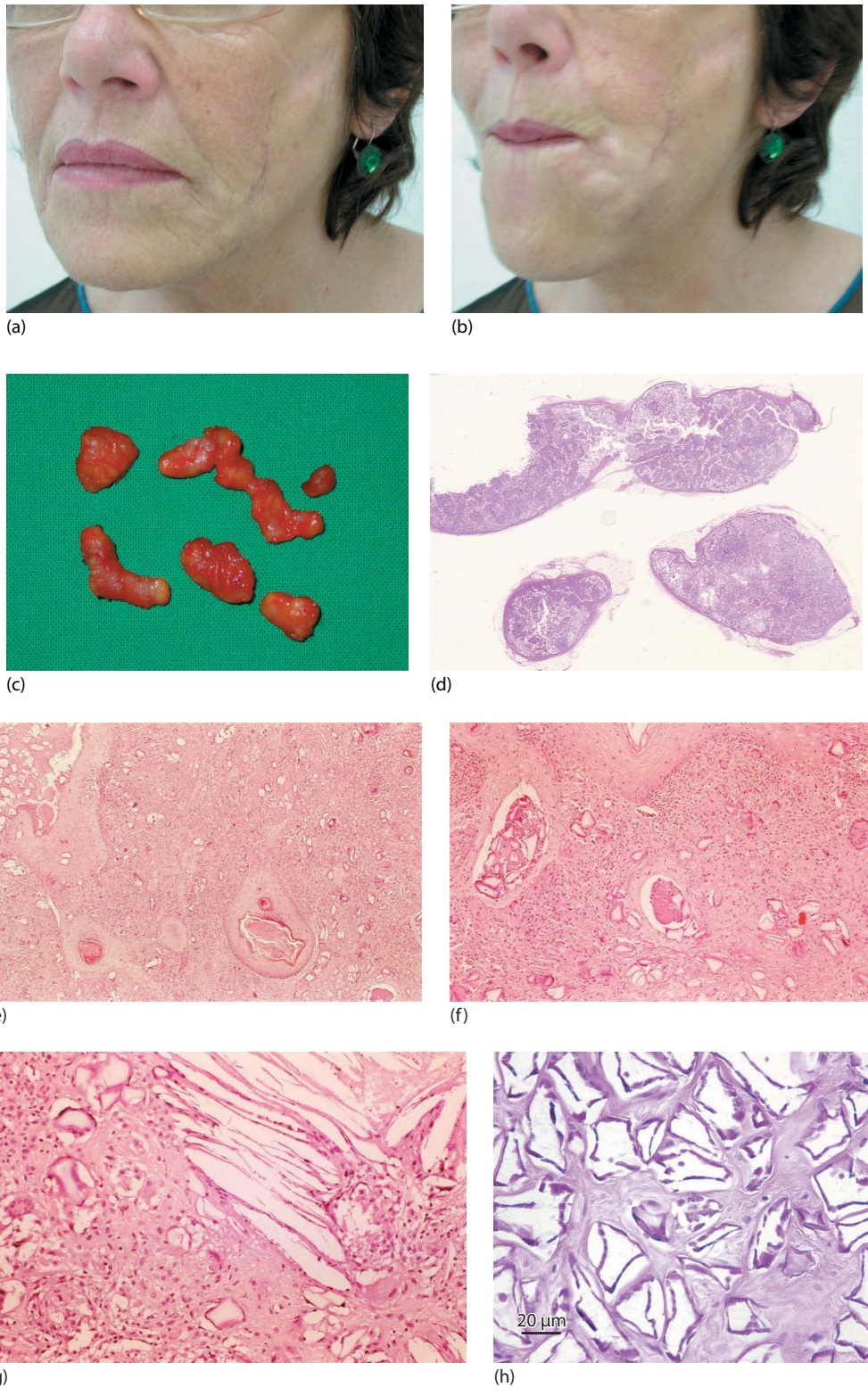


Figure 56.11 (a and b) HEMA granulomas 2 years after injection. (c) Some granulomas extirpated from the perioral region. (d) Histopathology of HEMA nodules shows well-delimited granulomas surrounded by a fibrous pseudocapsule. HE stain, scanning magnification, ×4. (e) HEMA granuloma. There is a dense granulomatous infiltrate with epithelioid cell; some giant cells; many HEMA particles, which stand out by their polygonal appearance; and sinus and fistule tracks, the latter of which also containing HEMA particles. HE, ×100. (f) Higher magnification of the vicinity of a sinus with many HEMA particles, monstrous giant cells, and neutrophils. HE, ×200. (g) HEMA granuloma with particles and many slit-like, so-called cholesterol clefts. HE, ×200. (h) HEMA granuloma during treatment with intralesional triamcinolone acetonide plus 5-fluorouracil. There is little infiltrate and the connective tissue appears hyalinized. HE, ×200.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 56.12 Granuloma due to polymethylmethacrylate microspheres in collagen (Artecoll). (Courtesy of F. Bruins, Haarlem, the Netherlands.)

Figure 56.13 Late complication of Profill demonstrating serious fat atrophy after initial inflammation. (Courtesy of P. André, Paris, France.)

Paraffin and Other Mineral Oil and Lipid Derivatives

Crude substances such as vaseline, paraffin, lanolin, cod liver oil, or beeswax were used in the late nineteenth and early twentieth centuries. Despite initial satisfying results, long-term results were usually appalling due to skin hardening, swelling, granuloma formation, ulceration and fistulation, infections, abscesses, and even cancer development [1].

Paraffin is irreversible and no longer legally used as a filler although highly inflammatory granulomas after fraudulent use of paraffin or other oils containing vitamin E, sometimes also D and A, are still seen (Figure 56.14) [103]. Injection of paraffin into the penis caused sclerosing lipogranuloma characterized by fibrosis and deformation [104]. Histopathologically, the deep reticular dermis and subcutaneous fat are involved with a predominantly lobular panniculitis with a Swiss cheese appearance. The cystic spaces are surrounded by foamy histiocytes and giant cells. The collagen bundles in between are sclerotic (Figure 56.14).

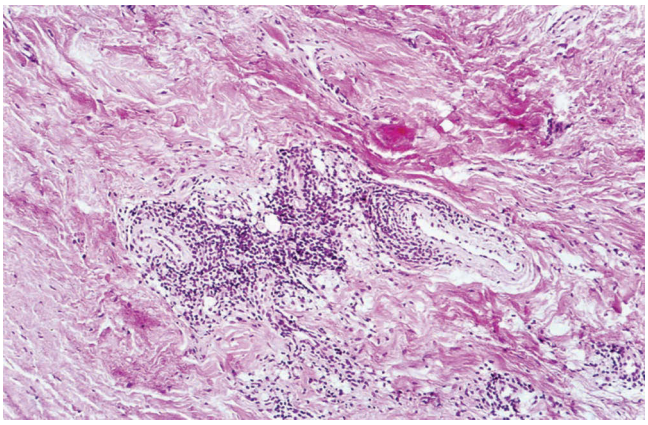


Figure 56.14 Siliconoma.

Vaseline and other mineral oils cause a very similar reaction [105–108].

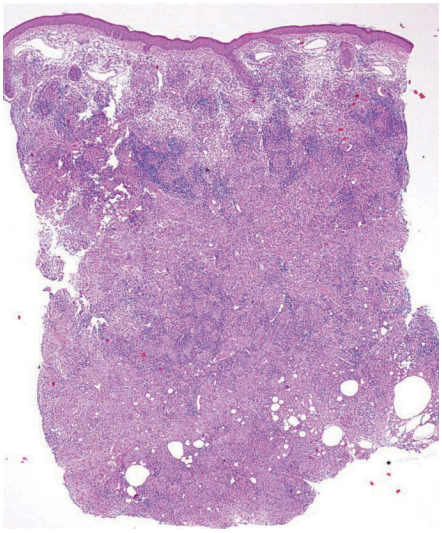
Whether ultrasound liquefaction of the fat where the inappropriate substance had been injected and subsequent extraction by a suction cannula helps to eliminate this material remains to be seen [109,110].

Silicone

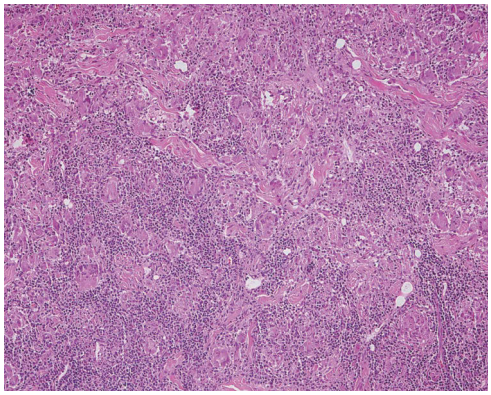
Silicone is another irreversible filler. It is a highly polymerized hydrophobic oil (Silikon 1000, Adatosil 5000, Biopolimero), gel (MDX 4-4011), or solid rubber consisting of dimethylsiloxane units. Silicone is generally well tolerated, but the occasional side effects may be dramatic and irreversible; this is the reason why it is banned for cosmetic use both in the European Union and the United States. Those still using silicone off-label claim that pure silicone [111] and proper microdroplet technique prevent adverse effects, but this is not generally accepted. Medical grade silicone oil is pure and sterile (Figure 56.16). The secret of good long-term results appears to be the injection of truly minute amounts [112–114]. A mixture of silicone with HA was recently described as "the optimal filler" [115].

Side effects are local and systemic. Minor complications are small nodules seen within a year after injection that are mainly due to too much substance. However, indurations and erythema with swelling are silicone granulomas that often only appear 2–12 years after injection. The differentiation between siliconomas, which consists almost exclusively of macrophages containing small droplets of silicone oil and contains virtually no inflammatory cells, and silicone granuloma with silicone containing macrophages, lymphocytes, and giant cells is somewhat artificial. Both respond to intralesional corticosteroids in most cases. Major complications are systemic with pneumonitis, acute respiratory distress syndrome, sudden death after intravascular injection, migration of large volumes of low-viscosity silicone oil, erysipelas-like reactions, blindness, loss of neurological functions, and death after silicone oil had been inadvertently injected into the ophthalmic or meningeal vessels.

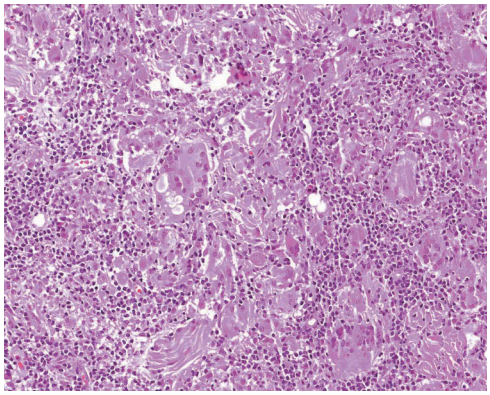
Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a)



(b)



(c)

Figure 56.15 (a) Scanning magnification of a punch biopsy of a patient who had herself autoinjected material that she had eluted from a hyaluronic acid–containing cream. There is a subepidermal edema and many granulomas all over in the dermis surrounded by lymphocytes. (b) Many small granulomas are distributed in a dense lymphocytic infiltrate. (c) Higher magnification shows a very dense lymphocytic infiltrate with epithelioid and many giant cells, some of which contain bleb-like spaces, probably from the ingested foreign material. (a through c: Courtesy of Department of Dermatology, Inselspital, University of Bern, Bern, Switzerland.)

Silicone Elastomer Particles (Bioplastique)

A silicone elastomer suspension in polyvinylpyrrolidone plasdone hydrogel was mainly used in urology and for vocal cord augmentation. It was shown to produce both lumps and granulomas [116,117].

GENERAL FEATURES OF THE HISTOPATHOLOGY OF ADVERSE FILLER EFFECTS

Many fillers have a specific morphology and/or staining pattern in the skin [51]. This is true for both acute reactions when the filler is still visible and late reactions like granulomas and infections with abscesses.

Bovine collagen is seen as a dense eosinophilic mass in the skin. It is not birefringent in contrast to human collagen fibers. Early "allergic" reactions usually show a lymphocytic infiltrate, which may turn into a granuloma with many epithelioid cells and some intermingled giant cells.

HA may sometimes be seen in the skin as a more or less structureless basophilic substance; this may correspond to the Tyndall effect when localized very superficially. Granulomas were relatively frequently seen in the early times of manufacturing of streptococcal HA, most probably due to the content of protein. This is nowadays very rare with this product. Another new brand caused many granulomas and abscesses. They consisted of a dense lymphocytic infiltrate with many giant cells, often of excessive size, as well as many eosinophils around basophilic HA. In case of abscesses and fistulation, foci of neutrophils are seen.

Matridex shows both HA and dextranomer beads in a cell-rich granuloma. The microspheres are perfectly round and darkly basophilic or purple, allowing the product to be identified.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

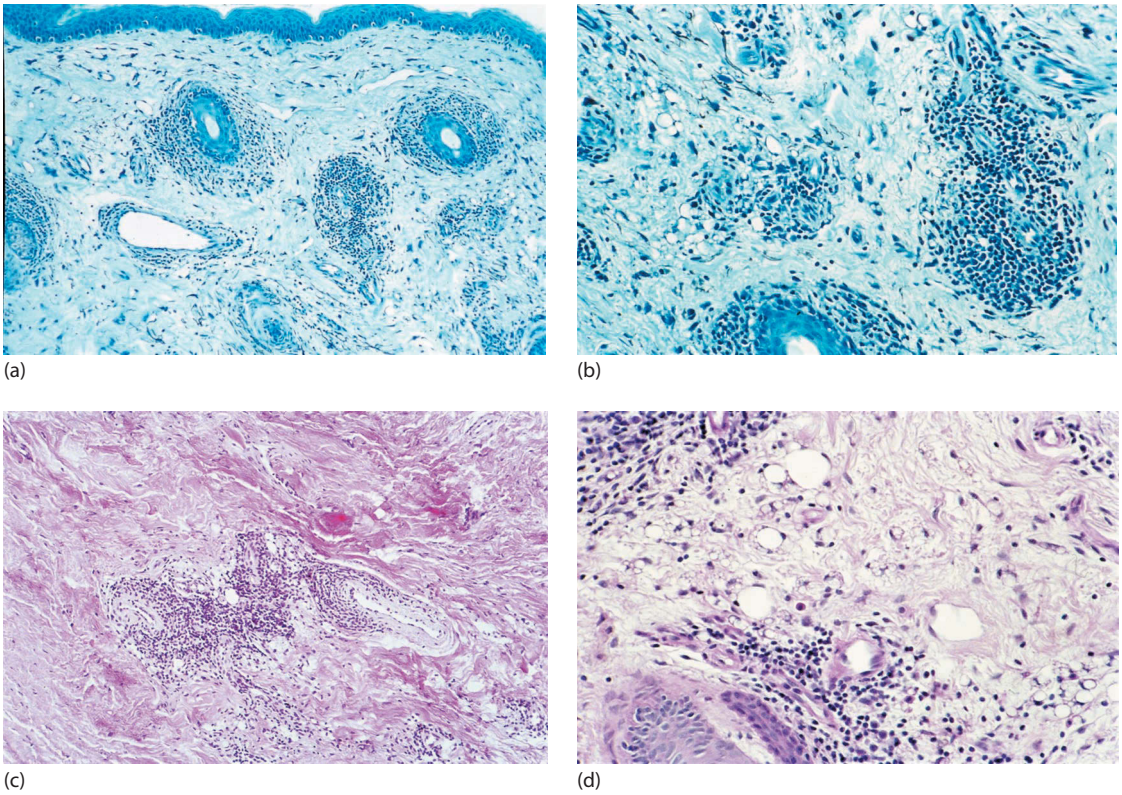


Figure 56.16 (a) Siliconoma showing perivascular lymphocytic infiltrates and an edematous reticular dermis. Methylene blue stain. ×100. (b) There are dense perivascular lymphocytic infiltrates and some relatively small round empty-appearing spaces. Methylene blue stain. ×200. (c) The connective tissue is very loose with many barely visible round spaces that are smaller than normal fat cells. Cresyl violet, ×100. (d) The connective tissue is loose and contains empty spaces that represent silicon oil droplets. Cresyl violet, ×400.

PLL is seen as a crystalloid material in epithelioid cell granulomas with giant cells often surrounded by fibrosis. The material is birefringent permitting its exact identification.

Acrylic hydrogel mainly causes late granulomas and no HA is seen any more. The acrylic particles are polyedric and seen in a dense granuloma with giant cells, many of which try to engulf the foreign bodies. Necrotic areas are frequent and often contain cholesterol clefts. Clinically visible fistulae correspond histopathologically to epidermal ingrowths also trying to engulf and transepidermally eliminate filler material.

PMMA (Artecoll, Artefill) is seen as round empty-appearing spaces in a fibrotic tissue. Although appearing to be of relatively uniform size, this depends on the section plane. In case of granuloma formation, epithelioid and giant cells are seen in addition.

PAAG is very well tolerated biologically. The main risk is infection that may cause abscesses and necroses. Granulomas show epithelioid and giant cells. The material is basophilic and does not exhibit a wavy structure often seen with HA.

Silicone oil causes granulomas with droplets of varying size, some of which are seen in epithelioid cells. Giant cells are rare as there are no particles. Often, dense lymphocytic infiltrates are seen in perivascular localization.

Sclerosing lipogranuloma is a characteristic feature of paraffin injection, mainly in the penis to increase its girth. It is characterized by a Swiss cheese–like aspect in a fibrotic tissue with lymphocytes, epithelioid, and giant cells. The empty spaces are of variable size.

The injection of vitamin E in different oils gives a similar histopathological picture, but as these injections are now mainly made in the face, particularly in the lips, by nonmedical persons, the changes are much more acute and the inflammatory component is more obvious in these cases.

GENERAL TREATMENT REMARKS

Prevention is always better and easier than treatment—this rationale is also true for filler side effects. After identifying the exact nature of an adverse side effect, the appropriate therapy has to be chosen. Early side effects like injection pain, immediate swelling, and edema usually do not require specific treatment. Placement of too much material or in the wrong area requires immediate massage or removal, if possible. Lump formation after CAH injection in the lip is a technical fault as well as too superficial injection. Proper training before starting to inject is mandatory.

HA can be dissolved with hyaluronidase. Most preparations are of animal origin, and there is the theoretical

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

possibility of a sensitization. It is wise to use one preparation to get experience with as the dosage may vary among different drugs. The effect is usually seen within hours, and reinjection is possible after 24 hours, so small doses are recommended in the beginning.

The problem is the treatment of late and delayed adverse effects. First, the responsible substance has to be identified. This is often impossible as the patients do not know or are reluctant to disclose which filler had been injected. Once a granuloma has developed, it is to be assumed that granulomas will continue to develop as long as the foreign material is in the skin. Whether attenuated total reflectance/Fourier transform infrared analysis spectroscopy [118] really allows fillers to be reliably identified remains to be seen. Another validated method is the histological examination of sections, which yields quite specific changes with most different fillers [51,119].

The differentiation of infectious from noninfectious granulomas is possible with radioactive-labeled leukocytes. In case of infection, antibiotics have to be given long enough and in doses capable of containing the infection.

Granulomas often respond to intralesional injection of a mixture of 250 mg 5-fluorouracil/mL and 10 mg triamcinolone acetonide/mL plus mepivacaine 1 mL, which is given first twice, then once weekly, plus allopurinol 300–600 mg/day. TNF-a inhibitors have not yet gained much acceptance in the treatment of granulomas.

CONCLUSION

Fillers belong to the most frequently used substances in aesthetic medicine. The "consumers" are not sick patients, but healthy persons expecting to look better after the procedure. Any adverse effect, whether immediate, late, or delayed and temporary or irreversible, is a catastrophe for them and potentially for the treating physician. All measures have to be taken to avoid them; the physician must be well trained, use the best product, and respect indications, contraindications, proper aseptic injection techniques, and adequate localization for each specific filler. The patient has to follow the physician's recommendations after treatment. The best would be to give a "filler pass" to the patient that notes which filler was when and where injected. Despite all precautions, adverse effects may occur. Take them seriously and never dismiss a patient's concerns. Treatment should be instituted as soon as possible [120].

REFERENCES

1. Haneke E. Risks of permanent fillers. *Expert Rev Dermatol* 2009; 4:271–283.
2. Haneke E. Skin rejuvenation without a scalpel. Fillers. *J Cosm Dermatol* 2006; 5:164–174.
3. DeLorenzi C. Complications of injectable fillers, part I. *Aesthet Surg J* 2013; 33:561–575.
4. Ionescu A, Wutscher E, Brambilla E, Schneider-Feyrer S, Giessibl FJ, Hahnel S. Influence of surface properties of resin-based composites on in vitro *Streptococcus mutans* biofilm development. *Eur J Oral Sci* 2012; 120:458–465.
5. Haneke E. Soft tissue augmentation with injectable fillers and implants. In: Vuyk HD, Lohuis PJFM, eds. *Facial Plastic Surgery*. London, U.K.: Hodder Arnold, 2006, pp. 167–180.
6. André P, Lowe NJ, Parc A, Clerici TH, Zimmermann U. Adverse reactions to dermal fillers: A review of European experiences. *J Cosmet Laser Ther* 2005; 7:171–176.
7. Cohen JL. Understanding, avoiding, and managing dermal filler complications. *Dermatol Surg* 2008; 34(Suppl 1):S92–S99.
8. Lazzeri D, Agostini T, Figus M, Nardi M, Pantaloni M, Lazzeri S. Blindness following cosmetic injections of the face. *Plast Reconstr Surg* 2012; 129:995–1012.
9. Park SW, Woo SJ, Park KH, Huh JW, Jung C, Kwon OK. Iatrogenic retinal artery occlusion caused by cosmetic facial filler injections. *Am J Ophthalmol* 2012; 154:653–662.
10. Glaich AS, Cohen JL, Goldberg LH. Injection necrosis of the glabella: Protocol for prevention and treatment after use of dermal fillers. *Dermatol Surg* 2006; 32:276–281.
11. Hirsch RJ, Cohen JL, Carruthers JD. Successful management of an unusual presentation of impending necrosis following a hyaluronic acid injection embolus and a proposed algorithm for management with hyaluronidase. *Dermatol Surg* 2007; 33:357–360.
12. Narins RS, Jewell M, Rubin M, Cohen J, Strobos J. Clinical conference: Management of rare events following dermal fillers: Focal necrosis and angry red bumps. *Dermatol Surg* 2006; 32:426–434.
13. Kleydman K, Cohen JL, Marmur E. Nitroglycerin: A review of its use in the treatment of vascular occlusion after soft tissue augmentation. *Dermatol Surg* 2012; 38:1889–1897.
14. Fulton J, Caperton C, Weinkle S, Dewandre L. Filler injections with the blunt-tip microcannula. *J Drugs Dermatol* 2012; 11:1098–1103.
15. Fiore R 2nd, Miller R, Coffman SM. Mycobacterium mucogenicum infection following a cosmetic procedure with poly-ʟ-lactic acid. *J Drugs Dermatol* 2013; 12:353–357.
16. Christensen L, Breiting V, Bjarnsholt T, Eickhardt S, Høgdall E, Janssen M, Pallua N, Zaat SA. Bacterial infection as a likely cause of adverse reactions to polyacrylamide hydrogel fillers in cosmetic surgery. *Clin Infect Dis* 2013; 56:1438–1444.
17. Beljaards RC, de Roos KP, Bruins FG. NewFill for skin augmentation: A new filler or failure? *Dermatol Surg* 2005; 31:772–776.
18. Rohrich RJ, Monheit G, Nguyen AT, Brown SA, Fagien S. Soft-tissue filler complications: The important role of biofilms. *Plast Reconstr Surg* 2010; 125:1250–1256.
19. Gleeson CM, Lucas S, Langrish CJ, Barlow RJ. Acute fatal fat tissue embolism after autologous fat transfer in a patient with lupus profundus. *Dermatol Surg* 2011; 37:111–115.
20. Weinkle S. Efficacy and tolerability of admixing 0.3% lidocaine with dermicol-P35 27G for the treatment of nasolabial folds. *Dermatol Surg* 2010; 36:316–320.
21. Sclafani AP, Romo T 3rd. Collagen, human collagen, and fat: The search for a three-dimensional soft tissue filler. *Facial Plast Surg* 2001; 17:79–85.
22. Bassetto F, Turra G, Salmaso R, Lancerotto L, Del Vecchio DA. Autologous injectable dermis: A clinical and histological study. *Plast Reconstr Surg* 2013; 131:589e–596e.
23. Saray A. Porcine dermal collagen (Permacol) for facial contour augmentation: Preliminary report. *Aesthet Plast Surg* 2003; 27: 368–375.
24. Monstrey SJ, Pitaru S, Hamdi M, Van Landuyt K, Blondeel P, Shiri J, Goldlust A, Shoshani D. A two-stage phase I trial of Evolence30 collagen for soft-tissue contour correction. *Plast Reconstr Surg* 2007; 120:303–311.
25. Braun M, Braun S. Nodule formation following lip augmentation using porcine collagen-derived filler. *J Drugs Dermatol* 2008 June; 7:579–581.
26. Clifford P, Clark III. Animal based hyaluronic acid fillers: Scientific and technical considerations. *Plast Reconstr Surg* 2007; 120:275–325.
27. Mummert ME. Immunologic roles of hyaluronan. *Immunol Res* 2005; 31:189–206.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

28. Stern R, Asari AA, Sugahara KN. Hyaluronan fragments: An information-rich system. *Eur J Cell Biol* 2006; 85:699–715.
29. Wright AJ, Day AJ. Hyaluronan in immune processes. *Adv Exp Med Biol* 2005; 564:57–69.
30. Goomer RS, Leslie K, Maris T, Amiel D. Native hyaluronan produces less hypersensitivity than cross-linked hyaluronan. *Clin Orthop Relat Res* 2005; 434:239–245.
31. Enríquez Merino J. Perhidroescualeno y colágeno-polivinilpirrolidona: Un nuevo matrial de relleno. Ensayo clínico con 20 pcientes. *Dermatol Cosmet Med Quir* 2013; 11:19–22.
32. Escobar Francisco SA, Rodríguez Ruiz XC. Tratamiento de surcos, depresiones cutáneas y líneas de expresión con perhidroescualeno CLG-PVP. *Dermatol Cosmet Méd Quir* 2013; 11:104–111.
33. Figueiredo VM. A five-patient prospective pilot study of a polycaprolactone based dermal filler for hand rejuvenation. *J Cosmet Dermatol* 2013; 12:73–77.
34. de Melo F, Marijnissen-Hofsté J. Investigation of physical properties of a polycaprolactone dermal filler when mixed with lidocaine and lidocaine/epinephrine. *Dermatol Ther* 2012; 2:13.
35. Moulonguet I, de Goursac C, Plantier F. Granulomatous reaction after injection of a new resorbable filler Novabel. *Am J Dermatopathol* 2011; 33:710–711.
36. Niamtu J III. Filler injection with micro-cannula instead of needles. *Dermatol Surg* 2009; 35:2005–2008.
37. Rodriguez JM, Xie YL, Winthrop KL, Schafer S, Sehdev P, Solomon J, Jensen B, Toney NC, Lewis PF. Mycobacterium chelonae facial infections following injection of dermal filler. *Aesthet Surg J* 2013; 33:265–269.
38. Grippaudo FR, Pacilio M, Di Girolamo M, Dierckx RA, Signore A. Radiolabelled white blood cell scintigraphy in the work-up of dermal filler complications. *Eur J Nucl Med Mol Imaging* 2013; 40:418–425.
39. Colbert SD, Southorn BJ, Brennan PA, Ilankovan V. Perils of dermal fillers. *Br Dent J* 2013; 214:339–340.
40. Alijotas-Reig J, Fernández-Figueras MT, Puig L. Inflammatory, immune-mediated adverse reactions related to soft tissue dermal fillers. *Semin Arthritis Rheum*, 2013; 43:241–258.
41. Talbot SG, Parrett BM, Yaremchuk MJ. Sepsis after autologous fat grafting. *Plast Reconstr Surg* 2010; 126:162e–164e.
42. Sykes JM, Tapias V, Pu LL. Autologous fat grafting viability: Lower third of the face. *Facial Plast Surg* 2010; 26:376–384.
43. Taupin A, Labbé D, Nicolas J, Debout C, Benateau H. Lipofilling and weight gain. Case report and review of the literature. *Ann Chir Plast Esthet* 2010; 55:238–242.
44. Delay E, Garson S, Tousson G, Sinna R. Fat injection to the breast: Technique, results, and indications based on 880 procedures over 10 years. *Aesthet Surg J* 2009; 29:360–376.
45. Teimourian B. Blindness following fat injections. *Plast Reconstr Surg* 1988; 82:361.
46. Dreizen NG, Framm L. Sudden unilateral visual loss after autologous fat injection into the glabellar area. *Am J Ophthalmol* 1989; 107:85–87.
47. Egido JA, Arroyo R, Marcos A, Jiménez-Alfaro I. Middle cerebral artery embolism and unilateral visual loss after autologous fat injection into the glabellar area. *Stroke* 1993; 24:615–616.
48. Feinendegen DL, Baumgartner RW, Vuadens P, Schroth G, Mattle HP, Regli F, Tschopp H. Autologous fat injection for soft tissue augmentation in the face: A safe procedure? *Aesthet Plast Surg* 1998; 22:163–167.
49. Sclafani A, Romo T, Jacono AA, McCormick SA, Cocker R, Parker A. Evaluation of acellular dermal graft in sheet (Alloderm) and injectable (micronized Alloderm) forms for soft tissue augmentation: Clinical observations and histologic findings. *Arch Fac Plast Surg* 2000; 2:130–136.
50. De Coninck A, Personal communication, 2008.
51. Requena L, Requena C, Christensen L, Zimmermann US, Kutzner H, Cerroni L. Adverse reactions to soft tissue fillers. *J Am Acad Dermatol* 2011; 64:1–34.
52. Tutrone WD, Cohen JL. Dissolving collagen fillers. Enzymatic degradation of some problematic filler circumstances may now include collagens. *J Drug Dermatol* 2009; 8:1140–1141.
53. André P. Evaluation of the safety of a non-animal stabilized hyaluronic acid (NASHA-Q-Medical Sweden) in European countries: A retrospective study from 1997 to 2001. *J Eur Acad Dermatol Venereol* 2004; 18:422–425.
54. Rodrigues-Barata AR, Camacho-Martínez FM. Undesirable effects after treatment with dermal fillers. *J Drugs Dermatol* 2013; 12:e59–e62.
55. Buntrock H, Reuther T, Prager W, Kerscher M. Efficacy, safety, and patient satisfaction of a monophasic cohesive polydensified matrix versus a biphasic nonanimal stabilized hyaluronic acid filler after single injection in nasolabial folds. *Dermatol Surg* 2013; 39:107–1105.
56. Micheels P. Human anti-hyaluronic acid antibodies: Is it possible? *Dermatol Surg* 2001; 27:185–191.
57. Lupton JR, Altster TS. Cutaneous hypersensitivity reaction to injectable hyaluronic acid gel. *Dermatol Surg* 2002; 26:135–137.
58. Altman RD, Moskowitz R, the HaylganO Study Group. Intraarticular sodium haluronate (Hyalgan®) in the treatment of patients with osteoarthritis of the knee. *J Rheumatol* 1998; 25:2203–2212.
59. Calvo M, Tornero P, De Barrio M, Mínguez G, Infante S, Herrero T, Baeza ML. Erythema multiform due to hyaluronic acid (Go-on). *J Investig Allergol Clin Immunol* 2007; 17:127–128.
60. Brody HJ. Use of hyaluronidase in the treatment of granulomatous hyaluronic acid reactions or unwanted hyaluronic acid misplacement. *Dermtol Surg* 2005; 31:893–897.
61. Bachmann F, Erdmann R, Hartmann V, Wiest L, Rzany B. The spectrum of adverse reactions after treatment with injectable fillers in the glabellar region: Results from the injectable filler safety study. *Dermatol Surg* 2009; 35:1629–1634.
62. Schuller-Petrović S, Pavlović MD, Schuller SS, Schuller-Lukić B, Neuhold N. Early granulomatous foreign body reactions to a novel alginate dermal filler: The system's failure? *J Eur Acad Dermatol Venereol* 2013; 27:121–123.
63. Eppley BL, Summerlin DJ, Prevel CD, Sadove AM. Effects of a positively charged biomaterial for dermal and subcutaneous augmentation. *Aesthet Plast Surg* 1994; 18:413–416.
64. Massone C, Horn M, Kerl H, Ambros-Rudolph CM, Brunasso AMG, Cerroni L. Foreign body granuloma due to Matridex injection for cosmetic purposes. *Am J Dermatopathol* 2009; 31:197–199.
65. Huh SY, Cho SY, Kim KH, An JS, Won CH, Chang SE, Lee MW, Choi JH, Moon KC. A case of complication after Matridex® injection. *Ann Dermatol* 2010; 22:81–84.
66. Yang J-H, Lee S-L, Won C-H, Chang S-E, Lee M-W, Choi J-H, Moon K-C. Foreign body granuloma caused by hyaluronic acid/dextranomer microsphere filler injection. *Int J Dermatol* 2012; 51:1517–1518.
67. Apikian M, Roberts S, Goodman GJ. Adverse reactions to poly-L-lactic acid injection in the periorbital area. *J Cosmet Dermatol* 2007; 6:95–101.
68. Palm MD, Woodhall KE, Butterwick KJ, Goldman MP. Cosmetic use of poly-L-lactic acid: A retrospective study of 130 patients. *Dermatol Surg* 2010; 36:161–170.
69. Zimmermann US, Clerici TJ. The histological aspect of fillers complications. *Semin Cutan Med Surg* 2004; 23:24–250.
70. Marmur ES, Al Quran H, De Sa Earp AP, Yoo JA. A five-patient satisfaction pilot study of calcium hydroxylapatite injection for treatment of aging hands. *Dermatol Surg* 2009; 35:1978–1986.
71. Daines SM, Williams EF III. Complications associated with injectable soft-tissue fillers. A 5-year retrospective review. *JAMA Facial Plast Surg* 2013; 15:226–231.
72. Daley T, Damm DD, Haden JA, Kolodychak MT. Oral lesions associated with injected hydroxyapatite cosmetic filler. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012; 114:107–111.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

73. Dadzie OE, Mahalingam M, Parada M, El Helou T, Philips T, Bhawan J. Adverse reactions to soft tissue fillers—A review of the histological features. *J Cutan Pathol* 2008; 35:536–548.
74. Reddy KK, Brauer JA, Anolik R, Bernstein L, Brightman LA, Hale E, Karen J, Weiss E, Geronemus RG. Calcium hydroxylapatite nodule resolution after fractional carbon dioxide laser therapy. *Arch Dermatol* 2012; 148:634–636.
75. Cohen JC, Reisacher W, Malone M, Sulica L. Severe systemic reaction from calcium hydroxylapatite vocal fold filler. *Laryngoscope*, 2013; 123:2237–2239.
76. Christensen LC, Breiting VA, Aasted A, Jörgensen A, Kebuladze I. Long term effects of polyacrylamide hydrogel (PAAG, Interfall/Contura SA) in human breast tissue. *Plast Reconstr Surg* 2003; 111:1883–1888.
77. Leung KM, Yeoh GPS, Chan KW. Breast pathology in complications associated with polyacrylamide hydrogel (PAAG) mammoplasty. *Hong Kong Med J* 2007; 13:137–140.
78. Kalantar-Hormozi A, Mozafari N, Rasti M. Adverse effects after use of polyacrylamide gel as a facial soft tissue filler. *Aesthet Surg J* 2008; 28:139–142.
79. Reda-Lari A. Augmentation of the malar area with polyacrylamide hydrogel: Experience with more than 1300 patients. *Aesthet Surg J* 2008; 28:131–138.
80. Cheng NX, Wang YL, Wang JH, Zhang XM, Zhong H. Complications of breast augmentation with injected hydrophilic polyacrylamide gel. *Aesthet Plast Surg* 2002; 26:375–382.
81. Lee CJ, Kim SG, Kim L, Choi MS, Lee SI. Unfavorable findings following breast augmentation using injected polyacrylamide hydrogel. *Plast Reconstr Surg* 2004; 114:1967–1968.
82. Zarini E, Supino R, Pratesi G et al. Biocompatibility and tissue interactions of a new filler material for medial use. *Plast Reconstr Surg* 2004; 114:934–942.
83. Malik S, Mehta P, Adesanya O, Ahluwalia HS. Migrated periocular filler masquerading as arteriovenous malformation: A diagnostic and therapeutic dilemma. *Ophthal Plast Reconstr Surg* 2013; 29:e18–e20.
84. Jones DH, Carruthers A, Fitzgerald R, Sarantopoulos GP, Binder S. Late-appearing abscesses after injections of nonabsorbable hydrogel polymer for HIV-associated facial lipoatrophy. *Dermatol Surg* 2007; 33(Suppl 2):S193–S198.
85. Goldan O, Georgio I, Grabov-Nardinii G, Regev E, Tessone A, Liran A, Haik J, Mendes D, Orenstein A, Winkler E. Early and late complications after a nonabsorbable hydrogel polymer injection: A series of 14 patients and novel management. *Dermatol Surg* 2007; 33(Suppl 2):S199–S206.
86. Lemperle G, Morhenn V, Charrier U. Human histology and persistence of various injectable filler substances for soft tissue augmentation. *Aesthet Plast Surg* 2003; 27:354–366; discussion 367.
87. Bergeret-Galley C, Latouche X, Illouz YG. The value of a new filler material in corrective and cosmetic surgery. DermaLive and DermaDeep. *Aesthet Plast Surg* 2001; 25:249–255.
88. Sidwell RU, Dhillon AP, Butler PE, Rustin MH. Localized granulomatous reaction to a semi-permanent hyaluronic acid and acrylic hydrogel cosmetic filler. *Clin Exp Dermatol* 2004; 29:630–632.
89. Angus JE, Affleck AG, Leach ICH, Millard LG. Two cases of delayed granulomatous reactions to the cosmetic filler DermaLive, a hyaluronic acid and acrylic hydrogel. *Br J Dermatol* 2006; 155:1077–1078.
90. Rossner M, Rossner F, Bachmann F, Wiest L, Bzany B. Risk of severe adverse reactions to an injectable filler based on a fixed combination of hydroxyethylmethacrylate and ethylmethacrylate with hyaluronic acid. *Dermatol Surg* 2009; 35:367–374.
91. González-Vela MC, Armesto S, González-López MA, Fernández-Llaca JH, Val-Bernal JF. Perioral granulomatous reaction to Dermalive. *Dermatol Surg* 2008; 34:986–988.
92. Gamo R, Pinedo F, Vicente J, Naz E, Calzado L, Ruiz-Genao D, de la Fuente EG, Alvarez G, Arranz E, López-Estebaranz JL. Keratoacanthoma-like reaction after a hyaluronic acid and acrylic hydrogel cosmetic filler. *Dermatol Surg* 2008; 34:954–959.
93. Weyand B, Menke H. Case report: Adverse granulomatous reaction (granuloma formation) and pseudomonas superinfection after lip augmentation by the new filler DermaLive. *Eur J Plast Surg* 2008; 30:291–295.
94. Hoffman AS. Synthetic polymeric biomaterials. In: Gebelein CG, ed. *Polymeric Materials and Artificial Organs*. Washington, DC: American Chemical Society, 1984, pp. 13–29.
95. Dansereau A, Hamilton D, Kavouni A et al. A report on the safety of and satisfaction with particle-based fillers, specifically polymethylmethacrylate microspheres suspended in collagen. *Cosmet Dermatol* 2008; 21:151–156.
96. Cohen SR, Berner CF, Busso M et al. ArteFill: A long-lasting injectable wrinkle filler material—Summary of the U.S. Food and Drug Administration trials and a progress report on 4- to 5-year outcomes. *Plast Reconstr Surg* 2006; 118(Suppl 3):S64–S76.
97. Solomon P, Sklar M, Zener R. Facial soft tissue augmentation with Artecoll(®): A review of eight years of clinical experience in 153 patients. *Can J Plast Surg* 2012; 20:28–32.
98. Haneke E. Polymethyl methacrylate microspheres in collagen. *Semin Cutan Med Surg* 2004; 23:227–232.
99. Wu W, Chayavichitsilp P, Hata T. Extremely delayed granulomatous reaction to soft-tissue injectables (polymethyl methacrylate). *J Am Acad Dermatol* 2012; 67:e206–e207.
100. Fischer J, Metzler G, Schaller M. Cosmetic permanent fillers for soft tissue augmentation: A new contraindication for interferon therapies. *Arch Dermatol* 2007; 143:507–510.
101. Conejo-Mir JS, Sanz Guirado S, Angel Muñoz M. Adverse granulomatous reaction to Artecoll treated by intralesional 5-fluorouracil and triamcinolone injections. *Dermatol Surg* 2006; 32:1079–1081.
102. Odo MEY, Odo LM, Nemoto NCF, Cucé LC. Treatment of nodules caused by polymethylmethacrylate. A pilot study. *Dermatol Surg* 2008; 32:1079–1081.
103. Kamouna B, Kazandjieva J, Balabanova M, DourmishevV L, Negentsova Z, Etugov D, Nikolova A, Miteva L, Haneke E. Oil soluble vitamins—Illegal use as fillers for lip augmentation. *Facial Plast Surg* 2014; 30:635–643.
104. Foucar E, Downing DT, Gerber WL. Sclerosing lipogranuloma of the male genitalia containing vitamin E: A comparison with classical "paraffinoma." *J Am Acad Dermatol* 1983; 9:103–110.
105. Akkus E, Iscimen A, Tasli L, Hattat H. Paraffinoma and ulcer of the external genitalia after self-injection of vaseline. *J Sex Med* 2006; 3:170–172.
106. Nyirady P, Kelemen Z, Kiss A, Banfi G, Borka K, Romics I. Treatment and outcome of vaseline-induced sclerosing lipogranuloma of the penis. *Urology* 2008; 71:1132–1137.
107. Al-Ansari AA, Shamsodini A, Talib RA, Gul T, Shokeir AA. Subcutaneous cod liver oil injection for penile augmentation: Review of literature and report of eight cases. *Urology* 2010; 75:1181–1184.
108. Hohaus K, Bley B, Köstler E, Schönlebe J, Wollina U. Mineral oil granuloma of the penis. *J Eur Acad Dermatol Venereol* 2003; 17:585–587.
109. Maxwell GP, Gingrass MK. Ultrasound-assisted lipoplasty: A clinical study of 250 consecutive patients. *Plast Reconstr Surg* 1998; 101:189–202.
110. Zocchi ML. Ultrasonic assisted lipoplasty. Technical refinements and clinical evaluations. *Clin Plast Surg* 1996; 23:575–598.
111. Seward AC, Meara DJ. Industrial-grade silicone injections causing intermittent bilateral malar swelling: Review of safety and efficacy of techniques and products available. *J Oral Maxillofac Surg* 2013; 71:1245–1248.
112. Webster RC, Fuleihan NS, Hamadan US, Gaunt IM, Smith RC. Injectable silicone: Report of 17,000 facial treatments since 1962. *Am J Cosmet Surg* 1986; 3:41–48.
113. Benedetto AV, Lewis AT. Injecting 1000 centistoke liquid silicone with ease and precision. *Dermatol Surg* 2003; 29:211–214.
114. Zappi E, Barnett JG, Zappi M, Barnett CR. The long-term host-response to liquid silicone injected during soft tissue augmentation procedures: A microscopic appraisal. *Dermatol Surg* 2007; 33:S186–S192.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

115. Fulton J, Caperton C. The optimal filler: Immediate and long-term results with emulsified silicone (1,000 centistokes) with cross-linked hyaluronic acid. *J Drugs Dermatol* 2012; 11:1336–1341.
116. Eppley BL, Sidner RA, Sadove AM. Adequate preclinical testing of bioplastique injectable material? *Plast Reconstr Surg* 1992; 89:157–158.
117. Baijens L, Speyer R, Linssen M, Ceulen R, Manni JJ. Rejection of injectable silicone "Bioplastique" used for vocal cord augmentation. *Eur Arch Otorhinolarangol* 2007; 264:565–568.
118. Persichetti P, Palazzolo D, Tenna S, Poccia I, Abbruzzese F, Trombetta M. Dermal filler complications from unknown biomaterials: Identification by attenuated total reflectance spectroscopy. *Plast Reconstr Surg* 2013; 131:597e–603e.
119. Eversole R, Tran K, Hansen D, Campbell J. Lip augmentation dermal filler reactions, histopathologic features. *Head Neck Pathol* 2013; 7:241–249.
120. Haneke E. What is new in long-lasting fillers. *Touch Briefings Eur Dermatol* 2008; 3:57–58.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Platelet-rich plasma from science to clinical results

Sabine Zenker

INTRODUCTION

The human aging process is complex. Platelet-rich plasma (PRP) can be used for skin regeneration and rejuvenation.

With the aging process, the epidermal layer changes less than the dermis where the number of cells and their reproductive activity slows down [1]. Consecutively, the levels of collagen, hyaluronic acid, and glycosaminoglycans decrease. Collagen accounts for as much as approximately 70% of the skin's dry weight and plays a pivotal role in maintaining the skin's structure. Collagen which exists in the following subtypes: Type I and Type III collagen are present in the highest amounts, Type IV collagen which is the main component of the lamina densa, Type VII collagen which is present at the dermal–epidermal interface, and Type V collagen which is found pericellularly [2].

Collagen changes in a prominent way during the aging process: in morphology, in its amount, and in its fiber arrangement, which becomes cross-linked, fragmented, and curled [3].

Clinically speaking, aging skin loses its firmness, elasticity, glow, and tone: it tends to sag, thins, becomes more wrinkled, dull and less glowy, and becomes less hydrated.

CONCEPTS IN AESTHETIC DERMATOLOGY

An important concept in aesthetic dermatology is that of controlled stimulation of the skin's structures. Multiple modalities for skin rejuvenation are available nowadays (Figure 57.1): from home care to medical treatments such as cosmeceuticals, chemical peels, laser technologies, filler injections (hyaluronic acid, calcium hydroxylapatite, polycaprolactone etc.), radiofrequency, needling, jet injections, cosmeceuticals, carboxytherapy, and hyperbaric oxygen—and PRP [4–10].

PLATELETS

Platelets, also known as thrombocytes, are small, irregularly shaped clear cell fragments, 2–3 μm in diameter [11] derived from fragmentation of precursor megakaryocytes. The average life span of a platelet is normally just 5–9 days. Platelets are suspended in the human peripheral blood and are involved in hemostasis, forming blood clots to prevent excessive bleeding.

Platelets contain alpha and dense granules. These alpha granules contain P-selectin, platelet factor 4, transforming growth factor 4 and β1, platelet-derived growth factor (PDGF), fibronectin, B-thromboglobulin, fibrinogen, and coagulation factor V [12]: platelets are a natural source of growth factors. Furthermore, they secrete cytokines, chemokines, and other inflammatory mediators [13–16]. Once activated, platelets excrete the contents of these granules into their canalicular systems and into the surrounding blood.

PLATELET ROLE IN WOUND HEALING

To understand the mode of action of PRP in aesthetics, it is helpful to revise the wound healing cascade.

After an injury, platelets degranulate within 10 minutes to assist the formation of a clot, releasing growth factors into the local environment; 95% of the presynthesized existing platelet growth factors are present in the wound within the first hour: in this first phase of wound healing, inflammation [17,18], and clotting take place in order to obtain hemostasis (this clot mostly consists of thrombocytes). During the second phase, the exudation, various factors are released to attract cells that phagocytose debris and bacteria and release factors that initiate the third phase, the proliferative phase of wound healing [19]. Here, fibroplasia and granulation tissue formation occurs. Thanks to the vascular ingrowth caused by platelets, macrophages come into play just as the direct influence of platelets begins to subside. Platelets are the pacemakers for wound healing (Figures 57.2 through 57.4).

PLATELET-RICH PLASMA

PRP may be defined as a preparation of plasma, generated by centrifugation, having a platelet concentration above the normal for venous blood. PRP not only contains platelets but also many other ingredients such as growth factors, chemokines, cytokines and other components (glucose, mineral ions, proteins such as cell adhesion molecules including fibrin, fibronectin, and vitronectin, and albumin). The activated thrombocytes, once injected, then release those factors. Platelets also carry on their surface a number of signaling molecules.

Focusing on the growth factors of interest for PRP, the following have been shown to be released by activated platelets [20–22]:

1. *PDGF* has its main origin in the platelets and affects fibroblast proliferation and chemotaxis, mitogenesis of the mesenchymal stem cells and endothelial cells, and promotes the synthesis of extracellular matrix and hyaluronan production.

2. *Transforming growth factor* α and β (TGFα,β) has its main origin in the platelets and promotes cell mitosis (fibroblasts),

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

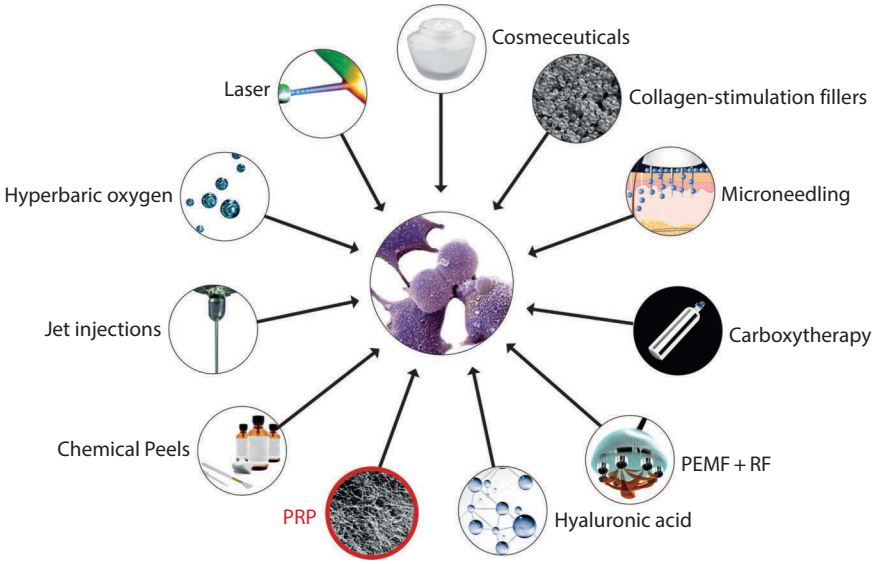


Figure 57.1 Skin rejuvenation treatments.

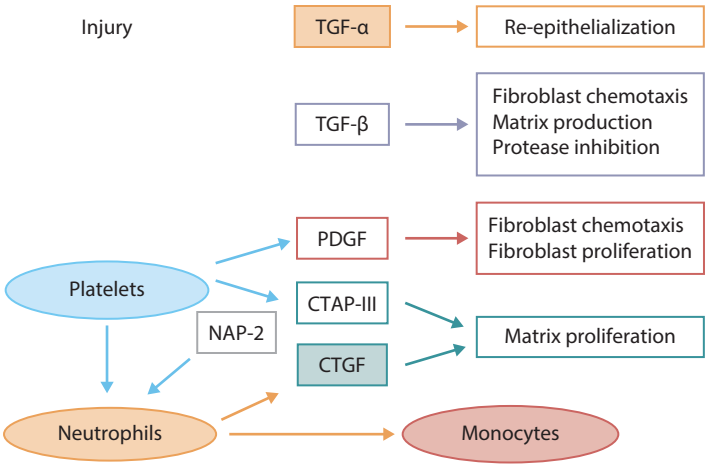


Figure 57.2 Chemical process of wound healing. (From Falabella A and Falanga V, Wound healing, in: Freinkel RK and Woodley DT, eds., *The Biology of the Skin*, Parthenon Publishing, New York, 2001, pp. 281–297. With permission.)

collagen production, stimulation of DNA synthesis, expression of antimicrobial peptides, keratinocyte stimulation, and angiogenesis.

3. *Vascular endothelial growth factor* (VEGF) stimulates angiogenesis and endothelial cell proliferation.

4. *Epidermal growth factor* (EGF) regulates cell growth, stimulates the proliferation and differentiation of the epidermal cells, promotes granulation tissue formation, and costimulates angiogenesis.

5. *Fibroblast growth factor* (FGF 1,2) stimulates fibroblast chemotaxis, angiogenesis, matrix (collagen fiber) deposition, and wound contraction.

The activated platelets will synthesize and release those growth factors over the next 7–10 days once this whole cascade has started (Figure 57.5; Reference 21).

So taking it all together, PRP is a complex process that results in attraction of mesenchymal stem cells and endothelial cells, differentiation of fibroblasts and osteoblasts, upregulation other growth factors on cells such as macrophages, synthesis of the extracellular matrix and collagen, promotion of cell mitosis, stimulation of DNA synthesis and of angiogenesis, etc.

Since PRP is an autologous material, it is inherently safe and free of transmissible diseases such as HIV and hepatitis [22]

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

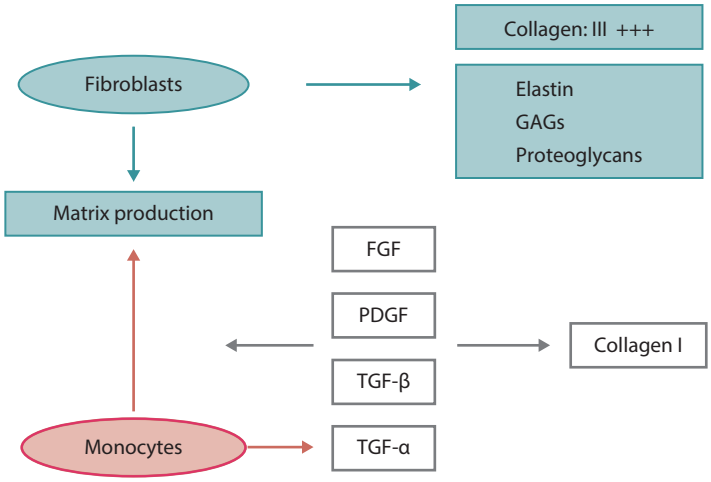


Figure 57.3 Role of fibroblasts in wound healing. (From Falabella A and Falanga V, Wound healing, in: Freinkel RK and Woodley DT, eds., *The Biology of the Skin*, Parthenon Publishing, New York, 2001, pp. 281–297. With permission.)

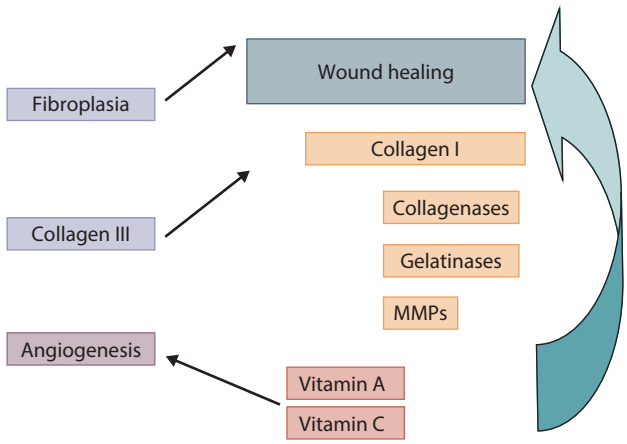


Figure 57.4 Factors contributing to wound healing. (From Falabella A and Falanga V, Wound healing, in: Freinkel RK and Woodley DT, eds., *The Biology of the Skin*, Parthenon Publishing, New York, 2001, pp. 281–297. With permission.)

and it is not carcinogenic. PRP is autologous, non-immunogenic, noninfectious, and is a readily available source of bioagents. Platelet preparations are convenient, and the harvesting process has been greatly simplified in recent years.

PLATELET-RICH PLASMA IN MEDICINE

As autologous PRP promotes local tissue growth and repair, it has—over the years—attracted attention in various medical fields including, initially, orthopedic and dental surgery.

As early as 1990, autologous human platelet-derived wound healing factors (HPDWHFs) were proposed as wound healing agents for recalcitrant skin ulcers, working by promoting the formation of granulation tissue in the early healing phase. This conclusion was based on studies in 23 patients with 27 skin ulcers who had shown no signs of healing after an average period of 25 weeks of conventional wound care. Strikingly, 100% healing was seen in an average of 10 weeks after the application of HPDWHF [22–33].

Mishra et al. conducted a study on knee tendonitis in patients unresponsive to other treatments, including surgery in some cases, and obtained 77% pain reduction at 6 months after PRP injections [34].

In implantology, PRP optimizes regeneration of bone: Marx et al. showed significant enhancement of bone

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

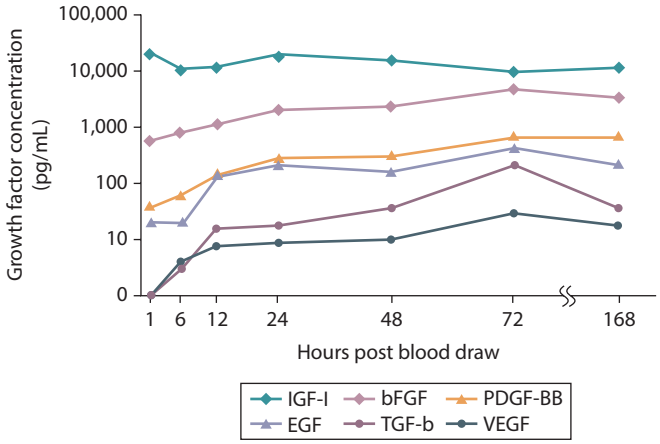


Figure 57.5 Controlled GF release over time. There is a 5–10× increase in each growth factor indicating increased stability within the PRFM over 7 days. (Copyright Selphyl™.)

density after 6 months compared to the control group (n-44), 55% versus 74% [21].

PLATELET-RICH PLASMA IN AESTHETICS

Study Data

In recent years, PRP has been used for a range of dermatological indications including wound healing, fat grafting, alopecia, scar revision, and skin regeneration by dermal augmentation. A modest benefit exists for aesthetic indications, such as skin rejuvenation [35].

The best scientific evidence for PRP as a stand-alone aesthetic therapy can be found for the mesotherapy-like injections used for skin rejuvenation.

Cho et al. showed that, in photoaged mice (ultraviolet B irradiation for 8 weeks), wrinkles were significantly reduced in the PRP-injected group. Biopsy results indicated that the dermal layer was thicker in the PRP-injected group. In an *in vitro* assay, fibroblast proliferation and collagen production were increased in the experimental group by growth factors in the PRP [36].

Cho et al. recently showed *in vitro* that PRP induces increased expression of G1 cell cycle regulators, type I collagen, and matrix metalloproteinase-1 (MMP-1) in human skin fibroblasts [37].

Further to this, Kim et al. evaluated the effects of PRP on human dermal fibroblasts: in this study, the effects of both activated PRP (aPRP) and activated platelet-poor plasma (aPPP) were investigated on the remodeling of the extracellular matrix, a process that requires activation of dermal fibroblasts; their results showed that both aPRP and aPPP stimulated cell proliferation, with peak proliferation occurring in cells grown in 5% aPRP. Additionally, aPRP and aPPP each increased the expression of type I collagen, MMP-1 protein, and mRNA in human dermal fibroblasts [38].

Topical application of PRP-derived growth factors stimulates the rejuvenation of photoaged facial skin, improving its clinical appearance and inducing new collagen synthesis [39,40].

A histological study by Scalfani et al. showed that platelet-rich fibrin matrix (PRFM) injections in the upper arm induced collagenesis, angiogenesis, and adipogenesis; 7 days after treatment, he found new collagen deposition and 19 days after injection the formation of new blood vessels as well as stimulation of subdermal adipocytes [41].

Amgar [42] tried to evaluate the efficacy of this facial skin treatment through objective biometric parameters, including anisotropy, transepidermal water loss (TEWL), microrelief, and hydration. This study, which included 37 female patients, demonstrated an average of 24% improvement in the anisotropy coefficient after the third week. The TEWL and microrelief parameters also improved significantly ($p < 0.05$ in all parameters tested).

A more clinical approach was chosen by Redaelli [43]; he did 23 sessions of mesotherapy-wise injection of the face and neck and evaluated the results clinically by improvement score, photographic score, and patient's doctor's satisfaction scores. He stated that "overall, the results were satisfactory but that further work needs to be carried out to investigate its exact mechanism of action."

Ablative CO_2 fractional resurfacing is a therapeutic intervention for the treatment of acne scars, although this technique is associated with prolonged surgical site erythema and edema, which may adversely affect the daily lives of patients. Jung-Im et al. [44] were able to show that PRP has a benefit for wound healing after skin resurfacing by fractional carbon dioxide laser (FCL): the melanin index (MI) was lower (statistically significant difference at day 3 [$p = 0.05$]), erythema resolved quickly (a significant difference was observed at day 1, but the erythema index [EI] did not change significantly) and biopsy specimens from the PRP-treated side showed an overall increase in dermal thickness and thicker collagen bundles than those from the control side.

Looking at combination therapies with PRP, there are some data: Ghwadat et al. compared adjuvant use of PRP with fractional carbon dioxide laser for correction of acne scars. The author compared PRP (intradermal injections and topical application) after fractional carbon dioxide laser. The results were that combined treatment had significantly better response ($p = 0.03$), fewer side effects, and shorter downtime ($p = 0.02$). So they concluded that the combination of topical PRP and FCL is an effective, safe modality in the treatment of atrophic acne scars with shorter downtime and better tolerability [45].

A most recent study evaluated the effect of PRP in the treatment of dark circles: "the improvement in infraorbital color homogeneity was statistically significant ($p = 0.010$), but no statistically significant changes were observed in melanin content, stratum corneum hydration, wrinkle volume, and visibility index [46]." So again and also for this indication, further studies are needed to establish the best treatment protocol for this indication.

PRP seems to increase the skin's elasticity: in a study conducted by Shin et al. [47], "PRP combined with fractional laser increased subject satisfaction and skin elasticity and decreased the EI. PRP increased the length of the dermoepidermal junction, the amount of collagen, and the number of fibroblasts."

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

The combination of fractional ablative carbon dioxide (CO_2) laser resurfacing showed a beneficial effect as well: Na et al. [48] found more rapid healing and reduced erythema after ablative fractional CO_2 laser resurfacing combined with the application of autologous PRP (significantly faster recovery of TEWL was seen on the PRP-treated side). The EI and MI on the PRP-treated side were lower than on the control side. Biopsy specimens from the PRP-treated side showed thicker collagen bundles than those from the control side.

And Lee et al. [49] showed that the treatment with PRP after ablative CO_2 fractional resurfacing enhances recovery of laser-damaged skin and synergistically improves the clinical appearance of acne scarring.

In a more recent study (2014), Nofal et al. showed improvement of acne scars by combining PRP with other treatment modalities. The study aimed to evaluate the efficacy and safety of intradermal injection of PRP, 100% focal TCA, and a combination of skin needling plus topical PRP for the treatment of atrophic acne scars. Nofal et al. [50] showed that all 3 groups showed statistically highly significant improvement in the degree of acne scars after treatment ($p < .001$). No major adverse effects were observed in the studied groups.

From my personal experience in treating patients with PRP for many years, I have found that combination therapies, such as PRP with microneedling, are helpful for skin rejuvenation. Evidence and consensus are still lacking on how to achieve best results.

Handling and Quality Aspects

Coagulation: Immediately after the activation of the platelets in the PRP-harvesting tube (by addition of calcium chloride), fibrin polymerization is initiated and growth factors are released [51–54]. That is why PRP must be developed in an anticoagulated state and should be used for reinjection within 10 minutes of clot initiation.

Some PRP harvesting kits may still contain thrombin from bovine origin; therefore, the end product cannot be categorized as autologous. Others use a chemical buffer to separate the plasma and the red cells and are not delivering a pure PRP (Figure 57.6).

Differences of harvesting kits: There exist significant differences among the commercial PRP preparations [55,56] such as the volume of autologous blood required, time and speed of centrifugation, nature of plasmaphoresis (choice of density gradient separation media: dependent on design of gel separator), addition of an activating agent, pH, final platelet, growth factor, and leukocyte concentrations.

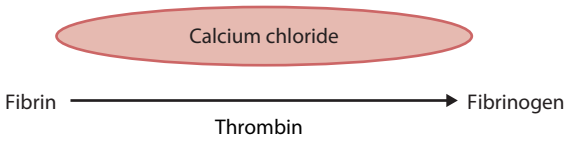


Figure 57.6 PRP activation.

Centrifugation: It has been established that excessive acceleration decreases the integrity of the platelet membrane, leading to premature activation, and further that platelets should be left intact in order to release the growth factors in a sustained way. Thus, for more than 400 G values, 5% of platelets are activated [57,58] and 40%–70% of them become activated at 3000 G.

Purity: The purity of the final PRP product is an important aspect of the quality of the PRP: extracellular hemoglobin oxidizes and thereby heme and reactive ferric oxide are released [59,60]. Thus, free radicals are generated that lead to inflammation, vascular injury, and cell death; additionally, free heme can lead to hemosiderin staining from iron oxide [61].

Leukocytes release MMPs and produce oxygen radicals/cytokines (catabolic or inflammatory); thrombin significantly increases leukocyte IL-1β production, which can lead to tissue damage, inflammation, and impaired healing as well as local pain [62].

Most methods for isolating PRP use anticoagulants to prevent clot formation [63] such as acid citrate dextrose-A (ACD-A) and citrate phosphate dextrose: once the pH is lowered (ACD-A has a pH 4–5), injection pain increases. So, a more physiological pH is desirable in PRP preparations.

Platelet concentration: What is the optimal concentration of platelets in the final PRP product? It has been shown that a sufficient cellular response to platelet concentrations was seen first when a four- to fivefold increase over baseline platelet numbers was achieved [64]. A similar study by Lui et al. [65] showed that fibroblast proliferation and type I collagen production were also enhanced by increasing platelet concentrations. Some publications suggest that PRP should achieve a three- to fivefold increase in platelet concentration over baseline [66,67].

Weibrich et al. [68] looked at platelet counts as well as different growth factors (PDGF, TGFb1, IGF1) and found a substantial variation in the growth factor content of PRP. They concluded that the factors influencing this are still worthy of further investigation and that a technique whereby the growth factor content could be rapidly assessed in PRP may be of therapeutic benefit. The platelet and consequent growth factor availability also depend on the particular harvesting kit: Mazzucco et al. [69] found that "similar methods for platelet gel preparation revealed different performances concerning growth factor recovery and the kinetics of its release from the gel. It is unclear whether these noticeable differences are important for clinical management."

To summarize, the following aspects of PRP preparations may be desirable: a low blood draw, a short centrifugation time, a three- to fivefold consistent increase in platelet concentration over baseline, a physiological pH for minimal pain and maintenance of cellular integrity, low red and, possibly, low white cell counts in the final PRP, and physiological and controlled activation.

Clinical Evaluation

PRP in aesthetics is typically used as an intradermal injection material for skin regeneration by dermal augmentation (Figures 57.7 through 57.10). A typical clinical protocol would include three sessions at monthly intervals using meso-wise injections such as epidermal mesotherapy, micropapular

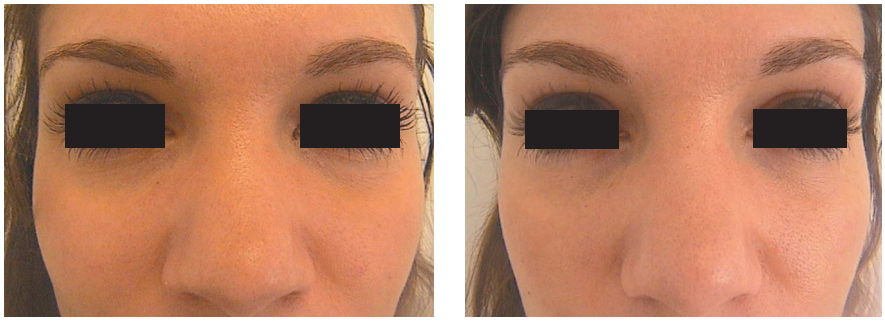
Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

System, company	Whole blood volume, mL	Anticoagulant	Centrifuge force, *g*	Centrifuge time, minutes	Final volume of PRP, mL
Cascade, MTF	18	Sodium citrate, 2 mL	1100	6	7.5
GPS III, Biomet	55	ACD-A, 5 mL	1100	15	6.0
Magellan, Arteriocyte	26	ACD-A, 4 mL	1200	17	6.0

Figure 57.7 Protocols for tested platelet-rich plasma separation systems. (From Castillo TN et al., *Am J Sports Med*, 39(2), 266, February 2011. With permission.)

(a) (b)

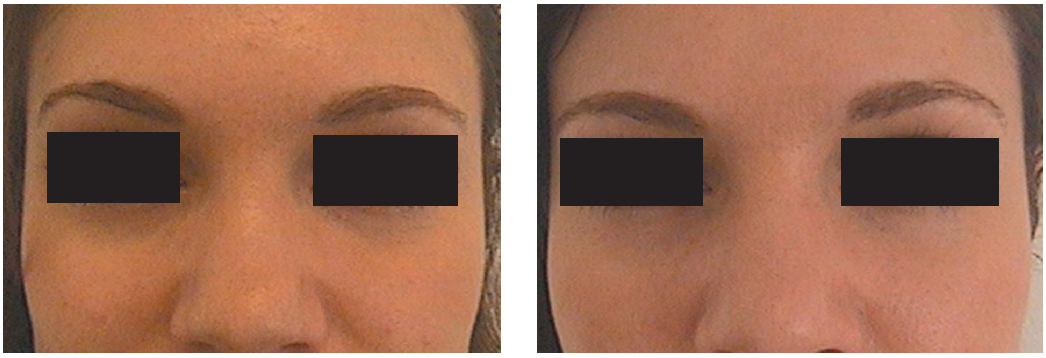
Figure 57.8 Whole face PRP injection by intradermal wheals: (a) before and (b) after three treatments, with 1 month between treatments by MyCells-kit.



(a) (b)

Figure 57.9 Whole face PRP: (a) before and (b) after Selphyl®-PRFM-kit.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b)

Figure 57.10 Whole face PRP: (a) before and (b) after Selphyl®-PRFM-kit.

technique, nappage, and point-by-point technique covering the whole of the area to be treated (face, neck, décolleté, hands, etc.).

To evaluate the immediate effect of PRP injections into the dermis, we tried to image the immediate effect of hypervascularization by confocal laser scanning microscopy and have been able to show that—by filming the injection site prior and directly post injection—the injected area reacts with an increase of vascularization (Figure 57.11).

To evaluate the long-term collagen remodeling effect, we have measured the collagen remodeling effect using a 20 MHz ultrasound in a single case study: the patient had received three PRP treatments one month apart in the mesotherapy mode. Also, 20 MHz evaluations were performed on the nasolabial fold as well as on the tear trough deformity (Figure 57.12): 1 and 2 months after the treatment, the increase in skin thickness and increase in skin density were not consistent nor significant (Figures 57.13 and 57.14).

Overall, and despite the fact that PRP has been used since 2005 within cosmetology objective, scientifically measurable evaluations are still rare [35,70,71]. In my clinical experience, after having performed many PRP treatments: PRP as a stand-alone treatment does not have a convincing collagen stimulating potential nor a filling potential for wrinkles and folds that will be able to compete with filler treatments directly. On the other hand, a smooth complexion and a skin quality improvement is described by almost every patient treated by PRP. The future will show how this effect might be improved.

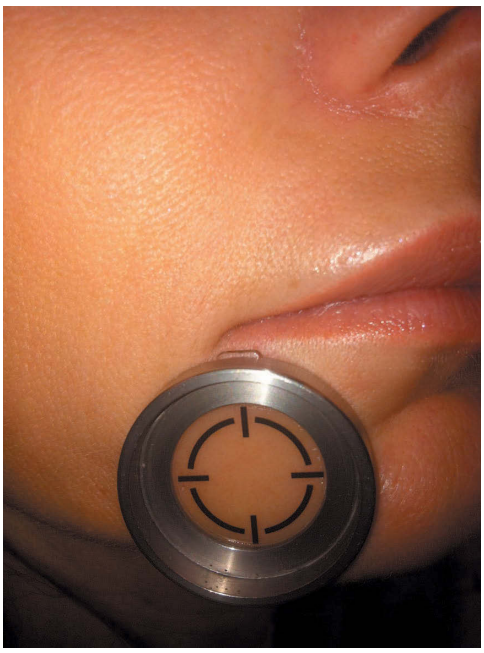


Figure 57.11 Objective evaluation by confocal laser scanning microscopy of the effect of PRFM on skin vascularization.

Figure 57.12 Measurements of density and thickness were made at the nasolabial fold and tear trough.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

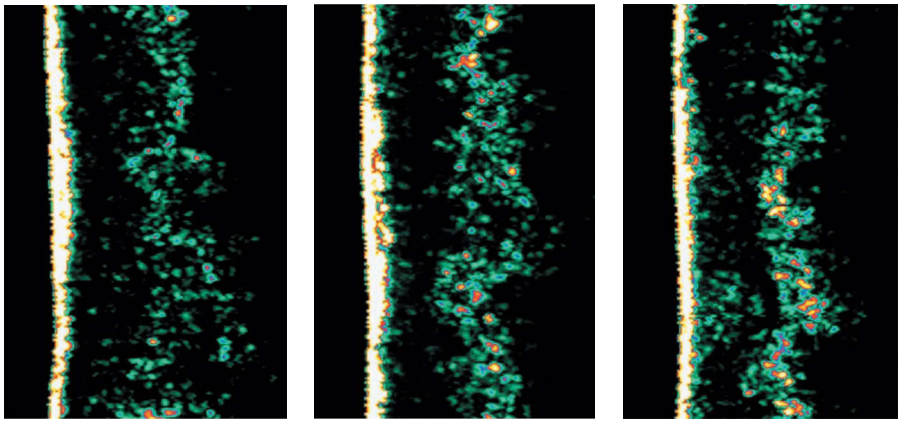


Figure 57.13 (a) Left nasolabial before therapy: density, 14.2; skin thickness (μm), 1606.3. (b) Left nasolabial 1 month after therapy: density, 17.9; skin thickness (μm), 1632.7. (c) Left nasolabial 2 months after therapy: density, 19.01; skin thickness (μm), 1448.3.

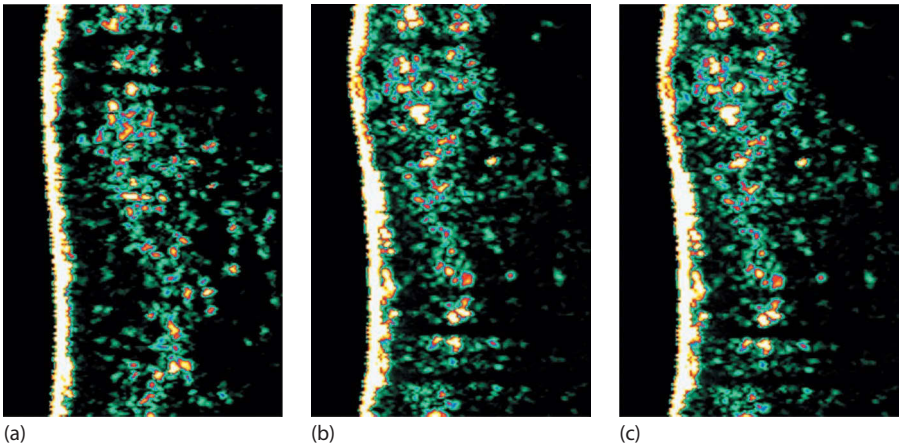


Figure 57.14 (a) Left lower eyelid before therapy: density, 22.1; skin thickness (μm): 1448.3. (b) Left lower eyelid 1 month after therapy: density, 30.4; skin thickness (μm): 1171.8. (c) Left lower eyelid 2 months after therapy: density, 40.3; skin thickness (μm): 1053.3.

CONCLUSION

PRP has a proof of concept in many *in vitro* studies. Generally speaking, the understanding of the mode of action of PRP is well shown; *in vivo* studies explored evidence about the principles of wound healing and tissue regeneration properties induced and enhanced by PRP. But when it comes to aesthetics, an evidence-based proof of the efficacy of PRP and a consensus on best treatment parameters and protocols for combination are still missing. Much clinical data confirms that PRP treatments do result in a smoother complexion and an overall improvement in skin quality. Very often, only the subjective aspect has been evaluated based on the patient's or the physician's subjective level of satisfaction.

REFERENCES

1. Robert L. An original approach to ageing: An appreciation of Fritz Verzar's contribution in the light of the last 50 years of gerontological facts and thinking. *Gerontology* 2006; 52:268–274.
2. Oikarinen A. Connective tissue and aging. *Int J Cosmet Sci* 2006; 26:107.
3. Fisher G, Varani J, Voorhees JJ. Looking older: Fibroblast collapse and therapeutic implications. *Arch Dermatol* 2008 May; 144(5):666–672.
4. Tiedke J, Marks O. Stimulation of collagen production in human fibroblasts. *Cosmet Sci Technol* 2007; 2007:15–18.
5. Berlin AL, Hussain M, Goldberg DJ. Calcium hydroxylapatite filler for facial rejuvenation: A histologic and immunohistochemical analysis. *Dermatol Surg* 2008; 34:S64–S67.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

6. Grimes F. Fibroblast biology in the three dimensional collagen matrices. *Trends Cell Biol* 2003; 13:264–269.
7. Fisher GH, Jacobson LG, Bernstein LJ, Kim KH, Geronemus RG. Nonablative radiofrequency treatment of facial laxity. *Dermatol Surg* 2005; 31:1237–1241.
8. Omi T, Sato S, Numano K, Kawana S. Ultrastructural observations of chemical peeling for skin rejuvenation (ultrastructural changes of the skin due to chemical peeling). *J Cosmet Laser Ther* 2010 February; 12(1):21–24.
9. Longo C, Galimberti M, De Pace B, Pellacani G, Bencini PL. Laser skin rejuvenation: Epidermal changes and collagen remodeling evaluated by in vivo confocal microscopy. *Lasers Med Sci* 2013 May; 28(3):769–776.
10. Brismar K, Lind F, Kratz G. Dose-dependent hyperbaric oxygen stimulation of human fibroblast proliferation. *Wound Repair Regen* 1997; 5(2):147–150.
11. George JN. Platelets. *Lancet* 2000; 355:1531–1539.
12. Harrison P, Cramer EM. Platelet alpha-granules. *Blood Rev* 1993; 7(1):52–62.
13. Rendu F, Brohard-Bohn B. The platelet release reaction: Granules' constituents, secretion and function. *Platelets* 2001; 12:261–273.
14. Reed GL. Platelet secretion. In: Michelson AD, ed. *Platelets*. San Diego, CA: Elsevier Science, 2002, pp. 181–195.
15. Hato T, Ginsberg MH, Shattil SJ. Integrin·IIb,3. In: Michelson AD, ed. *Platelets*. San Diego, CA: Elsevier Science, 2002, pp. 105–116.
16. Weyrich AS, Zimmerman GA. Platelets: Signaling cells in the immune continuum. *Trends Immunol* 2004; 25(9):489–495.
17. Falabella A, Falanga V. Wound healing. In: Freinkel RK, Woodley DT, eds. *The Biology of the Skin*. New York: Parthenon Publishing, 2001, pp. 281–297.
18. Wagner DD, Burger PC. Platelets in inflammation and thrombosis. *Thromb Vasc Biol* 2003; 23:2131–2137.
19. Diacovo TG, Puri KD, Warnock RA, Springer TA, von Andrian UH. Platelet-mediated lymphocyte delivery to high endothelial venules. *Science* 1996; 273(5272):252–255.
20. Eppley BL. Platelet quantification and growth factor analysis from platelet-rich plasma: Implications for wound healing. *Plast Reconstr Surg* 2004; 114:1502.
21. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR. Platelet rich plasma: Growth factor enhancement for bone grafts. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998; 85:638.
22. Hom DB, Linzie BM, Huang TC. The healing effects of autologous platelet gel on acute skin wounds. *Arch Facial Plast Surg* 2007; 9:174–183.
23. O'Connell SM, Impeduglia T, Hessler K, Wang XJ, Carroll RJ, Dardik H. Autologous platelet-rich fibrin matrix as cell therapy in the healing of chronic lower-extremity ulcers. *Wound Repair Regen* 2008; 16(6):749–756.
24. Atri SS, Misra J, Bisht D, Misra K. Use of homologous platelet factors in achieving total healing of recalcitrant skin ulcers. *Surgery* 1990; 108:508–512.
25. Lariviere B, Rouleau M, Picard S, Beaulieu AD. Human plasma fibronectin potentiates the mitogenic activity of platelet-derived growth factor and complements its wound healing effects. *Wound Repair Regen* 2003; 11:79–89.
26. Herouy Y, Mellios P, Bandemir E et al. Autologous platelet-derived wound healing factor promotes angiogenesis via αvβ3 integrin expression in chronic wounds. *Int J Mol Med* 2000; 6:515–519.
27. Margolis DJ, Kantor J, Santanna J, Strom BL, Berlin JA. Effectiveness of platelet releasate for the treatment of diabetic neuropathic foot ulcers. *Diabetes Care* 2001; 24:483–488.
28. Tarroni G, Tessarin C, De Silvestro L et al. Local therapy with platelet-derived growth factors for chronic diabetic ulcers in haemodialysis patients. *G Ital Nefrol* 2002; 19:630–633.
29. Yamaguchi Y, Yoshikawa K. Cutaneous wound healing: An update. *J Dermatol* 2001; 28:521–534.
30. Brown GL, Nanney LB, Griffen J et al. Enhancement of wound healing by topical treatment with epidermal growth factor. *N Engl J Med* 1989; 321:76–79.
31. Du Toit DF, Kleintjes WG, Otto MJ, Mazyala EJ, Page BJ. Soft and hard-tissue augmentation and platelet-rich plasma. Tissue culture dynamics, regeneration and molecular biology perspective. *Int J Shoulder Surg* 2007; 1:64–73.
32. Du Toit DF. The Specialist Forum. State of the Art rejuvenation and normal wound healing with platelet-rich plasma growth factors. Part 1 and 2. 2007; 7:36–42.
33. Eppley BL. Platelet-rich plasma: A review of biology and applications in plastic surgery. *Plast Reconstr Surg* 2006; 118:147e.
34. Mishra A, Woodland J, Vieira A. Treatment of tendon and muscle using platelet-rich plasma. *Clin Sports Med* 2009; 28:113–115.
35. Lynch MD, Bashir S. Applications of platelet-rich plasma in dermatology: A critical appraisal of the literature. *J Dermatolog Treat* 2016 June;27(3):285–289.
36. Cho JM, Lee YH, Baek RM, Lee SW. Effect of platelet-rich plasma on ultraviolet b-induced skin wrinkles in nude mice. *J Plast Reconstr Aesthet Surg* 2011; 64:e31–e39.
37. Cho JW, Kim SA, Lee KS. Platelet-rich plasma induces increased expression of G1 cell cycle regulators, type I collagen and matrix metalloproteinase-1 in human skin fibroblasts. *Int J Mol Med* 2012 January; 29(1):32–36.
38. Kim DH, Je YJ, Kim CD, Lee YH, Seo YJ, Lee JH, Lee Y. Can platelet-rich plasma be used for skin rejuvenation? Evaluation of effects of platelet-rich plasma on human dermal fibroblast. *Ann Dermatol* 2011 November; 23(4):424–431.
39. Fitzpatrick RE, Rostan EF. Reversal of photodamage with topical growth factors: A pilot study. *J Cosmet Laser Ther* 2003; 5:25–34.
40. Kakudo N, Minakata T, Mitsui T, Kushida S, Notodihardjo FZ, Kusumoto K. Proliferation-promoting effect of platelet-rich plasma on human adipose-derived stem cells and human dermal fibroblasts. *Plast Reconstr Surg* 2008; 122:1352–1360.
41. Scalfani AP, McCormick SA. Induction of dermal collagenesis, angiogenesis and adipogenesis in human skin by injection of platelet-rich fibrin matrix. *Arch Facial Plast Surg.* 2012 March–April; 14(2):132–136.
42. Amgar G, Bonnet C, Butnaru A, Herault-Bardin F. Using objective criteria to evaluate cosmetic effects of platelet rich plasma. *Prime J* 2011 November–December; 1:23–30.
43. Redaelli A, Romano D, Marcianó A. Face and neck revitalization with platelet-rich plasma (PRP): Clinical outcome in a series of 23 consecutively treated patients. *J Drugs Dermatol* 2010 May; 9(5):466–472.
44. Jung-Im NA, Choi JW, Choi HR et al. Rapid healing and reduced erythema after ablative fractional carbon dioxide laser resurfacing combined with the application of autologous platelet-rich plasma. *Dermatol Surg* 2011;37:463–468.
45. Gawdat HI. Autologous platelet rich plasma: Topical versus intradermal after fractional ablative carbon dioxide laser treatment of atrophic acne scars. *Dermatol Surg* 2014 February;40(2):152–161.
46. Mehryan P, Zartab H, Rajabi A et al. Assessment of efficacy of platelet-rich plasma (PRP) on infraorbital dark circles and crow's feet wrinkles: A recent study does evaluate the benefit of PRP on the treatment of dark circles. *J Cosmet Dermatol* 2014 March;13(1):72–78.
47. Shin MK, Lee JH, Lee SJ, Kim NI. Platelet-rich plasma combined with fractional laser therapy for skin rejuvenation. *Dermatol Surg* January 30, 2012; 38(4):623–630.
48. Na JI, Choi JW, Choi HR, Jeong JB, Park KC, Youn SW, Huh CH. Rapid healing and reduced erythema after ablative fractional carbon dioxide laser resurfacing combined with the application of autologous platelet-rich plasma. *Dermatol Surg* 2011; 37(4):463–468.
49. Lee JW, Kim BJ, Kim MN, Mun SK. The efficacy of autologous platelet rich plasma combined with ablative carbon dioxide fractional resurfacing for acne scars: A simultaneous split-face trial. *Dermatol Surg* 2011 July; 37(7):931–938.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

50. Nofal E, Helmy A, Nofal A et al. Platelet-rich plasma versus CROSS technique with 100% trichloroacetic acid versus combined skin needling and platelet rich plasma in the treatment of atrophic acne scars: A comparative study. *Dermatol Surg* 2014 August;40(8):864–873.
51. Kanaide H, Uranishi T, Nakamura M. Effects of divalent cations on the conversion of fibrinogen to fibrin and fibrin polymerization. *Am J Hematol* 1982; 13:229–237.
52. Martineau I, Lacoste E, Gagnon G. Effects of calcium and thrombin on growth factor release from platelet concentrates: Kinetics and regulation of endothelial cell proliferation. *Biomaterials* 2004; 25:4489–4502.
53. Valeri CR, Saleem B, Ragno G. Release of platelet derived growth factors and proliferation of fibroblasts in the releasates from platelets stored in the liquid state at 22 degrees C after stimulation with agonists. *Transfusion* 2006; 46:225–229.
54. Brass EP, Forman WB, Edwards RV, Lindan O. Fibrin formation: Effect of calcium ions. *Blood* 1978; 52:654–658.
55. Martin P, Leibovich SJ. Inflammatory cells during wound repair: The good, the bad and the ugly. *Trends Cell Biol* 2005; 15:599–607.
56. Castillo TN, Pouliot MA, Kim HJ, Dragoo JL. Comparison of growth factor and platelet concentration from commercial platelet-rich plasma separation systems. *Am J Sports Med* November 4, 2012.
57. Bagamery K. Are platelets activated after a rapid, one-step density gradient centrifugation? Evidence from flow cytometric analysis. *J Clin Lab Haematol* 2005 February; 27(1):75–77.
58. Zimmermann R, Jakubietz R, Jakubietz M et al. Different preparation methods to obtain platelet components as a source of growth factors for local application. *Transfusion* 2001; 41:1217–1224.
59. Sadrzadeh SM, Graf E, Panter SS, Hallaway PE, Eaton JW. Hemoglobin. A biologic fenton reagent. *J Biol Chem* 1984; 259:14354–14356.
60. Kumar S, Bandyopadhyay U. Free heme toxicity and its detoxification systems in human. *Toxicol Lett* 2005; 157:175–188.
61. Belcher JD et al. *Antioxid Redox Signal* 2010; 12(2):233–248.
62. Sundman EA. Growth factor and catabolic cytokine concentrations are influenced by the cellular composition of platelet-rich plasma. *Am J Sports Med* 2011; XX(X):1–6.
63. Lei H, Gui L, Xiao R. The effect of anticoagulants on the quality and biological efficacy of platelet rich plasma. *Clin Biochem* 2009; 42:1452–1460.
64. Haynesworth SE, Kadiyala S, Liang LN et al. Mitogenic stimulation of human mesenchymal stem cells by platelet release suggest a mechanism for enhancement of bone repair by platelet concentrates. *48th Meeting of the Orthopedic Research Society*, Boston, MA, 2002.
65. Lui Y, Kalén A, Risto O, Wahlström O. Fibroblast proliferation due to exposure to a platelet concentrate in vitro is pH dependent. *Wound Repair Regen* 2002; 10:336.
66. Marx RE. Plateletconcentrate: A strategy for accelerating and improving bone regeneration. In: Davies JE, ed. *Bone Engineering*. Toronto, Ontario, Canada: University of Toronto, 2000, pp. 447–453.
67. Kevy SV, Jacobson MS. Comparison of methods for point of care preparation of autologous platelet gel. *J Extra Corpor Technol* 2004; 36:28.
68. Weibrich G, Kleis WK, Hafner G, Hitzler WE. Growth factor levels in platelet-rich plasma and correlations with donor age, sex, and platelet count. *J Craniomaxillofac Surg* 2002 April; 30(2):97–102.
69. Mazzucco L, Balbo V, Cattana E, Guaschino R, Borzini P. Not every PRP-gel is born equal. Evaluation of growth factor availability for tissues through four PRP-gel preparations: Fibrinet, RegenPRP-Kit, Plateltex and one manual procedure. *Vox Sang* 2009 August; 97(2):110–118.
70. Borzini P, Mazzucco I. Platelet-rich plasma (PRP) and platelet derivatives for topical therapy. What is true from the biologic view point? *ISBT Sci Ser* 2007; 2:272–281.
71. Leo MS, Kumar AS, Kirit R et al. Systematic review of the use of platelet-rich plasma in aesthetic dermatology. *J Cosmet Dermatol* 2015 December;14(4):315–323.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Fat grafting

Olivier Claude and Pierre André

BACKGROUND

The first autologous grafts of adipose tissue were carried out at the end of the nineteenth century. In 1893, Neuber [1] had already published his technique: removal of small grafts of fat from the arm (no bigger than the size of an almond), followed by transplantation on to the face. In 1911, Bruning [2] described the first reinjection technique using a syringe to correct secondary deformities in rhinoplasty. These techniques only produced temporary results and were replaced by fatty tissue flaps with vascular pedicle for grafting that proved more durable. It was not until 1950 that Peer [3] published the first study on the autograft of adipose tissue. He found a persistence of 50% in the volume injected at a year. In 1953, Bames [4] was the first to publish his breast augmentation technique using fat grafts in treatments for breast hypoplasia.

But the real revolution took place in 1974 when Fischer [5] developed the first technique for liposuction, a technique that would advance under the influence of Illouz [6] and Fournier [7]. The new technique made it easy to obtain adipose tissue in large quantities. The idea of reinjecting part of it quickly arose. It was appealing: an autologous filler finally on hand among our surgical equipments. From the 1980s onward, numerous articles were published. The techniques presented were sometimes very different and the results were often contradictory. French doctors were among the first to show interest in this technique. However, it was in North America that its beneficial role was revealed and where the necessary techniques were actually developed to achieve the best results, notably optimizing durability and reproducibility [8–12]. Then in 1994, Coleman introduced his own technique as LipoStructure©, which is based upon the atraumatic manipulation of the fat transplant. He emphasizes that at each stage of removal centrifugation and reinjection need to be carried out with the minimum of traumatism in order to ensure the best survival rate of the adipocyte grafts. This technique finally made it possible to obtain the results anticipated. It was rapidly adopted and then modified, which has allowed the indications of the technique to become more extensive [13–16] and for it to become popular in our surgical units. Now, it is routinely used in plastic surgery, notably for facelifts, hands, or the gluteus region. Its use for the treatment of breast hypoplasia has produced some valuable results but has also sparked off some debate. Some people fear that the reinjection of fatty tissue could make it difficult to detect breast cancer in mammograms. Delay and Coleman [17,18] have shown that the quality of screening by a radiologist, specialized in breast oncology, who could use also MRI is not impaired. However, breast augmentations using fat grafts need to be carried out by specialized surgeons and then only on patients who have no past record or family history of breast cancer. Candidates considering this surgery should have also had a preoperative breast examination and mammography without any anomaly (BI-RADS 1 or 2, ACR) and have accepted to attend postoperative clinical and radiological checkups.

Autologous adipose tissue grafting is sometimes limited by the lack of retrievable tissue when large amounts are required. Over the last 10 years, a number of teams have been carrying out research to find a means of increasing the volume available using tissue engineering [19–20]. A set amount of fat is cultivated *in vitro*, allowing significant volumes to form from preadipocytes within a matter of weeks. Other research teams have focused on the ubiquitous properties of mesenchymal stem cells contained in fat samples. Adipocytes, osteoblasts, chondrocytes, and myocytes can also be cultivated [21–24].

PHYSIOLOGICAL DESCRIPTION

The adipose tissue is an energetic stock in the form of triglycerides. The physiology of the fat cell is complex and not yet fully understood. The adipocyte is a large cell of approximately 80 µm, coming from an undifferentiated multipotent mesenchymal cell that turns into an adipoblast, then a preadipocyte. The adipoblast stocks the fat in lipid compartments, and the preadipocyte brings together the coalescing lipid droplets that then take on a mulberry appearance (morula stage) and develop into an adipocyte, which contains a central lipid droplet that pushes the nucleus out toward the periphery. The change in the adipocyte depends on the energetic balance and hormonal conditions [25,26].

Triglycerides make up 99% of the lipids' weight. There is only a small amount of free fatty acids, diglycerides, cholesterol, and phospholipids. The adipocytes group together forming microlobules. These microlobules then merge to become secondary lobules, which measure approximately 1 cm in diameter. All of these lobules are separated by septa where the blood and lymph vessels pass. The exchanges between vessels and adipocyte cells take place in close proximity.

Hormones play a decisive role in the regulation of lipolysis. Insulin produced by the pancreas favors lipogenesis, whereas adrenaline and other catecholamines favor lipogenesis in the event of stress or exertion [27]. There are alpha- and beta-adrenergic receptors on the surface of the adipocytes. The alpha receptor inhibits lipolysis, while the beta receptor induces it. Depending on the location of the fat, these receptors might possibly be distributed differently. The quantity of adipocytes appears to be relatively determined in the first years of our life. Obesity is also often related to adipocyte hypertrophy even if hyperplasic obesity is more commonly found in children. In fact, adipocyte hyperplasia from preadipocytes remains a possibility throughout life [26].

Recent studies have shown that adipocytes are not only passive cells for triglyceride storage. They also have an

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

extremely active metabolism from their secretion of "adipokines," which are biologically active molecules involved in the energetic balance and glycerolipid metabolism. Both the adipocytes and the nonadipocyte cells of the tissue participate in this function of secretion. The adipokines act locally in autocrine or paracrine mode and remotely (endocrine effect) on the target tissues of the muscle, the liver, and the hypothalamus [28]. Leptin is another hormone secreted by the adipocytes from the Ob gene, which has an essential role in the hypothalamus, controlling food intake and body weight. It also regulates appetite in relation to adipose tissue mass and acts as a satiety hormone by hypothalamic feedback. Equally important is the role leptin plays in angiogenesis by stimulating the endothelial cells during the microvascularization of the adipose tissue. Leptin also acts locally by regulating the quantity of fat mass [29].

The adipocytes also secrete numerous other molecules, in particular tumor necrosis factor-alpha and also interleukin-6, as well as a large number of angiogenic factors that potentially limit the fatty acids locally from entering the adipose tissue and contribute to its vascularization in association with the leptin hormone [30].

It has been shown that a transgenic mouse without white adipose tissue showed major anomalies (diabetes, fatty liver, hypertriglyceridemia, organomegaly) that led to its premature death [31]. An adipose tissue graft transferred onto these mice allowed their metabolic problems to be resolved in less than a month [32].

Similar findings have been made using adipose tissue grafts on the human body, showing that they are not simply a product for restoring volume but also for improving the quality of the surrounding tissue. Adipose tissue grafts make a remarkable improvement in cutaneous trophicity either in cosmetic indications, notably for the face and hands, or in reconstructive surgery [33–36]. Rigotti has also shown that radiodystrophy treatment, and even radionecrosis treatment and breast tumor surgery, can be made less complicated with the use of subcutaneous injections of autologous fat [37].

The exact physiology of fat grafts is still to be specified, but the significance of both the action of mesenchymal stem cells and transfers of angiogenic growth factors has already been shown [38]. Recent studies have indicated that it might be possible to enhance the transplant graft with stem cells or PRP [39,40]. These improvements in technique are charting completely new ground where our results can be optimized. Standardization should in turn lead to an even higher survival rate in adipocytes and an improvement in the trophicity of receptor tissues.

TECHNIQUE

Carrying out an autologous adipose tissue graft is relatively simple and swift. Several techniques have been written about in detail, but all of them emphasize the importance of an atraumatic manipulation of the fat transplant throughout each stage. The technical reference remains that of Sydney Coleman's, whose standardization of LipoStructure has ensured constant and durable results.

Harvesting

A correlation between where the fat graft donor site is located and the quality of the graft take in the receptor site has never been made. A site for liposuction is therefore chosen for its maximum potential to improve the silhouette. The site is generally in the trochanteric or saddlebag region, the hips, the abdominal region, or the inner parts of the thighs or knees. The operation is carried out under local anesthetics (lidocaine with epinephrine), or general anesthetics when the fat grafts are larger, in a surgical unit. Lidocaine with epinephrine has been shown not to affect the survival of adipocytes or the quality of the fat graft [41]. When using general anesthetic, an infiltration of the adipose tissue with epinephrine serum is carried out, allowing harvesting with the least hemorrhaging possible. The removal is carried out using an atraumatic blunt suction cannula of 2–2.5 mm in diameter attached to a 10 mL syringe. Innovation in the last few years has led to more slender cannulas being used for harvesting and reinjection, with the aim of improvement in adipocyte graft survival. By exerting a gentle negative pressure manually and back and forth motions, fatty tissue can be harvested for transfer.

Centrifugation

The syringes are then placed in the centrifuge after their plungers have been removed and luer-lock stopcocks have been put into place. Centrifugation is carried out for 2–3 minutes at 3000 revolutions per minute. The sample is separated into three phases (see Figure 58.1):

1. *The upper or supernatant phase*: Oil containing triglycerides from damaged adipocytes. It is removed by packing with neurosurgical compresses.
2. *The lower phase*: Made up of blood and liquid infiltration. It is removed by letting it drain away after removal of the luer-lock stopcock.
3. *The intermediate phase*: Corresponding to the fat phase containing viable adipocytes. Only this part of the sample can be used for the adipocyte grafts. The bottom third of this phase is made up of the stromal fraction that has a high density in stem cells. It will be used on the zones, like the periorbital area, where an optimal graft take is desired.

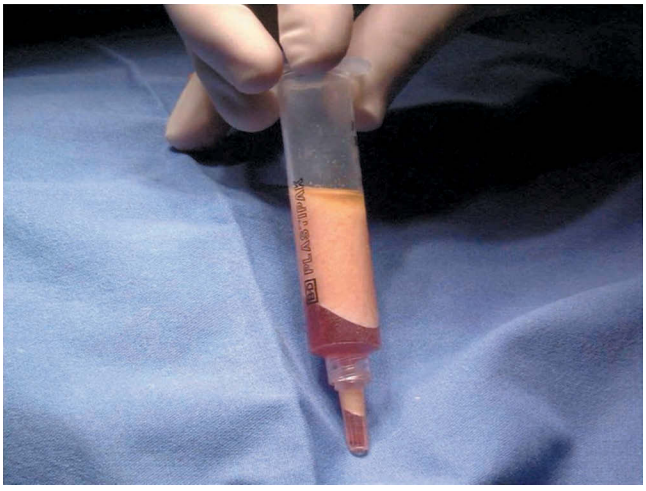


Figure 58.1 The three layers after centrifugation of the harvested fat.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Reinjection

The content from the intermediate phase is then transferred into 1 mL syringes before being reinjected using blunt-tipped cannulas of between 0.7 and 1.2 mm. If the surgery is carried out under local anesthesia, it should be kept to a minimum so as to avoid modifying the contours or traumatizing any of the recipient tissue. The use of a general anesthetic requires a moderate infiltration of epinephrine serum and the vasoconstrictor effect helps to prevent bruising as well as diminish the risk of fat embolism. The fat is injected in small quantities using the retrotracing technique without positive pressure. Each 1 mL syringe enables some 20 transmissions, each time using a different tunnel. Then an actual 3D lattice is organized at depth up until the surface. The adipocytes that are transferred then have the best use of the local vascular network, which ensures the viability of the graft.

When a larger volume of fat is injected, there is a risk of granulomas or fat necrosis. When all the different stages are followed in adherence to the principle of atraumatic manipulation of the fat transplant, overcorrection is not necessary. Massage on the injected area should be avoided due to the risk it presents for losing control of the site where the fat has been placed; massage, however, could be carried out with careful skill if a possible inconsistency is discerned.

There have been case studies published about the periorbital area that report postinjection blindness as a result of accidental arterial embolization. It should be noted that different lipofilling techniques were being used in those studies from the technique that is being recommended here. They were carried out using excessive positive pressure on a single entry point and needles, instead of cannulas with blunt tips, were used [42]. Vasoconstriction of the receptor site by epinephrine serum infiltration is also an important measure to be taken to prevent this rare complication. It also requires the use of blunt-tipped cannulas with side openings and injection of the fat by retrotracing with continuous movements and without positive pressure.

Postoperative follow-up is most often simple: the donor site can be sensitive and ecchymotic, whereas the receptor site can often present with light resolving edema within a few days. The result should be considered as definite from the sixth month after any signs of edema have disappeared. A new session can eventually be considered in case of partial graft take.

INDICATIONS AND RESULTS

The indications for adipocyte grafts are numerous and concern both cosmetic and reconstructive plastic surgery. In cosmetic plastic surgery, adipocyte grafts can be used alone or together with other surgical techniques. The objective is either aesthetic enhancement or restoration of a youthful appearance, or both, by restoring smooth volumes and improving cutaneous trophicity.

Isolated Use on the Face

- *Cheekbones and tear troughs*: A young adult presents with a cheekbone (malar area) that is highly projected, following an axis from the base of the wing of the nose to the root of the helix. The lid-cheek junction should be imperceptible with a cheekbone projection above the vertical axis, passing through the cornea in profile view (positive vector). Aging often leads to a decrease in periorbital volume due to ptosis tissue, which can be corrected during a facelift, but also because of multitissular resorption (bone, muscular, fat, and subcutaneous). The loss in volume, mainly in fat, unmasks the fat pockets on the lower eyelids, deepens the tear troughs, and diminishes fullness in the middle third of the face. LipoStructure of the malar area and tear troughs not only restores smooth volumes but also improves the trophicity of the lower eyelids (color and texture) and can also cover vessels that might appear with age and the color change in the orbicularis muscle, sometimes visible in delicate skin. It also reinforces the lower eyelid by supporting it and thereby raising the position of its free edge as well as reducing round eye and scleral show, notably in its lateral part.
- *Upper eyelid and temple*: A hollow upper orbit gives an aged, undernourished, or ill look. Restoring fullness in the upper eyelid and the lateral part of the eyebrow has a very dynamic and youthful effect (see Figures 58.2 and 58.3). Temple fat also tends to diminish with aging. The filling injection can ensure a smooth transition between the eyebrows, the temple, and the cheekbone equally allowing bone contours to be covered, notably the lateral orbital rim, which may have taken on a skeletal or even dead-like appearance.
- *Nasolabial folds and marionette lines*: Facial aging leads to an accentuation of the nasolabial folds and the appearance of marionette lines, often giving a severe and sometimes contorted look or rictus. The adipocyte graft on this area should not be reduced to filling the main nasolabial fold but should also treat the areas immediately adjacent to it to prevent secondary folds appearing. Attention must be paid to these sides so as to avoid accentuating the original fold. It should be carried out as from two or three openings with perpendicular and longitudinal cross deposits in the subcutaneous plane. The patient should be advised that the marionette lines are always more difficult to correct than that of the nasolabial fold.

(a)

(b)

Figure 58.2 (a) and (b) Before and after fat grafting of the upper eyelid, the brow, and the temporal area.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 58.3 (a) and (b) Before and after fat grafting of the upper eyelid, the brow, and the temporal area.

Figure 58.4 (a) Before and (b) after fat grafting of the chin and the jawline.

- *Chin and jawline*: The fatty tissue transfers also allow an increase in chin projection, redefining its contours, notably with median depression. They can also be used to replace alloplastic implants in small volumes. A cervical liposuction to allow a maximal improvement in the cervical chin angle is most often included (see Figure 58.4). Improving the shape of the jawline requires filling in the prejowl depression and treating the jowl with microliposuction, restoring a smooth contour.
- *Lip*: One of the main objectives is to evert the dry red area of the lip or vermilion by carrying out a transfer on the superficial submucosal layer, avoiding an intramuscular injection that would thicken the lip without enhancing it. The lower lip is raised along its entire length but while insisting on paramedian projections that contain the slight central depression. The upper lip will be filled in similarly but in "negative" in relation to the lower lip, indeed prioritizing the central area and the juxtacommissural areas.

Combined Use on the Face

The techniques described earlier for grafting adipose tissue on to the face are mainly used on young patients aged between 20 and 40 years old, presenting with a concave-shaped face that tends to have a less attractive appearance and show early aging. They can also be used on patients over 40 years old, whose facial aging is mainly due to loss in volume from multitissular resorption. Such concave-shaped faces are most often characterized by fat loss in the periorbital and malar areas. These patients should be treated with a combined use of techniques to receive optimum and natural results. Facelifts allow a tightening of the flaccid tissues and in particular of the lower third of the face, correcting the jowl and redefining the cervical-chin area (see Figures 58.5 and 58.6); at the start of the surgery, a fat tissue transfer allows the loss of volume to be restored in the tear troughs, the cheekbones, the upper eyelid, the lips, the nasolabial folds, the chin, and the temple area. A cervical-facial lift carried out alone would tend to flatten the face of these patients, leaving them with an unnatural appearance. The preoperative analysis is then essential because it makes it possible to differentiate between those facelift patients who require only cervical-facial lifting and those who could be treated with a combined use of lifting and fat tissue transfer techniques (see Figures 58.7 and 58.8). Such an analysis would be greatly assisted by past photos of the patient, which would help to define the aging process of their face and thereby guide surgical strategy. In practice, fat transfers are carried out in most of our facelift as fat resorption is a near, inevitable part of aging.

Body

- *Hand*: The hand is a tool for basic communication and is the second area that people see after the face. Increasing numbers of patients who have had facelifts now ask to have corrective surgery on the dorsal face of their hands. The adipocyte graft allows for a strict subcutaneous superficial filling to cover the dorsal veins and the tendons that give away the patient's age [43].
- *Buttocks*: There is a growing demand for enhancement in the gluteal area. Silicone implants most often give good

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figures 58.5 (a) and (b) After facelift with fat grafting of the malar area, the nasolabial fold, the marionette folds, and the jawline.

(a) (b)

Figures 58.6 (a) and (b) After facelift with fat grafting of the malar area, the nasolabial fold, the marionette folds, and the jawline.

(a) (b)

Figure 58.7 (a) and (b) After facelift with fat grafting of the chin, the nasolabial fold, the marionette folds, and the jawline.

results but they are made up of a foreign material and mainly correct only the upper part of the buttock. The adipocyte graft makes a correction possible using autologous material that is selectively placed where there is a lack of projection (see Figure 58.9). The patient, however, needs to have enough fat to be able to obtain the projection and the shape they have chosen for successful grafting [44]. The technique will equally be lightly modified using notably 10 mL syringes for the reinjection so as not to prolong operating time unnecessarily. Similarly, decanting or filtering the fat sample instead of using centrifugation is sometimes preferred. The percentage of successful graft take is slightly lower, but the surgery needs to take place within a reasonable time limit [45,46]. More localized corrections

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 58.8 (a) and (b) After facelift with fat grafting of the chin, the nasolabial fold, the marionette folds, and the jawline.

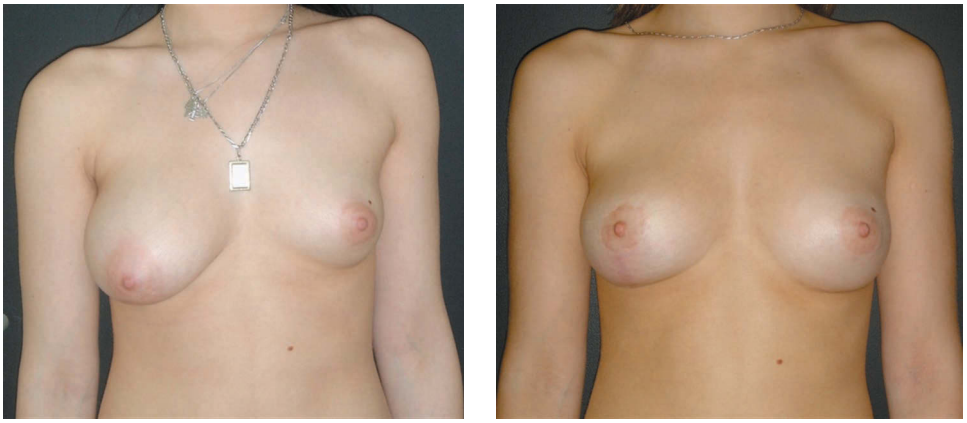
(a) (b)

Figure 58.9 (a) Before and (b) after buttock fat grafting with liposuction of the waist.

can likewise be carried out on the buttocks such as congenital skin depression, iatrogenic (corticoid injection), or posttraumatic treatments.

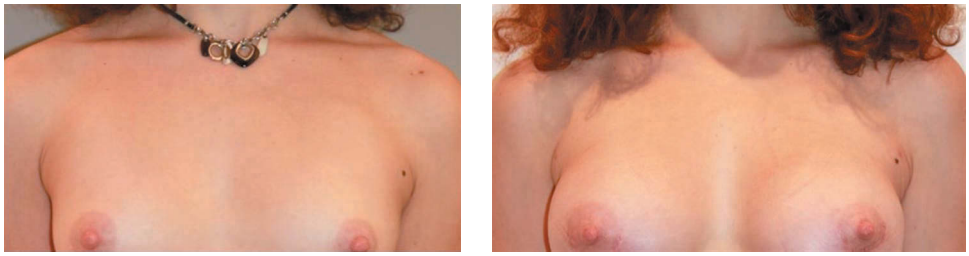
- *Genital organs*: The penile adipocyte graft is also becoming more and more common. It allows an increase in penile circumference of 2–3 cm on average without modifying the length. Such modification would require more invasive surgical techniques.
- *Breasts*: This technique allows breast augmentations to be made while improving the global silhouette using liposuction. In addition to these cosmetic indications, its application in breast reconstruction is very appealing. However, there are two requirements that limit the extensive use of this technique: the required operating time is longer than it is for breast implants and a sufficient stock of autologous fat is necessary to obtain the desired result [16,47]. Fat transfers are particularly interesting in breast asymmetry treatments (see Figure 58.10). They avoid putting in more than a single implant and withstand the aging process more than breasts that have not undergone enlargement. For thin patients, a combined use of breast implants and fat grafting in the décolleté area softens the prosthetic contours (see Figure 58.11). A smooth transition between the implant and the chest gives a natural and glamorous cleavage as a result of the autologous enlargement.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b)

Figure 58.10 Asymmetric breasts: (a) before and (b) after breast fat grafting of the left side and breast lift of the right side.



(a) (b)

Figure 58.11 Composite breast augmentation: (a) before and (b) after breast implants and fat grafting of the cleavage area.

CONCLUSION

Adipose tissue grafting is now a standardized technique that produces reproducible and long-lasting results. The fat acts as the ideal filler, combining the safety of resorbable fillers and the permanency of nonresorbable fillers without the disadvantage of it being a foreign substance. Apart from its capacity to restore volume, it also improves the texture of the surrounding tissues, notably because of stem cells and growth factors transfer. Autologous fat transfer has therefore become one of the key techniques for aesthetic treatments to provide rejuvenation and beautification.

REFERENCES

1. Neuber F. Fettatransplantation. *Chir Kongr Verhandl Dtsch Gessellsch Chir* 1893; 22:66.
2. Bruning P. Contribution à l'étude des greffes adipeuses. *Bull Acad R Med Belgique* 1919; 28:66.
3. Peer LA. Loss of weight and volume in human fat grafts. *Plast Reconstr Surg* 1950; 5:217.
4. Bames H. Augmentation mammoplasty by lipo-transplant. *Plast Reconstr Surg* 1953; 11:404–408.
5. Fischer A, Fischer GM. Revised technique for cellulitis fat. *Bull Int Acad Cosmet Surg* 1977; 2:40.
6. Illouz YG. Body contouring by lipolysis: A 5-year experience with over 3000 cases. *Plast Reconstr Surg* 1983 November; 72(5):591–597.
7. Fournier PF. Facial recontouring with fat grafting. *Dermatol Clin* 1990 July; 8(3):523–537.
8. Toledo LS. Syringe liposculpture: A two-year experience. *Aesthet Plast Surg* 1991 Fall; 15(4):321–326.
9. Ellenbogen R. Fat transfer: Current use in practice. *Clin Plast Surg* 2000 October; 27(4):545–556.
10. Guerrerosantos J. Simultaneous rhytidoplasty and lipoinjection: A comprehensive aesthetic surgical strategy. *Plast Reconstr Surg* 1998 July; 102(1):191–199.
11. Guerrerosantos J. Long-term outcome of autologous fat transplantation in aesthetic facial recontouring: Sixteen years of experience with 1936 cases. *Clin Plast Surg* 2000 October; 27(4):515–543.
12. Trepsat F. Periorbital rejuvenation combining fat grafting and blepharoplasties. *Aesthet Plast Surg* 2003 July–August; 27(4):243–253.
13. Trepsat F. Volumetric face lifting. *Plast Reconstr Surg* 2001 October; 108(5):1358–1370; discussion 1371–1379.
14. Jauffret JL, Champsaur P, Robaglia-Schlupp A, Andrac-Meyer L, Magalon G. Arguments in favor of adipocyte grafts with the S.R. Coleman technique. *Ann Chir Plast Esthet* 2001 February; 46(1):31–38.
15. Mojallal A, Breton P, Delay E, Foyatier JL. Greffes d'adipocytes: Applications en chirurgie plastique et esthétique. In *Encyclopédie Médico-Chirurgicale*. Paris, France: Elsevier SAS, Techniques chirurgicales—Chirurgie plastique reconstructrice et esthétique, 2004, pp. 4–125.
16. Coleman SR, Saboeiro AP. Fat grafting to the breast revisited: Safety and efficacy. *Plast Reconstr Surg* 2007 March; 119(3):775–785; discussion 786–787.
17. Gosset J, Guerin N, Toussoun G, Delaporte T, Delay E. Radiological evaluation after lipomodelling for correction of breast conservative treatment sequelae. *Ann Chir Plast Esthet* 2008 April; 53(2):178–189.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

18. Katz AJ, Llull R, Hedrick MH, Futrell JW. Emerging approaches to the tissue engineering of fat. *Clin Plast Surg* 1999 October; 26(4):587–603, viii.
19. Zhu W, Nelson CM. Adipose and mammary epithelial tissue engineering. *Biomatter* April 1, 2013; 3(2):e24630.
20. Stosich MS, Mao JJ. Adipose tissue engineering from human adult stem cells: Clinical implications in plastic and reconstructive surgery. *Plast Reconstr Surg* 2007 January; 119(1):71–83; discussion 84–85.
21. Schipper BM, Marra KG, Zhang W, Donnenberg AD, Rubin JP. Regional anatomic and age effects on cell function of human adipose-derived stem cells. *Ann Plast Surg* 2008 May; 60(5):538–544.
22. Lin SD, Wang KH, Kao AP. Engineered adipose tissue of predefined shape and dimensions from human adipose-derived mesenchymal stem cells. *Tissue Eng Part A* March 24, 2008; 14(5):571–581.
23. Flynn L, Prestwich GD, Semple JL, Woodhouse KA. Adipose tissue engineering with naturally derived scaffolds and adipose-derived stem cells. *Biomaterials* 2007 September; 28(26):3834–3842.
24. Poznanski WJ, Waheed I, Van R. Human fat cell precursors. Morphologic and metabolic differentiation in culture. *Lab Invest* 1973 November; 29(5):570–576.
25. Dugail I, Ferre P. Développement du tissu adipeux. In *Encyclopédie Médico-Chirurgicale*. Paris, France: Elsevier SAS, Endocrinologie-Nutrition, 2002, p. 10-506-A-10.
26. Dugail I, Ferre P. Métabolisme du tissu adipeux blanc. In *Encyclopédie Médico-Chirurgicale*. Paris, France: Elsevier SAS, Endocrinologie-Nutrition, p. 10-506-B-10.
27. Guerre-Millo M. Adipose tissue secretory function: Implication in metabolic and cardiovascular complications of obesity. *J Soc Biol* 2006; 200(1):37–43. Review.
28. Bouloumié A, Lolmède K, Sengenès C, Galitzky J, Lafontan M. Angiogenesis in adipose tissue. *Ann Endocrinol* 2002 April; 63(2 Pt 1):91–95.
29. Abderrahim-Ferkoune A, Bezy O, Chiellini C et al. Characterization of the long pentraxin PTX3 as a TNFalpha-induced secreted protein of adipose cells. *J Lipid Res* 2003 May; 44(5):994–1000.
30. Moitra J, Mason MM, Olive M et al. Life without white fat: A transgenic mouse. *Genes Dev* October 15, 1998; 12(20):3168–3181.
31. Gavrilova O, Marcus-Samuels B, Graham D, Kim JK, Shulman GI, Castle AL, Vinson C, Eckhaus M, Reitman ML. Surgical implantation of adipose tissue reverses diabetes in lipoatrophic mice. *J Clin Invest* 2000 February; 105(3):271–278.
32. Coleman SR. Structural fat grafting: More than a permanent filler. *Plast Reconstr Surg* 2006 September; 118(Suppl 3):108S–120S.
33. Haack J, Friedman O. Facial liposculpture. *Facial Plast Surg* 2006 May; 22(2):147–153.
34. Klinger M, Marazzi M, Vigo D, Torre M. Fat injection for cases of severe burn outcomes: A new perspective of scare remodeling and reduction. *Aesthet Plast Surg* 2008 May; 32(3):465–469.
35. Caviggioli F, Klinger F, Villani F, Fossati C, Vinci V, Klinger M. Correction of cicatricial ectropion by autologous fat graft. *Aesthet Plast Surg* 2008 May; 32(3):555–557.
36. Rigotti G, Marchi A, Galiè M, Baroni G, Benati D, Krampera M, Pasini A, Sbarbati. A. Clinical treatment of radiotherapy tissue damage by lipoaspirate transplant: A healing process mediated by adipose-derived adult stem cells. *Plast Reconstr Surg* April 15, 2007; 119(5):1409–1422; discussion 1423–1424.
37. Lu F, Mizuno H, Uysal CA, Cai X, Ogawa R, Hyakusoku H. Improved viability of random pattern skin flaps through the use of adipose-derived stem cells. *Plast Reconstr Surg* 2008 January; 121(1):50–58.
38. Zhu M, Zhou Z, Chen Y, Schreiber R, Ransom JT, Fraser JK, Hedrick MH, Pinkernell K, Kuo HC. Supplementation of fat grafts with adipose-derived regenerative cells improves long-term graft retention. *Ann Plast Surg* 2010 February; 64(2):222–228.
39. Jin R, Zhang L, Zhang YG. Does platelet-rich plasma enhance the survival of grafted fat? An update review. *Int J Clin Exp Med* April 12, 2013; 6(4):252–258.
40. Shoshani O, Berger J, Fodor L, Ramon Y, Shupak A, Kehat I, Gilhar A, Ullmann Y. The effect of lidocaine and adrenaline on the viability of injected adipose tissue—An experimental study in nude mice. *J Drugs Dermatol* 2005 May–June; 4(3):311–316.
41. Danesh-Meyer HV, Savino PJ, Sergott RC. Case reports and small case series: Ocular and cerebral ischemia following facial injection of autologous fat. *Arch Ophthalmol* 2001 May; 119(5):777–778.
42. Coleman SR. Hand rejuvenation with structural fat grafting. *Plast Reconstr Surg* 2002 December; 110(7):1731–1744; discussion 1745–1747.
43. Roberts TL 3rd, Weinfeld AB, Bruner TW, Nguyen K. "Universal" and ethnic ideals of beautiful buttocks are best obtained by autologous micro fat grafting and liposuction. *Clin Plast Surg* 2006 July; 33(3):371–394.
44. Murillo WL. Buttock augmentation: Case studies of fat injection monitored by magnetic resonance imaging. *Plast Reconstr Surg* 2004 November; 114(6):1606–1614.
45. Perén PA, Gómez JB, Guerrerosantos J, Salazar CA. Gluteus augmentation with fat grafting. *Aesthet Plast Surg* 2000 November–December; 24(6):412–417.
46. Panfilov DE. Augmentative phalloplasty. *Aesthet Plast Surg* 2006 March–April; 30(2):183–197.
47. Zheng DN, Li QF, Lei H, Zheng SW, Xie YZ, Xu QH, Yun X, Pu LL. Autologous fat grafting to the breast for cosmetic enhancement: Experience in 66 patients with long-term follow up. *J Plast Reconstr Aesthet Surg* 2008 July; 61(7):792–798.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Liposuction

Daniela Pulcini and Olivier Claude

BACKGROUND AND HISTORY

Liposuction is routinely employed by plastic surgeons concerned with removing subcutaneous adipose deposits in various areas in the body to improve figure flaws and create a more balanced physique [1–4]. In 2013, liposuction was the second most frequently performed cosmetic surgical procedure, with 313,011 patients undergoing lipoplasty. In the past 15 years, liposuction has seen a 77% increase in its number of surgeries performed. Furthermore, suction lipectomy is the most common aesthetic surgical procedure performed in men [5]. Indeed, liposuction consistently ranks among the most common aesthetic surgery procedures. The aspiration of fat using blunt cannulas and negative pressure suction was first popularized in Europe in the late 1970s [6]. Three French surgeons, Drs. Yves-Gerard Illouz, Pierre Fournier, and Francis Otteni, were the first to present their lipoaspiration experience at the 1982 American Society of Plastic and Reconstructive Surgeons annual meeting in Honolulu, Hawaii. Subsequent to Illouz's presentation, over the years, many alterations and modifications have been employed to minimize risk and improve cosmetic outcome of the contouring procedure of liposuction [7–11].

PERTINENT ANATOMY

The subcutaneous fat throughout the body is divided into superficial and deep layers or compartments separated by Scarpa's fascia, or the superficial fascial equivalent. However, for the purposes of liposuction and body contouring, subcutaneous fat is arbitrarily divided into three layers: superficial, intermediate, and deep. The anatomy of the subcutaneous adipose tissue varies throughout the body. Some areas of the body have both a deep adipose compartment and a superficial adipose compartment, which are separated by a discrete subcutaneous fascia. The superficial fat in the trunk and thigh consists of smaller lobules, tightly organized within vertically oriented, thin, fibrous septa. The deep fat consists of larger lobules arranged more loosely within widely spaced and more irregularly arranged septa [12]. In these areas, the deep layer of fat is the target for liposuction. The overlying superficial fat is relatively thin and will act as a protective layer to hide small contour deformities, especially for the inexperienced liposuction surgeon. In contrast, other areas of the body that are commonly suctioned (arms, lower legs) have only one layer of fat. Suctioning these areas with smaller cannulas will help to avoid contour irregularities. The importance of this distinction is that the superficial layer is rarely violated. If this layer is treated, there is a significantly increased risk of vascular compromise and/or contour irregularities. The relative consistency and thickness of each of these separate layers vary in different anatomic areas. This contrasts with the fat of the inner thigh, which is not as fibrous and is less compact. This information is crucial for an aesthetic surgeon to perform safe and appropriate suctioning of the targeted area and to minimize potential contour irregularities and skin necrosis. Anatomic zones of adherence should be identified and marked during the preoperative consultation. These are areas of relatively dense fibrous attachment to the underlying deep fascia that help define the natural shape and curve of the body. It is important to recognize these zones because they are high-risk areas for contour irregularities after surgical intervention if not properly respected.

PREOPERATIVE PLANNING

Patient selection is a critical determinant of a good aesthetic surgical result, especially in body contouring. Not all patients who request liposuction are good candidates. In 2004, the Committee on Patient Safety of the American Society of Plastic Surgeons published the first "Practice Advisory on Liposuction" to help guide appropriate selection and treatment of patients seeking liposuction, which was subsequently updated in 2009 [13,14]. Patients should be generally healthy and demonstrate a commitment to long-term lifestyle changes including both healthy diet and exercise [15]. Additionally, patient goals and expectations should be appropriate and realistic. Furthermore, patients who are either obese or who have generalized adiposity, adolescents, and patients with certain preexisting medical conditions that place them in preclusive risk may not be suitable candidates. Venous thromboembolism, the most common cause of mortality during suction lipectomy, should be managed with preoperative risk stratification and treatment, as necessary. The American Society of Plastic and Reconstructive Surgeons recently published "Evidence-Based Practices for Thromboembolism Prevention" to guide risk stratification and implementation of preventative measures. The consultation begins with an assessment of the patient's goals [16]. Physician–patient dialogue is paramount in this evaluation; understanding patients' goals and setting expectations is key. The surgeon then provides the patient with a realistic appraisal of what can and cannot be accomplished with liposuction. Some patients may require alternative procedures (such as an abdominoplasty) or liposuction combined with an open surgical procedure. A detailed weight history is an important part of any liposuction consultation. Ideal candidates are at a stable weight with a working diet and exercise regimen in place. Patients who have a history of frequent or significant weight fluctuations are at high risk for weight gain after liposuction. Maintaining a stable weight and practicing a diet and exercise regimen for at least 6–12 months indicates the necessary commitment to lifestyle

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

change. Appropriate candidates for liposuction are not morbidly obese, are at a stable weight, and have incorporated the aforementioned lifestyle changes into their preoperative regimen. It is the responsibility of the surgeon to address all concerns, expectations, and goals with the patient before the procedure to establish realistic expectations of the procedure. Liposuction is contraindicated in patients who are pregnant or in poor general medical health. Patients with morbid obesity, cardiopulmonary disease, body image perception issues, unrealistic expectations, wound-healing difficulties, or extensive or poorly located scars should be excluded from consideration for liposuction [17].

PHYSICAL EXAMINATION

A thorough physical examination is always performed. The assessment of the amount and thickness of the adipose layer in areas that concern the patient are appraised critically. If the abdomen is being considered for treatment, the amount of intra-abdominal fat must be considered along with careful assessment for hernias. In males, most of the abdominal protuberance frequently can be internal, with only smaller amounts of subcutaneous tissue. The skin should have an appropriate inherent elasticity to recoil and contract after removal of fat. Stretch marks are a strong indication of poor elasticity, as is delayed rebound after manual stretching. Significant skin overhang is also a prime indicator of the need for adjunctive procedures (abdominoplasty, thigh lift) because the removed fat accentuates the redundant skin, forming an unsightly pannus. These adjunctive procedures decrease the risk of contour deformities and possible skin irregularities. Document areas of cellulite and point them out to the patient so that he or she understands that these areas are not altered significantly by the procedure and in fact may be accentuated postoperatively. The pinch test is a relatively simple estimate to check for the amount of fat that can be removed. Gently pinching the subcutaneous tissue between the thumb and index finger provides a width between the two fingers that should be at least 1 in. before improvement can be expected (except in the neck and face area). If too little subcutaneous fat is left postprocedure, contour deformities and difficulties with skin elasticity can result. Several areas need to be treated with extreme caution and liposuction should be avoided in these areas due to increased risk of complications. Such areas include the gluteal crease, lateral gluteal depression, distal posterior thigh, middle medial thigh, and inferolateral iliotibial band. These areas have increased susceptibility to superficial contour deformities due to minimal amounts of deep fat and adherence of the more superficial layer to the underlying fascia of the muscle. Also discuss and evaluate proposed port sites with the patient. To minimize risk of contour abnormalities with liposuction, multiple port sites are required to approach each problem area. For the medial thigh, the authors use the medial inguinal area for one of the port access sites. The saddlebag, infragluteal region (banana fold), and posterior thigh are accessed best with gluteal crease and lateral trochanteric port sites. Lateral flank, hip roll, and saddlebag sites also can be accessed through lateral trochanteric, flank, and midline back sites. Abdominal access can be achieved through umbilical port sites with inguinal and subcostal sites if necessary. The physical examination is best performed with the patient in front of a full-length mirror. At the initial evaluation, high-quality medical photographs should be obtained, with anterior, posterior, and lateral views as well as anterior and posterior oblique views. Professional medical photography can be a very useful tool for accurate and consistent pre-/postoperative documentation. During this visit, computer images are reviewed that allow the patient to establish realistic expectation. The patient should understand that imaging is for educational purposes only and is not a guarantee of the final result.

INFORMED CONSENT

The informed consent process is necessary to protect the patient and the surgeon. Informed consent should be regarded by the surgeon not only as a legal responsibility but also as a mutually beneficial transaction. The patient is informed of the risks, benefits, and available alternatives to the procedure being considered. A well-informed patient knows what to expect in the postoperative period. If there is a postoperative complication, the patient will recall that it was a possibility and it is more likely that the doctor–patient relationship will remain intact. The risks for liposuction include, but are not limited to, bleeding, infection, pain, thermal injury, seroma, dyspigmentation, paresthesias, contour irregularities, and dysesthesias.

MARKING AND POSITIONING

Make markings using a surgical marker to indicate areas to be treated while the patient is in the standing position. Most surgeons use topographic-type markings to indicate areas of maximal bulge centrally with successive concentric circles farther away to indicate adjacent areas where the liposuction should be tapered gently at the periphery. Once the patient is recumbent, lipodystrophic areas become distorted and shift, making discerning the areas to be treated much more difficult. Thus, the patient must be marked prior to positioning, almost always in the standing position. If the patient also understands the markings, he or she can help confirm the areas of treatment and can be involved in the decision-making process, which helps increase patient satisfaction. Zones of adherence and depressions frequently are drawn with a marker of another color to indicate avoidance areas. Port sites also should be marked with the patient in the standing position. This allows for placement in strategic areas that can be camouflaged by undergarments, shorts, or skirt lines. Plan 2–3 port sites for each problem area to allow cross-tunneling aspiration to minimize surface abnormalities. Patient positioning should be planned before the procedure. Positioning depends on which areas are being suctioned. When several body areas are to be suctioned, an intraoperative position change is necessary. If the procedure is performed under local anesthesia, it often makes sense to prep the patient circumferentially while the patient is standing and then have the patient lie down on a sterile drape. The patient can rotate on the operating table as necessary throughout the procedure. When the procedure is performed under general anesthesia, the patient is first prepped in the prone position, which allows easy access to the back, flanks, buttocks, lateral thighs, and the posterior aspect of the entire lower extremity. A soft hip roll is placed beneath the iliac crest to elevate the treatment areas of the bed, and either pillow or longitudinal rolls are used to support the upper chest.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

ANESTHESIA

In the authors' practice, most lipoplasty procedures are performed under general anesthesia with the tumescent or superwet technique. This allows both ease of repositioning and minimal or no use of lidocaine to prevent toxicity issues postoperatively. Additionally, the authors use body warmers and blankets when possible, along with warmed infusate solution, to help maintain core temperature. To aid in the prevention of deep vein thrombosis or pulmonary embolism, pneumatic compression devices are used in all patients when the procedure is anticipated to last longer than 1 hour.

INFILTRATION AND OPERATIVE TECHNIQUE

Liposuction was first practiced as a "dry" technique, meaning that nothing was done to prepare the fat prior to suctioning it from the subcutaneous plane. As one might expect, hemorrhagic complications were common. Illouz is credited with developing the "wet" technique, which he described as a "dissecting hydrotomy," wherein he instilled normal saline, water, and hyaluronidase in the hope of creating a weak hypotonic solution to lyse the adipocyte cell wall [18]. Hetter is credited with adding lidocaine and dilute epinephrine to the wetting solution [23]. Jeffrey Klein, a dermatologist, developed and coined the term tumescent technique, which is now used for the infiltration of large volume, dilute lidocaine with epinephrine solution for the purpose of performing liposuction with low blood loss [19]. The importance of infiltration of wetting solution cannot be overstated.

Historically, four types of wetting solutions have been used for liposuction: dry, wet, superwet, and tumescent. The essential difference between these techniques focuses on the amount of infusate introduced into the tissues and the resultant blood loss as a percentage of aspirated fluid. The dry technique involves no infused fluid and results in approximately 25%–40% blood loss of the volume removed. The wet technique uses infiltration of 100–300 mL of fluid (with or without epinephrine) into each site to be treated, resulting in a reduction in blood loss of 10%–30% of aspirate without epinephrine and 15% with epinephrine. These two techniques have fallen out of favor and have been replaced by superwet and tumescent techniques due to levels of blood loss. The superwet technique involves instillation of fluid with epinephrine in equal volume to the amount to be removed, for example, 1:1 ratio. Ranges of blood loss have been reported at 1%–4% of aspirate. The tumescent technique involves infusions of fluid with epinephrine until the targeted tissue is engorged and tense with fluid (estimated at 2–3 mL/mL removed). Blood loss estimates have been approximated at 1% or less. The American Society of Plastic Surgeons Practice Advisory Committee has recommended use of the superwet technique to reduce the need for infiltrating solutions and the surgical risk. Approximately 50%–70% of the infused fluid is estimated to remain at the end of the lipoplasty procedure. The two major formulas for tumescent infiltration for liposuction are the tumescent formula (Klein) and modified tumescent formula (Hunstad). The tumescent formula combines 1 L of normal saline with 50 mL of 1% lidocaine, 1 mL of 1:1000 epinephrine, and 2.5 mL of 8.4% sodium bicarbonate. In this formula, the bicarbonate is added to counteract the acidic nature of the saline solution to decrease the pain of the injection and increase analgesic potency [14].

Alternatively, the modified formula is composed of 1 L of lactated Ringer solution with the same lidocaine and epinephrine solution as in the standard formula. Because the pH of the lactated Ringer solution is higher than that of the saline solution, the need for the bicarbonate is obviated. In both concentrations, a final concentration of lidocaine of 0.05% and epinephrine of 1:1,000,000 is created. Some surgeons omit the lidocaine component of the solution when the patient is undergoing general anesthesia to further reduce potential lidocaine toxicity issues. The authors also take the additional measure of warming the injectate to 38°C–40°C to help maintain core body temperature and prevent hypothermia. Infiltration begins by creating a small stab incision, just enough to accommodate the infiltration needle. Alternatively, some use an awl or punch device to attempt to decrease bleeding at the local site. Blunt-tipped cannulas of varying lengths are used to infiltrate the fluid into the desired deep subcutaneous adipose layer using either a handpiece or foot pedal to control administration. When using the tumescent technique, infuse the fluid until the skin is uniformly distended and firm at the operative site. After 8–10 minutes, the skin should become blanched from the vasoconstriction. Commonly, back pressure causes transient spurting of fluid from the ports. Pretunneling can help increase cannula control by establishing desired planes of fat removal before suction is activated. This concept, delineated by Mladick, involves using a larger cannula (6 mm on the trunk/extremities and 3–4 mm on the face) that is passed many times without suction into the most superficial layer of the desired area of removal. This helps prevent inadvertent removal in the subdermal fat layer, which can result in contour irregularities. Ultimately, this can assist in increasing precision in accurate and safe removal of fat. Cross-tunneling is an additional technique helpful in improving cosmetic results of lipoplasty. The technique of cross-tunneling involves the use and creation of at least two port sites at right angles to one another to treat an area of adiposity. The use of multiple port sites provides for better contouring and feathering of edges and allows for more thorough treatment of problem areas. Fat layers generally are treated from deep to superficial in sequence. Parallel tracks are developed in standard fashion, and as the procedure is moved more superficially, cannula size can be decreased along with suction intensity to help decrease risk of irregularity to surface layers. Take care to keep the tip openings facing downward or deep to prevent suction of superficial fat near the dermis, which can result in dimpling. Additionally, moving the tip more rapidly helps prevent dermal deformity. A technique called mesh undermining can also be used to recontour transition and treatment area edges. A blunt cannula is used without suction and is passed laterally into surrounding transition areas, loosening adjacent tissue and softening the edge of treated and untreated areas.

FLUID MANAGEMENT

During liposuction, fluid shifts can manifest in both extremes of fluid status: hypovolemia due to under correction or pulmonary edema and/or congestive heart failure due to over correction. Monitoring urine output with a Foley catheter and constant dialogue between the anesthesia provider and the surgeon should be maintained throughout the procedure to ensure optimal fluid management. Four crucial elements should guide intraoperative fluid correction: intravenous fluid maintenance (body weight dependent), third space losses, volume of

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

wetting solution infiltrated, and the total volume of lipoaspirate [27]. Even higher regard for fluid management is required for large-volume liposuction. In 2006, Rohrich et al. [36] proposed guidelines to aid in this management:

1. Preoperative fluid losses should be repleted as needed and at the discretion of the surgeon and anesthesiologist.
2. Maintenance fluids and fluid boluses should be administered during surgery based on the patient's vital signs and urine output.
3. Superwet technique should be employed.
4. An additional 0.25 mL of lactated Ringer's solution should be given intraoperatively for every 1 mL of aspirate.

INSTRUMENTATION AND CURRENT DEVICES

An extensive number of liposuction cannulas are available to the surgeon that can be used depending on the area, volume, and type of tissue to be treated. Currently, the most frequently used cannulas are either based upon the Mercedes design (contains 3 windows, 120° apart, with a blunt tip; see Figure 59.1) or have downward-facing openings to prevent suctioning of superficial fat, which can create undesirable contour irregularities. Most cannulas used are blunt tipped to limit damage to surrounding soft tissues.

Cannula shaft lengths also vary significantly to allow for proper access to the area to be treated. Areas such as the face and neck are best treated by shorter lengths, while the thighs, hip, back, and abdomen often are treated by longer length cannulas to obtain sufficient reach. Smaller cannula sizes and openings allow for more controlled fat removal with less opportunity for development of contour deformities. Generally, for larger treatment areas, such as the truncal area, 3–6 mm cannulas are used, while in areas that require removal of smaller amounts, such as the face and neck, 1.5 and 2.4 mm cannulas are frequently used. Other tips (e.g., tiger-tip cannula, saber-toothed cannula) also have been created to help allow for more aggressive removal, especially after secondary procedures or with tough fibrous tissue. Other styles of cannula (e.g., loop-de-loop, pickle fork) have been constructed to treat areas of cellulite, disrupting the septa. Several of these also provide mechanisms to reinject fat after aspiration to correct contour and irregularities. Recently, power-assisted cannulas, with a protected rotating tip, have been developed (e.g., MicroAire®, MicroAire Surgical Instruments, Charlotteville, VI) to assist in easier removal of fat with less physical strain on the operating surgeon [8]. There are a number of tools available to the liposuction surgeon. Each tool has its advantages and disadvantages, and some surgeons simply prefer one tool or technique over another. The following discussion is only an introductory comparison, not an in-depth analysis, of the techniques discussed. Traditional suction-assisted lipoplasty (SAL) became popular in the United States in the 1980s. The technique uses varying diameter, blunt-tip cannulas attached via large-bore tubing to a source of high vacuum, which effectively suctions fat through a hole or holes in the tip of the cannula. Syringe SAL is a variation whereby fat is aspirated with a cannula attached to a syringe. Suction is created when the plunger is withdrawn, collecting the fat into the syringe. This technique is frequently used if fat is to be reinjected in other locations. SAL has a long track record and is considered the "gold standard" tool for liposuction. Traditional SAL cannulas are typically bendable and come in many sizes and tip configurations, and most hospital operating rooms and surgery centers own this type of equipment [20]. SAL is an excellent technique for smaller-volume cases and removal of soft fat. It is a less efficient tool for the removal of fat from more fibrous areas and requires a fair amount of physical effort on the part of the surgeon, which becomes a disadvantage in larger-volume cases. Bruising is expected as a result of disruption of blood vessels by the shearing and suction forces. Cross-tunneling is a necessary step with SAL in order to avoid contour irregularity, which one study reported to be as high as 20% [29]. The most frequently reported unsatisfactory results in this study were insufficient fat removal and excessive waviness.

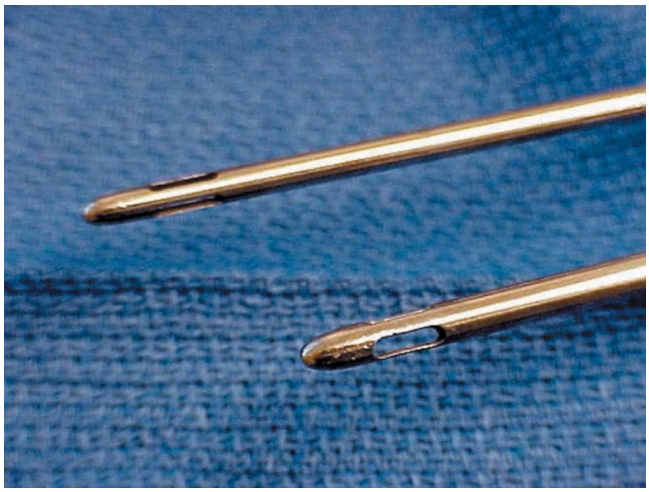


Figure 59.1 Mercedes-tip design liposuction cannulas.

Ultrasound-assisted liposuction (UAL) is a form of liposculpting that employs ultrasonic energy to allow for a more selective tissue lipolysis. Zocchi [33] initially described the technique, where he utilized a two-stage process of selective tissue lipolysis using an ultrasonic probe followed by traditional SAL to evacuate the fat. The selective adipose lipolysis seen in UAL can be attributed to the transformation of electrical into mechanical energy via an ultrasonic probe that vibrates at frequencies in excess of 16 kHz. This oscillating sound wave produces a negative pressure vector that overcomes molecular forces selectively within adipose tissue leading to cavitation and cellular fragmentation [31]. The large-scale cellular disruption is later aspirated in a second-stage liposuction. Rohrich et al. [39] confirmed that UAL generates significantly higher levels of several intracellular adipocyte enzymes than SAL, confirming the notion that adipocytes are mechanically lysed in larger amounts. One of the reported benefits of UAL over other forms of energy and thermal-assisted SAL is cavitation formation of the air bubbled in the tumescent fluid. This process results in a "crowbar" effect of streaming intact fat cells and adipocyte-derived stem cells so that these can then be used for successful fat grafting. Supporters of UAL claim that adipocyte cavitation prior to SAL decreases blood loss and operative time while providing for less ecchymosis and discomfort as well as improved contouring in areas with an abundance of fibrous tissue, such as the back and chest [33,34]. While the evidence to substantiate claims of decreased operative time and ecchymosis are mixed, several studies have confirmed that UAL is effective in cases of secondary liposuction as well as liposuction in

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

fibrotic areas such as the male flank or chest area. Power-assisted liposuction (PAL) was developed in the late 1990s to address some of the concerns about UAL. PAL is basically traditional SAL powered by a reciprocating cannula. The main advantages of PAL over SAL are its efficiency in fibrous areas and its ease of operation for the surgeon. There is no particular salvage of fibroconnective tissue or neurovascular structures as there is with UAL. The main advantage of PAL over UAL is that there is no heat generation. UAL is safe and effective when the surgeon is properly trained and the procedure is performed properly. PAL is an excellent tool for surgeons who remain uncomfortable with the potential for heat and the more powerful tool. Laser-assisted liposuction (LAL) was first described in 1994 by Apfelberg et al. LAL utilizes the principles of selective photothermolysis to preferentially lyse adipocytes while leaving surrounding structures unaffected. The disadvantages of LAL include the potential for thermal injury, high costs of equipment, and prolonged procedural time. Initial studies evaluating first-generation laser devices showed, in randomized trials, no increased cosmetic benefits of LAL when compared with traditional SAL. The emerging laser technology utilizes varying wavelengths with different effects on the surrounding environment, leading to promising dermal physiologic changes with decreased complication [21].

Radio frequency–assisted liposuction (RFLAL) energy is a high-frequency oscillating electrical current (1 million cycles/s) applied to the tissue to create a thermal effect. RFAL is responsible for dissolving fat cells, which leads to the creation of small channels in the fatty tissue. Furthermore, RFAL causes dermal physiological responses including immediate contraction of the collagen fibers, subdermal remodeling, and neocollagen formation. RFAL is a computer-controlled, bipolar RF device that simultaneously coagulates fat, aspirates the liquefied fat, and contracts the fibroseptal network. The first such technological advance to employ RF for lipolysis is the BodyTite™ system (Invasix Ltd, Yokneam Illit, Israel). The internal electrode of the BodyTite is a hollow Mercedes-tip suction cannula/electrode and is silicone coated, except for the tip. The tip delivers RF, which flows to an external circular electrode that slides along the surface of the skin, in tandem with the internal electrode. This contact surface creates lower power density in the upper dermal layer and closes the RF current loop by receiving the energy through the skin. Furthermore, the external electrode has an imbedded thermal sensor that measures real-time skin temperature 10 times per second, leading to uniform heating of the subreticular dermis, which aids in the denaturation and remodeling of collagen. This is an important concept and ensures patient safety by avoiding thermal injury that can result in deep burns and pathological scarring. In addition, the pericanalicular temperature, high and low dermal impedance, and the external electrode contact are measured. There are safety RF cutoffs for each of these measured parameters, which greatly reduce the risk of a thermal injury. While a theoretical disadvantage of the RFAL system is thermal injury to the surrounding dermal structures, there have been no reports of this within the peer-reviewed literature. Reported complications have been minimal and include bruising, surface irregularities, and pain. The RFAL system shows promise and has a significant amount of international experience and data. FDA approval is pending [35,36].

BODY AREAS TREATABLE WITH LIPOSUCTION

Numerous body areas are amenable to liposuction given the plethora of equipment now available. Today's patient can be treated from head to toe. The face and neck can be successfully treated with liposuction, although fat injection instead of aspiration is increasingly popular. The trunk, including the abdomen, back, breast, and posterior hips (flanks), and the lower extremities, including the knees, calves, and ankles, have all been successfully treated with liposuction. The upper arm is also well suited for UAL or SAL when the skin is not too loose. The buttocks can be successfully treated but should be approached with some degree of caution. Creation of a flat or ptotic buttocks is not only unsightly, but usually requires excisional measures to repair.

Neck

Liposuction in the neck region is often performed with traditional SAL and small cannulas. Access is typically via a submental incision and often is just posterior to the mandible on either side. Overzealous treatment of this area may result in hollowing and skeletalization of the neck or potential neuropraxia of the marginal mandibular nerve (Figures 59.2 through 59.5).

(a) (b)

Figure 59.2 (a) This 45-year-old woman presented with cervical steatomery after massive weight loss; (b) 6 months after cervical liposuction combined with a facelift. (Courtesy of Dr. Olivier Claude.)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 59.3 (a) This 45-year-old woman presented with cervical steatomery after massive weight loss; (b) 6 months after cervical liposuction combined with a facelift. (Courtesy of Dr. Olivier Claude.)

(a) (b)

Figure 59.4 (a) This 62-year-old woman presented with jowls with excess of facial skin; (b) 7 months after jowl liposuction combined with a facelift. (Courtesy of Dr. Olivier Claude.)

(a) (b)

Figure 59.5 (a) This 62-year-old woman presented with jowls with excess of facial skin; (b) 7 months after jowl liposuction combined with a facelift. (Courtesy of Dr. Olivier Claude.)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Arms

Liposuction of the arms is usually suited to patients with an excess of 1.5 cm of fat by the pinch test. Patients with less fat and more skin excess may benefit from excisional surgery rather than liposuction. Proximal access may be achieved through a posterior axillary incision. The area where the arm joins the trunk may be accessed either through this incision or a back access incision if the back is being treated as well.

Back

The anatomy of the subcutaneous fat and skin of the back is different from other regions of the trunks and extremities; it has a very thick dermis and a dense, fibrous characteristic to the underlying fat. Access incision sites will depend on the distribution of lipodystrophy and can be placed medially or laterally; the incisions should be placed in the bra/bathing suit line for the best cosmetic result.

Abdomen

Subcutaneous abdominal fat is amenable to all of the various modalities of liposuction. We reserve superficial liposuction for the linea alba or for correction of secondary deformities. Access to the abdominal region may be conducted through an umbilical incision, bilateral lower abdominal incisions, and/or suprapubic incisions (Figures 59.6 and 59.7).

Hip/Flanks

This common area of suctioning in both men and women is accessible through the bilateral or single midline paraspinous region and/or incision in the lateral gluteal fold. Suctioning in this area can provide excellent results, and all modalities have proved effective. The fat is loose and in some cases fibrous, with thick overlying skin.

Thighs and Buttocks

Liposuction of the thighs is one of the most difficult procedures; overaggressive treatment may result in an unsatisfactory contour. Because the majority of contour irregularities occur within the thigh region, again it is of paramount importance to recognize and understand the significance of the thigh zones of adherence: the lateral gluteal depression; the gluteal crease; the posterior, inferior, and distal lateral thigh; and the mid-inner thigh.

(a) (b)

Figure 59.6 (a) This 21-year-old woman presented with android steatomeries; (b) 7 months after abdominal and waist liposuction. (Courtesy of Dr. Olivier Claude.)

(a) (b)

Figure 59.7 (a) This 21-year-old woman presented with android steatomeries; (b) 7 months after abdominal and waist liposuction. (Courtesy of Dr. Olivier Claude.)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

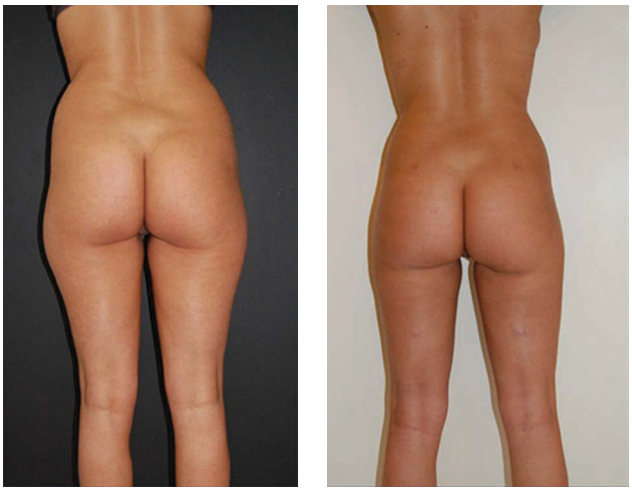
Access incisions are placed asymmetrically to avoid an operated look. This area is most easily accessed through paraspinous or gluteal access incisions. Excessive contouring of the lateral proximal posterior thigh may result in an extension of the gluteal fold in women and masculinization of the gluteal area. The surgeon must exercise special care when addressing the proximal posterior thigh. Aggressive suctioning in this difficult area may result in disfiguring skin rolls and redundancy (Figures 59.8 and 59.9).

Knees

Treatment of the knees varies depending on the patient's anatomy. Isolated fat of the knee medially is easily treated through a posterior incision with the patient in the prone position. For patients with suprapatellar fullness, the incision placed within a skin fold anteriorly.

POSTOPERATIVE CARE AND PREVENTION OF COMPLICATIONS

Compression garments are worn at all times for the first 2 weeks followed by nightly for an additional 2 weeks. The majority of small-volume patients can be counseled that they may return to work in 3–5 days, whereas generally 7–10 days is needed for patients undergoing larger-volume procedures. Most patients will return to regular activities in 3–4 weeks. Safe lipectomy depends not only on the intended action of the surgeon but also on the management of risk and prevention of complications. Gargan and Courtiss [32] broke these risks into two distinct subgroups: undesirable sequelae include surface contour irregularities, dysesthesia, edema, ecchymosis, and discoloration, while potential complications include excessive blood loss, hematoma, seroma, infection, thrombosis, fat emboli, and skin necrosis.



(a) (b)

Figure 59.8 (a) This 25-year-old woman presented with gynoid steatomeries; (b) 6 months after saddle bag, inner thigh, abdominal, and waist liposuction. (Courtesy of Dr. Olivier Claude.)

(a) (b)

Figure 59.9 (a) This 25-year-old woman presented with gynoid steatomeries; (b) 6 months after saddle bag, inner thigh, abdominal, and waist liposuction. (Courtesy of Dr. Olivier Claude.)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Notably, dysesthesia of the treatment area is to be expected rather than considered an avoidable consequence of suction lipectomy. Typically, a 3–6 months waiting period will allow for normal sensation to return. Contour irregularities that are evident during the operation should be immediately addressed by fat grafting. Postoperatively, contour irregularities that arise should be treated conservatively for at least 6 months with massage therapy. Depending on the severity of the irregularity, methods of correction include liposuction of areas of prominence or adjacent to areas of depression, fat grafting, or even dermolipectomy. More severe consequences of lipectomy include not only morbidity but also mortality. In a review by Grazer and de Jong [38] of 1200 active board-certified plastic surgeons, there were 95 fatalities in nearly 500,000 lipectomy procedures, producing a mortality rate of 19 in 100,000 with 23% attributable to pulmonary embolism. In a discussion of these findings, Rohrich and Muzaffar [39] suggested the following safety guidelines in liposuction:

1. Appropriate patient selection (American Society of Anesthesiologists class I, with ideal body weight)
2. Use of superwet technique
3. Meticulous monitoring of volume status (urinary catheterization, non-invasive hemodynamic monitoring, constant communication with anesthesiologist)
4. Judicious fluid management
   a. *For aspirate <5 L*: Maintenance of fluid plus subcutaneous infiltrate
   b. *For aspirate >5 L*: Maintenance of fluid plus subcutaneous infiltrate plus 0.25 mL on intravenous crystalloid per 1 mL of aspirate >5 L
5. Overnight monitoring of large-volume (>5 L total aspirate) liposuction patients in appropriate health-care facility
6. Use of pneumatic compression devices in cases performed under general anesthesia or lasting longer than 1 hour
7. Maintaining total lidocaine doses below 35 mg/kg (wetting solution)

RISKS AND POSSIBLE COMPLICATIONS

Any surgical procedure has risks. Fortunately, serious complications are rarely associated with liposuction procedures. The most significant complications have been attributed to concurrent sedation or general anesthesia or fluid shifts secondary to large-volume liposuction. Fatalities have been associated with other concurrent surgical procedures, for example, abdominoplasty performed with abdominal liposuction. In an American Society for Dermatologic Surgery study of 15,336 patients [40], no deaths were noted. In addition, no reports of pulmonary emboli, viscous perforation, thrombophlebitis, hypovolemic shock, seizures, or toxic reactions were described. Four cases of toxic shock syndrome were recognized, but overall, the prevalence of infection ranged from 0.34% to 0.6%. Skin irregularity ranged from 0.26% to 2.1%. The rate of hematoma or seroma was only 0.17%–1.6%, the rate of unacceptable scarring was 0.02%, the rate of sensory nerve impairment was 0.03%–2.6%, and the rate of contact dermatitis was 0.12%. In another recent survey of 261 dermatologic surgeons having performed 66,570 liposuction procedures, no deaths were reported.

OUTCOME AND EVOLUTION

Recent outcome studies show that 80% of patients were satisfied with their liposuction results, and 53% rated their appearance as excellent or very good. Interestingly, weight gain is common after liposuction and is seen in 43% of patients, with the abdomen serving as the most common location of recurrence. Three-quarters of patients rate discomfort as mild to moderate, with 60% indicating that the pain lasted less than 7 days [41].

CONCLUSION

Over the past 30 years, there have been many advances in surgical technique and patient-related standards for liposuction. Liposuction is a surgical procedure that can produce superb aesthetic results when performed properly. Careful aspiration, use of the smart hand, triangulation, and fluid management are all important parts of the liposuction procedure. Final outcomes depend on both the skill of the surgeon and the healing response of the patient. Liposuction is an extremely popular cosmetic procedure in today's body-conscious society. Indeed, liposuction is a very powerful tool; nevertheless, sculpting the human body by removal of the perfect amount of fat, and leaving behind the perfect amount of fat, is an art [25].

REFERENCES

1. Fournier P. Popularization of the technique. In: Hetter GP, ed. *Lipoplasty: The Theory and Practice of Blunt Suction Lipectomy*, 2nd ed. Boston, MA: Little Brown, 1990, pp. 35–38.
2. Agris J, Varon J. *Suction-Assisted Lipectomy-Clinical Atlas*. Houston, TX: Terico, 1983.
3. Illouz Y. *Liposuction: The Franco-American Experience*. Beverly Hills, CA: Medical Aesthetics, 1985.
4. Kesselring U. Regional fat aspiration for body contouring. *Plast Reconstr Surg* 1983; 72(5):610–619.
5. Hetter G, ed. *Lipoplasty: The Theory and Practice of Blunt Suction Lipectomy*. Boston, MA: Little, Brown &Co, 1984.
6. Field L. Liposuction surgery: A review. *J Dermatol Surg Oncol* 1984; 10(7):530–538.
7. Newman J. Liposuction surgery: Past-present-future. *Am J Cosmet Surg* 1984; 1(1):19–20.
8. Courtiss E. Suction lipectomy: A retrospective analysis of 100 patients. *Plast Reconstr Surg* 1984; 73(5):780–786
9. Teimourian B, Fisher J. Suction curettage to remove excess fat for body contouring. *Plast Reconstr Surg* 1981; 68(1):50–58.
10. Newman J, Dolsky R. Complications liposuction surgery. *Am J Cosmet Surg* 1985; 2(1):8–12.
11. Courtiss E. Suction lipectomy of the neck. *Plast Reconstr Surg* 1985; 76(6):882–889.
12. Shippert R. The dynamics of fat break down and the role of progressive diameter cannula technique and suction assisted lipectomy. *Am J Cosmet Surg* 1984; 181:15–18.
13. Fournier P, Otteni F.Liposuction in body sculpturing the dry procedure. *Plast Reconstr Surg* 1983; 72(5):598–609.
14. Brown SA, Lipschitz AH, Kenkel JM et al. Pharmacokinetics and safety of epinephrine use in liposuction. *Plast Reconstr Surg* 2004 September; 114(3):756–763.
15. Hetter GP. The effect of low dose epinephrine on the hematocrit drop following lipolysis. *Aesthet Plast Surg* 1984; 8(1):19.
16. Iverson RE, Lynch DJ. Practice advisory on liposuction. *Plast Reconstr Surg* April 15, 2004; 113(5):1478–1490; discussion 1491–1495.
17. Karcenty B, Lentini A, Le Nen D, Henry AS, Ta P, Trimaille A, Hu W. Pediatric lower extremity reconstruction. *Ann Chir Plast Esthet* 2003; 5:399–404.
18. Klein JA. The tumescent technique for liposuction surgery. *Am J Cosmet Surg* 1987; 4:263.
19. Klein JA. Tumescent technique for regional anesthesia permits lidocaine doses of 35 mg/kg for liposuction. *J Dermatol Surg Oncol* 1990; 16:248.
20. Fodor PB. Power-assisted lipoplasty versus traditional suction-assisted lipoplasty: Comparative evaluation and analysis of output. *Aesthet Plast Surg* 2005; 29:127.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

21. Scuderi N, Paolini G, Grippaudo FR et al. Comparative evaluation of traditional, ultrasonic, and pneumatic assisted lipoplasty: Analysis of local and systemic effects, efficacy, and costs of these methods. *Aesthet Plast Surg* 2000; 24:395–400.
22. Rohrich RJ, Kenkel JM, Janis JE et al. An update on the role of subcutaneous infiltration in suction-assisted lipoplasty. *Plast Reconstr Surg* 2003; 111:926.
23. Hatef DA, Brown SA, Lipschitz AH et al. Efficacy of lidocaine for pain control in subcutaneous infiltration during liposuction. *Aesthet Surg J* 2009; 29:122–128.
24. Samdal F, Amland PF, Bugge JF. Plasma lidocaine levels during suction-assisted lipectomy using large doses of dilute lidocaine with epinephrine. *Plast Reconstr Surg* 1994; 93:1217–1223.
25. Rohrich RJ, Broughton G II, Horton B et al. The key to long-term success in liposuction: A guide for plastic surgeons and patients. *Plast Reconstr Surg* 2004; 114:1945–1952.
26. Seruya M, Venturi ML, Iorio ML et al. Efficacy and safety of venous thromboembolism prophylaxis in highest risk plastic surgery patients. *Plast Reconstr Surg* 2008; 122:1701–1708.
27. Stephan PJ, Kenkel JM. Updates and advances in liposuction. *Aesthet Surg J* 2010; 30:83–97; quiz 98–100.
28. Hatef DA, Brown SA, Lipschitz AH et al. Efficacy of lidocaine for pain control in subcutaneous infiltration during liposuction. *Aesthet Surg J* 2009; 29:122–128.
29. Ahmad J, Eaves FF III, Rohrich RJ et al. The American Society for Aesthetic Plastic Surgery (ASAPS) survey: Current trends in liposuction. *Aesthet Surg J* 2011; 31:214–222.
30. Kenkel JM, Lipschitz AH, Shepherd G et al. Pharmacokinetics and safety of lidocaine and monoethylglycinexylidide in liposuction: A microdialysis study. *Plast Reconstr Surg* 2004; 114:516–524; discussion 525–526.
31. Rohrich RJ, Leedy JE, Swamy R et al. Fluid resuscitation in liposuction: A retrospective review of 89 consecutive patients. *Plast Reconstr Surg* 2006; 117:431–435.
32. Gargan TJ, Courtiss EH. The risks of suction lipectomy. Their prevention and treatment. *Clin Plastic Surg* 1984; 11:457–463.
33. Zocchi ML. Ultrasonic assisted lipoplasty. Technical refinements and clinical evaluations. *Clin Plast Surg* 1996; 23:575–598.
34. Rohrich RJ, Morales DE, Krueger JE et al. Comparative lipoplasty analysis of in vivo-treated adipose tissue. *Plast Reconstr Surg* 2000; 105:2152–2158; discussion 2159.
35. Maxwell GP, Gingrass MK. Ultrasound-assisted lipoplasty: A clinical study of 250 consecutive patients. *Plast Reconstr Surg* 1998; 101:189–202; discussion 203.
36. Rohrich RJ, Beran SJ, Kenkel JM, Adams WPJ, Di Spaltro F. Extending the role of liposuction in body contouring with ultrasound-assisted liposuction. *Plast Reconstr Surg* 1998; 101:1090–1102; discussion 1117.
37. Beckenstein MS, Grotting JC. Ultrasound-assisted lipectomy using the solid probe: A retrospective review of 100 consecutive cases. *Plast Reconstr Surg* 2000; 105:2161–2174; discussion 2175.
38. Grazer FM, de Jong RH. Fatal outcomes from liposuction: Census survey of cosmetic surgeons. *Plast Reconstr Surg* 2000; 105:436–446; discussion 447–448.
39. Rohrich RJ, Muzaffar AR. Fatal outcomes from liposuction: Census survey of cosmetic surgeons. *Plast Reconstr Surg.* 2000; 105:447–448.
40. Goyen MR. Lifestyle outcomes of tumescent liposuction surgery. *Dermatol Surg* 2002; 28:459–462.
41. Levesque AY. Daniels MA, Polynice A. Outpatient Lipoabdominoplasty. Review of the literature and practical considerations for safe practice. *Aesthet Surg J* September 1, 2013; 33(7):1021–1029.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Laser lipolysis

Franck Marie P. Leclère, Serge Mordon, and Mario A. Trelles

INTRODUCTION

Attempts to reduce localized adiposity through diet or exercise alone are often unsuccessful, and liposuction remains one of the most common cosmetic surgical procedures in North America with over 400,000 procedures performed in 2006 [1]. Though it is a common surgical cosmetic procedure, liposuction is not without shortcomings [2], including blood loss, bruising, and long operating time. The term liposuction is imprecise because it regroups the following techniques: suction-assisted lipoplasty (SAL), ultrasound-assisted lipoplasty, power-assisted lipoplasty (PAL), and laser-assisted lipolysis (LAL).

SAL was introduced by Fisher and Fisher in Italy in 1975 [3]. The procedure, based on the use of a blunt-tipped, blind cannula, multiple incisions, and a crossed back and forth tunneling movement, was then developed and modified into Illouz's *wet technique* [4] and Klein's tumescent anesthesia [5]. The step from general anesthesia to tumescent anesthesia was crucial in order to reduce side effects such as blood loss, postoperative pain, and edema and to increase the patient's satisfaction [5,6]. Additional advances followed in the field of SAL, including the development of external and internal ultrasound [7–9], and PAL [10]. Of the three techniques, PAL is the most commonly used owing to low cost, easy penetration of fibrous fat, and a low incidence of seromas and burns mostly related to ultrasound [11]. However, both SAL and PAL are mechanical procedures that require significant force to regularly perforate fibrous tissue. The local damage caused by the cannula can be transmitted along the septa and the vessels to areas other than the area of treatment [12]. The procedure can also result in irregular contouring and skin laxity. Since its introduction in 1992, LAL has been steadily on the rise. After its U.S. Food and Drug Administration (FDA) approval in October of 2006 [13], studies have continued to underline its numerous advantages over conventional techniques.

In this chapter, a short overview of the technique's history is presented. The mechanism of action and advantages of laser lipolysis are discussed. Finally, a large place is accorded to the dosimetry.

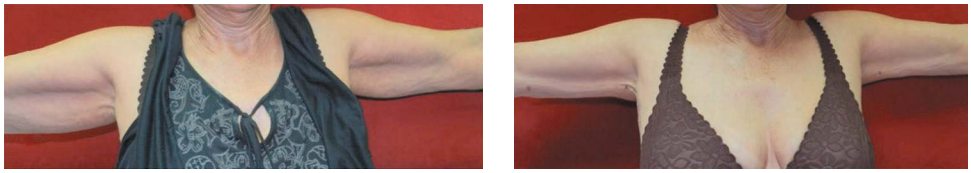
From the Pioneer Work of Apfelberg to the Mathematical Model of Mordon

Apfelberg et al. published the pioneer work on laser lipolysis in 1992 [14], and 2 years later, this team conducted the first multicenter trial studying neodymium-doped yttrium aluminum garnet (Nd:YAG) laser-assisted liposuction with the following parameters [15]: 40 W power and 0.2 second pulse duration. The 600 µm fiber used in their studies was encased within a 4 or 6 mm cannula. Their LAL work produced decreased ecchymosis, pain, and edema compared to the conventional technique. Moreover, less effort was needed for the surgeon. Between 2000 and 2003, Goldman [16], Blugerman [17], and Schavelzon [18] demonstrated the effects of the pulsed 1064 nm Nd:YAG laser on fat tissue, vessels, and dermis, introducing the concept system for laser lipolysis. In 2003, Badin et al. [19] demonstrated more precisely the histological changes after thermal damage by the laser: disruption of adipocyte membranes, coagulation of blood vessels, and reorganization of collagen. Badin underlined that LAL was less traumatic due to smaller cannula size as well as the unique tissue reaction of the Nd:YAG system, which improved skin retraction. A large cohort study of 1734 patients was published in 2002 by Goldman [20]; it underlined the reduced blood loss and ecchymosis as well as the better efficacy of LAL compared to conventional techniques. Complementary proof of fat reduction and skin retraction with LAL were provided by Kim and Geronemus [21] with the help of magnetic resonance imaging. After a long period of discussion, the FDA finally approved the LAL technique: done with a 6 W Nd:YAG laser manufactured by Deka and distributed by Cynosure. After this critical date, the number of studies increased and numerous wavelengths and corresponding devices were used to reach effective lipolysis and skin retraction. In 2007, our team detailed a mathematical model of laser lipolysis that evaluated a 980 nm diode device with a 1064 nm Nd:YAG device [22]. Our study concluded that heat, rather than a particular wavelength, led to lipolysis and skin tightening. We determined that an internal temperature range of 48°C–50°C was sufficient to induce skin tightening. In 2008, McBean and Katz presented the first study to demonstrate via India ink tattoo the skin-tightening effect of laser lipolysis with the sequential use of 1064–1320 nm wavelengths [23]. In 2009, DiBernardo et al. presented the first EBM II study on LAL; they treated 10 female patients using, sequentially, the 1064 and 1320 nm of the Nd:YAG laser on one side of the abdomen and liposuction alone on the other side [24]. Three months after treatment, the skin tightening was significantly higher on the laser-treated side. They concluded that LAL has a statistically significant effect on tightening of the skin in the abdominal area when compared to liposuction alone. Since this report, the number of studies and wavelengths used in the literature has grown. The technique is now widely used. Our experience is based on six studies [25–30] (Figures 60.1 through 60.3); while most of the indications are usually the same with the conventional technique, LAL is largely better for (1) location that demonstrates unwanted fatty tissue and modest skin laxity like submental areas or cankles, (2) fibrous areas such as the male breast, and (3) revisional surgeries after the conventional technique.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

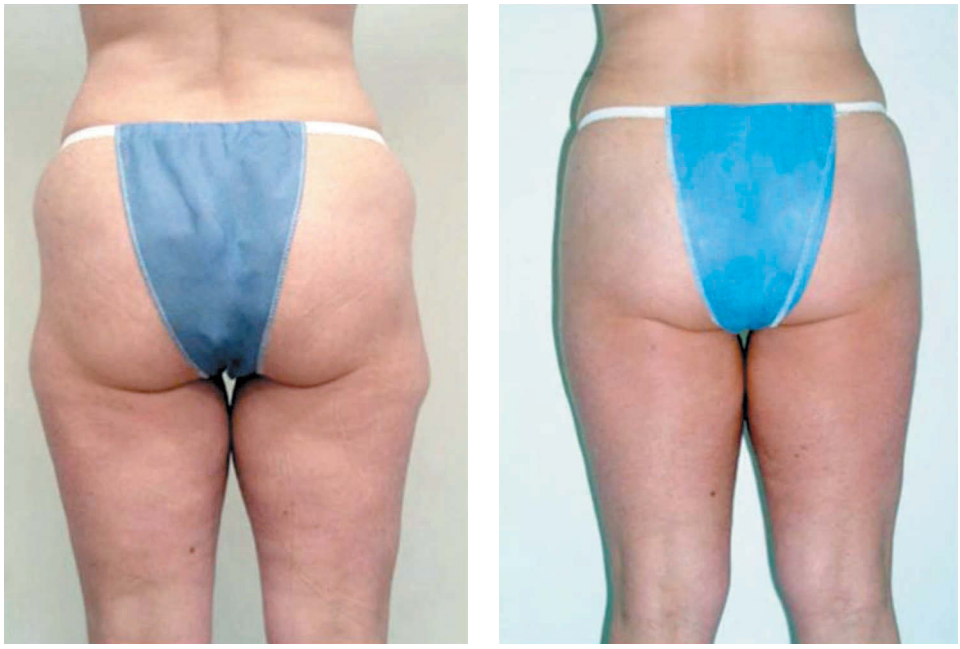
(a) (b)

Figure 60.1 Male, 38 years of age, gynecomastia Rhorick degree III, BMI 32.5. (a) Before LAL, there is notable flaccidity and areola–nipple enlargement. (b) Six months after LAL, there is further reduction of breast volume without changes in the BMI. Notice the decrease in the areola diameter and skin contraction and firmness.



(a) (b)

Figure 60.2 Female, 68 years of age. (a) Before LAL, arm flaccidity, and evident sagging skin. (b) Six months after LAL.



(a) (b)

Figure 60.3 Female, 37 years of age. (a) Before LAL of the buttocks and trochanter areas. (b) Results 6 months after LAL.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Mechanisms of Action

The efficacy of laser lipolysis is determined by the type of wavelength and energy delivered on tissue. Different wavelengths including 924, 968, 980, 1064, 1319, 1320, 1344, 1470, and 1440 nm have been selected for laser lipolysis in an attempt to specifically target fat, collagen (water), and blood vessels. According to the theory of selective photothermolysis, these chromophores will preferentially absorb laser energy on the basis of their absorption coefficients at specific wavelengths.

Photoacoustic, photomechanical, and photothermal effects are additional theorized mechanisms of action in laser lipolysis. According to our experience with several clinical trials and histological examinations, heat is the primary stimulant for lipolytic and skin-tightening effects. Our mathematical analysis [22] and additional thermoregulatory studies [31,32] have demonstrated that an internal temperature between 48°C and 50°C must be reached for collagen denaturization and subsequent skin tightening. External skin temperatures between 38°C and 41°C were identified as safe and efficacious.

Advantages of Laser Lipolysis

When the optimal temperature is reached, numerous studies have underlined that LAL provides disruption of adipocyte membranes, coagulation of blood and lymphatic vessels, and reorganization of collagen. As a consequence, laser lipolysis features excellent patient tolerance and satisfaction, reduced down time, as well as having the benefit of dermal tightening. The thermal action of the beam makes the movement of the cannula easier with less effort and fatigue for the surgeon [25–30]. The treatment of areas where fat removal is difficult, as in the case of arms or gynecomastia, is facilitated by the small diameter of the microcannula containing the laser fiber. In our experience, ecchymosis is usually observed in all patients but resolved in less than 10 days. Additional complications reported in the literature include infection and burns. However, most of these complications are directly associated with the learning curve. In order to help the surgeon avoid burning tissue while achieving satisfactory outcomes, technological advances have been incorporated to some systems. These developments are discussed in the next section.

Dosimetry

Due to the relatively narrow window between heat accumulation that denatures proteins and stimulates collagen due to dermal–epidermal thermal effects, burns are an inherent risk. To homogenize the energy delivered, two systems have been designed. Cynosure has developed the system SmartSense™ [26]. This system contains an accelerometer that automatically adjusts the laser power. In other words, if the surgeon moves the cannula too slowly, the power is automatically reduced, and without movement, the power is zero. Recently, *Osyris* has developed the LipoControl™ [33]. Using a 3D magnetic tracking system of the cannula, this system knows the position and speed of the cannula at all times, thereby controlling the laser power emitted as a function of speed. Moreover, LipoControl is able to inform the surgeon of the delivered energy in each portion of the treated area. These two systems represent a first level of control assistance for dosimetry during laser lipolysis. With LipoControl, the amount of energy delivered into the tissue is no longer globally defined depending on the treated area, but locally defined depending on the thickness of the treated tissue. It is therefore a custom lipolysis based on dosimetry. The interest for dosimetry in a laser lipolysis procedure is multiple. Overall, it avoids both overdosing and underdosing. Without complementary tools, it has been relatively difficult to estimate the volume to be treated and, consequently, the laser energy needed. With the help of dosimetry, the surgeon is able to deliver a custom energy level without reaching levels of higher energy thresholds that can cause thermal damage. In this developing technique, it is very interesting to see how technological evolutions have refined the original procedure and its outcomes.

Reasons for Limited Development of Laser-Assisted Lipolysis over the World

Besides the risk of burns claimed by some surgeons, two aspects explain the limited global development of LAL. The price of the equipment can be initially prohibitive. The affordability of new instruments, their rapid payback, and the aforementioned benefits should contribute to a wider use of this powerful tool. Some authors have previously highlighted the long learning curve of the procedure. However, two points will greatly help the beginner. On the one hand, the new technologies that can help to determine the required dosimetry are on the rise and will help the young surgeons to reach the threshold level of energy while avoiding the risk of thermal damage. On the other hand, there is a high interest to improve laser teaching. In Europe, with the development of the Diplome Interuniversitaire de Laser, it is now possible to rapidly acquire experience and discuss problems with experienced surgeons in laser technologies.

Conclusions

LAL appears to be a safe, more effective, and reproducible alternative to conventional lipoplasty. With this developing technique, it is very interesting to see how technological evolutions have refined the original technique and its outcomes. The search should continue to reduce operator effect, downtime, and bleeding to achieve fine tissue sculpture. Finally, to definitively establish the technique compared to conventional liposuction, more double-blind multicenter studies must be undertaken.

REFERENCES

1. Katz B, McBean J. The new laser liposuction for men. *Dermatol Ther* 2007; 20:448–451.
2. Fuente del Campo AF, Rojas Allegretti E, Fernandes Filho JA, Gordon CB. Liposuction: Procedure for focal volume reduction and body contour remodeling. *World J Surg* 1998; 22:981–986.
3. Fischer A, Fischer GM. Revised technique for cellulitis fat reduction in riding breeches deformity. *Bull Int Acad Cosmet Surg* 1977; 2:40–46.
4. Illouz YG. Surgical remodeling of the silhouette by aspiration lipolysis or selective lipectomy. *Aesthet Plast Surg* 1985; 9:7–14.
5. Klein JA. Tumescent technique for regional anesthesia permits lidocaine doses of 35 mg/kg for liposuction. *J Dermatol Surg Oncol* 1990; 16:248–263.
6. Klein J. Tumescent technique. *Am J Cosmet Surg* 1987; 4:263–267.
7. Coleman WP III. The history of liposuction and fat transplantation in America. *Dermatol Clin* 1999; 17:723–727.
8. Zocchi M. Ultrasonic liposculpturing. *Aesthet Plast Surg* 1992; 16:287–298.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

9. Silberg BN. The technique of external ultrasound-assisted lipoplasty. *Plast Reconstr Surg* 1998; 101:552–560.
10. Gross CW, Becker DG, Lindsey WH, Park SS, Marshall DD. The soft-tissue shaving procedure for removal of adipose tissue. A new, less traumatic approach than liposuction. *Arch Otoryngol Head Neck Surg* 1995; 121:1117–1120.
11. Coleman WP III. Powered liposuction. *Dermatol Surg* 2000; 26:315–318.
12. Blondeel PN, Derks D, Roche N, Van Landuyt KH, Monstrey SJ. The effect of ultrasound-assisted liposuction and conventional liposuction on perforator vessels in the lower abdominal wall. *Br J Plast Surg* 2003; 56:266–271.
13. http://www.fda.gov/consumer/updates/liposuction082007.html.
14. Apfelberg D. Laser-assisted liposuction may benefit surgeons and subjects. *Clin Laser Mon* 1992; 10:259.
15. Apfelberg DB, Rosenthal S, Hunstad JP et al. Progress report on multicenter study of laser-assisted liposuction. *Aesthet Plast Surg* 1994; 18:259–264.
16. Goldman A, Schavelzon DE, Blugerman GS. Laser lipolysis: Liposuction using Nd:YAG laser. *Rev Soc Bras Cir Plast* 2002; 17:17–26.
17. Blugerman GB. Laser lipolysis for the treatment of localized adiposity and "cellulite." *Abstracts of World Congress on Liposuction Surgery*, Dearborn, MI, 2000.
18. Schavelzon DS, Blugerman G, Goldman A et al. Laser lipolysis. *Abstracts of the Tenth International Symposium on Cosmetic Laser Surgery*, Las Vegas, NV, 2001.
19. Badin A, Moraes L, Gondek L et al. Laser lipolysis: Flaccidity under control. *Aesthet Plast Surg* 2002; 26:335–339.
20. Goldman A, Schavelzon D, Blugerman G. Laser lipolysis: Liposuction with Nd:YAG laser. *Rev Soc Bras Laser Med* 2002; 2:15–17.
21. Kim KH, Geronemus RG. Laser lipolysis using a novel 1,064 nm Nd:YAG Laser. *Dermatol Surg* 2006; 32:241–248.
22. Mordon SR. Mathematical modeling of laser lipolysis. *Biomed Eng Online* 2008; 7:10.
23. McBean JC, Katz B. A pilot study of the efficacy of a 1064 nm and 1320 nm sequentially firing Nd:YAG laser device for lipolysis and skin tightening. *Lasers Surg Med* 2009; 41:779–784.
24. DiBernardo BE, Reyes J. Evaluation of skin tightening after laser-assisted liposuction. *Aesthet Surg J* 2009; 29:400–407.
25. Trelles M, Bonanad E, Moreno-Moraga J, Alcolea J, Mordon S, Leclère FM. Laser-assisted lipolysis for gynecomastia: Safe and effective skin retraction. *Rev Col Bras Cir* 2013; 40:23–31.
26. Leclère FM, Moreno-Moraga J, Mordon S, Servell P, Unglaub F, Kolb F, Rimareix F, Trelles MA. Laser-assisted lipolysis for cankle remodelling: A prospective study in 30 patients. *Lasers Med Sci* 2014; 29:131–136.
27. Leclère FM, Trelles M, Moreno-Moraga J, Servell P, Unglaub F, Mordon SR. 980-nm laser lipolysis (LAL): About 674 procedures in 359 patients. *J Cosmet Laser Ther* 2012; 14:67–73.
28. Moreno-Moraga J, Trelles MA, Mordon S, Unglaub F, Bravo E, Royo de La Torre J, Sanz I, Servell P, Betrouni N, Leclère FM. Laser-assisted lipolysis for knee remodelling: A prospective study in 30 patients. *J Cosmet Laser Ther* 2012; 14:59–66.
29. Trelles MA, Mordon SR, Bonanad E, Moreno Moraga J, Heckmann A, Unglaub F, Betrouni N, Leclère FM. Laser-assisted lipolysis in the treatment of gynecomastia: A prospective study in 28 patients. *Lasers Med Sci* 2013; 28:375–382.
30. Reynaud JP, Skibinski M, Wassmer B, Rochon P, Mordon S. Lipolysis using a 980-nm diode laser: A retrospective analysis of 534 procedures. *Aesthet Plast Surg* 2009; 33:28–36.
31. Dudelzak J, Hussain M, Goldberg DJ. Laser lipolysis of the arm, with and without suction aspiration: Clinical and histological changes. *J Cosmet Laser Ther* 2009; 11:70–73.
32. DiBernardo BE, Reyes J, Chen B. Evaluation of tissue thermal effects from 1064/1320 nm laser-assisted lipolysis and its clinical implications. *J Cosmet Laser Ther* 2009; 11:62–69.
33. Sadick NS, Rochon P, Mordon S. Advantages of real-time magnetic tracking of the cannula for controlled laser assisted lipolysis (LAL). *Lasers Surg Med* 2010; 42:65.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Soft tissue lifting by suspension sutures

Konstantin Sulamanidze, Marlen Sulamanidze, and George Sulamanidze

SUTURE DEVELOPMENT

At the beginning of the 1990s, rapidly developing, minimally invasive aesthetic surgery split off from plastic and aesthetic surgery, making it more affordable and democratic. This factor allowed a multimillion army of patients, wishing to eliminate aesthetic manifestations of ageing, to safely make plans to visit a specialist for implementation of rejuvenating interventions. Formerly, the majority of them would never have dared to address the surgeon for facelift implementation, dooming them to slow ageing. Among the numerous trends of minimally invasive aesthetic surgery, came suture methods for treating appearance deformations. Colleagues' interest in these methods steadily began growing, and scientific publications on these themes began appearing in reputable periodicals, and even in separate sessions at congresses, symposiums, and scientific conferences.

The first information in the scientific literature on the use of sutures with the purpose of face and neck soft tissue lifting dates back to the middle of the 1950s when Buttkewitz [1] demonstrated a correction of the flabby buccolabial fold by suture.

In 1970, René Guillemain published an article [2] describing a similar technique named the "curl lift." He used a long Reverdin needle with the help of which he tightened a tendon in the zygomatic region, and the lower one-third of the face and the upper region of the neck were lifted. With the patient under local anesthesia, a suture was laid in the subcutaneous tissue and firmly fixed to dense structures above and below. This technique was not widely used, though results were quite satisfactory.

In a book by Mario Gonzales Ulloa [3], a similar technique of lifting facial tissue by means of nylon sutures is described.

In 2002, Sassaki and Cohen [4] published a similar technique with two needles. They used it simultaneously with a classic facelift for improvement and strengthening of the result and also independently in the closed procedure process.

In 2003, Maximiliano Mendez Florez [5] published an article in which he suggested a suture lifting technique with the use of a double-edged needle of his own construction, and a special manipulation to simplify the operation. The double-edged needle suggested by Mendez is analogous to the needle used many years ago by upholsterers. Needles with nib points on both sides, curved or straight, small or big, but with the fastener along the center, were often used in general practice and plastic surgery in the past.

In 1982, the Italian plastic surgeon Sergio Capurro also wrote about the double-edged needle [6,7].

In 1986, the Japanese surgeons Akira Yahai, Osama Fukuda, and Sinichi Abayashi published their technique of using a curved double-edged needle with the fastener along the center [8]. Two double-edged needles also were used by orthopedic surgeons (meniscus surgery) and plastic surgeons (cleft palate surgery).

Double-edged needles with nylon sutures were also used for cirsodesis and cosmetic surgery for upper blepharoplasty by Koo Boo-Chai [9,10], who began using this suture technique since as far back as 1952.

Jo Mathay [11], in the Philippines, used subcuticular sutures to narrow wide nose tips. Nikolai Serdev also [12,13] described a similar technique, the distinctive feature of which was a cannula of his original construction and a method of laying it under the skin.

LIFTING TECHNIQUES

An invaluable contribution in the popularization of suture lifting methods among plastic and aesthetic surgeons worldwide belongs to Pierre Fournier, who in his publications and presentations at various congresses and scientific conferences assisted in spreading these methods [14–16].

The first publication dates back to 1968 (Figure 61.1) when German colleagues patented a barbed suture, the barbs being multiple small incisions made along the length of the suture. They advocated its use for the percutaneous repair of Achilles tendon rupture. Analogous sutures were suggested by American surgeons in 1997 (Figure 61.2). Two years later Aptos "cog" (i.e. barbed) threads were patented (Figure 61.3) [17], since when they have been widely used by surgeons in many fields [18–22].

Face and neck soft tissue lifting by means of barbed sutures with the purpose of rejuvenation were suggested for the first time by us in 1998 [23–25] (Figure 61.4). The name Aptos (antiptosis) was later conferred on all the products and technologies of minimally invasive lifting developed and introduced by us.

The first experiments we carried out with sutures were on with barbs directed to one side (Figure 61.5). Through a small incision in the temple region, several sutures were inserted subcutaneously and sewed to temporal muscle fascia (Figure 61.6). In a similar way, soft tissues of submaxillary

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

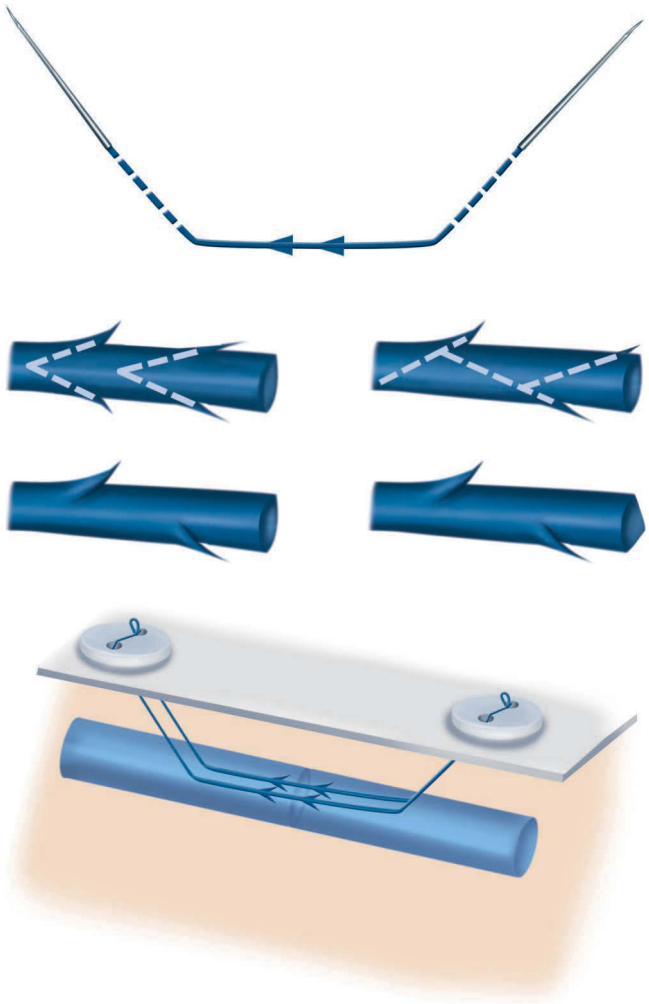


Figure 61.1 German barbed threads (patented 1968) for suturing of an Achilles tendon rupture.

and neck cervical regions were lifted by fastening the suture's upper end to the mastoid periosteum. Striving for minimization of interventional trauma, several sutures were introduced through one incision in different directions (Figure 61.7).

Then, in the same year 1998, this technique underwent improvement: a no-needle suture was implanted under the skin by means of a needle guide (Figures 61.8 and 61.9). Such a suture achieved lifting and elevating of soft tissues.

In 2002, we again returned to the idea of using a single product, that is, a needle with a suture attached, distinguished by the presence of two needles to the ends of which was connected one suture with convergent barbs—Aptos thread 2G (Figures 61.10 and 61.11). This device allowed a doubling of the suture arm and so the strength and stability of the lifting. An important innovation from this time was also that these needles were paired by a temporary joint in such a way that, their points made a single unit. These paired needles allowed entry through a single puncture, without obtaining skin retraction in the place of the suture bend: both needles were inserted into the skin by the same single point; they were separated under the skin at the necessary depth and only then were laid in different directions.

The next stage of our researches was the creation of the double-edged needle with a smooth suture fastened to the needle in its middle part—Aptos Needle (Figure 61.12).

Such suture materials and methods of use were used by our colleagues not only in aesthetic surgery but also in plastic surgery [26–29]. By means of various modifications of the Aptos Needle, minimally invasive aesthetic operations for suturing soft tissues of the middle zone of the face, submaxillary and cervical regions (2003), chin, extended and stretched lobules, and ptosis of breast were developed (2004).

The successful combination of Aptos thread 2G and Aptos Needle is our latest development—Aptos Needle 2G (Figures 61.13 and 61.14).

Lifting by implementation of the operation by means of Aptos Needle 2G is stronger and more stable.

Our approach to the lifting of kinetically active zones ("sorrow" wrinkles, angles of mouth) is crucially different, as a hard facelift in such cases is ineffective and subject to early recurrence. For the elimination of involutive changes in these zones, we used an elastic facelift by means of a spiral suture made from a special memory-retaining polypropylene—Aptos spring (Figures 61.15 and 61.16) [30,31].

STUDIES

Beginning from 2001, attention was paid to investigate anatomical, histological, functional, and clinical aspects of these studies in laboratory animals and people [32,33], as well as analysis of complications and negative outcomes [34,35]. We have implemented a double-blind placebo-controlled investigation of suture lift effectiveness [36]. The group under investigation included 32 patients, who had suture lift by various Aptos methods from one side of the face, the neck, the chest, extremities, and the body. The contra-lateral side was treated by placebo or another method. Necessary observations were made (e.g., photographing, questioning, expert conclusions, ultrasonic scanning, Doppler). After some time (in each case it was different) and after repeated interventions, symmetry was restored.

Aptos suture lifts, especially needleless Aptos thread, and methods of its use turned out to be the most successful and most asked-for method among the specialists. Their popularity allowed the development of other minimally invasive Aptos products especially for dermatologists: Aptos Elegance, Excellence Visage, Nano Spring, and Nano Vitis. Excellence Visage sutures (Figure 61.17) are made from polycaprolactone copolymer and lactic acid. After implantation in the tissues, this material undergoes biodegradation by hydrolysis and in time (within 1½ year) the sutures completely dissolve. In their place a fibrous network develops, the formation of which is connected not only with the presence of the foreign body (suture) but with gradual elimination of microquantity of L-lactic acid during the biodegradation process, which stimulates neocollagenesis.

Aptos Nano (Figure 61.18) is a plaited suture thread made from resorbable materials without any fixing elements. Three weeks after placement such suture becomes unplaited (Figures 61.18 and 61.19), uplifting tissues above itself. It is much thinner and is meant not for lifting but for armoring of the skin. This method is mainly meant for dermatological cosmetologists.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

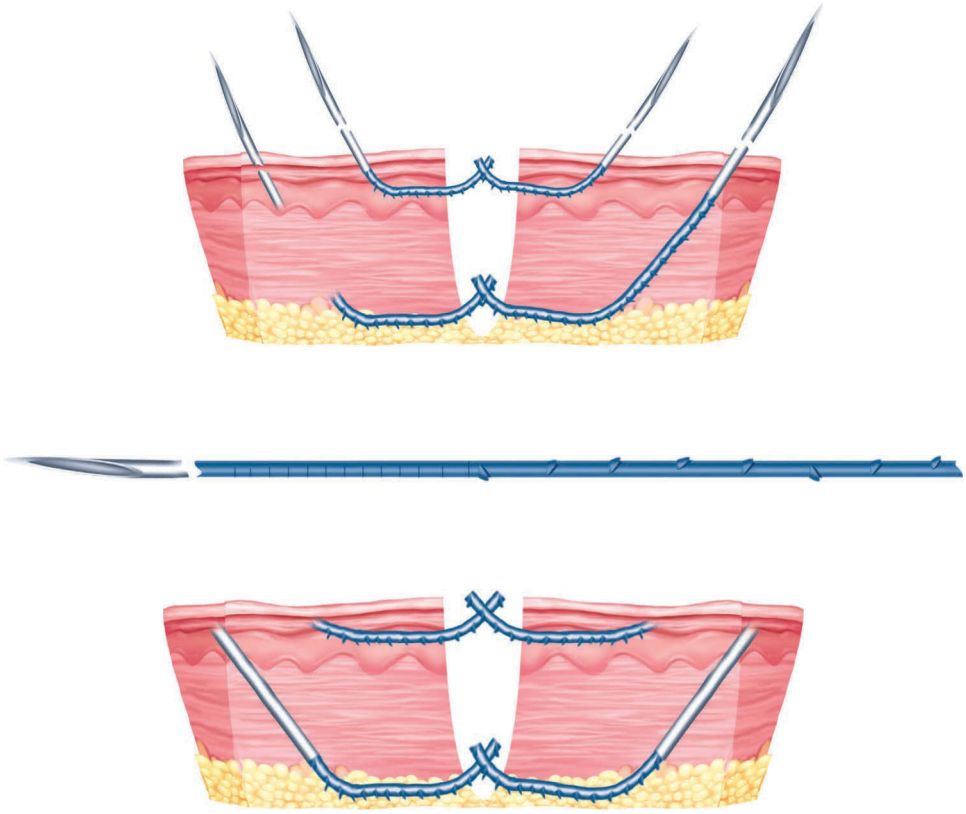


Figure 61.2 American barbed threads (patented 1997) for suturing wounds by continuous cosmetic suture.

Figure 61.3 Aptos cog (i.e., barbed) threads (patented 1998) for suturing wounds by continuous cosmetic suture. 1, Thread length is 10–50 cm; 2, base of the cog; 3, cog is 1 mm; 4, needle or canule are from 7–17 cm; 5, angle of the cog is 10 –15°; 6, thickness of the thread is 2/0 or 3/0; 7, length between cogs is 0.5 mm.

Figure 61.4 Aptos cog (i.e., barbed) threads (patented 1998) for lifting of soft tissues.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

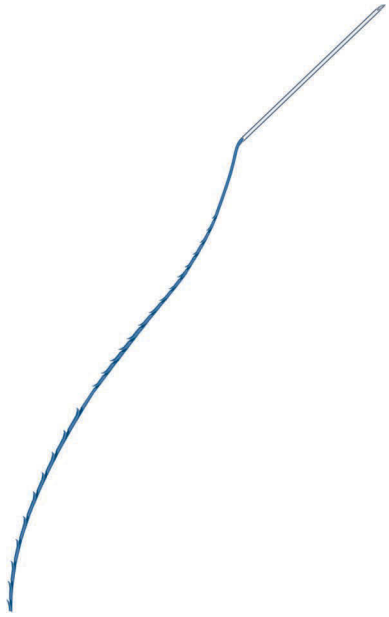


Figure 61.5 Barbed thread for lifting soft tissues without mobilization of the skin.

Figure 61.6 Markings for mid-face-lifting with several barbed threads using small cut.

Figure 61.7 Markings for mid-face-lifting with barbed thread.

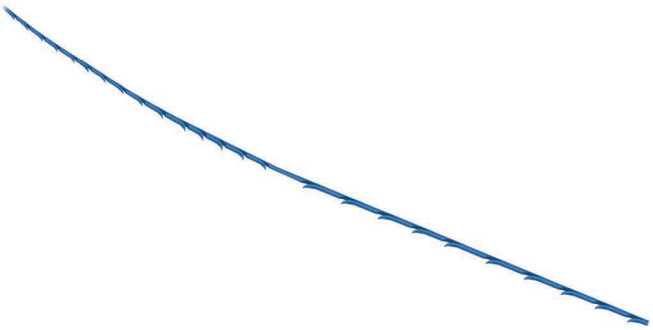


Figure 61.8 First-generation Aptos thread for lifting soft tissues without an incision.

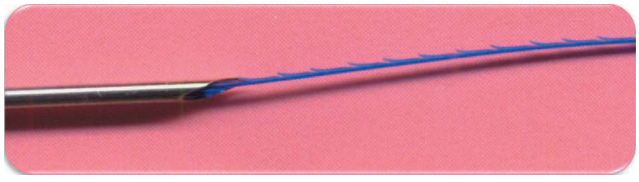


Figure 61.9 Needle for insertion of the first-generation Aptos threads.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

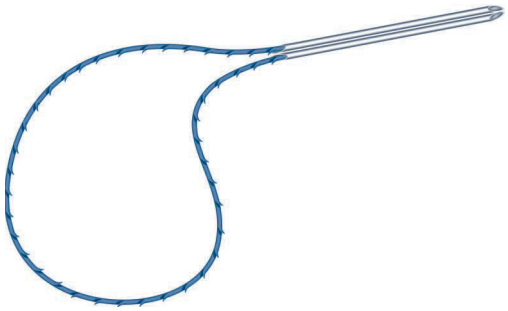


Figure 61.10 Patented second-generation Aptos thread for lifting soft tissues.

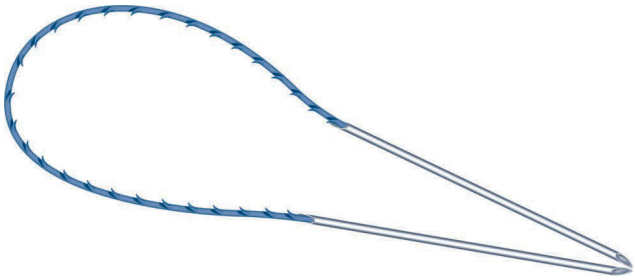


Figure 61.11 Patented second-generation Aptos thread for lifting soft tissues.

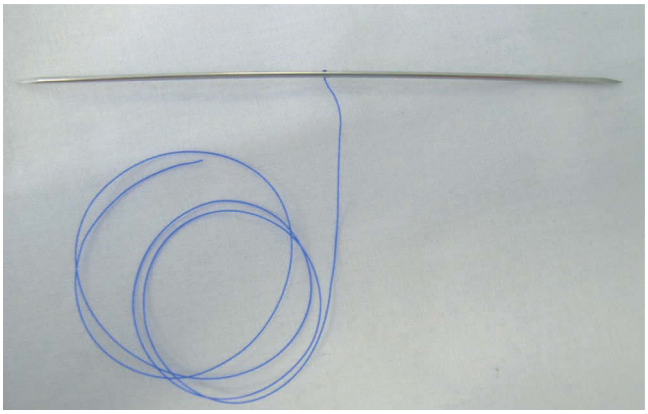


Figure 61.12 Double-edged needle with smooth suture.

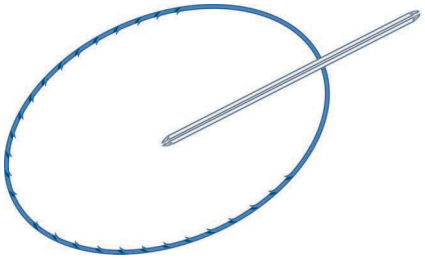


Figure 61.13 Double-edged needle with barbed suture.

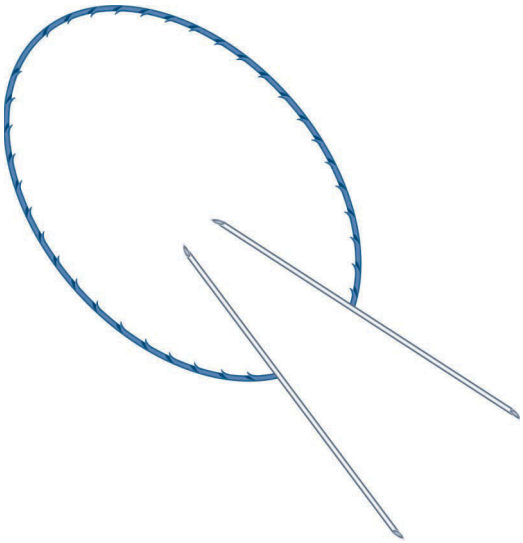


Figure 61.14 Double-edged needle with barbed suture.

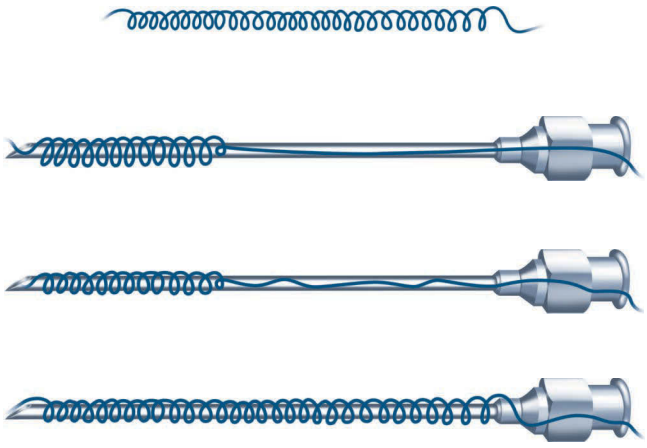


Figure 61.15 Elastic spiral Aptos threads (2003).

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 61.16 Elastic spiral Aptos threads (2003).

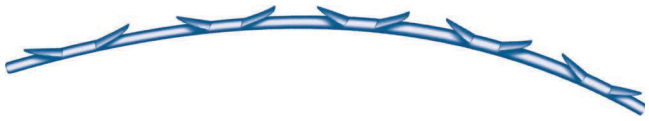


Figure 61.17 Absorbable threads with opposite direction barbs.

Figure 61.18 Absorbable threads for armoring.

Figure 61.19 Absorbable threads for armoring.

Histological investigations conducted at Petrovsky, Scientific Center of Surgery of Russia, showed after placement of absorbable plaited or barbed sutures:

1. An increase in capillary numbers as compared with the areas away from the sutures (Figures 61.20 through 61.22).
2. Capillaries look overfilled with blood, i.e., having open lumen. It is possible to considers a persistent hyperemia phenomenon in the region of Aptos suture implantation. Presumably, it is possible to talk about an improvement in tropism in these areas.
3. Fibroblasts of friable connective tissue are in a functionally active state: nucleus and cytoplasm volume is increased; chromatin is finely dispersed.
   a. With toluidine blue staining of the friable layer of connective tissue, where Aptos sutures are placed, the number of fat cells is increased.
   b. It is known that decreasing hyaluronic acid quantity has a negative impact on the immune status of the skin and that intradermal injection improves skin structure.

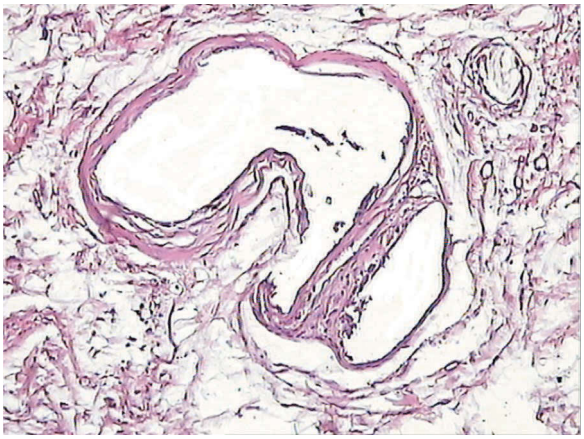


Figure 61.20 Forty days after insertion in subcutaneous.

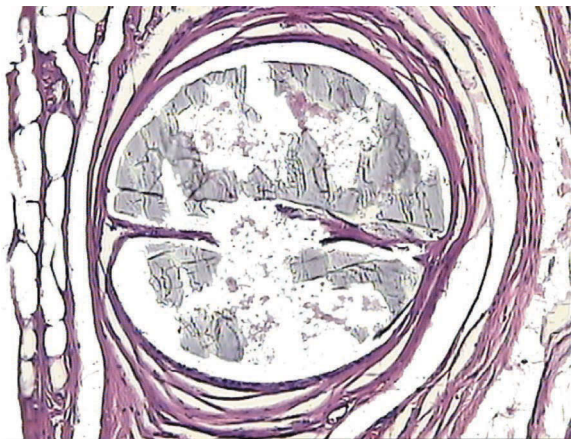


Figure 61.21 Eight months after insertion in subcutaneous: 40% of absorption.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 61.22 One year after insertion in subcutaneous: Total absorption.

We also conducted histological investigation after placement of smooth suture (classic suture material):

- Smooth suture after 40 days is encircled by a thin connective tissue capsule.
- Elastic fibers are not present.
- It differs from the capsule around Aptos sutures in that it is thinner and more mature, owing to the less irritant effect of smooth sutures.
- In the tissues surrounding smooth sutures, there is an increased quantity of small blood vessels but hyperemia is much less expressed than around Aptos sutures.
- Around smooth sutures, there are fewer fat cells.

Aptos methods have not avoided critical publications nor complications and negative results [37–39], but among these were also apparently hostile reports favoring alternative methods [40–43]. At the same time, there appeared authoritative analytical articles and books [44–49], which have called for continuous investigation of these suture lifting methods.

CLINICAL CONSIDERATIONS

With the aim of lessening operative trauma, cannulas with rounded, blunt ends are suggested. Typically, a cannula of 17 cm length and 20 G thickness is used.

To decrease the trauma of the intervention itself, a suture is penetrated under the skin only by an injection. Such an approach allows a fan structure placement, for example, on the face, of five sutures through one injection in the lateral area of the face.

Indications for lifting by Excellence Visage in the face and neck are slight to moderate skin flabbiness and ptosis of soft tissues (without excess skin):

- Ptosis of the entire brow or just its lateral one-third
- Sagging and separation of buccal–zygomatic region of soft tissues
- Nasolabial folds, "wrinkles of marionette," caused or aggravated by hanging soft tissues
- Deformation of face oval, mental regions, "double chin" (in cases of hypertrophy of fatty tissue, first local fatty tissue reduction is necessary)
- Age-related changes of neck, developing against the background of atrophic skin
- Atrophic subcutaneous changes with uneven skin relief
- Facial asymmetry

Contraindications include:

- Autoimmune diseases
- Severe somatic diseases
- Blood diseases
- Collagenoses
- Ischemic heart disease
- Levels II and III arterial hypertension
- Hemophilia
- Psychotic and neurotic disorders
- Inflammation phenomena and tumors in the region of intervention
- Inclination to formation of keloidal and hypertrophic scars
- Blood diseases (hemophilia), taking anticoagulants
- Exacerbation of any chronic diseases
- Pregnancy and lactation
- Previously injected of non-biodegrading injection implants in the procedure zone
- Individual intolerance of the injectables

PREOPERATIVE

It is desirable to stop taking anticoagulants and non-steroidal anti-inflammatories, because of their influence on blood coagulability, for approximately one week prior to the procedure.

Before the procedure, it is necessary to ascertain the desires of the patient, collect anamnesis, reveal indications, and exclude probable contraindications; special attention should be paid to cosmetic procedures and operations conducted previously. The main point of method should be explained to the patient; the desired results should be discussed as well as the probable complications related to the placement of threads. The patient signs the informed consent, and afterward, photos are made in the five standard projections.

The procedure of thread lifting should be performed in a separate room (treatment or dressing room, small operating room) with observance of the rules of asepsis. The following are the required materials: two pairs of sterile gloves, disposable caps, masks, sterile drapes, skin antiseptic agents (e.g., Cutasept, octenisept), disposable sterile surgical coat, medium-size sterile bedsheet (e.g., 60 × 40 cm), sterile scissors, tray, sterile syringe or 10 mL syringe with 29 G needle (insulin needle), 2 capsules of articaine (1.7 mL) and 6 mL of lidocaine with adrenaline solution 1:200,000, one pack of Excellence Visage threads for placing into one zone, and adhesive strips (Steri-Strips or Omnistrip).

The preoperative marking is made in the vertical position (standing or sitting). The place of initial puncture of the skin, the lines where threads are laid, and the final points are to be marked by a black or red marker (Figure 61.23).

The patient should be dressed in a disposable coat and a cap (Figure 61.24). Also, before the procedure, it is recommended to remove cosmetics by special means for the

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 61.23 Preoperative marking.

Figure 61.24 Preoperative procedures.

removal of makeup. After the preliminary preparation, the patient is laid on an operating chair or couch with a slightly lifted head.

The surgeon should at least two times scrub hands with an antiseptic agent solution and put on sterile gloves.

Processing the skin of patient should be done with an antiseptic agent solution at least two times in the direction from center to periphery, including neck and decollete areas, auricles, and partilly the part of the head covered by hair (Figure 61.25).

Afterwards, the skin should be thoroughly dried by a sterile drape. The operative field is then localized by sterile drapes or bedsheets.

OPERATIVE

The main rules are not to place sutures in active mimic zones, but to pass several zones simultaneously, stipulate individual properties of skin, and provide relief to tissues. For Excellence Visage suture placement, one injection is enough in the lateral regions of the face.

In the location of the initial incision/puncture, up to 0.5 mL of articaine or other anesthetic agent is injected, and up to 1 mL into the final points. Local anesthesia is to be performed either after initial puncture by an infiltration cannula, which is included in the set of threads, or by a carpule injection needle of 30–41 mm. Infiltration of tissue happens either while the needle (or cannula) moves forward or while it moves backward. It is necessary to avoid extreme infiltration of tissues. For anesthetization of the tissues to which we are supposed to put 10 Excellence Visage sutures, an average of 3 capsules with a volume of 1.7 mL were used.

There are 10 threads preloaded into cannulas in the Excellence Visage set, cannulas for infiltration anesthesia, and an injection needle for initial puncture. According to the marking, the skin is held and the initial puncture of skin is done, and the hypodermic fatty tissue is slightly separated by the needle in the direction of the laying of threads. The surgeon should take the cannulas with preloaded threads, tuck the end of thread into the cannula, put the cannula into the point of initial puncture, and lay it along the marked line. Threads should be laid in the hypodermic layer. During introduction of the cannula in order to avoid emergence of retractions of skin, it is necessary to avoid an extremely superficial introduction. While introducing the cannula, there are resistances in the hypodermic fatty tissue—those are the septa of the subcutis separating fatty compartments. It is necessary always to control by palpation the position of the cannula under the skin. While passing the threads along the marked circuit, the tissues are moved along the cannula, in accordance with the marking. When the cannula with preinstalled thread comes to the final intended point, the cannula is removed by tightening and fixing of tissues in the direction of the desired vector of traction. The end of the thread, which goes beyond the puncture, is to be cut, for which purpose the thread should be slightly stretched and at the same time the skin should be moved aside (Figure 61.26). The remaining threads are placed in the same way.

POSTOPERATIVE

The patient's postoperative treatment protocol is as follows:

- After the procedure the puncture wounds are treated with antiseptic agent and sterile strips (Steri-Strips, Omnistrip).
- Cold packs are helpful for 24 hours after the procedure.
- It is recommended to avoid hot beverages for 2–3 days or alcohol for 2 weeks.

After the procedure, the patient is advised to treat the puncture wounds at home by means of alcoholic solutions for the next 3 days. For a week, it is recommended to limit the activity of the facial muscles, to abstain from massaging, to restrain from fitness exercises, to refrain from visiting bathhouses, saunas, and pools. Thermal procedures on the implantation regions should be abstained for more than 1 month; also, deep massaging, physiotherapy, and any subcutaneous manipulations are also prohibited for 2 months after the operation.

In case of pain, it is possible to use analgesics to speed up hematoma resolution with the use of the recommended

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 61.25 (a–d) Antiseptic processing of the skin.

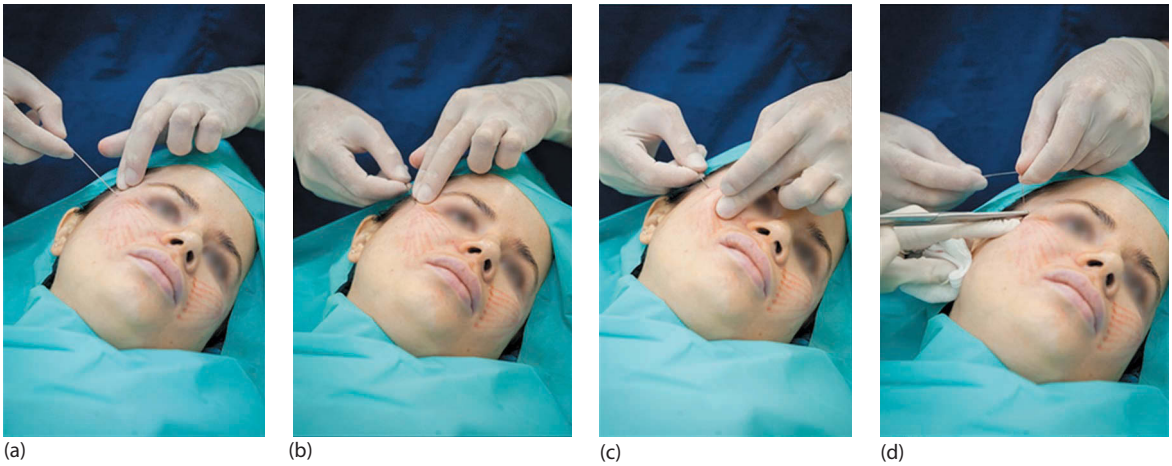


Figure 61.26 (a–d) Operative technique.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 61.27 (a) Patient, 34 years old, before soft lifting of the middle zone of the face with the use of absorbable Aptos threads. Results (b) after operation and (c) after 6 months.

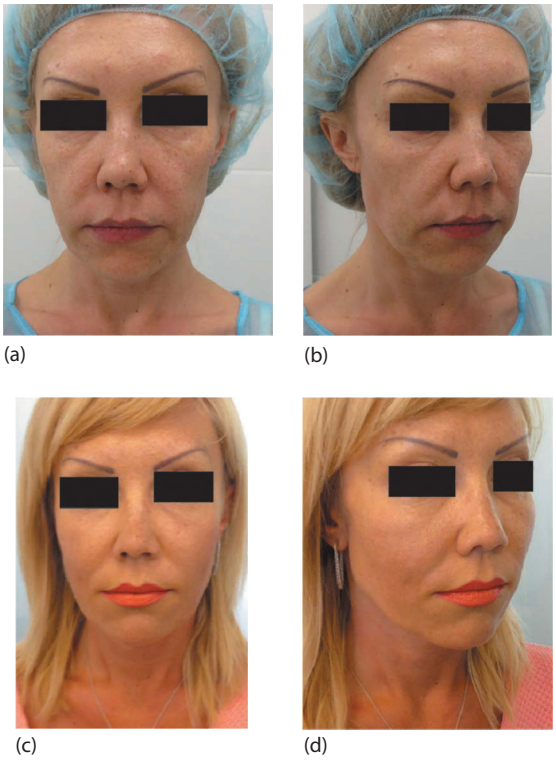


Figure 61.28 (a and b) Patient, 41 years old, to undergo soft lifting of the middle zone of the face with the use of absorbable Aptos threads. (c and d) Results after 8 months.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 61.29 (a) Patient, 43 years old, to undergo cheekbone area lifting by nonabsorbable second-generation Aptos thread. (b) Result after 2 years.

(a) (b) (c)

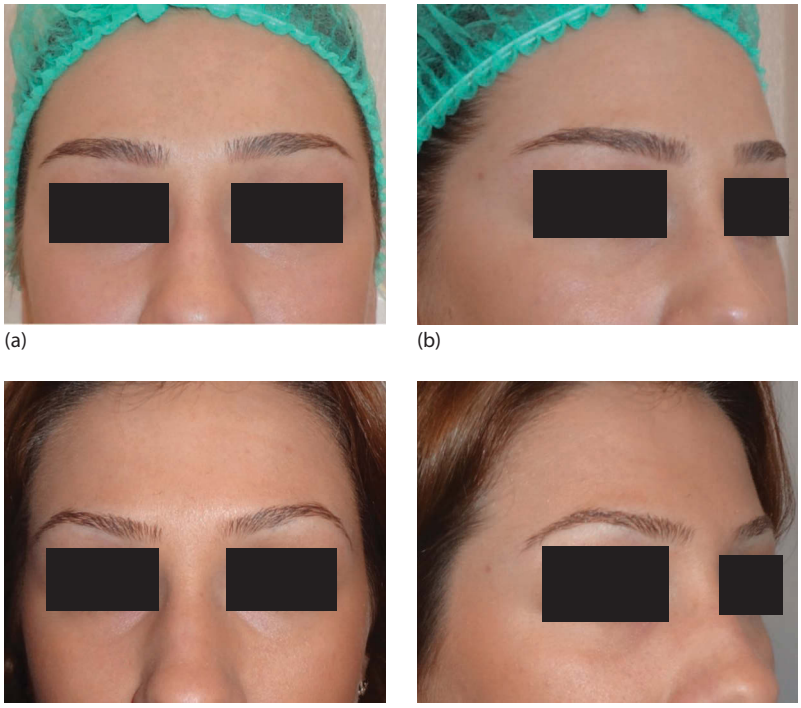
(d) (e) (f)

Figure 61.30 (a–c) Patient, 63 years old, after lower face liposuction and full face thread lifting with absorbable and nonabsorbable Aptos threads. (d–f) Result after 2 years.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 61.31 (a) Patient 49 years old. (b) Result after brow lifting with Aptos threads.



(a) (b)

(c) (d)

Figure 61.32 (a and b) Patient, 26 years old. (c and d) Result 1 year after brow lifting with absorbable threads.

preparations and procedures for diminishing edemas (Traumeel, heparin, microcurrent therapy, etc.).

In case of the placement of more than one package of Excellence Visage or lowered immunity, it is desirable to take antibiotics of cephalosporin group 3–4 days after the operation. Repeated visits to the doctor are planned on the 3rd, 7th, and 14th day after the procedure.

During 17 years of experience with Aptos thread lifting, we have done more than 1.5 million procedures. Figures 61.27 through 61.32 detail some cases from our practice.

REFERENCES

1. Buttkewitz H. Die Nadeltechnik der subcutanen Gewebsraffung einer schnittlosen Korrekturmethode bei kosmetischen Brust- und Gesichtoperationen. *Centralbl Chir* 1956; 81:1185.
2. Guillemain R. Le "Curl Lift". *Chir Plast Estét* 1970 March; 4.
3. Gonzalez-Ulloa M. *The Aging Face*. Piccin Nuova Libraria S.p.A., Padova; 1987.
4. Sassaki GH, Cohen AT. Meloplication of the malar fat pad by cable-suture technique for midface rejuvenation. Outcome study (392 cases-6years experience). *Plast Reconstr Surg* 2002; 110(2):635–654.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

5. Florez MM, Rossani German A, Ivan Hernandez P. Face up: Minilifting subcutaneo no quirurgico con suturas de polipropileno (personal communication).
6. Capurro S Jr. Rivista Italiana di Chirurgia Plastica: Un ago a due punte Atti del. *32 Congresso Nazionale della Societa Italiana di Chirurgia Plastica*, September 13–17, 1983, Palermo, Italy.
7. Capurro S Jr. The double tipped needle. *Plast Reconstr Surg* 1987 June; 79(6):1006.
8. Yanai A, Fukuda O, Hiribayashi S. Double-tipped center threading suture needle for subcuticular suturing. *Plast Reconstr Surg* 1986 September; 78(3):411–413.
9. Boo-Chai K. Buried mattress sutures placed transconjonctivally. Oriental cosmetic blepharoplasty. Further experience with cosmetic surgery of the upper eyelid. *Transactions of the Third International Congress of Plastic Surgery*, October 13–18, 1963, Washington, DC, International Congress Series No. 66, Excerta Medical Foundation, Amsterdam, the Netherlands, pp. 518–524.
10. Boo-Chai K. Plastic construction of the superior palpabral fold. *Plast Reconstr Surg* 1973; 31:74.
11. Mathay J. Personal observation. Makati Medical Center Manila, Philippines, PA.
12. Serdev N. Serdev suture for scarless buttock lift and ultrasonic liposculpture of the buttocks. *Int J Cosmet Med Surg* 2003; 1:1–8.
13. Serdev N. Scarless Serdev suture methods in brow and face lifts. Cirugia ambulatoria de levantamiento de gluteos mediante una sutura sin cicatrices de incision. *Int J Cosmet Med Surg* 2003; 1:9–15.
14. Fournier Pierre F. Le lifting invisible. Revue de la Societe Francaise de Chirurgie esthetique et du Syndicat National des chirurgiens de chirurgie esthetique, December 2003, XXVII 113, pp. 9–20.
15. Fournier Pierre F. Histoire de 1''aiguille a deux pointes. Revue de la Societe Fransaise de Chirurgie esthetique et du Syndicat National deschirurgiens de chirurgie esthetique, June 2004, Numero 115.
16. Fournier P. Les variants dans la technique du Curl Lift. *La revue de chirurgie esthetique de langue Francaise* 2004 December; XXVIII(117):35–38.
17. Sulamanidze M, Michailov G. Surgical thread for plastic surgery operations. European Patent EP 1,075,843 A1, priority: 03.03.1999.
18. Robinson JK. Suspension sutures in facial reconstruction. *Dermatol Surg* 2003 April; 29(4):386–393.
19. Murtha A, Kaplan A, Paglia M, Mills B, Feldstein M, Raff G. Evaluation of a novel technique for wound closure using a barbed suture. *Plast Reconstr Surg* 2006; 117:1769.
20. Sulamanidze M. Commentary to the article entitled Murtha AP et al. Evaluation of a novel technique for wound closure using a barbed suture. *Plast Reconstr Surg* 2007 July; 120(1):349–350.
21. Sulamanidze M, Sulamanidze G. A new variant of the continuous surgical wound suturing technique. *Ann Plast Reconstr Aesthet Surg* 2006; 3:54–59.
22. Warner PJ, Gutowski GA. Abdominoplasty with progressive tension closure using a barbed suture technique. *Aesthet Surg J* 2009 May–June; 29(3):221–225.
23. Sulamanidze MA, Sulamanidze GM. Flabby, ageing face. A new approach. *Second Congress on Aesthetic and Restorative Surgery*, February 1998, Moscow, Russia, p. 15.
24. Sulamanidze MA, Fournier PF, Paikidze TG, Sulamanidze GM. Removal of facial soft tissue photosis with special threads. *Dermatol Surg* 2002 May; 28:367–371.
25. Sulamanidze M, Paikidze T, Sulamanidze G. Utilisation du fil "APTOS" dans le lifting facial. *La Revue De Chirurgie Esthetique de Langue Francaise* 2001; 25(103):17–22.
26. Sulamanidze M, Sulamanidze G. Lifting of soft tissues: Old philosophy, new approach—A method of internal stitching (Aptos needle). *J Jpn Soc Aesthet Surg* 2005; 42(5):182.
27. Sulamanidze M, Sulamanidze G, Sulamanidze C, Vozdvijensky I. Low-invasive lifting of lower region of face and neck by Aptos Needle method. Aptos Needle. *Plast Surg Cosmetol* 2012; (3):383–393.
28. Sulamanidze MA, Sulamanidze GM, Sulamanidze KM. Mastopexy—How to achieve stabile results—New approaches. *Aesthet Surg* 2011; 10(2):257–265.
29. Borovikov A, Sulamanidze M, Sulamanidze G, Sulamanidze C. Remote result of suture lifting of chest. Clinical observation. *Plast Surg Cosmetol* 2012; (2):203–209.
30. Sulamanidze M, Sulamanidze G. Aptos spring—A new concept of lifting. *J Jpn Soc Aesthet Surg* 2005; 42(5):183.
31. Sulamanidze M, Sulamanidze G, Vozdvijensky I, Sulamanidze K, Kajaia A. New method of elastic suture facelifting. *Aesthet Med* 2010; 9(3):275–280.
32. Adamyan A, Skuba N, Sulamanidze M, Khusnutdinova Z. Morphological foundations of facelift using APTOS filaments. *Ann Plast Reconstr Aesthet Surg* 2002; 3:19–27.
33. Prokudin S, Saban I, Gaziulina O. Anatomic grounding of suture facelift use. *XII International Conference on Aesthetic Medicine*, January 2013, Moscow, Russia.
34. Sulamanidze M, Sulamanidze G, Sulamanidze C, Vozdvijensky I. Avoiding complications with suture lifting methods. *Aesthet Surg J* 2011 November; 31(8):863–875.
35. Sulamanidze M, Sulamanidze G, Vozdvijensky I, Sulamanidze K, Aziayn E. Prevention and complication treatment experience during suture rejuvenation of face and neck. *Aesthet Med Messenger* 2011; 10(4):27–35.
36. Sulamanidze M, Gubanova, E, Sulamanidze G, Sulamanidze C. Preliminary results of double blind placebo-controlled investigation of suture lifting effectiveness. Aptos. *XIII International Congress on Applied Aesthetics and Cosmetology*, April 2013, Kiev, Ukraine.
37. Winkler E, Goldan O, Regev E. Stenssen duct rupture (sialocele) and other complications of the Aptos thread technique. *Plast Reconstr Surg* 2006; (118):1468–1471.
38. Helling E, Okpaku A, Wang P, Levine R. Complications of facial suspension sutures. *Aesthet Surg J* 2007 March–April; 27(2):155–161.
39. Beer K. Delayed complications from thread-lifting: Report of a case, discussion of treatment option and consideration of implications for future technology. *Dermatol Surg* 2008; 34:1120–1123.
40. Wu W. Advances in stitch lift. *Second Regional Conference in Dermatological Laser and Facial Cosmetic Surgery*, January 20–22, 2006, Hong Kong, China, Programme Book, p. 30.
41. Rachel JD, Lack EB, Larson B. Incidence of complications and early recurrence in 29 patients after facial rejuvenation with barbed suture lifting. *Dermatol Surg* 2010; 36:348–354.
42. Benito J, Pizzamigio R, Teodorou D, Arvas L. Facial rejuvenation and improvement of malar projection using sutures with absorbable cones: Surgical technique and case series. *Aesthet Plast Surg* 2011; 35:248–253.
43. Sasaci G, Komorowska-Timek E, Bennett D, Gabriel A. An objective comparison of holding, slippage, and pull-out tensions for eight suspension sutures in the malar fat pads of fresh-frozen human cadavers. *Aesthet Surg J* 2008 July–August; 28(4):238–396.
44. Flynn J. Suture suspension lifts: A review. In: Niamtu III J, eds. Minimally invasive cosmetic surgery. *Oral & Maxillofac Surg Clin* 2005; 17(1):65–76.
45. Paul M. Use of sutures with thorns in aesthetical plastic face surgery: Development of theoretical grounding and methods of practical application. In: Eisenmann-Klein M, Neuhann-Lorenz C, eds. *Innovations in Plastic Surgery*. London, UK: Springer, 2007, Chapter 28, pp. 265–273.
46. Khustutdinova Z. Correction of involutive changes of face by "Aptos" suture. MS thesis, Moscow, Russia, 2002.
47. Matarasso A, Pfeifer T. The use of modified sutures in plastic surgery. *Plast Reconstr Surg* 2008 August; 122(2):652–658.
48. Sulamanidze M, Sulamanidze G. Aptos suture lifting methods—10 Years of experience. *Clin Plast Surg* 2009 April; 36(2):281–306.
49. Sulamanidze M, Sulamanidze G, Sulamanidze C, Borovikov A. Remote results of low-invasive interventions on the face are compared with deep lifting. *Plast Surg Cosmetol* 2013; (1):383–393.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

62

Blepharoplasty

Serge Morax

Palpebral cosmetic surgery can be defined as the ensemble of surgical procedures whose objective is to refashion, reposition, readjust, reduce, or transplant palpebral skin and muscular and fatty tissues with a normal structure both functionally and histologically.

During a blepharoplasty, other complementary adjuvant procedures can be performed at the same time or subsequently in order to improve the procedure's results.

These actions fall within the scope of the upper and midface rejuvenation treatment (surgery of the look), whether being adjunct surgeries such as temporal forehead lift, brow lift, and cheek lift and adjuvant treatments such as the reduction of the crow's feet and glabellar and forehead wrinkles; the lifting of an eyebrow using botulinum toxin and the filling of certain tissues by injecting absorbable products (hyaluronic acid), and/or autologous fat (lipostructure).

PALPEBRAL AND UPPER FACE EXAMINATION (TABLE 62.1) [1–3]

- *The forehead–facial region*: One notes the area of the scalp implantation (separation of the upper and lower forehead) and the existence of horizontal and vertical forehead wrinkles in the glabellar region (lion wrinkles). The assessment of the eyebrow's position and its eventual ptosis often increase dermatochalasis, which then extends in the superolateral and lateral canthal region, thereby underlining the importance in such cases of the eyebrow's tail repositioning, in addition to upper blepharoplasty (Figure 62.1).
- *The upper eyelid*: The examination assesses the quantity of excess skin (cutaneous or blepharochalasis) and the existence of fat pads either in the internal compartment or in the medial compartment (preaponeurotic fat pad) better visualized by a gentle pressure on the globe (Figure 62.2).

A lateral prolapse must evoke a ptosis of the lachrymal gland.

The research of ptosis has to be quantified both by the height of the palpebral fissure and by the study of muscular function.

The eyelid's movements allow us to establish the position of the palpebral fold (modification of the Asian palpebral fold).

PALPEBRAL, LOWER, AND MIDFACE EXAMINATION (TABLE 62.1) [1–3] (FIGURE 62.2)

Three levels are individualized:

1. The lower eyelid
2. The lid/cheek junction (tear trough area)
3. The *jugal* (cheek) region

The lower eyelid examination includes static and dynamic examination in up gaze and down gaze and further testing.

- Usually, the free edge of the eyelid levels with the corneal limbus in primary position.
- The presence of a scleral show, retraction, or ectropion must alert the surgeon and modify the operative technique.

The lower eyelid laxity is evaluated by the *Snap test*.

- One notes the existence of excess skin, cutaneomuscular surplus, and herniated fat highlighted by applying a gentle pressure on the globe while asking the patient to look upward.
- Three fat pads can be isolated: internal, medial, and lateral.
- We evaluate the importance of the orbicularis oculi muscle by forced contraction of the eyelids.
- Opposing the thick, fatty, cystic skins to the thinner hypopigmented skins permits identifying the skin type.

The lid/cheek junction (tear trough) is inspected with the upmost attention: all accentuation of the tear trough valley in the form of cavity can benefit from fillings or lipostructure.

- The presence of fine wrinkles, eye bags, and pseudo malar bags is noted.
- The existence of palpebral circles and/or hyperpigmentation of the orbitonasal area will not be directly treated through blepharoplasty, but will eventually benefit from further treatment such as laser resurfacing.

At a jugal level, particular attention is paid to the suborbicularis ocular fat (SOOF) position to the position of a displaced or atrophic cheekbone with volume loss, any anomaly of the bone structure in the form of a retromaxilla or an infraorbital rim hypoplasia, generating a retraction with scleral show of the lower eyelid, even more frequent when the globe is pseudo-exophthalmic, during a transcutaneous blepharoplasty.

A standard ophthalmological assessment including a background screening and certain parameters is essential prior to any palpebral cosmetic surgery.

Once the assessment is completed, classification and surgical indications can be carried out.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Table 62.1 Medical Examination Record for Potential Candidate to a Plastic Surgery Procedure Age, Sex, Race, Pigmentation, Anterior Procedures

Questioning	Motive of the consultation
Ophthalmology history	Visual and refractive disorders, organic anomalies (SA-SP), dry eye, malocclusion, facial paralysis, oculomotor disorders, glaucoma, vascular incident, dysthyroid ophthalmopathy, corneoconjunctival lesions, sole eye
General history	Anesthesia incidents, allergy Coagulation disorders *Medication regimen*: aspirin, anticoagulants, antidepressants, etc. Anterior lid and face surgical procedures
Examination	*OPH*: visual acuity, anterior segment, posterior segment, ocular tension, lachrymal secretions, motility
Facial examination	Forehead/brow Upper eyelid Muscular and skin excess Presence of spots Palpebral fold anomalies Ptosis (value of the RPS) Excessive laxity of the superior lid Lachrymal gland ptosis Downward unrolling of the eyelid Degree of occlusion Lower eyelid Muscular and skin excess Presence of wrinkles Fat pads (C.M.L.) Lid's free edge laxity Ectropion and/or entropion Scleral show, round eye retraction Dark circles, pigmentation Hollowness below the eye bags Protrusion of the orbital rims *Pseudo malar bags* Lateral canthus, crow's feet Medial canthus, lachrymal punctum position
Additional photographic exams	

(a) (b)

Figure 62.1 (a) Eyebrow ptosis; (b) reposition of the eyebrow by traction on the temporal area. Excellent candidate for a temporal forehead lift.

UPPER EYELID BLEPHAROPLASTY

Palpebral Fold [2,3]

Ptosis

The upper eyelid blepharoplasty can be performed either by itself or in association with complementary procedures involving the eyebrow, forehead, lower eyelid, or the rest of the face.

A surface procedure using different agents can be associated to the *conventional* surgery.

Several cases can be described: simple excess of skin or skin–muscle (dermatochalasis); anomaly of the skin surface such as spots, wrinkles, and pigmentation; palpebral fold anomaly; presence of additional ptosis; internal fat pad

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

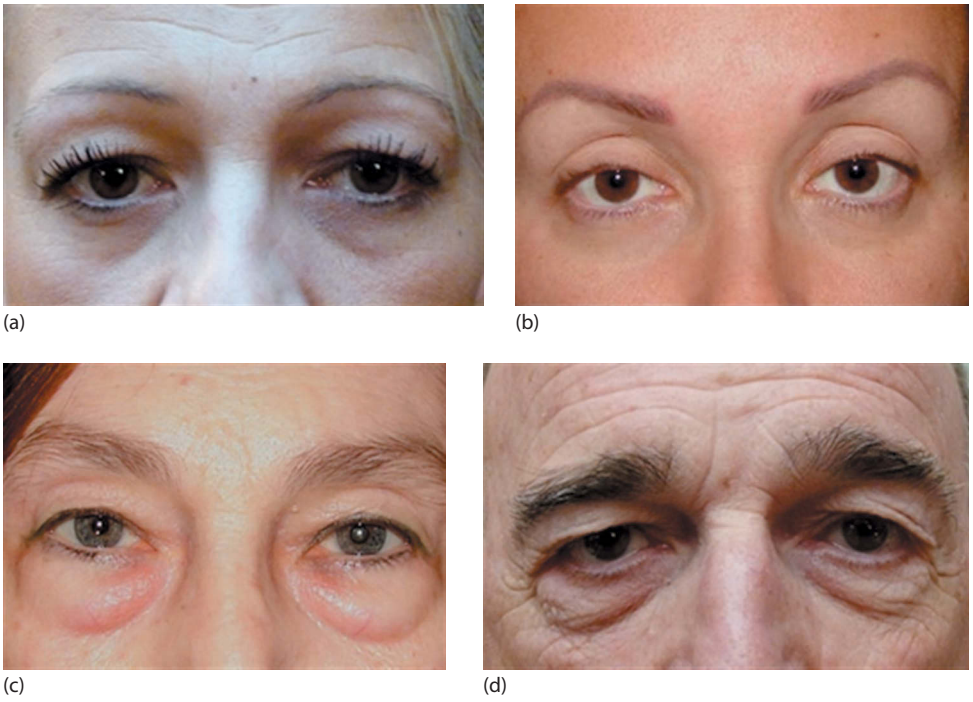


Figure 62.2 (a) Caucasian woman with important dermochalasis; (b) Caucasian woman with high crease (or supratarsal sulcus), high brow position; (c) woman with important fat pad herniation. Excellent candidate for transconjunctival blepharoplasty. (d) Caucasian man with brow ptosis, upper eyelid dermatochalasis, inferior eyelid fat pad herniation, and lateral canthal dystopia.

Table 62.2 Classification and Operative Indication: Upper Face—Upper Eyelid

Excess skin, cutaneomuscular excess	Skin and/or muscle removal
Lipoptosis	Internal fat removal
	Preaponeurotic fat bag removal (caution risk for hollow eyelids)
Upper lid fine wrinkles	Laser resurfacing
	Peeling
Palpebral fold malposition and anomalies	Palpebral fold reconstruction
Associated palpebral malposition	Simultaneous ptosis correction
"Ptosis"	Action on the laxity (shortening the lid's free edge and/or lateral canthoplasty)
Eyebrow:	Submuscular fat removal in the course of the blepharoplasty
Browplasty (brow lift)	Brow lift:
Brow ptosis	In the course of the temporal lift by endoscopic route or not
	In the course of the blepharoplasty (internal pexy)
	By botulinum toxin injection
Wrinkles in the glabellar region	Botulinum toxin
	Weakening of the corrugator muscle
	Facelift
	Blepharoplasty
Lachrymal gland prolapse (ptosis)	Repositioning of the lachrymal gland

and/or preaponeurotic fat pad lipoptosis; lachrymal gland prolapse; and brow ptosis.

All these clinical pictures can be more or less associated, requiring combined treatment (Table 62.2).

Operative Techniques

Strict local anesthesia or enhanced by neuroleptic analgesia will be preferred whenever possible, permitting better control of hemostasis, better appreciation of the dosage of cutaneous and fatty resection, and the possibility of verifying muscular functions throughout the procedure (Figures 62.3 through 62.5).

Conventional Blepharoplasty

Includes the following stages:

- Skin marking of the resection area. Performed with a fine tip marker on the patient in a supine or sitting position after skin antisepsis. It is composed of two lines in accordance with the following principles:
  - *First line*: Marking the palpebral fold adapting to a patient's morphology (the palpebral fold is located higher up in women than in men and lower in Asian) starting straight above the lacrimal punctum and extending to the lateral canthus. Generally, this fold

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 62.3 (a) Marking the palpebral fold; (b) pinching excess skin; (c) skin marking of the resection area and local anesthesia infiltration; (d) incision skin and orbicularis between the two lines.

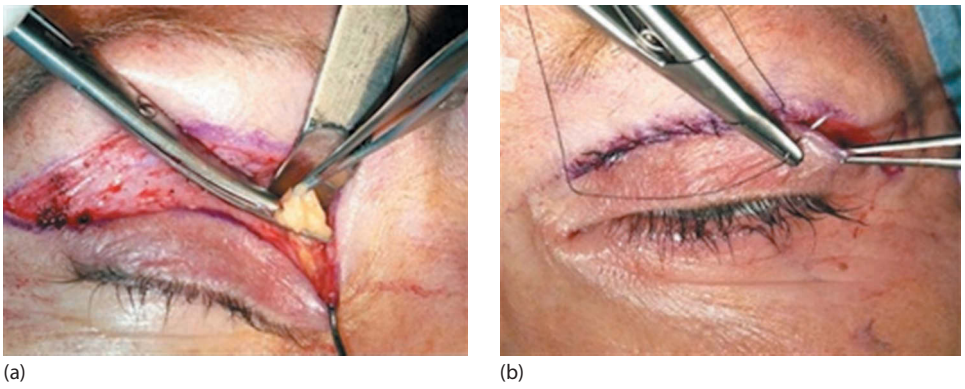


Figure 62.4 (a) Excision of internal fat pad; (b) 6.0 monofilament running sutures.

is situated at 8–10 mm of the eyelid's free edge in the central portion.

- *Second line*: Following the assessment of the importance of the cutaneous resection, which can be confirmed by pinching the excess skin (pinch technique) without producing any unintended palpebral opening.

When measured, the excess skin is generally around 10 mm.

This upper line must remain distant from the eyebrow on approximately 10 mm so that when finishing the procedure, the skin integument between the eyelid's edge and eyebrow will measure at least 20 mm.

Both markings should be joining in the canthi area:

- Medially, straight above the lacrimal punctum, depending on the importance of the excess skin, the lower mark will join the upper mark in a slightly angled upward trait, while always remaining at a proper distance from the inner canthus (in order to avoid epicanthus).
- Laterally, the trait is slightly angled upward and outward, following the lower eyelid's curve, and may follow the path of a crow's feet wrinkle depending on the cases.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 62.5 (a) Caucasian woman with dermatochalasis; (b) result after upper eyelid blepharoplasty.

This line must not exceed the lateral orbital rim and remain at distance from the incision mark of the lower eyelid on at least 5 mm in order to avoid any unsightly scar.

In the case of excess skin located above the lateral orbital edge, a complementary procedure by brow lift will be preferred to an external palpebral cutaneous resection.

- Local anesthesia performed while sedated: Infiltration is performed with a 30 G needle and 2 mL syringes; the solution is Xylocaine + adrenaline at 1% or 2% (2% lidocaine + epinephrine) injected in the submuscular expanded tissue plan.
- Skin incision is made with a no. 15 blade along the different markings, followed most of the time by a monobloc cutaneomuscular resection performed with scissors, electrocautery, or CO_2 laser.
- The orbital septum is opened, thus exposing the internal fat pad, and resection is performed in function of the quantity of fat, which can be assessed by applying a gentle pressure on the globe in order to increase the protrusion.
- Mono- or bipolar cauterization of the base of the resected fat.

From case to case and especially in the case of upper lid heaviness, resection is function of the quantity of retroseptal fat, after opening the septum and being careful not to harm the eyelid's levator aponeurosis.

- *Skin suture* can be performed in several ways:
  - 6-0 or 7-0 monofilament or 6-0 silk interrupted stitches
  - 6-0 silk or 6-0 or 7-0 monofilament classic overlock stitches
  - 6-0 monofilament or 6-0 absorbable thread subcutaneous overlock stitches, which has the advantage of reducing small cutaneous outgrowths along the scar line and avoiding tunnels

An early removal of the sutures is performed between the fifth and eighth day.

Once the procedure is over, a cream is applied on the scar, and cold serum pads are applied on the eyes a few hours after the procedure for about 48 hours, in order to reduce the postoperative swelling.

Associated Procedures

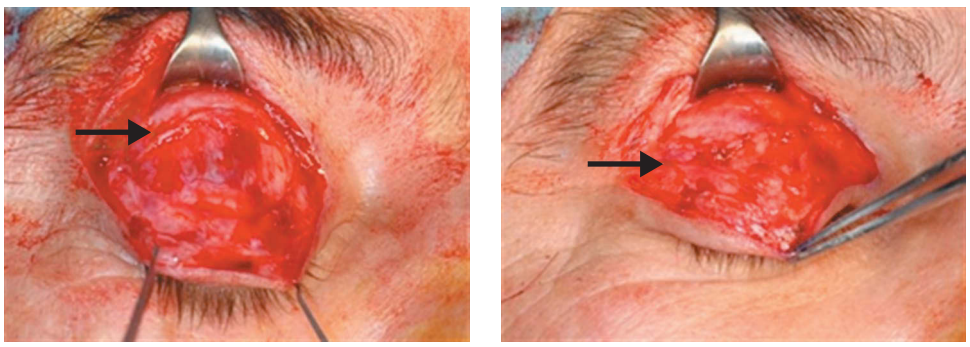
Involutional Ptosis [4] (Figures 62.6 and 62.7)

A slight involutional ptosis associated to excess skin is frequently observed in older patients.

This ptosis is generally accompanied by very good muscular function and benefits from an aponeurotic ptosis surgery.

Operative technique includes the following stages:

- Execution of the blepharoplasty
- Incision of the septum on the whole length of the eyelid
- Orbital fat reflection



(a) (b)

Figure 62.6 (a) Levator aponeurosis disinsertion; (b) repositioning the aponeurosis on the tarsus.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 62.7 (a) Involutional ptosis with overaction of the eyebrow; (b) result after ptosis surgery.

- Inspection of the levator aponeurosis from the upper to the lower part in order to respect the pretarsal muscular insertion
- Recognition of the dehiscence or uninsertion
- Repositioning of the aponeurosis on the tarsus upper edge with a few stitches of 6-0 Vicryl and per-operatory control of the curve and height
- Repositioning of the septum without suturing—closure of the blepharoplasty

Lachrymal Gland Prolapse (Dacryopexy Treatment)

Technique

- Recognition of the lachrymal gland prolapse by the protrusion in the superolateral angle of the eyelid, entirely reducible by digital pressure

In the course of the blepharoplasty:

- Opening the septum in the superolateral part (often dehiscent)
- Approach of the lachrymal gland cavity
- Repositioning of the lachrymal gland in the orbital region and reattachment to the superior orbital rim with 5-0 Vicryl stitches
- Reinforcement of the septum
- Closure of the blepharoplasty

Eyebrow Ptosis Correction by Internal Brow Lift (Blepharopexy)

Using the blepharoplasty approach:

- Superior dissection in the submuscular plane up to the ROOF by rising 1–5 cm above the supraorbital edge
- Setting up medial and lateral 4-0 nonabsorbable stitches, joining together the muscular deep face of the eyebrow's lower edge with the frontal bone periosteum, at approximately 1–1.5 cm above the arcus marginalis
- Verification of the symmetrical characteristic of this eyebrow lift
- Closure of the blepharoplasty

Other brow ptosis techniques are available such as the direct approach with subciliary excision, endoscopic, or coronal frontal lift techniques.

Vertical and Glabellar Wrinkles Treatment
(Lion's Wrinkle by Blepharoplasty Approach)

After performing skin and orbicular excision, during the blepharoplasty, the dissection is extended upward and inside the suborbicularis plane in order to expose the superior-orbital rim.

Exposition of the depressor supercilii by identifying its vertical fibers extending from their osseous insertion to the head of the eyebrow.

The depressor is resected, and the corrugator is exposed with its upward- and outward-angled direction.

The muscular body is laterally severed, before its penetration in the frontal plane and the orbicular, medially outside of the supratrochlear nerve.

Palpebral Fold (Superior Eyelid Crease) [2]

Usually present, the palpebral fold can be missing in certain Asians.

More pronounced in younger persons, the palpebral fold is an important element of plastic surgery, both by its presence, curve, and symmetry.

Anatomical reminder: The palpebral fold is composed of an elastic fiber network, emanating from a fascia (conjoint fascia composed by the fusion of the levator aponeurosis and the septum).

It is generally situated 2 or 3 mm underneath this junction.

Its height is variable.

Situated at 8–12 mm of the eyelid's free edge in Caucasians, it is situated lower in men. It should be situated between 2 and 5 mm from the eyelids' free edge in Orientals, when existing.

There is no correspondence between the height of the tarsus and the location of the palpebral fold.

Surgical Principle It is through suturing that we recreate and reinforce a palpebral fold by an adherence between the pretarsal orbicularis and the supratarsal fibrous aponeurotic plane.

Indication: Lack of palpebral fold, palpebral fold malposition, asymmetric palpebral folds, Asian palpebral fold, etc.

Operative Technique

- Skin marking of the fold at the desired position, while patient is looking down after traction of the brow
- Blepharoplasty
- Incision of the orbicularis on all of the upper lid's length and excision of a pretarsal orbicularis flap at the future palpebral fold's level
- Implementation of three to five supratarsal stitches
- Simple suture by charging skin and lower lip orbicularis then in depth, the levator aponeurosis above the tarsus and again the orbicularis and the skin of the upper lip

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

This suture creates a much more pronounced fold, and the deep moorage upper position tightens the skin and the pretarsal orbicularis.

The eyelid's closure is performed with simple interrupted stitches or superficial overlock stitches.

Variation When a less pronounced but more natural-looking fold is wanted, the sutures will only attach the orbicularis of the inferior flap to the levator aponeurosis at approximately 1–2 mm above the tarsus.

LOWER EYELID BLEPHAROPLASTY

General

The goal of a lower lid blepharoplasty is to rejuvenate the eyelid's appearance while preserving its shape, position, and function and avoiding further complications such as round eye, scleral show, and ectropion.

The choice of the surgical procedure will essentially depend on the different anatomic and clinical forms (see Table 62.3 classification).

Techniques [2,3]

Lower Blepharoplasty by Anterior Approach (Figures 62.8 through 62.10)

Subciliary and Retromuscular Approach This technique is especially indicated in subjects with herniated fat and with little excess skin, wrinkles, folds, muscular surplus, and lateral canthal dystopia.

- Marking the incisions on the skin at 2–3 mm underneath the free edge of the eyelid

  The marking extends laterally following the path of a wrinkle at the level of the lateral canthus, slightly angled downward, not exceeding 5–15 mm in relation to the lateral canthus.
- Local anesthesia using 2–3 mL of 2% lidocaine + adrenaline injected in eyelid's inferior border and in the submuscular space associated with topical anesthesia of the conjunctiva (26 or 29 G needle).
- An opaque glass plate can protect the eyeball, avoiding photophobia.
- Installation of 4-0 silk traction at the palpebral margin level.
- Skin incision, starting underneath the lachrymal punctum up to the lateral canthus.
- At first, subcutaneous tissue detachment is performed in order to preserve the pretarsal orbicularis, guaranteeing a good static of the eyelid's free edge.
- Downward traction of the skin flap and opening the orbicularis in its central part at 3–4 mm of the eyelid's free edge.
- Dissection underneath the preseptal orbicularis up to the infraorbital rim (a natural cleavage plane exists between the deep face of the orbicularis and septal plane).
- The skin–muscle flap is reflected with a Desmarres retractor and the septal plane and the underlying fat is identified.
- The septum is opened and the herniated fat is excised. We proceed by applying a gentle digital pressure on the globe, which protrudes the greasy clusters surplus.
- The thin capsule surrounding the fat is opened, facilitating the extraction of the fat pads. The fat pad situated in front of the orbital rim is clamped and excised. Bipolar cauterization is applied on the forceps. Only then, the forceps can be safely removed without any risk of hemorrhage. The same process is applied to the three different fat pads in relation to their importance and surgical indication, starting with the central fat pad, then the medial fat pad, and finally, the lateral fat pad.
- Repositioning of the skin–muscle flap and excision.

  To avoid any abusive resection, which is the source of descent of the eyelid, the flap is draped without any tension and the patient is looking upward. The muscle–skin surplus draping the zone of incision is excised starting by the temporal segment up to the nasal segment.

Table 62.3 Classification and Operative Indication: MidFace–Lower Eyelid

Excess skin	Skin removal
Cutaneomuscular excess	Skin–muscle removal
Lipoptosis	Lipectomy by conjunctival approach
Lipoptosis and cutaneous and cutaneomuscular surplus	Lipectomy by conjunctival approach + anterolateral cutaneous blepharoplasty or anterior myocutaneous blepharoplasty with lipectomy
Lipoptosis, myocutaneous surplus, external canthus release (round eye, hyper laxity)	Anterior myocutaneous blepharoplasty with lipectomy + lateral canthoplasty
Scleral show with lipoptosis	Transconjunctival lipectomy Lateral canthoplasty and/or posterior lamellae lengthening
Subpalpebral depression (crease at the level of the tear trough)	Filling with Hyaluronic acid Lipostructure
Mesofacial descent Descent of the cheekbone Tissue atrophy	Cheek lift ("jugal" lift) Lipostructure
Skeletonization	
Senile eyelids	Action on the laxity (shortening the free edge and/or lateral canthoplasty)
Superficial fine lines Deep wrinkles "crow's feet"(dynamic mimic lines) Deep static cutaneous wrinkles	Chemical peel, CO_2 laser, erbium, botulinum toxin, bioabsorbable filling products (hyaluronic acid), autologous fat reinjection (lipofilling)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

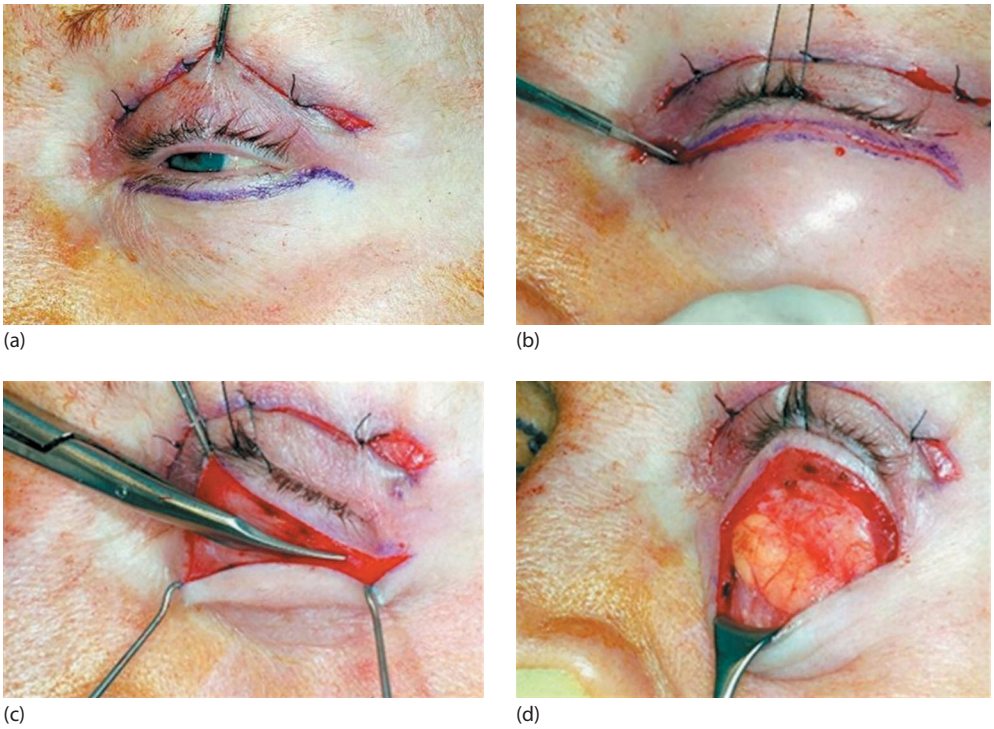


Figure 62.8 Lower blepharoplasty by anterior approach. (a) Marking the incision; (b) skin incision; (c) opening the orbicularis; (d) retraction of the skin–muscle flap and identification of the fat.

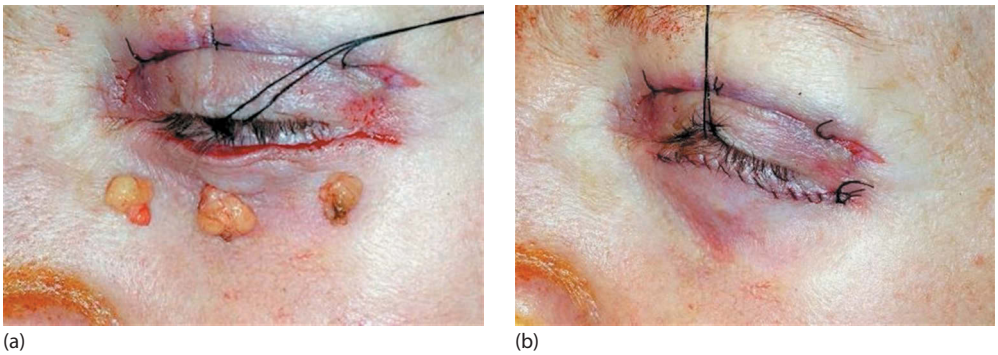


Figure 62.9 (a) Fat resection. The three pockets; (b) running sutures.

If skin resection is not necessary, a 3 mm strip of orbicular is excised from the flap's upper part in order to avoid an unsightly scar.

- The incision is closed with a 6-0 silk or monofilament overlock stitches.
- Removal of the silk traction and installation of cold compresses for 2 hours, then for a 20-minute period separated by a 20-minute free interval during daytime for 24–48 hours.
- At night, a cortisone cream is applied on the scar. Bandages on the eyes are not required, allowing visual function monitoring.
- Sutures are removed on the fourth/fifth day and eventually replaced by Steri-Strips during 3 days.

Premuscular Cutaneous Approach: This technique is not frequently used because the orbicular cutaneous adhesions make it more laborious to dissect and more hemorrhagic than the retromuscular approach.

Postoperative cutaneous creasing can occur by cutaneous retraction and disturb the lymphatic drainage.

Indication: Blepharoplasty associated to an important skin surplus.

A few other details should be pointed out in comparison to the retromuscular approach:

- Marking the skin incision at 2 mm of the eyelid's free edge
- Lidocaine 2% + adrenaline widely infiltrated on the area of the future incision and extended to the whole eyelid

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 62.10 (a) Caucasian woman with dermatochalasis and inferior eyelid fat pad; (b) result after four-eyelid procedure.

- Cutaneous incision and dissection of the skin flap that is separated from the adherent underlying muscular plane up to the infraorbital rim
- Excision of the fat pads by using the same technique than the retromuscular approach
- Excision of the cutaneous surplus
- Suture with monofilament or 6-0 silk overlock stitches

Variation: In the case of an orbicular muscle hypertrophy (discovered when the patient smiles and looks upward), the patient can be offered a thinning of the orbicular muscle while keeping a certain distance with the palpebral margin. This procedure can be extended to the whole surface of the muscle when the skin flap is reflected downward.

Lower Transconjunctival Blepharoplasty (Lipectomy by Conjunctival Approach) [2,3] (Figures 62.11 and 62.12)

The transconjunctival approach consists in an incision through the conjunctive below the tarsus, which allows a faster removal of the fat pads while avoiding any modification of the orbicularis oculi muscle's skin or of the septum.

Two kinds of approach can be isolated:

1. The preseptal approach, which consists in a conjunctival incision on the lower rim of the tarsus
2. The modified retroseptal approach

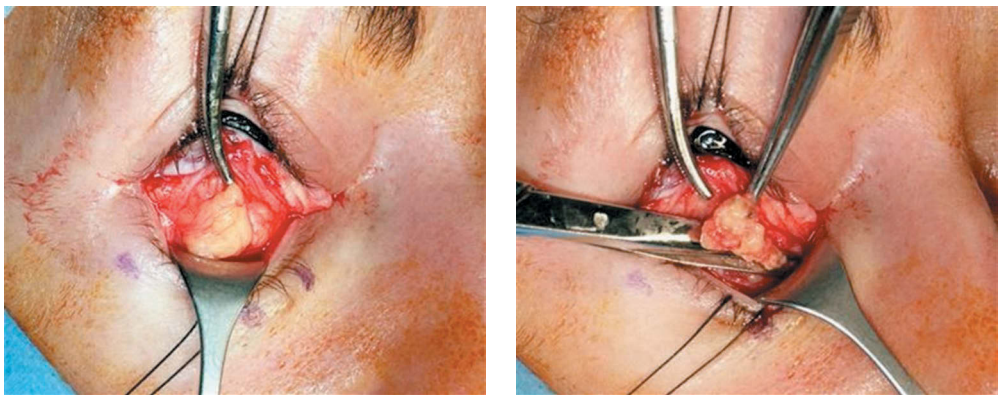
The main advantage of this technique is avoiding scars (particularly for black skin) and any secondary palpebral retraction. In the case of a lipoptosis associated to a scleral show, a lipectomy by conjunctival route can be offered in addition to the elongation of the posterior lamella.

Operative indications: lipoptosis without any associated skin–muscle affliction.

When scars are observed on the anterior lamellae, a revision surgery for residual lipoptosis can be performed.

Operative Technique

- Injection of 3 mL of 2% lidocaine + adrenaline by conjunctival route while separating the anterior cutaneomuscular lamella from the conjunctiva Muller septal posterior lamellae, associated to topical anesthesia of the bottom of the conjunctival bag.
- Installation of a protective glass lid and a 4-0 silk traction at the palpebral margin level.
- Eversion of the eyelid on a Desmarres lid retractor.
- Incision of the conjunctival plane and of the capsulopalpebral fascia on the lower border of the tarsus and on all of the palpebral length.
- Separation of the conjunctival plane and the orbicular plane. While the palpebral margin and muscle skin plane are retracted, the conjunctival mullerian flap is pulled in the opposite direction with two forceps.



(a) (b)

Figure 62.11 Lower eyelid transconjunctival blepharoplasty: (a) exposition of the fat pad; (b) excess of the fat pad after coagulation.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 62.12 (a) Woman with important fat pad herniation; (b) result after lipectomy by conjunctival approach (no surgery on the skin).

- Dissection until contact with lower orbital edge.
- Opening of the septal plane and excision of the central, medial, and lateral herniated fat pads, with cauterization of their base.
- Repositioning of the conjunctival plane on the inferior edge of the tarsus without suturing.

Variation: *Lipectomy by conjunctival and retroseptal route.*

The fat pads are much closer from the inferior oblique muscle.

The conjunctival incision is deeper and lower, parallel to the conjunctival bag.

After applying a gentle pressure on the globe toward the back, the fat pads can be seen in the bottom of the conjunctival bag, and as soon as the incision is made, they easily herniate.

Then, they are dissected, clamped, severed, and cauterized by using the same technique than the preseptal approach.

The procedure ends with the repositioning of the lower eyelid and a soft compression by applying cold pockets on the eye for approximately half an hour.

An ophthalmic solution, an antibiotic cream, and/or cortisone cream can be applied on the bottom of the conjunctival pad.

Specific Techniques

Some surgical procedures can be associated during a lower blepharoplasty by anterior or posterior approach. These procedures depend essentially on clinical and anatomical forms:

Lower Blepharoplasty with Fat Repositioning on the Infraorbital Edge [5,6] *Principle*: Transposition of fat in the form of a septo fat flap fixated to the infraorbital rim, the malar curve, and SOOF region below the orbital orbicularis in order to correct the subpalpebral crease (nasopalpebral and palpebromalar creases and folds, tear trough).

Indication: Augmentation of the tear trough in the form of the accentuation of the palpebrojugal fold and subpalpebral creases (nasopalpebral and palpebromalar creases).

Technique: The approach used can be transconjunctival, but it is preferable to use a transpalpebral approach, which allows a better exposition.

- Opening the septum as low as possible
- Detachment up to the periosteum of the infraorbital rim while leaving the SOOF and the orbital orbicularis muscle forward
- Transposition of the three fat pads and fixation to the orbital rim's periosteum with 6-0 Vicryl stitches

Lipectomy by Conjunctival Approach and Skin Excision: The goal of this dual approach (anterior and posterior) is to avoid any large detachment of the skin and orbicularis muscle, sources of edemas, bruises, and retraction.

1. By transconjunctival route, we remove the fat pads.
2. By transcutaneous route, the surplus is treated by the following technique:
   a. Measuring the excess skin to remove by a simple pinch with forceps (pinch technique) while asking the patient to look upwards.
   b. Excision of the excess skin with scissors without any dissection.
   c. Suture by 6-0 monofilament or silk overlock stitches.

Notes: A lateral canthoplasty is associated in the case of excessive laxity.

Lower Blepharoplasty and Hyperlaxity: This hyperlaxity must be inspected prior to any blepharoplasty and is sometimes already accompanied by an ectropion.

In the course of the blepharoplasty by anterior approach, the skin and the orbicularis muscle must be sparingly resected.

At the same time, hyperlaxity will be treated either by a full-thickness resection of the lid's edge (1) near the outer angle or by lateral canthoplasty (2).

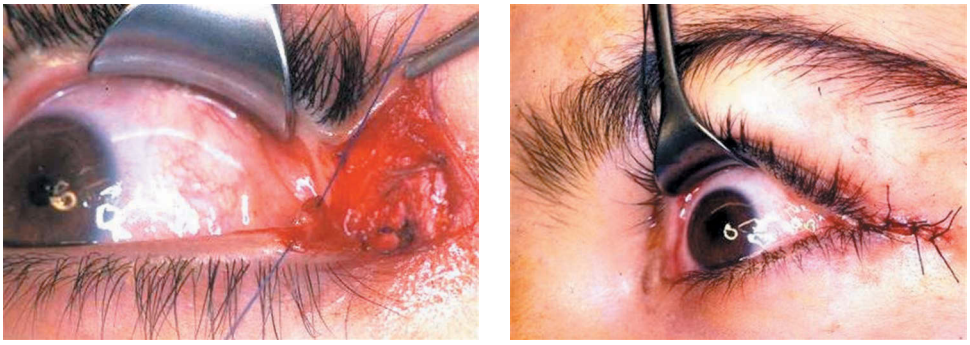
Full-Thickness Resection of the Eyelid's Free Edge (1): It has a pentagon shape near the outer angle at approximately 6 mm of the lateral canthus. The length of the horizontal segment depends on the importance of the laxity.

The suturing takes place at the palpebral margin level by 2 or 3 6-0 silk stitches and at the tarsoorbicularis level by a 6-0 Vicryl overlock stitches or interrupted stitches.

Lateral Canthoplasty (2): [7] (Figure 62.13): Often, a patient will exhibit age-related laxity of the lower lid margin.

The principle is to stabilize the eyelid fissure to correct the horizontal laxity.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b)

Figure 62.13 Lateral canthoplasty: (a) anchoring the lateral part of the tarsus to the periosteum of the lateral orbital rim; (b) suture the skin.

Technique

- Lateral canthotomy
- Inferior cantholysis over the superficial and deep portion of the lateral canthal tendon
- Drap under mild tension the free lower lid segment against the globe
- Excise skin, orbicularis, lashes, and conjunctiva between the lateral tarsal plate and the point where the new lateral canthus will be
- Anchor the lateral portion of the tarsus to the periosteum of the lateral orbital rim using a 5-0 Vicryl suture

Lower Blepharoplasty and Malar Bags: Malar bags are most of the time due to excess skin and/or muscular surplus that relapse below the medial orbital rim. It can sometimes be a genuine lymph edema.

Many techniques are available; they all have the merit of highlighting, most of the time, their own deficiencies:

- *The classic subcutaneous anterior lower blepharoplasty* with a large detachment up to the infraorbital bone rim and fixation of the flap to the lateral orbital rim
- More recently, *the supraperiosteal mesolift with jugal and canthal fixation* (see mesofacial lift)
- Only the direct incision of the *malar pocket*, at the price of a thin scar, can sometimes solve this problem and give acceptable results.

The Midface Lift [7–10] With aging, the SOOF descends. The orbicularis itself weakens. This can lead to malar bags.

In combination with pseudoherniation of orbital fat, a double convexity deformity results.

The midface lift addresses the aging changes that occur in the triangular area from the nasolabial fold to the eyelids.

- Eyelid fat protrusion
- Laxity and sagging of the eyelid skin and midface skin
- Descent of subcutaneous face and midface structures
- Nasojugal groove (tears trough)

Surgical procedure includes

- Lower eyelid blepharoplasty by anterior approach with an extended skin–muscle flap
- Fat transposition
- Midface lift

Surgical steps of the cheek lift

Two steps are very important:

1. Anchoring of the canthus, which mainly controls the shape of the eyelid fissure.
2. Anchoring of the cheek flap itself, which really supports the lower lid and cheek. It redrapes the cheek and also provides a sling-like support for the lower lid and reposition eyelid fat by tension of the flap.

Technique

- Subciliary incision.
- Dissection of a skin–muscle flap down to the orbital rim.
- Continue the dissection below in a subperiosteal plan (after the incision of the periosteum at the inferior orbital rim) until the inferior malar border, laterally to the anterior third of the zygomatic arch.
- Elevate the cheek tissue from the cheek bone.
- Anchor the lateral canthus at the level of the inferior pupil edge and inside the lateral orbital RIM (depending of on enophthalmic or exophthalmic eye).
- Anchor the inferior arc of the orbicularis muscle in the cheek lift flap: this supports the lower lid and the cheek.
- To isolate a portion of the inferior area of the orbicularis muscle, a subcutaneous dissection is performed down to the inferior edge of the muscle.
- Double anchoring is necessary:
  - The base of the orbicularis muscle is anchored at the level of the lateral canthus in the periosteum.
  - The tip is fixed in the deep temporal fascia.
  - Excise the excess skin over the lateral half of the lid margin.

Variants The dissection can be done in a subperiosteal plane [10].

CONCLUSION

Eyelid blepharoplasty has evolved considerably, and today's oculoplastic surgeon has the ability to rejuvenate not just the eyelids but also the entire periorbital complex with procedures targeting the brow, midface, and skin quality.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 62.14 (a) Man with a right upper eyelid high crease (deep sulcus); (b) result after autologous fat injection (lipofilling).

Standard blepharoplasty technique does not completely address periocular rhytides.

To avoid such complications [11] like round eye, scleral show, and ectropion, it is important to combine blepharoplasty with other surgical procedures like canthoplasty, canthopexy, and adjunctive procedures as

- Superficial resurfacing
- Botox injection
- Volume injection (Figure 62.14)

REFERENCES

1. Perkins SW, Prischmann J. The art of blepharoplasty. *J Facial Plast Surg* 2011 February; 27(1):58–66.
2. Adenis J-P, Morax S. *Pathologie orbito-palpebrale—Rapport S.F.O.* Paris, France: Masson, 1998, pp. 261–309.
3. Reynaud JP, Bardot J, Fogli A, Malet T, Saboye J. *Chirurgies esthétiques des paupières: Rapport Sofcpre*. Paris, France: Elsevier Masson, 2008.
4. Morax S. Ptosis et complications. In: Adenis JP, Morax S, eds. *Pathologie orbito-palperale—Rapport S.F.O.* Paris, France: Masson, 1998, pp. 227–253.
5. Hamra ST. The role of orbital fat preservation in facial aesthetic surgery. A new concept. *Clin Plast Surg* 1996 January; 23(1):17–28.
6. Loeb R. Fat pad sliding and fat grafting for leveling lid depressions. *Clin Plast Surg* 1981 October; 8(4):757–776.
7. Mc Cord C. Lower blepharoplasty and primary cheeklift. In: Chen W, Khan J, Mc Cord C, eds. *Color Atlas of Cosmetic Oculofacial Surgery*. Butterworth-Heinemann, Elsevier Inc., 2004, pp. 109–139.
8. Le Louarn C, Buthiau D, Buis J. Rajeunissement facial et lifting malaire concentrique: Le concept du FACE RECURVE®. *Ann Chir Plast Esthet* 2006; 51:99–121.
9. Botti G, Botti C, Cella A, Gualdi A. Correction of the naso-jugal groove. *Orbit* 2007 September; 26(3):193–202.
10. Kestemont P. La technique de suspension palpébromalaire par utilisation du muscle orbiculaire des paupières. *Ann Chir Plast Esthet* 2009; 54:425–434.
11. Morax S, Touitou V. Complications of blepharoplasty. *Orbit* 2006; 25:1–26.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

PART IV

The Aesthetic Facelift

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Facelift: Identity and attractiveness reconstruction

Thierry Besins

INTRODUCTION: THE CURRENT STATE OF THE ART

All facial rejuvenation procedures, whether medical or surgical, aim to give the impression that the patient is younger rather than actually making the patient younger. This is the plain truth.

Our treatments aim to modify age perception codes in this respect.

This presupposes a fair and artistic analysis of the patient's face, always divided into two phases:

1. Analyzing which facial zones *seem young* and should not, or should hardly, be touched so as not to *damage* them
2. Analyzing which indicators *give an impression of age* and, consequently, determining which therapeutic procedures are better suited, whether medical, surgical, or mixed

New therapeutic and non-invasive approaches have proved efficient, and consequently, surgery is no longer the prevailing procedure, having almost been blacklisted.

Industry seized the opportunity to launch an aggressive (and successful) marketing campaign over the past 10 years based on various key themes:

1. No more surgery and its brutal, bloody, painful, and dangerous overtones, with clichéd results.
2. Non-surgeons are encouraged to practice on the same level as surgeons.
3. Lastly, smooth, natural, and seamless results and no seclusion period.

No patient can resist such (sales) arguments, at least not at first!

Is surgery out of fashion? Absolutely not! But it benefits from a better defined scope of indications. The overwhelming emergence of rejuvenating medical treatments has caused surgery to evolve both in terms of technique and indications. Our therapeutic tools allow us to provide better care as well as better and seamless treatments, and, thanks to the combination of medical and surgical treatments, results are optimized, more harmonious, and, therefore, more "natural looking."

The emergence of such a broad range of therapeutic options (fillers, myorelaxation toxins, fat autografts, autologous blood derivatives, and chemical or energy surface treatments) has caused a very important evolution in care regimens:

1. Facial rejuvenation is not just the prerogative of surgery anymore (a perfect result not being achievable via surgery only).
2. Mutilating procedures such as the forehead lift, and aggressive eyelid surgeries have almost entirely vanished from surgical programs and are now only carried out in very specific cases.
3. Surgical procedures are increasingly carried out in instances where only surgery may correct the problem. They are better codified and above all more conservative.
4. The current trend is to use surgery for the lower part of the face (neck, jowls, oval), where it is still indispensable, and to treat the central part using medical treatments or autologous fat.
5. This evolution testifies to our effort to continuously perfect our results, which often depend on small aesthetic details that we very gladly take into account, now, guaranteeing a seamless result.

This is all the better for our art as well as for our patients. Congresses are swarmed with cases that are deemed to be incomplete, whereas they were seen as *excellent* just a few years ago.

Our art is experiencing a new breath of passion after becoming increasingly dull and glum due to being riddled by numerous inadequacies, and we were aware of it. Our mentors all confessed (in private) to feeling guilty about performing facelifts.

Better understanding of facial aging, combined with new therapeutic tools, has given us a more enthusiastic and positive outlook, and consequently, we are able to achieve results of unquestionably high quality.

Surgery, nonetheless, remains mysterious, unpredictable, and even philosophically challenging at times; this, however, is a different, though essential, matter, and we would rather overlook it for the time being. Perfect surgical results, matching our concepts as well as our patients' wishes, cannot be achieved without a great deal of luck.

PATIENT'S APPEARANCE

Our specialty (both medical and artistic) is very challenging, not to say impossible to carry out.

We are the doctors and surgeons of appearance! Indeed, our task is to turn our patients' unwanted appearance into their expected appearance!

What defines a unwanted appearance? Who is it unwanted by, and why?

What defines one's expected appearance? Though it is deemed understood, the appreciation of one's new image depends on too many subjective factors to be *guaranteed*. Only a fortunate set of circumstances may yield the perfect expected result. In order to maximize our chances of success, we must improve our odds.

The only underlying objective behind any cosmetic surgery-related decision is to make the patient happier once the

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

procedure is done. The objective technical quality of the result is entirely different from its emotional quality, especially from the point of view of the patient's feelings. Satisfaction depends on many factors and more specifically on three key aspects:

1. Satisfaction derived from well carried out, well followed up work, of good objective quality: this is the *material* result, which depends of the surgeon's *technical* skills.
2. Satisfaction brought about by positive changes that can be enjoyed in one's daily life on a personal, professional, and emotional level following surgery. This is successful identity reconstruction and depends on the surgeon's *artistic* and *psychological* skills.
3. And lastly, whether one likes it or not, a good *return on investment*, these procedures being costly and closer to an investment (whether acknowledged or not) in an ill-defined notion rather than an indulgence.

Improving one's appearance in order to improve one's well-being is a notion that many psychiatrists and psychologists would laugh at. Identity reconstruction (or restoration) in order to improve one's standard of living is a process that entails several other reconstruction steps, but it is crucial to schedule the surgery at the right time, particularly when it pertains to morphology; age-related reconstruction is more controversial; aging is an unavoidable process, yet people secretly dream of turning back the hands of time, whereas the procedure only really aims to create an illusion! In such a specific context, it is essential to distinguish between quests for eternal youth (negative requests) and desire for mild reconstruction in order to harmonize well-being and appearance (positive requests).

The secret of well-being lies in the balance of being and appearing. Such balance is fundamental to the charm, power, and *universal* seduction that constitute the invaluable gift known as charisma.

Charisma is a mysterious attribute that evokes the fascination of others, it has nothing to do with age or beauty!

This much sought-after natural virtue is often requested by patients. A strong identity is an essential component of charisma. No treatment should be performed that may adversely affect a patient's charisma.

In a nutshell, we aim to rebuild people's identities. The purpose of our surgical procedures is construction or reconstruction.

Lastly, we must never forget that emotional quality always outweighs technical quality.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Development of a therapeutic program: Some rules

Thierry Besins

Good therapeutic planning is essential for a successful surgery.

All of the patient's physical, psychological, and personal data should be analyzed.

Before deciding to proceed with surgery, the patient should take the time to reflect on five questions in a specific order; the answers to which shall be based on listening, examination, and preoperative consultations that shall occur as often as required by the complexity of the case both from a psychological and physical point of view

Understanding who is sitting in front of me, do I know my patient (it is essential to devote sufficient listening time)? I personally cannot make a surgical decision if I do not know who my patient is.

- Do I understand the request?
- Am I objectifying the request?
- Am I able, given the amount of knowledge I have, to provide a positive solution?
- Considering the projected result that only I know, will the patient be satisfied?
- Lastly, does the patient have the resources to face the difficulties inherent to a surgical procedure (pain, discomfort, complications, very subjective and random postoperative recovery period, and appreciation of the result)?

Operative planning (the choice and multiplicity of procedures) depends on two essential facts: objective physical facts and subjective psychological facts. A few simple rules can be followed

Finalizing therapeutic planning depends mainly on the patient's psychological state, so too does patient satisfaction.

The decision whether to refrain from performing the surgery or not and to perform minimal procedures or heavier ones depends on the patient's profile, mental health, and motivation.

For patients with a strong identity and obvious charisma, the surgeon should proceed with extreme caution before treating certain areas (typically the centrofacial area, where the nose and eyes are located) as the risk of impairing the said identity and charisma is high, regardless of the technical quality of the procedure.

Fragile and depressed patients should not undergo procedures. The point of facial cosmetic surgery is to provide rebirth rather than change. However, the patient needs to be ready for this process and should be strong enough to accept temporary "destruction."

IMPLEMENTING THERAPEUTIC PLANNING DEPENDS ON THREE ESSENTIAL FACTORS

1. *The patient's motivation to rectify a particular cosmetic "problem"*: The level of satisfaction (given a good technical result) is proportional to the level of motivation—very motivated, very satisfied; fairly motivated, fairly satisfied; not motivated, not satisfied. This is a fundamental point: nobody can be satisfied with a purchase of something they don't want. The cosmetic enhancement will not be perceived as something positive and, therefore, will cause dissatisfaction or disappointment. Similarly, specific requests, which can be simple details, should always be taken into consideration, as they often constitute the patient's main expectations. The surgeon should always discuss the relevant therapeutic options.
2. *The patient's identity*: Some procedures involve the risk of modifying a patient's identity (aggressive facelifts, temporal facelifts, any surgery carried out around the eye area). Such a risk can only be taken when dealing with patients whose identity is relatively unformed so that a certain degree of change or *transformation* is actually hoped for; this usually applies to patients for whom appearance prevails over being and who never completely matured toward the adult stage. In conclusion, with several possible therapeutic planning options available, the psychological profile of the patient should be the determining factor regarding the appropriate choice to be made. The stronger the identity and charisma, the smaller and above all more risk-free the procedure should be, apart from the neck area that is not part of the identity triangle.
3. *The patient's psychological strength*: Before any identity reconstruction, there is destruction. This destructive phase happens during the surgical procedure, and, the postoperative phase and its various post-traumatic stages, which all surgeons are familiar with. It is typically proportional to the scope of the *work* carried out. In this instance too, the whole process should depend on our patient's physical and psychological strength, with "fragile" patients being spared as much as possible.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

CONCLUSION

Well prepared therapeutic planning allows the surgeon to perform the procedure with peace of mind, and helps minimize the need for last-minute changes with consequent risk of mistakes. Appropriate choices should be made following consultations, and with a clear head rather than in the operating theater.

Well-prepared therapeutic planning, taking into account all psychological and physical information pertaining to the patient, guarantees, provided good techniques are used, a high degree of patient satisfaction.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Practical anatomy for face-lifts

Philippe Kestemont and Jose Santini

INTRODUCTION

Studying the face and neck's surgical anatomy with the aim of performing face-lifts pertains, on the one hand, to the face's superficial structures as modified by aging (and which would benefit from surgical repositioning) and, on the other hand, to regional anatomical elements that are not directly concerned but that are to be identified and preserved during the course of the surgical procedure.

The anatomical structures that are mobilized during face-lifts are the skin, the subcutaneous fat tissue, the mimetic or dermal muscles, and the cervicofacial submuscular aponeurotic system (SMAS).

This chapter does not aim to be comprehensive but provides the reader with a condensed and practical overview of current anatomical knowledge in an area characterized by the complexity of its structures and the subtle way it functions. These static and dynamic elements are fundamental to our expressions and to our relationships with other people.

This chapter focuses on face-lifts and, therefore, mentions neither the facial skeleton nor the eyelids.

SKIN AND FAT TISSUE

The skin shows signs of aging in the form of wrinkles and folds that appear as a consequence of the forces applied to it, particularly in the areas in which the underlying dermal muscles adhere. It is essential to carry out a quality analysis of the dermal state in order to determine the usable detachment surface as well as to assess the said detachment's trophic risks. In practice, cutaneous detachment is greater for older patients and can be very limited for middle-aged patients who show good SMAS function.

Dermal hypodermic aging is visible on the neck through the appearance of wrinkles that are secondary to orthostatic occurrences. Orthostatic wrinkles are strictly speaking secondary to cervical flexion–extension movements and appear around the age of 30 in the form of two or three superior cavity wrinkles. The ptosis of the cutaneous fatty covering is concentrated in the jugal lateral region and increases the lines in the junction area between the cheek and the periorificial region. The nasolabial line is the most important one (Figure 65.1).

Fat Tissue [1–4]

Taking into account the subcutaneous fat tissue is an essential step. The layer of fat totally covers the superficial SMAS in the laterofacial and cervical regions. Its width varies from one region to another, and even from one cosmetic unit to another. Some areas may contain thicker and denser fatty deposits: the malar and submental fatty deposits.

In short, one distinguishes facial fat, that assists trophicity and helps the face resist the aging process, and cervical fat that modifies the cervical outline and disturbs, in particular cases of very heavy necks, the corrective action obtained by reapplying tension on the SMAS–platysma flap.

Over time, facial fat tissue undergoes two evolutions: melting and ptosis.

Facial fat can be divided into two categories for each facial region (lateral and central): deep fat and superficial fat. These fat compartments have their own behavior (Figures 65.2 and 65.3):

- The deep temporal fat, in continuity with Bichat's fat pad (deep jugal fat) via the masticatory syssarcosis, will cause a ptosis and aggravate marionette lines.
- The periparotid fat is not subject to ptosis, the parotidocutaneous ligaments being highly adherent and this area not being very mobile.
- The external jugal fat superficial to SMAS and the masseter muscle, does not undergo any shearing movements and, therefore, remains quite stable over time in terms of volume and location.
- The malar fatty deposit lying against the jugal extension of the orbital orbicular muscle's orbital fascicle is subject to ptosis and atrophy over time, causing the appearance of the subpalpebral line and the valley of tears.
- The internal jugal fat slides down the nasolabial fold's adherences and creates the jowl.

The facial and neck skin and their fatty sublayer are of varying aspect, thickness, and quality according to two major and distinct regions:

1. The *periorificial craniofacial region, the embryological origin of which is the sphincter colli profundus* (Figure 65.4), is the facial dynamic support. The area of the face with the thinnest skin is found around the orbits, the nose, and the oral cavity, with very little fat tissue lying against the dermal muscles.

   There is a lot of adherence between these superficial muscles and the dermis.

   This distinctive characteristic is the cause of the thin periorificial wrinkles referred to as *expression lines*.

   On the eyelids, the skin is particularly thin and features very little subcutaneous fat tissue, which shouldn't be confused with the retroseptal endo-orbital fat pads.

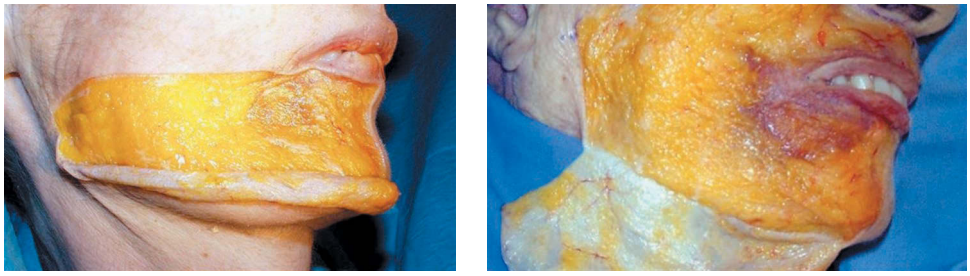
Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 65.1 A 70-year-old woman. (a) Classic aspect of aging skin, in the perioral area, and the neck. (b) Correction 3 years after a face-lifting, lipofilling, and hyaluronic acid in the lips.

(a) (b)

Figure 65.2 (a) MRI view of a 52-year-old patient. Magnetic resonance imaging, the fat tissue is white in this view. Note the precise limit of subcutaneous fat in the periorificial craniofacial region and the lateral cervicofacial region. (b) Photographic view of the same patient, note that the limit of the muscular central face and fatty lateral face is the border of the eyes, the nose, the nasolabialfold, and the marionnette lines.



(a) (b)

Figure 65.3 (a) Young cadaver dissection. (b) Old cadaver dissection. Look at the fat tissue in the perioral area. Note the difference between a young face and an old face. There is no more fat around the lateral labial commissure.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

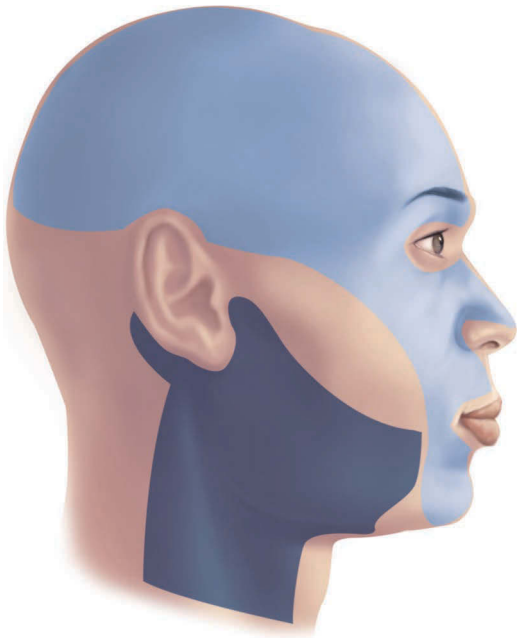


Figure 65.4 Embryological origin. The *sphincter colli profundus* (light blue) and the *platysma primitif* (dark blue).

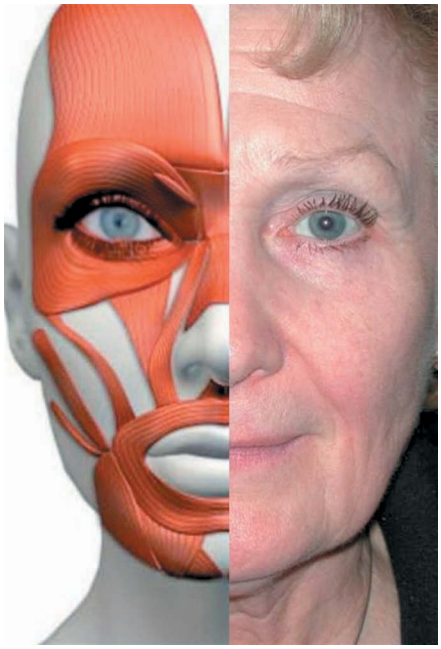


Figure 65.5 Facial skin muscles. (Courtesy of L. Vignol and P. Kestemont.)

2. The *cervicofacial region, the embryonic origin of which is the primitive platysma* (Figure 65.4), is characterized by a lot of subcutaneous fat tissue and thicker skin. The sublayer is aponeurotic and muscular and represented by the SMAS–platysma. This is a more static region of the face, theoretically less prone to developing wrinkles.

The subcutaneous fat tissue is distributed in the cheek and neck area, in a relatively thick and homogeneous layer, apart from the malar region where it is more voluminous, forming the *malar fatty deposit*.

DERMAL MUSCLES AND MUSCULAR AND APONEUROTIC STRUCTURES

In the periorbital region (Figure 65.5):

The eyebrows form a mobile structure that depends on two dermal muscular systems, an eyebrow raising system mainly composed of the frontal muscle and a lowering system comprising the eyelids' orbicularis muscles, the pyramid muscles, and the corrugator muscles.

The raising muscular aponeurotic complex consists of the combination of the galea aponeurotica, the frontal muscle, and the occipital muscle.

The frontal muscle, of a quadrangular shape measuring 6 × 7 cm, features medial fibers that connect at the glabella and cross the procerus muscle fibers. Its central and lateral fibers cover the corrugator muscle and cross the most peripheral fibers of the eyelid orbicular muscles' orbital portion. It is located between the galea and the skin, and its fibers are in contact with the subcutaneous tissue. The frontal muscle fibers start from the lower fixations, go upward, intertwine with the galea aponeurotica, and reach the occipital muscle in the posterior region. Its repeated contractions cause the creation of the horizontal forehead wrinkles.

The galea aponeurotica or epicranial aponeurosis covers the bony cranium's convexity. It is solidly affixed at the back, at the occipital tuberosity, and at the upper occipital line. It is separated from the external bone's periosteum by Meckel's space, allowing the scalp to move against the skull. Laterally, in the temporal area, it continues to the superficial temporal fascia, a mesenteriolum containing the facial nerve's superficial temporal vessels and temporal and frontal ramifications.

The eyebrow's lowering muscular complex is composed of the association of three distinct muscles:

The eyebrow muscle, or corrugator supercilii, is a deep dermal muscle. It is a thin yet powerful muscle with a deep medial origin in the glabellar eminence's periosteum and a more superficial transorbicular lateral insertion in the lid–eyebrow section. It lowers and draws together the eyebrows' internal thirds. Its repeated contractions cause the creation of the vertical glabellar wrinkles, or *lion wrinkles*.

The pyramid muscle, or procerus, is a medial expansion of the frontal muscle, covering the nose's bones and connecting to their distal part and to the triangular cartilages. It lowers the medial tip of the eyebrows. Its repeated contractions cause the creation of the glabellar horizontal wrinkles.

The *orbicularis oculi muscle* (OO) is one of the face's largest dermal muscles. It is wide, disc-shaped, and diaphragmatic and is a flat and slim muscular strip, sticking strongly to the skin, with ovalar fascicles. OO is characterized by the following:

- The *pars orbicularis*, the outer part of OO. It has no deep attachments. It is often larger than the usual depiction seen in standard manuals. Its repeated contractions cause the creation of crow's feet and oblique glabellar wrinkles. The latter appear as a result of the fibers' upper external contingent, referred to by some as *depressor supracilii muscle*.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 65.6 (a) Fresh cadaver dissection. Note the superficial musculoaponeurotic plane (SMAP). There is a continuity of the submuscular aponeurotic system (SMAS) and the platysma muscle. (b) 56-year-old woman, note the clinical limit of the SMAP.

- The *pars palpebralis*, the inner part of OO, adheres to the tarsus and connects deeply to the palpebral tendons. A muscular fascicle runs toward the posterior lacrimal ridge: Horner's muscle.
- OO plays an active role in the orbital region's lacrimal and lymphatic drainage.
- The orbitomalar line masks the inferior limit of the palpebral part of OO. This line separates the cheek from the orbital region. It also corresponds to the upper limit of the malar fatty deposit. There is a thin suborbicular fat layer in continuity with the jugal fat tissue: the suborbicularis oculi fat (SOOF), which constitutes a natural surgical dividing plane.

Regarding the Buccolabial Region

These muscles are disposed as stratums as described by Freilinger:

- A superficial layer composed of the small zygomaticus muscle (zygomaticus minor), the lip angle depressor muscle (depressor anguli oris), and the eyelid orbicular muscle (orbicularis oculi).
- A second layer composed of the greater zygomaticus muscle (zygomaticus major), the risorius muscle, the platysma muscle, and the lower lip depressor muscle.
- A third muscular layer composed of the lip orbicular muscle (orbicularis labii) and the upper lip raising muscle (levator labii superioris).
- A deep layer composed of the muscle mentalis, the mouth angle raising muscle (levator anguli oris), and the buccinator muscle.

Cervicofacial face-lifts are carried out according to an anatomical guiding principle: the cervicofacial SMAS, entirely corresponding to the platysmal fibromuscular layer and both its parts, the muscular platysma itself and the fibrous platysma (Jost). This set constitutes what we refer to as superficial musculoaponeurotic plane (Figure 65.6). It represents the SMAS's surgically *useful* part for the face-lift [5–8].

The SMAP is an aponeurotic and muscular layer, paired and symmetrical, covering the lower third of the face and the neck's lateral region. It is characterized by high dermal adherence.

There are three parts to the SMAP:

1. An anterior, chin-related part or fascicle, its fibers connecting to the labial corner lowering a muscle's fibers, from which they are surgically inseparable. The anterior side of this fascicle, which is also the anterior side of the platysma, is, with aging, responsible for platysmal bands or dewlaps.
2. A medial part, the fibers of which end in the modiolus and connect with the other endings of the labial muscles.
3. A posterior parotid and zygomatic part that is constituted by the SMAP's most fibrous portion, characterized by deep and strong adherence to the parotid fascia and attached to the zygomatic arch, at the top. This insertion represents an important fixed point: the *McGregor patch* (Figure 65.7).

FACE-LIFT PLANE OF MOTION AND DEEP ANATOMICAL STRUCTURE PLANE OF MOTION

Two planes of motion are used by the surgeon during the dissection of the laterofacial and cervical region in order to perform a face-lift:

1. The subcutaneous plane, or, more specifically, the subcutaneous fatty plane. Dissection in the plane allows the superficial fat and overlying skin to be mobilized as a unit and leaves the SMAS undisturbed. This plane is different from the subdermal plane used by the earliest authors.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

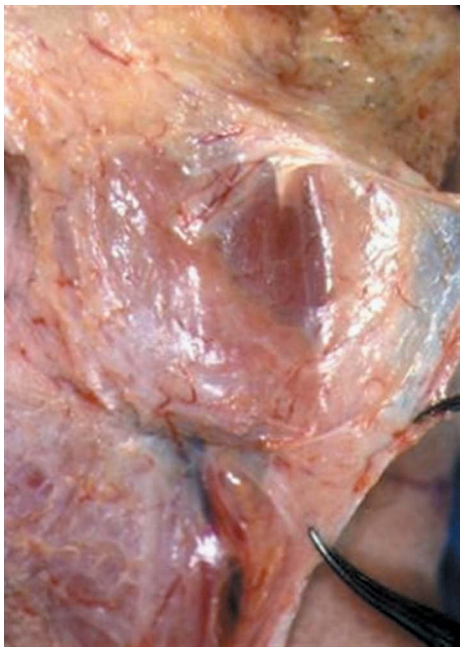


Figure 65.7 The McGregor patch. Posterior parotid and zygomatic ligaments that are constituted by SMAP's most fibrous portion, are responsible for the deep and strong adherence of the parotid fascia. This insertion represents an important fixed point.

2. The sub-SMAS plane, which, justifies characterization of the face-lift as *deep*, exposes the skeletal aponeurotic vascular and nervous elements, which are the most risk-prone structures in this type of face-lift. Such a dissection is easily made in the region covering the parotid gland's external fascia as it protects the facial nerve. It is more complex and requires more precision at the front of the gland, and at the external face of the masseter muscle which is covered by the parotid and masseter fascia. The deep dissection plane is more natural on the neck as this area corresponds to the SMAP's most mobile part.

Deep Aponeurotic Structures and *Cutaneous Ligaments* of the Face

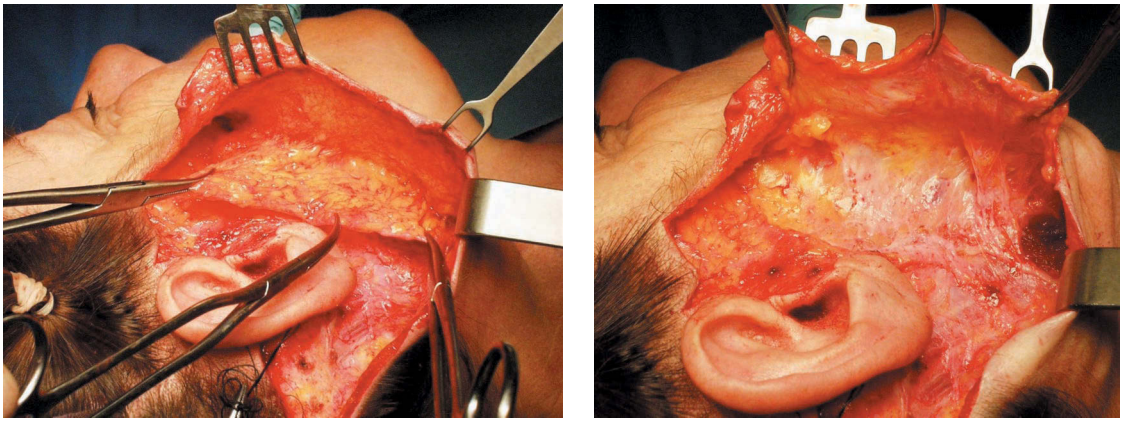
Lifting the SMAP uncovers the deep aponeurotic plane. Posteriorly lies the parotid gland and its fascia, anteriorly the masseter muscle and its fascia. Regarding the neck, the sub-SMAS plane, a plane of motion, follows the external surface of the deep cervical aponeurosis that covers the sternocleidomastoid muscle (SCM) and the submandibular gland's external surface.

There are areas where adherences are stronger between the deep aponeurotic plane and the SMAP's deep face. Such connective structures include the cutaneous parotid ligaments, the cutaneous masseter ligaments, and the cutaneous malar ligament or *McGregor patch*. Detachment of these areas is necessary in order to mobilize the SMAP but constitutes a real obstacle for the surgeon given their close relationship with the facial nerve's branches (Figure 65.8).

This zygomatic ligament has been described by McGregor and studied by Furnas and is commonly referred to as McGregor's patch. It constitutes the lower limit of the prezygomatic space, stretching from the medial part of the zygomatic minor to the lateral part of the zygomatic major, where it connects to the cutaneous masseter ligament's upper fibers.

One observes a condensation of pearly white fibers, 3 mm wide and 0.5 mm thick, located 4.5 cm to the front of the tragus. At the front of this main ligament, there can be a secondary ligament of the same width but of lesser thickness. Other smaller fibrous condensations are spread around both these structures. The ligament is 6–8 mm long, starting from the zygomatic osseous arcade and reaching the dermis. It maintains the facial mask at this level while giving it some mobility within the sagittal plane. It causes the appearance of the medial jugal fold.

A vascular pedicle and a sensory nerve ramus connect to the skin via the thickest ligament. The upper branch of the facial nerve's upper zygomatic ramus is directly located below the ligament and should not be confused with this sensory ramus.



(a) (b)

Figure 65.8 (a) Intraoperative view of a facelift, subdermis layer, look at the zygomatic cutaneous ligament. (b) Intraoperative view, sub-SMAS layer, look at the zygomatic cutaneous ligament.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

VASCULARIZATION AND INNERVATION

The face's arterial vascularization is subserved via two distinct networks:

1. A superficial network and a main network that depend on the external carotid artery
2. A deep network depending on the internal carotid artery

Both these systems are subject to anastomosis, explaining the facial skin's great vitality.

The facial artery, a continuation of the external carotid artery, becomes superficial by crossing the mandible's lower edge. As it crosses the face, it follows the nasolabial fold and continues its sinuous route through the muscular planes to the deep aspect of the platysma and zygomatic muscles. It turns into the labial and alar branches that are subject to anastomosis with the arteries of the opposite side of the midline. In the upper part of the fold, it becomes the angular artery that is subject to anastomosis in an inconstant manner with the ophthalmic artery's branches.

The superficial temporal artery begins in the parotid region via the split of the external carotid artery into the superficial temporal artery and the maxillary artery. It goes through the superficial temporal fascia, always at the back of the facial nerve's temporal and frontal branch. It features three collateral arteries, the transversal facial artery, the zygomatic and malar artery, and the medial deep temporal artery. It ends with a temporal and anterior frontal artery that joins the periorbital circle and a posterior temporoparietal artery that is subject to anastomosis once it reaches the deep contralateral arteries.

The internal maxillary artery contributes to the deep irrigation of the face. Among its 14 collateral arteries, one observes the buccal artery that irrigates the soft areas of the cheek and the suborbital artery that comes out of the suborbital cavity and irrigates the lower eyelid and the cheek.

The ophthalmic artery starts in the internal carotid artery. It takes part in the vascularization of the face by ending in the nasal artery, referred to as the angular artery. Two facial collateral arteries then appear: the suborbital, or external frontal artery, and the internal frontal artery, which goes up and is subject to anastomosis with the superficial temporal artery's temporal and frontal branch.

The face's venous system is superimposable on the arterial system. One observes a superficial network composed of the facial vein that connects to the internal jugular vein and the external jugular vein that connects with the subclavian vein. There is a deep venous network that communicates with the superficial network via the angular vein, linking the cavernous sinus to the facial vein.

Facial Innervation

Motor Innervation: The Facial Nerve

The extracranial facial nerve is protected in the posterior part of the cheek by the parotid gland and afterward by the parotid masseter fascia (Figure 65.9). As part of this intraglandular course, it is divided into a cervicofacial branch and a temporal facial branch that will in turn both be divided into five branches. They will first follow a facial intraparotid path before entering the mimic muscles.

The cervical ramus is the lowest and most posterior ramus, at the back and beneath the mandible's angle, innervating the platysma.

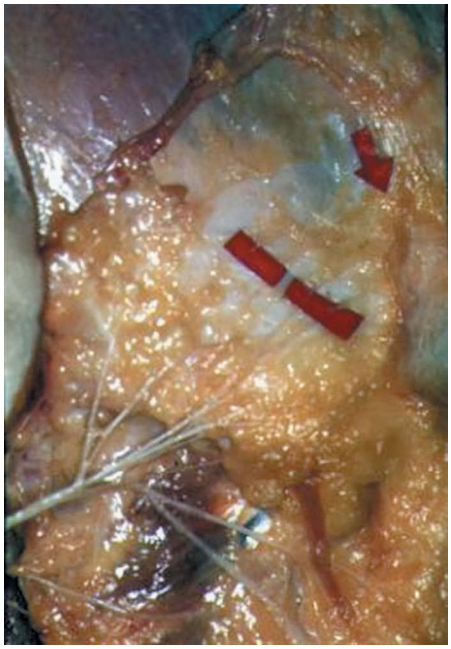


Figure 65.9 The facial nerve: live dissection.

The labiomental ramus can be single or divided in two, and its lowest branch will always be the largest one. It crosses the facial artery via its external face, becomes superficial, and turns into several motor branches for the deep aspect of the mentalis muscle, which lowers the labial corners and depresses the lower lip.

The buccal ramus is rapidly divided into two rami that continue below the parotid and masseter aponeurosis:

1. An upper ramus, slanting at the bottom and forward, at Stenon canal's lower edge, which innervates the lips' buccinator muscle via its superficial aspect
2. A lower ramus that innervates the lips' orbicular muscle via its deep aspect

The zygomatic ramus goes through the zygomatic arcade and is divided into three groups of rami:

1. The upper palpebral ramus that innervates the eyelids' orbicular muscle and the corrugator
2. The lower palpebral ramus that also innervates the eyelids' orbicular muscle
3. The suborbital ramus that innervates the zygomatic muscles and the other dermal muscles of the upper lip and the nose

Anastomoses are observed between the buccal ramus and the zygomatic ramus.

The temporofrontal ramus is the most vulnerable of the facial nerve's rami during facial surgery. Its course can be represented by a line passing 0.5 cm below the tragus and 1.5 cm above the eyebrow's lateral tip. Its different branches are subject to an anastomosis among themselves. It crosses the zygomatic arch approximately 2 cm in front of the tragus and reaches the temporal fascia where it continues below the superficial

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

temporal artery. It finally penetrates the frontal muscle via its deep aspect.

Sensory Innervation: The Trigeminal Nerve and the Great Auricular Nerve

Knowledge of this is indispensable in order to carry out local facial anesthesia.

The trigeminal nerve provides the sensory innervation of the face via its three branches:

1. The ophthalmic nerve that is itself divided into three branches
   a. The lacrimal nerve that innervates the lacrimal gland, the upper eyelid, the conjunctiva, and the eye's external angle
   b. The frontal nerve, divided into the supratrochlear nerve that innervates the eye's inner angle, the upper eyelid, the bridge of the nose, and part of the glabella, and the supraorbital nerve, which protrudes from the orbit either via a notch or a canal, in order to innervate the external angle of the eye, the upper eyelid, and the frontotemporoparietal region.
   c. The nasal nerve is divided into two branches, an internal one and an external one, which innervates the dorsal nasal region.
2. The maxillary nerve turns into an orbital ramus by going through the infratemporal region, which is divided into a lacrimopalpebral branch for the external part of the upper eyelid and a temporomaxillary branch for the upper temporal region. Then it arrives at the suborbital canal passes through the cavity of the same name below the orbit's lower edge, turning into the suborbital nerve that innervates the lower eyelid, the wing of the nose, the cheek, and the upper lip.
3. The mandibular nerve also turns into cutaneous branches, featuring particularly the lower dental nerve that goes through the canal of the same name and becomes the mentalis nerve that maintains the chin and lower lip's sensitivity. In the retrocondylar buttonhole, the mandibular nerve also turns into the auriculotemporal nerve, which innervates the tragus, the ear lobule, and the temporal region. This ramus comes from the mandibular nerve's posterior stem. The anterior stem becomes the buccal nerve, which innervates the cheek's skin.

The great auricular nerve belongs to the superficial cervical plexus, which comes from the C2 and C3 roots' anterior branches. It goes up and connects to the SCM's external face, on the superficial cervical aponeurosis, and behind the external jugular vein and becomes subcutaneous in the subauricular region. It innervates the ear lobule, the retroauricular region, and part of the cheek in the preauricular region (Figure 65.10).

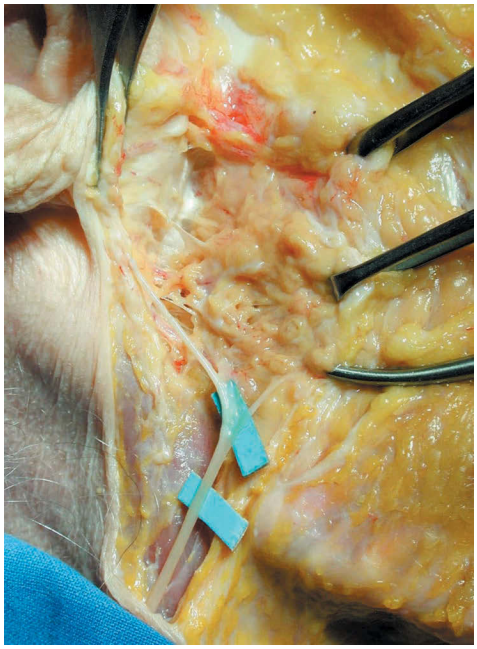


Figure 65.10 Dissection of the great auricular nerve. There is risk of injury during subplatysmal dissection.

REFERENCES

1. Hamra ST. The deep plane rhytidectomy. *Plast Reconstr Surg* 1990; 86(1):53–61.
2. Baker T, Gordon H, Stuzin J. *Surgical Rejuvenation on the Face*, 2nd ed. St. Louis, MO: Mosby, 1996.
3. Stuzin JM. Restoring facial shape in face lifting: Anatomic considerations and the role of skeletal support in facial analysis and midface soft tissue repositioning. In: Thaller SR, Bradley JP, Garri JL, eds. *Craniofacial Surgery*. New York: Informa Health Care, 2008, pp. 59–81.
4. Santini J, Kestemont P, Krastinova-lolov D. Anatomie des regions génienne et cervicale. Chirurgie Plastique de la Face, rajeunissement, embellissement. Concepts et pratiques. Rapport de la société française d; ORL et de Chirurgie de la face et du cou, Masson, 1999, pp. 27–54.
5. Mitz V, Peyronie M. The superficial musculo-aponeurotic system (SMAS) in the parotid and cheek area. *Plast Reconstr Surg* 1976; 58:80.
6. Mitz V. The superficial musculoaponeurotic system: A clinical evaluation after 15 years of experience. *Facial Plast Surg* 1992; 8(1):11–17.
7. Jost G, Levet Y. Parotid fascia and face lifting: A critical evaluation of the SMAS concept. *Plast Reconstr Surg* 1984; 74(1):42–51.
8. Jost G. SMAS in rhytidectomy. *Aesthet Plast Surg* 1982; 6(2):69–77.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Surgical rejuvenation: Cervico-facial lift technique using the superficial musculoaponeurotic plane technique

Philippe Kestemont and Jose Santini

ANESTHESIA AND INSTALLATION

The procedure is carried out under general anesthesia in order to avoid heavy infiltrations that modify reliefs. The intubation probe should be fixed using interdental thread in order for the cheeks to remain free and for the head to rotate. The infiltration (adrenalized Xylocaine) is limited to the areas concerned by the cutaneous incision and the strict subcutaneous detachment carried out at the beginning of the procedure (Figure 66.1).

OUTLINE OF ANATOMICAL MARKS AND OF THE INCISION'S COURSE (FIGURE 66.2)

The incision's outline is carried out carefully as it determines the final scarring. This incision has a general omega shape and features three segments:

1. A temporal segment very close to the sideburns.
2. A periauricular segment that follows the auricle's reliefs aims to maintain its autonomy at the tragus and to maintain its natural aspect at the lobule; in the retroauricular area, the incision follows the groove and reaches the retroauricular muscle's relief.
3. A horizontal posterior segment continuing across the scalp over 3 cm and ending on a small vertical counterincision that shall prove to be useful during cutaneous cutting in order to avoid an *ear-like* appearance at the end of the scar.

Marks matching major deep anatomical elements are often drawn on the skin: the upper edge of the platysma, the mandibular line, the subcutaneous detachment limits, and the zygoma's lower limit.

SUBCUTANEOUS DETACHMENT (FIGURE 66.3)

The subcutaneous detachment is performed from top to bottom; the incision is made using a cold knife with a no. 15 blade; the preauricular detachment is continued over 3 cm on the parotidian superficial musculoaponeurotic system (SMAS) outer face; such detachment is carried over to the malar area in order to free cutaneous malar ligament attachments.

The retroauricular detachment will progress according to deep structures: first, the mastoid's outer face, followed by the SCM's upper tip, and ending with the platysma's outer face. The identification of the platysma's posterior superior edge is an essential step as non-monitored sub-SMAS progression places the patient at risk of lower facial nerve branch injuries, particularly pertaining to the chin–labial ramus, which is the most exposed.

As a key aspect to be considered as part of such subcutaneous detachment, the surgeon must adapt the depth of the dissection according to skin thickness and to the presence of hair follicles. The detachment is carried out on a deeper plane in hairy areas (the temple and posterior scalp). The detachment is very superficial, very close to the dermis, and in the sublobular area due to the absence of subcutaneous fat (SCM dermal adherence).

The cervical subcutaneous detachment is adapted to cutaneous looseness; it is very limited in young patients as platysma contraction mobilizes their skin properly; it is more considerable in older patients, the cutaneous loosening being more substantial. During this time, thorough hemostasis monitoring is essential as subcutaneous bleeding is the main cause of postoperative hematomas.

SMAP FLAP DETACHMENT (FIGURE 66.4)

This detachment constitutes the key step in a deep facelift; the incision (carried out with an electric or cold knife) is carried out following an inverted L shape with both a horizontal and vertical segment:

- The horizontal incision follows the zygomatic arch's inner edge over approximately 3 cm; it uncovers deep fat tissue and the parotid gland's upper tip.
- The vertical incision is discreetly slanted toward the bottom and the back; it follows the outer face of the parotid gland and then the neck along the posterior edge of the muscular platysma and ends 4–5 cm below the gonion.

During this procedure, it is important not to injure the great auricular nerve nor the external jugular vein that is located in front of it.

The sub–superficial musculoaponeurotic plane (SMAP) detachment reaches the parotid's anterior edge in its facial portion; it separates the platysma from the SCM at the neck. The dissection is harder to perform at the face–neck junction, with regard to the gonion, as fibrous condensations form cutaneous mandibular ligaments in this area and therefore increase the injury risk of the facial nerve chin–labial ramus, which is not always protected by the parotid. This dissection may be performed in a less aggressive manner by using a Trepsat spatula.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 66.1 Technique: face lifting installation with general anesthesia.

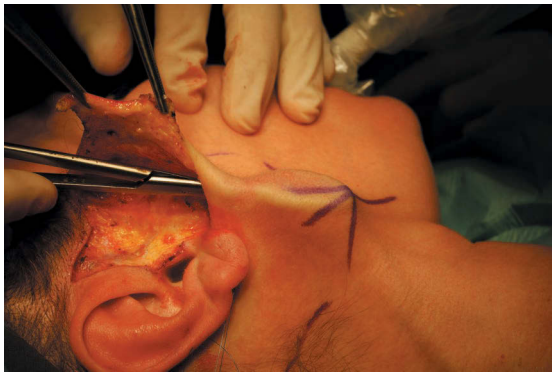
Figure 66.2 Mapping, landmarks, and periauricular incision.

SMAP TRACTION AND SUTURE

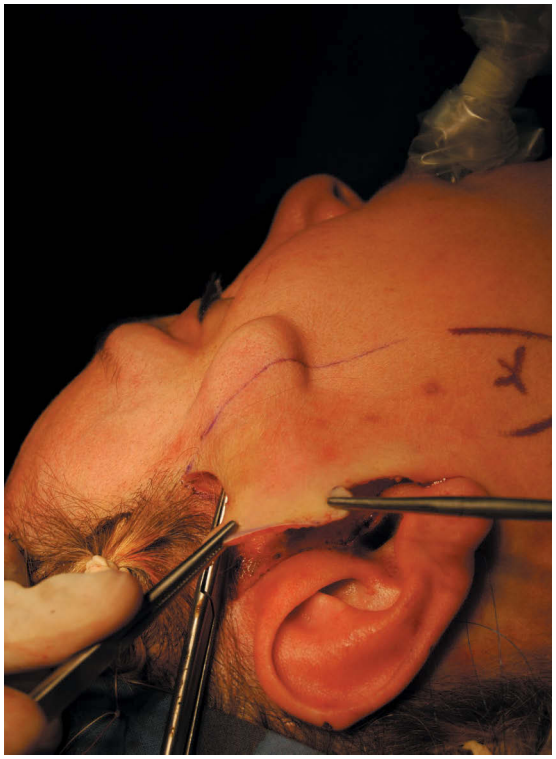
The mobilized SMAP flap will be stretched and pulled according to two vectors: a posterior oblique vector and an anterior vertical vector. This traction allows the carrying out of a posterior suture between the SMAP and the premastoid fibrous tissue. At the top, the SMAP is fixed to the initial subzygomatic section, which entails its shortening and length adaptation.

It is essential to check this procedure's efficiency, which corrects the mandibular area and must therefore outline the mandibular line again and make the dewlap disappear.

SMAP efficiency depends on the quality of its dissection as well as its intrinsic qualities (Figure 66.5).



(a)

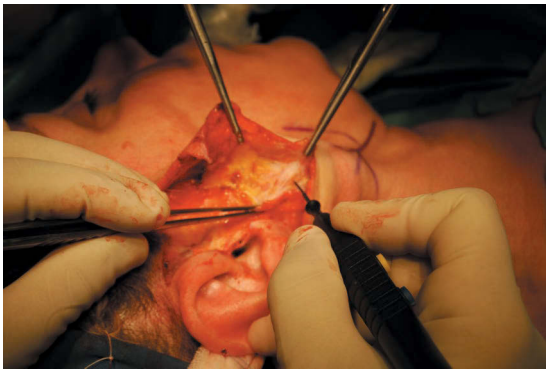


(b)

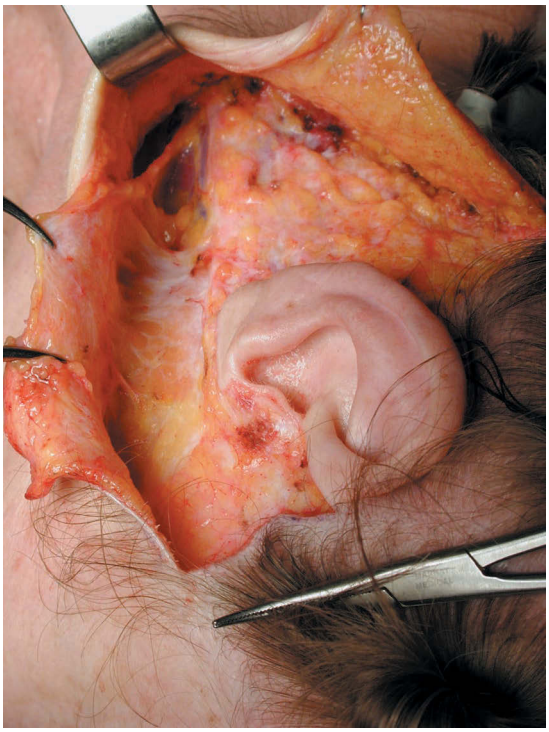
(c)

Figure 66.3 (a) Cervical sub cutaneous dissection, (b) mid cheek dissection under the malar fat pad, (c) cervical subcutaneous dissection. The extension will be adapted to the patient (age, skin quality, etc.).

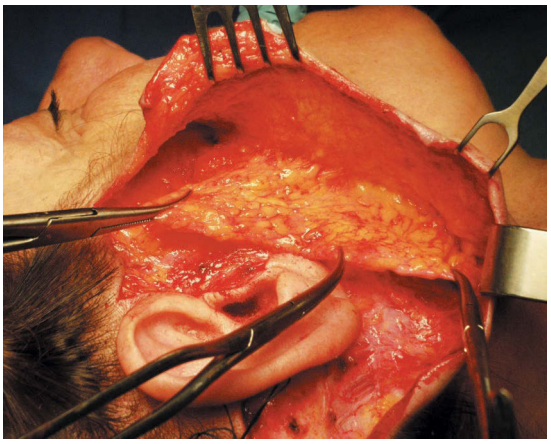
Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a)



(b)



(c)

Figure 66.4 (a) Sub-SMAS pre parotidien dissection, (b) sub-SMAP dissection until the masseter visibility, (c) visibility of a strong SMAP layer.

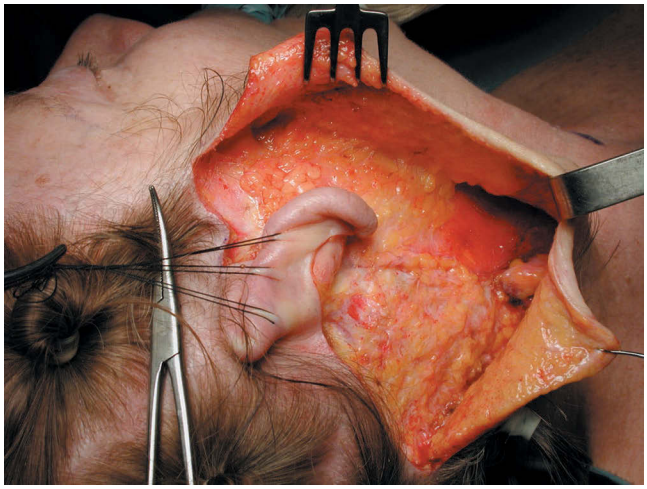


Figure 66.5 SMAP fixation with resorbable sutures.

Figure 66.6 Skin excess after SMAP fixation, with vertical and posterior vector.

CUTANEOUS RESECTION AND CLOSURE (FIGURES 66.6 AND 66.7)

The cutaneous cut is a very specific facelift-related procedure. It is hard to master in the beginning and must be reproduced in a systematized manner in order to be reproducible and symmetric and to avoid abusive tractions entailing cutaneous damage and scar migration (Figure 66.8).

Three distinct steps are to be considered as part of this process:

1. The facial flap is stretched using two pairs of pliers with a horizontal traction vector; excess skin is removed in order to uncover the incision outline for a single plane suture as part of a quality procedure. It is essential to maintain the tragus' autonomy with no cartilage plication.
2. *The posterior cut*: Once the cervical flap is pulled with a vertical traction vector, excess skin is removed while

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a)

(b)

Figure 66.7 (a) Pre auricular skin resection without any tension, (b) retro auricular skin resection without any tension.

Figure 66.8 Skin suture, silk, or Prolene.

ensuring that the hair line is maintained and as little scalp as possible is removed. The suture is carried out over two planes once the limits' hemostasis has been thoroughly checked.

3. *The lobule cut*: Its *personality* should be maintained, and its initial appearance should be restored, which entails perfect identification of the cheek attachment's shape.

No drainage is implemented unless when a high risk of hematoma appears as part of preoperative observations (Figure 66.9 through 66.13).

Figure 66.9 Fat dressing 24 hours.

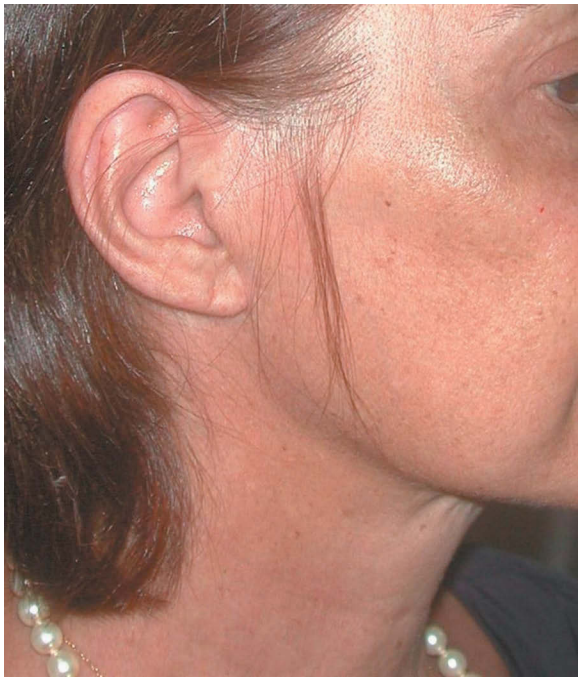


Figure 66.10 Final periauricular scar.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 66.11 (a) Sub-SMAP face lifting, with botulinum toxin in the platysma muscle, 1 month before surgery and every year, (b) result after 4 years.

Figure 66.12 (a) Sub-SMAP face lift, with submental lipoaspiration, (b) 4 years after surgery.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 66.13 Sub-SMAP face lifting and mental fat injection. Result after 1 week and 2 years.

BIBLIOGRAPHY

1. Mitz V, Peyronie M. The superficial musculo-aponeurotic system (SMAS) in the parotid and cheek area. *Plast Reconstr Surg* 1976; 58:80.
2. Mitz V. The superficial musculoaponeurotic system: A clinical evaluation after 15 years of experience. *Facial Plast Surg* 1992; 8(1):11–17.
3. Jost G, Levet Y. Parotid Fascia and face lifting: A critical evaluation of the SMAS concept. *Plast Reconstr Surg* 1984; 74(1):42–51.
4. Jost G. SMAS in rhytidectomy. *Aesthet Plast Surg* 1982; 6(2):69–77.
5. Hamra ST. The deep plane rhytidectomy. *Plast Reconstr Surg* 1990; 86(1):53–61.
6. Baker T, Gordon H, Stuzin J. *Surgical Rejuvenation on the Face*, 2nd ed. St. Louis, MO: Mosby, 1996.
7. Stuzin JM. Restoring facial shape in face lifting: Anatomic considerations and the role of skeletal support in facial analysis and midface soft tissue repositioning. In: Thaller SR, Bradley JP, Garri JL, eds. *Craniofacial Surgery*. New York: Informa Health Care, 2008, pp. 59–81.
8. Santini J, Kestemont P, Krastinova-lolov D. Anatomie des regions génienne et cervicale. Chirurgie Plastique de la Face, rajeunissement, embellissement. Concepts et pratiques. Rapport de la société française d; ORL et de Chirurgie de la face et du cou, Masson, 1999, pp. 27–54.
9. Owsley JG. SMAS-platysma face lift, a bidirectional cervicofacial rhytidectomy. *Clin Plast Surg* 1983; 10(3):429–440.
10. Mendelson BC. Surgical anatomy of the lower face: The premasseter space, the jowl and the labiomandibular fold. *Aesthet Plast Surg* 2008; 32:185–195.
11. Marten TJ, Facelift. Planning and technique. *Clin Plast Surg* 1997; 24(2):269–308.
12. Besins T. The RARE technique (reverse and repositioning effect): The renaissance of the again face and neck. *Aesthet Plast Surg* 2004; 28(3):127–142.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Surgical rejuvenation: The temporal lift

Henry Delmar and Thierry Besins

The goal is to elevate the tail of the eyebrow, in order to rejuvenate the look, by reducing excess skin on the upper eyelid, spreading and tightening the temporal skin, and, finally, inducing more light around the eyes.

Temporal lifting is in fact a way to carry out different improvements of the upper part of the face through a temporal incision (light malar elevation, temporal skin spreading, crow feet improvement, and, of course, eyebrow tail elevation), depending on the undermining and suspensions we can perform (Figures 67.1 through 67.3).

This lift is, in my opinion, the most difficult because you never know exactly what the final result will be nor the emotional result. We must bear in mind that we are working on identity and charisma through a modification of the look.

WHY IS THIS LIFT SO DIFFICULT? BECAUSE THE CHALLENGE IS NEARLY IMPOSSIBLE, AND THE PROCEDURE IS RISKY COMPARED TO STANDARD FACELIFTS:

1. The eyebrow is a cutaneous organ, and consequently, only a subcutaneous lift could be effective.
2. After the reattachment and scarring process, the new position of the eyebrow cannot be fixed because of the surrounding muscular contractions.
3. The eyebrow moves depending on the contractions of the corrugator, orbicularis, and frontalis muscles.
4. Consequently, we can't know the final position of the eyebrow till a few weeks or months after the surgery.
5. Furthermore, this surgery has a high rate of nerve complications (temporary or not), depending on how close the frontal branches are to the facial nerve.

THREE SURGICAL SOLUTIONS (TECHNIQUES) ARE AVAILABLE:

1. The subcutaneous plane alone that supposes a cutaneous resection (and hair sometimes)
2. The *bayonet* plane (deep first and then subcutaneous, 1 cm below the hair line)
3. The deep plane (along the deep temporal fascia and subperiosteal [lateral part of the forehead, temporal crest detachment, periorbital and medial third zygomatic detachment])

Both the deep and bayonet techniques allow hair preservation, because the skin or scalp excess must not be removed as the tension is deep and the skin is not concerned. The excess wave of superficial tissues will spread and will disappear over time if a limited undermining above has been performed (convexity of the skull).

In the *bayonet* technique (Figure 67.4), the superficial temporal fascia (galea) is opened 1 cm below the hair line, and the undermining is continued in a subcutaneous plane. The eyebrow elevation is fixed by suturing the upper edge of the divided galea to the deep temporal fascia at the expected level, with three stitches. The wave of exceeding tissue stays in place, is not removed, and will disappear in a few weeks (Figure 67.5, Videos 67.1 through 67.4).

The same principle of fixation is used in the complete deep and subperiosteal technique if a complete detachment of the periosteum has been performed (Video 67.5).

The *endoscopic temporal lifting* is not a technique; it is only an additional (light) tool used to gain better visibility of what the surgeon is doing. The principles and the surgery are of course the same.

INCISIONS (FIGURE 67.6)

- In front of the hairline, inside the hair or both in some cases (particularly in multiple prior surgeries).
- Unique or multiple, depending on the estimated vectors (Figure 67.7).
- In fact, there is no rule, depending on which vector the patient has chosen and the surgeon's advice: nearly horizontal, slanted, more vertical, or a combined choice.
- The location of the temporal crest gives an idea of the kind of fixation we will need depending on the quality of the underlying tissues at the upper part of the scar: bone or temporal fascia?

SOME RULES TO BE EFFICIENT

- The lifting *mannequin* by excising a band of hair and suturing the two edges without any undermining causes bad scars (enlargement), loss of hair, and poor lasting results (huge damages and poor or no results).
- Superficial undermining (subcutaneous) must be extended enough down to the eyebrow and around the temporal

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

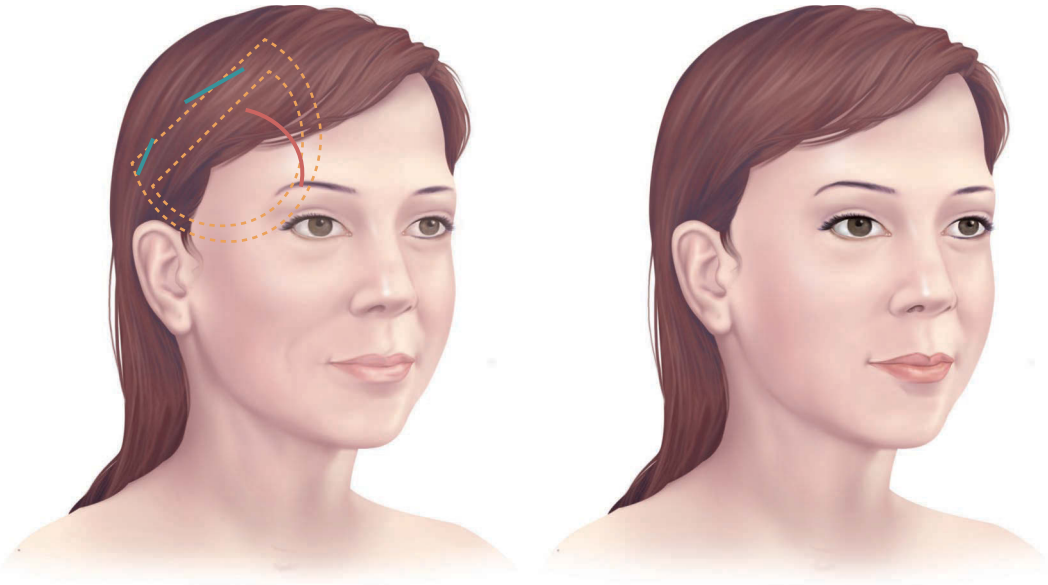


Figure 67.1 Underminings can be extended more or less, depending on which result we need.

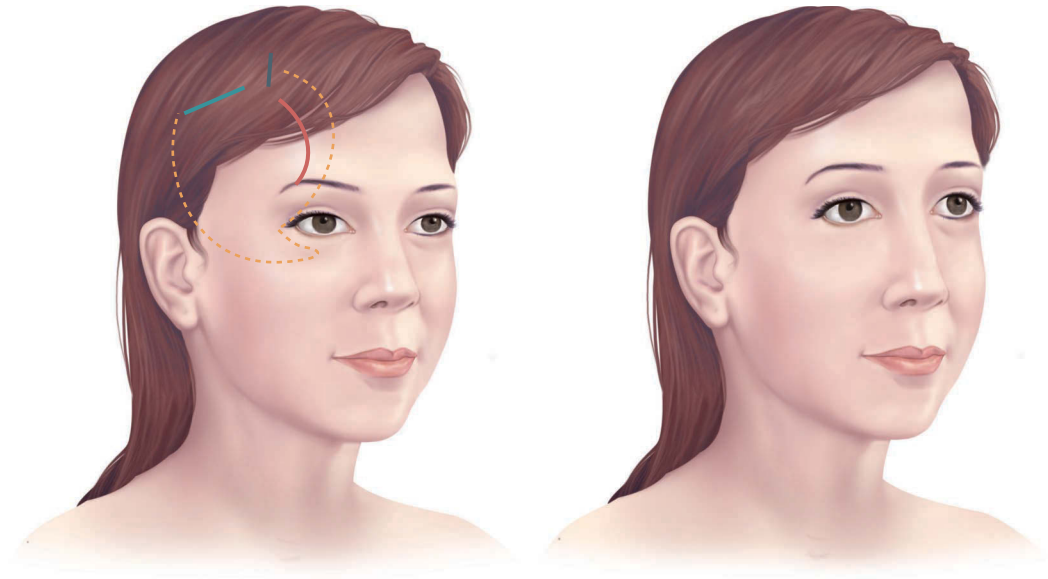


Figure 67.2 Deep or superficial extended undermining of the lateral cantus and the lower eyelid.

area and frontal area, which exposes fragile patients to the risk of necrosis (with or without hematomas).

- A deep plane cannot be efficient if all the periosteal attachments are released around the orbit, the zygomatic arch, and on the temporal crest, which induce a heavy postoperative period of 2–3 weeks!

INDICATIONS

A temporal lift can be performed alone or associated with a facelift: the separate incisions allow to respect the hairline and to avoid any hair removal.

The main difficulty is to appreciate the proportion of a true blepharochalasis and the degree of eyebrow ptosis.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

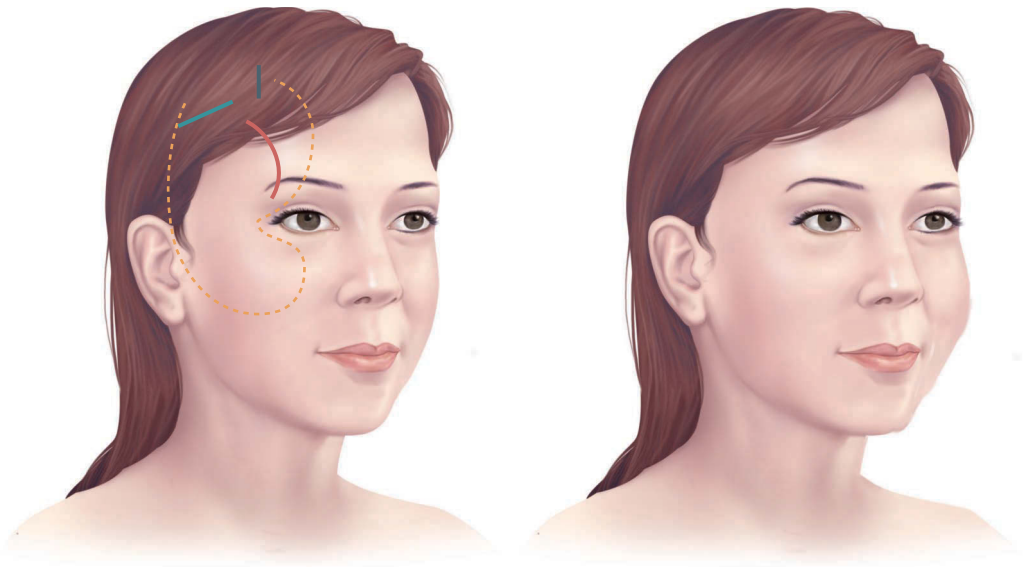


Figure 67.3 Deep (subperiosteal) extended undermining of the midface to produce a whole look and face rejuvenation.

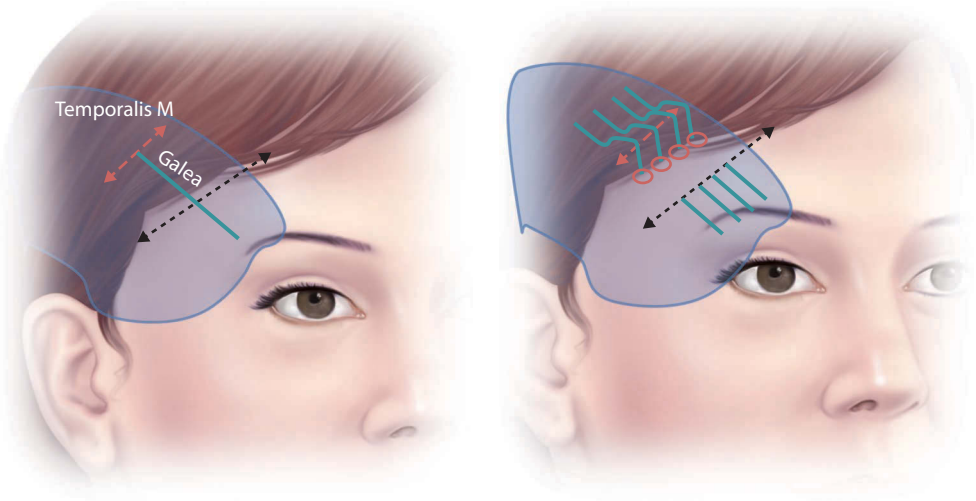


Figure 67.4 Biplane bayonet technique.

Figure 67.5 (a and b) Stitches from the galea to the deep temporal fascia. Notice the excess wave of tissues that is not removed.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

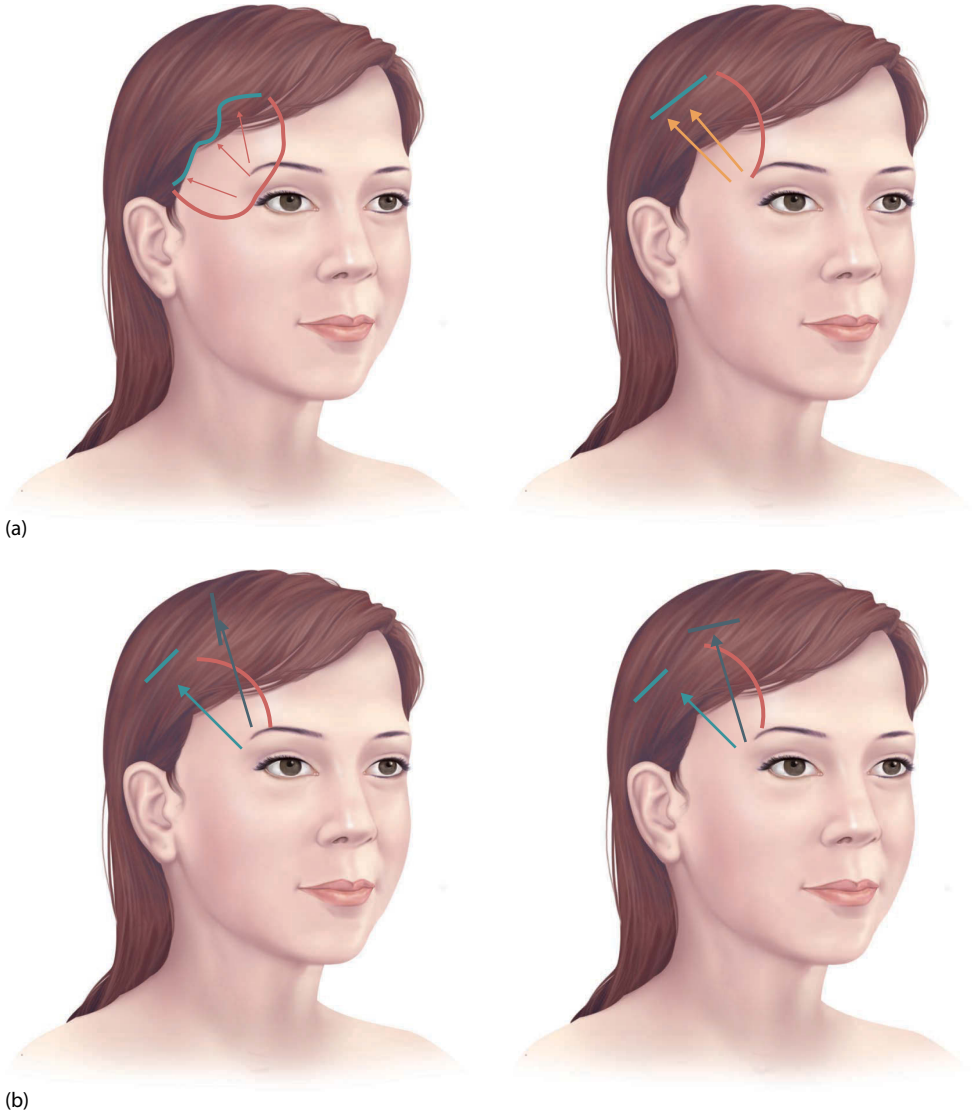


Figure 67.6 (a and b) Alternative incisions according with anatomic considerations and expected results.

For that, previous photos of the patient in its youth are the main mandatory documents in order to avoid identity destruction: Is there any sliding of the tail of the eyebrow or not?

Is the external blepharochalasis due to the descent of the eyebrow? If yes, the temporal lift is mainly indicated first.

Here are some results that we can obtain with a temporal lifting (Figures 67.8 through 67.12).

SYNTHESIS: CONCLUSION

We must keep in mind the dilemma of the temporal lifting.

The eyebrow is a *cutaneous* organ; thus, the only way to reach an efficient and permanent result should be a high cutaneous tension on the temporal skin, which means big subcutaneous undermining and an impressive resection of the skin (or the skin and hair).

That kind of technique, which is logical, can be efficient in particular cases of high temporal hairline and existing prehairline long scars and when prior surgery has been done with consequently loss of elasticity of the skin.

Unfortunately, in those cases, the risks of damages of the frontal nerve and necrosis must be kept in mind. This surgery becomes *a balance between the blood and nerve supply and beauty!*

The two deep or half-deep techniques (hair conservation) are less concerned by these risks but are more dependent on the negative effect of orbicularis contractions.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 67.7 (a and b) Wishes of the patient inducing the drawings of the main vector.

(a) (b)

Figure 67.8 (a) Before and (b) after an extended temporal lift.

The preoperative and permanent postoperative neutralization of this muscle with toxin is the logical key to guarantee a long-lasting result.

As usual a complete and exhaustive preoperative examination is necessary to make the best strategic choices as well as to comply with the patient's wishes (see Figure 67.7):

Vectors of elevation, which induce the localization of the scars to be effective
Quality of the hair and position of the hairline
Prior surgeries and scars that can modify the strategy
Localization of the temporal crest in order to know the kind of tissue on which fixation will be done (bone or deep temporal fascia)

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 67.9 (a) Before and (b) after extended deep temporal lift to the lateral cantus and orbital rim.

(a) (b)

Figure 67.10 (a) Before and (b) after an extended deep temporal lift.

(a) (b)

Figure 67.11 (a) Before and (b) after automatic inversion of the line of the eyebrow through a deep extended temporal lift.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 67.12 (a) Before and (b) impressive result of a deep subperiosteal lifting with huge midface undermining: rejuvenation of the face and aspect.

The choice of the undermining plane will depend on all these factors and, of course, on the patient's lifestyle (factors such as smoking).

We must always keep in mind that the temporal skin has a very poor blood supply compared to all the other areas of the face.

VIDEOS

Video 67.1. Useful subperiosteal undermining to get a good long-lasting result: http://goo.gl/XCZL1L

Video 67.2. Scar closing with staples (hair preservation): http://goo.gl/SdJaT3

Video 67.3. Bone fixation of stitches if Endotine device is not available: http://goo.gl/aaGy3s

Video 67.4. Fixation of the temporofrontal flap through the drilled bony tunnel: http://goo.gl/T7oNGY

Video 67.5. Fixation of the galea to the deep temporal fascia (for subperiosteal and bayonet technique): http://goo.gl/4zkNtG

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Surgical rejuvenation: Endoscopic brow lift

Henry Delmar

Repositioning the eyebrow is an integral part of periorbital rejuvenation.

Since the eyebrow is lower medially and/or laterally, there is a real excess of skin on the upper eyelids.

Endoscopic approach affords excellent exposure for release of periorbital adherences; myotomies and nerve preservation are facilitated through the magnification offered by the endoscope.

The operative sequence and considerations are shown in Video 68.1.

VIDEOS

Video 68.1. Endoscopic brow lift technique and result: http://goo.gl/avkr03

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Surgical rejuvenation: The midface lift

Henry Delmar

Since the first description of the masklift by Tessier [1] and Krastinova [2], there have been many proposals for lifting the middle third of the face. Because of this, its anatomy has gained an interest.

The functional and surgical anatomy of the middle third of the face brings out the specific features of this region, how it ages, and its suitable medical and surgical techniques.

The anatomical structures that make it up consist of deep and superficial fatty tissues and the facial muscles, which are sandwiched between the periosteum and skin. Each has a clearly defined function.

This chapter describes a modeling of aging that enables a detailed clinical approach and describes the treatment indications for the region.

The different surgical techniques are described, including low and high lifting, and their gingival or palpable approaches, implantable medical devices including sutures, and tensor threads are considered.

INTRODUCTION

The middle third of the face is an intuitively designed anatomical space, which is complex in its formation because of its anatomical features, some of which can be difficult to identify. Its anatomical architecture explains the changes that develop with aging, and its anatomical position, with many openings, gives it specific motor functions.

Aging of the middle third of the face that has the particular feature that lies next to the openings of the eye and mouth and aging of these openings, involving their own specific tissues, therefore interact with each other. This highlights the importance of taking a global look on facial aging and the approach to treatment.

This combined approach of descriptive anatomy [3–7], functional anatomy [8,9], tissue aging [10], and morphology forms the bases on which we will base a morphological modeling of aging of the middle third of the face. This modeling is a prerequisite to any decision about medical or surgical treatment.

Leaving skin traction aside and excluding liposculpture and mini- or noninvasive procedures, techniques for cheek lifting have been developed: low, high, high-tension, and combined lifting and lifting restricted to an aesthetic unit and by suture, tensor threads, or other implantable devices.

A detailed study of the principles of each of these will provide ideas about how they act and, therefore, enable the most appropriate technique for a given patient being chosen.

Using this more detailed approach to aging of the face, this process will allow us to achieve more natural results.

ANATOMY

Definition

The middle third of the face is defined arbitrarily by a superior horizontal line passing through the external canthus, separating it from the superior third, and by an inferior horizontal line, passing through the labial commissure, separating it from the lower third, the lower limit being the vertical midline of the face. The external limit is vertical, passing through the tragus. Our description of the middle third of the face will be restricted to a narrower region. The cephalic region is defined by the upper edge of the zygomatic arch and by a line passing through the canthi, including the lower eyelid, and the medial border, which is the lateral edge of the nose and the nasolabial fold to the labial commissure. The caudal limit returns to the tragus, which is the lateral border (Figure 69.1).

Units

The middle third of the face is conventionally divided into three subregions:

1. The malar region
2. The zygomatic region
3. The orbital region (Figure 69.2a)

The orbital region is located above the malar region and is delineated by the "palpable malar fold" that separates it from the lower eyelid against the orbicularis retaining ligament (ORL).

The malar region has three units that can be identified by their fixed points and retaining ligaments (Figure 69.2b):

1. "The nasolabial unit" is located above and parallel to its fold (also called the nasolabial protrusion that is delineated superiorly by the infraorbital ring).
2. "The lateral malar unit" is located against the malar eminence and is delineated laterally by the zygomatic region.
3. "The median malar unit" lies between these two spaces and is the classical "valley of tears." This triangular space takes on the shape of the underlying maxillomalar depression.

The nasolabial and median malar units are delineated by the facial vein. Its skin landmark is a line connecting the middle of the mandibular return and the medial canthus. This landmark is used to avoid injuries to the facial vein when needle injections are administered in the region.

The compartmentalization of the cheek is useful therapeutically as bolus injection of filler into each unit produces expansion that is restricted to the unit in question.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

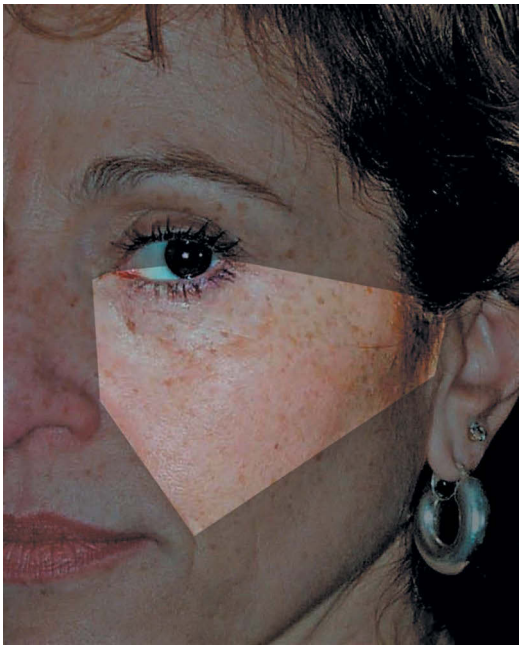


Figure 69.1 Schematic definition of the middle third of the face. The middle third of the face is an anatomical structure of two orientations: lateral and medial.

Anatomical Structures

The stratification of tissue structures in the middle third of the face is related to the embryonic expansion of the infraorbital part of the second brachial arch. This is no longer followed after the concentric convergence of the embryonic buds, which applies to the malar region, the area where the embryonic structures around the facial openings converge.

Generally, the tissue stratification in the malar region follows the same logical bases as everywhere else in the body, with the five basic layers:

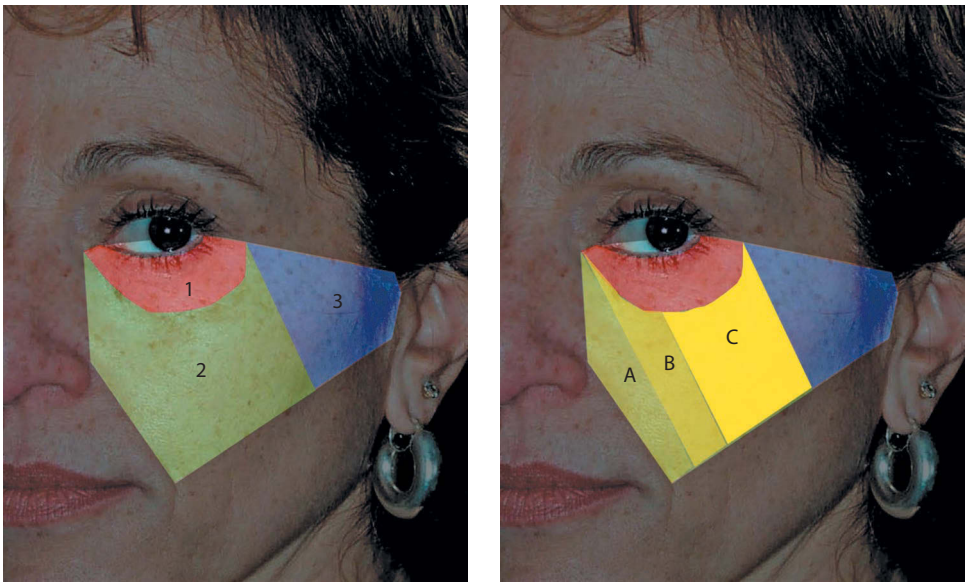
1. The skin
2. The superficial malar fat pad
3. The superficial or musculoaponeurotic fascia
4. The deep malar fat pad
5. The periosteum or muscular aponeurosis

Skeleton and Deep Muscles

The anterior surface of the skeleton of the cheek (Figure 69.3) contains the insertions for many muscle, ligament, and fat structures.

The inferior orbital border does not project uniformly. It contains the attachment for the arcus marginalis and preseptal muscle fibers of the orbicularis oculi muscle (OOM).

The convex area of the body of the zygoma has attachments for the muscles and ligaments of tissues that cover it. Caudally and medially, it has attachments for the quadratus



(a) (b)

Figure 69.2 (a) The regions of the middle third. The middle third of the face is composed of orbital mediocephalic part (1), medial malar portion (2), and a zygomatic lateral malar portion (3). (b) The malar region present describes three identifiable units per their fixed points and retaining ligaments: the nasolabial unit situated above and parallel to the fold (also called nasolabial groove) is limited cephalically by the palpebromalar fold (A), the lateral malar unit is situated next to the eminence malar and limited laterally by the zygomatic area (C), and the median unit malar is placed between these two areas and responds to the classic valley of tears in the aging process (B).

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

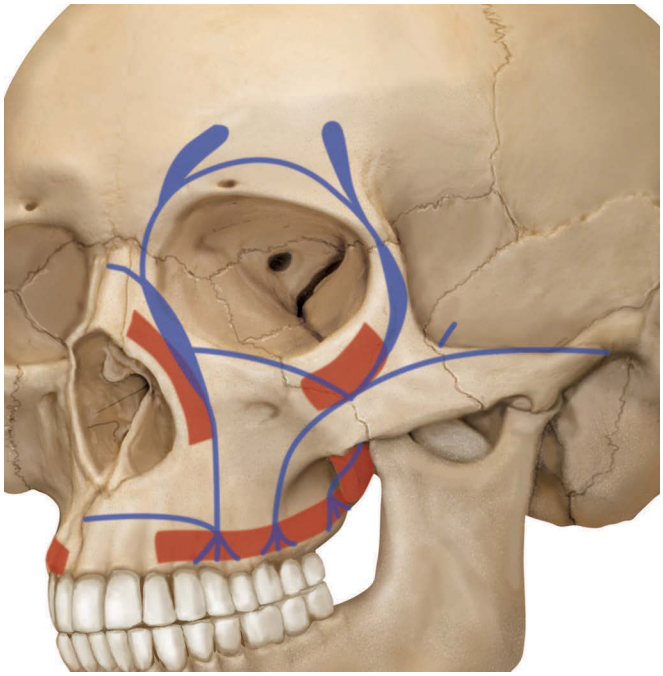


Figure 69.3 Forces supported by the maxillozygomatic skeleton. Sicher's pillars (shown in blue) are vertical and include the three pillars: pillar canine, malar pillar, and pillar pterygoid. Ombredanne's beams (shown in red) offer horizontal resistance of lower, middle, and upper pillars supporting Sicher's pillars. This bony architecture is likely to absorb vertical and horizontal forces and to oppose all mechanical stresses by creating a damping and stabilization system.

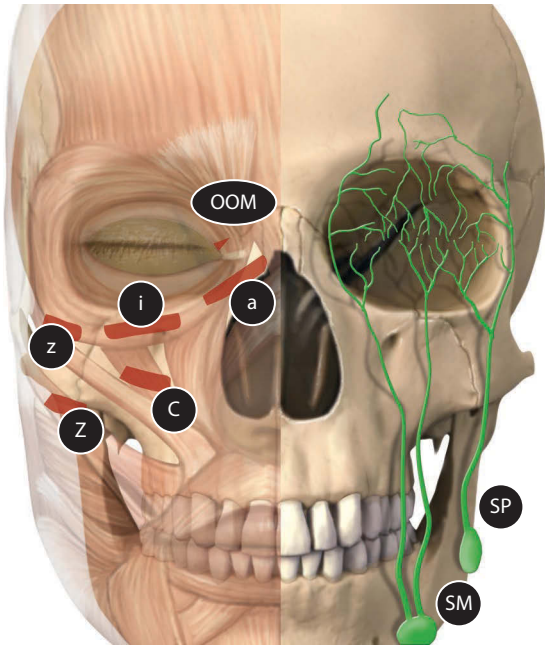


Figure 69.4 Diagram of the malar muscular insertions to the skeleton and the orbital lymphatic drainage. On the left, the bony insertions: the quadratus labii superioris (QLS) muscle is composed of three chefs—the angular muscle (a) that sends fibers to the nose wing and orbicularis oris muscle, the infraorbital muscle (i) that extends over the upper lip, and the zygomatic muscle (z) that is inserted laterally to the upper lip. The caninus muscle (C) and the zygomaticus muscle (Z) are moving toward the labial commissure. Above, the attachment of the orbicularis oculi muscle (OOM). On the right, double lymphatic network of the orbit passing through the parotid gland (SP) and the submaxillar node (SM).

labii superioris (QLS) and caninus muscles [11] (Figure 69.4). The QLS is made up of three bundles:

1. The angular bundle (levator labii superioris alaeque nasi muscle) that has fibers running to the wing of the nose and orbicularis oris muscle
2. The infraorbital bundle (QLS muscle) that extends over the upper lips between the angular bundle and the caninus muscle
3. The zygomatic bundle (levator anguli oris muscle) that inserts laterally onto the upper lip

The caninus and zygomaticus muscles run to the labial commissure. To recall, the zygomaticus minor muscle is considered to be an expansion of the OOM.

While most people understand the progressive expansion of the facial skeleton with aging, the expansion of the maxilla raises more conceptual problems. The maxilla undoubtedly loses height and projection [12] beneath the orbital border, although there are differences in opinion about the inferointernal part of the orbital border: according to Pessa et al. [13], the orbital arcade recedes, whereas Bartlett et al. [5] and Mendelson et al. [14] believe that the length of the inferior orbital cone does not change in, but relative expansion of the middle third occurs, with a slight increase in facial width, depth, and bony protrusions.

In summary, therefore, it is accepted that the facial skeleton is a dynamic structure and that these structural changes lead to morphological changes in the face.

Herein lies the importance of the clinical study of the malar vector.

It is

- One of the morphological components of the orbital region
- A predictor of the method of aging
- A source of problems or complications in inferior blepharoplasty and malar lifting

A vector is positive if the projection of the anterior point of the cheek, seen laterally, lies in front of the most anterior corneal point. Otherwise, it is negative (in which case it reflects inferior orbital recession).

Loss of projection of the bone and tissues covering it with aging reduces the vector. Similarly, recession of the edge of the inferior orbit (the negative pillar) is not really solved by manipulating soft tissues, but rather by an effect on the bone.

Superficial Planes of the Middle Third of the Face

Facial Muscles

These muscles are innervated by the facial nerve and are stratified into four layers according to Freilinger [15] and into five embryological layers:

- Layer 1: Risorius, platysma, and OOMs
- Layer 2: Depressor angularis oris muscle and the zygomatic bundle of the QLS

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

- Layer 3: Depressor labii inferioris, zygomaticus muscle, and the angular bundle of the QLS
- Layer 4: Orbicularis oris muscle and the infraorbital bundle of the QLS
- Layer 5: Mentalis muscle, caniculus muscle, and buccinator muscle

Orbicularis Oculi Muscle

The OOM of the inferior eyelid is divided into three concentric portions: the superficial portion is tarsal, the middle is septal, and the inferior is orbital. Each portion is notable by the thickness of the muscle that constitutes it.

The orbicular portion is a thick sheet that occupies two-thirds of the malar region (Figure 69.5).

Fatty Tissues

There are two fatty tissue planes in the cheek, one deep and the other superficial.

The deep fatty tissue comprises the following (Figure 69.6 through 69.8):

- The *deep malar fat pad* (*Delmar*[8]) or suborbicularis oculi fat (SOOF) pad (Aiache [16]), which is a infraorbicular fatty plane that adheres tightly to the periosteum (Figure 69.6) and contains fibrous bands that makes it denser than the superficial layer. It is delineated cranially by the ORL and disappears in the cheek in contact with the buccal expansion of Bichat's fat pad.
- The *orbital fat compartment* is thin and located above the ORL in the orbital area. It disappears with age, explaining the circle beneath the eyes.

The *superficial malar fat pad* is subcutaneous and is a very thick, wide sheet of fat that is compartmentalized as described earlier.

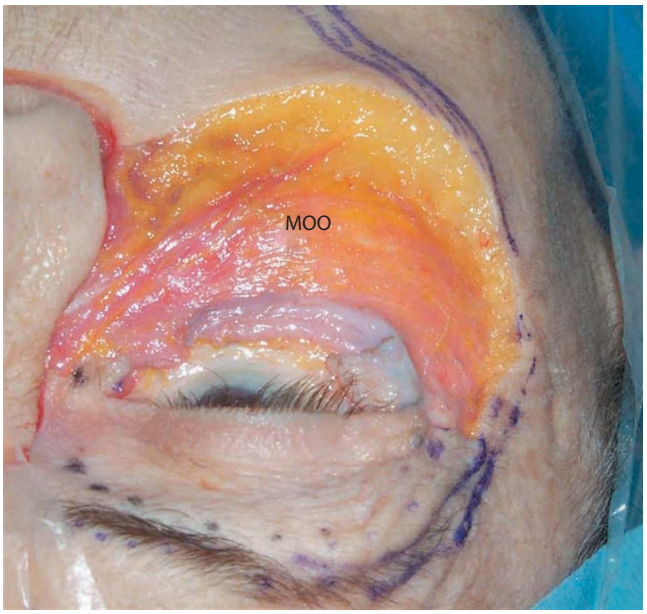


Figure 69.5 Dissection of the malar region. The orbicularis oculi muscle (OOM) occupies most of the malar region. There are many expansions of subcutaneous muscle as the OM.

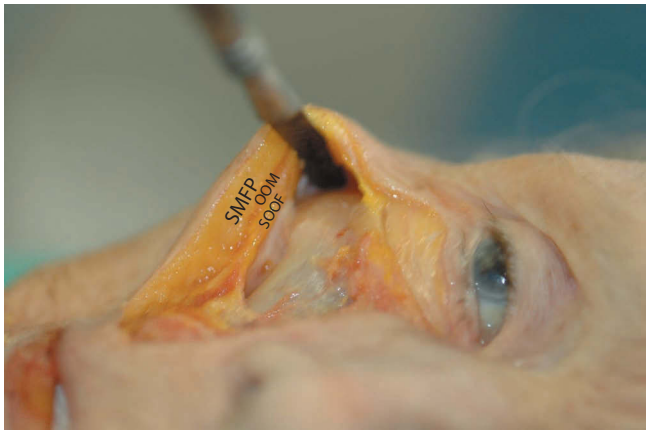


Figure 69.6 Dissection of the malar area. The suborbicularis oculi fat (SOOF) pad is the layer of deep malar fat pad that is interposed between the maxillozygomatic periosteum and the OOM. It surrounds the quadratus labii superioris and caninus muscles. Its function is an intermuscular syssarcosis. The superficial malar fat pad (SMFP), compartmentalized, plays a role as a pad in between the facial orifices, as in mimicry, in oral prehension.

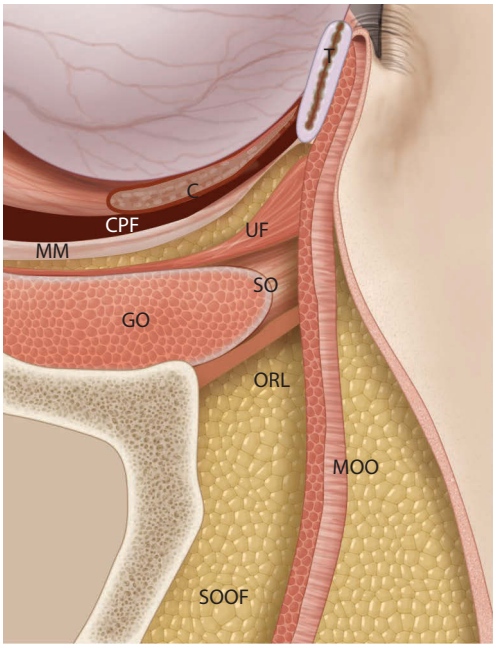
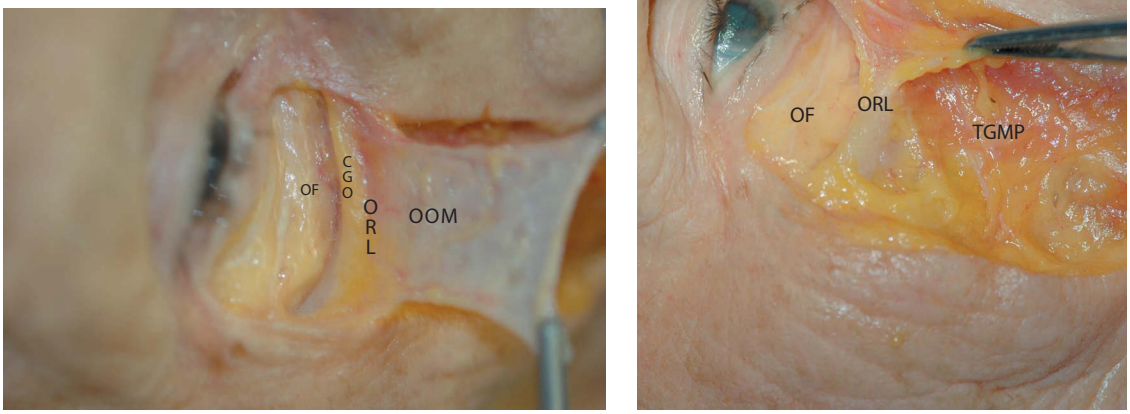


Figure 69.7 Vertical view of the lower eyelid. CPF, capsulopalpebral fascia; T, tarsus; MM, muscle Muller; C, conjunctiva; RC, retinaculi cutis; UF, upper fascia; SO, orbital septum; ORL, orbicularis retaining ligament; GO, orbital fat; CGO, orbital fat compartment.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b)

Figure 69.8 Anatomical dissection of the infraorbital area. (a) OF, orbital fat; CGO, orbital fat compartment; ORL, orbicularis retaining ligament; OOM, orbicularis oculi muscle. (b) TGMP, deep malar fat pad or suborbicularis oculi fat (SOOF) pad.

Supporting Fascia and Ligaments of the Middle Third

- The ORL arises slightly beneath the arcus marginalis and lower part of the orbital periosteum. This also plays a supportive role for the orbital portion of the OOM of the lower eyelid (Figure 69.9).
- The zygomatico-cutaneous ligament, described initially by Pessa, is delineated by the so-called "malar bag" described earlier [17,18].
- The Furnas supporting ligament, described later by Stuzin [19], is an area of convergence and fusion of the septa that is extremely tight at its bony origin and spreads out like the branches of a tree beneath the dermis.

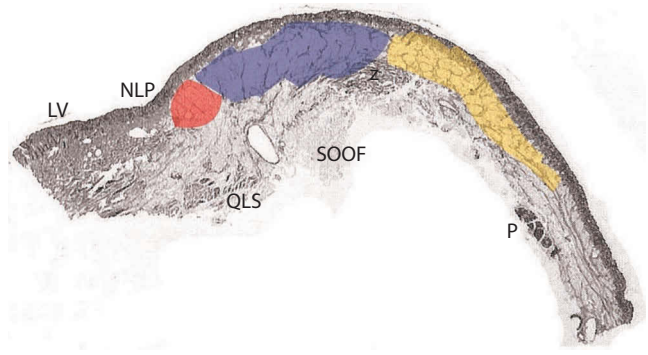


Figure 69.9 Horizontal histological section through the upper lip just below the nose. LV, upper lip; NLP, nasolabial fold; Z, zygomaticus muscle; P, parotid; QLS, quadratus labii superioris muscle; SOOF, suborbicularis oculi fat pad. In red, the nasolabial compartment. In blue, malar compartment. In yellow, the lateral temporojugal compartment.

The planes are superimposed on each other with looser or tighter areas of attachment. There are no shear planes but, instead, places where detachment is present.

This stratified organization of the successive layers is consistent throughout the middle third of the face apart from two areas:

1. The OOM, which has a bony insertion. This is not generally the case with a superficial muscle.
2. There is no fascia superficialis delineating the superficial from deep fat inside and beneath the zygomaticus muscle (Figure 69.10).

The three portions of the OOM have three functions: the tarsal portion has a lachrymal function, the septal portion has an occlusion function, and the orbital portion has a concentric function for the surrounding tissues, particularly in the inferior part, in order to raise the pommette. The OOM is mobile but also has tight attachments through the ORL and various fixed points.

In addition, the fixed palpable and nasal openings contrast with the considerable mobility of the mouth. In order to meet this anatomical and functional challenge, the zygomatic region is structured like a buffer zone with tissues of varying elasticity and mobility, made up of the superficial malar fat pad. Motor interdependency of the structures around the orifices, therefore, permits the different primary and secondary functions, such as the features of the face and changes in facial expression as it was described by Delmar [8].

AGING

The conclusions of the work carried out by Val Lambros [10] are explained by the presence of supporting ligaments in the face: during aging, the facial tissues do not migrate but, rather, the superficial structures become more mobile against the bone.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

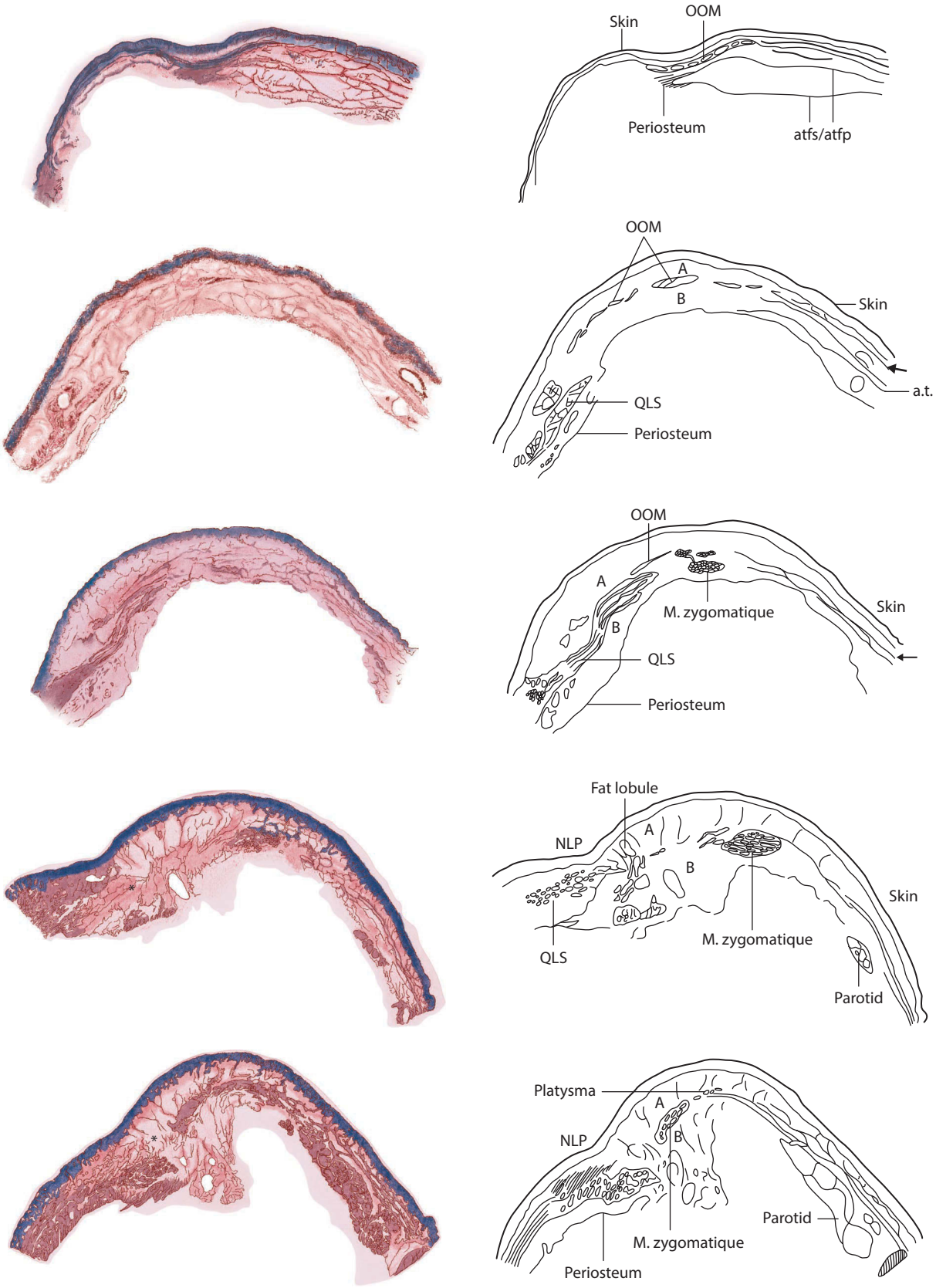


Figure 69.10 Histological horizontal cross view stepped in between the lower eyelid and upper lip (top to bottom). Deep fat is in continuity with the superficial fat: there is no any gliding space. QLS, quadratus labii superioris muscle; A, superficial malar fat pad; B, deep malar fat pad; atfs, deep layer of deep temporal fascia; atfp, superficial layer of deep temporal fascia.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Lambros' clinical findings confirm that the skin in the malar region is displaced slightly on standing with aging. Conversely, the morphological changes seen in aging are due to aging of cells and tissues and the resulting cascade of changes such as abnormalities of muscle balance and bone erosions, etc.

Is the term erosion correct? Is this wear or use? It is difficult to answer this without taking sides. It is conventionally considered that bone is subject to wear, whereas tissue structures change biologically. It is possible that repeated forces on some structures such as bone may lead to structural changes. Morphological modeling of aging, biomechanics, and biology are clearly future approaches to understand aging of the face and neck, particularly the middle third of the face.

Morphologically, what is seen is a series of waves, from above downward:

- An extraorbital wave involving the inferior orbital fatty pouches that form the *palpable pouches*
- The *malar pouch* through tissue distension and lymphatic dysfunction cranially delineating the suborbital ring and orbitopalpebral fold
- The *philtral ridge* separated from the above by the valley of tears and from upper lip by the nasolabial fold

These changes are influenced by the overall facial volume that follows the contour of the skeleton, becoming thinner and flatter. While a third of these waves are due to overweight, it is more difficult to work out the origin of the first two. For this reason, we propose to model the morphological aging of the face based on a number of clinical signs [20]. The inferior orbital ring and valley of tears form a more or less lateralized trace, depending on the volume of the face, creating a **Y** in aging as a result of skeletalization, a **λ** (lambda layer) in sagging, and a **U** in heaviness.

- *Model 1: Skeletonization (Figure 69.11).* The overall volume of the face becomes less than it was in young adults, lines are hollowed out, and the waves described earlier are pronounced. Wrinkles are often deep.

  Clinical signs: The Y sign, deep medialized valley of tears, and hollowed-out cheeks (Figure 69.14a).
- *Model 2: Sagging (Figure 69.12).* Overall facial volume is equivalent to that in a young adult; the face becomes heavier with tissue sagging and imbalance of width between the upper and middle third. The waves are less pronounced.

  Clinical signs: The λ sign, the valley of tears, is lateralized by the malar volume, and the cheeks are full (Figure 69.14b).
- *Model 3: Heaviness (Figure 69.13).* The face is full and round. Wrinkles are rarer. The eyelids appear hollower because of inflation of the face.

  Clinical signs: The U sign due to hollowing out of the infraorbital ring and filling of the cheek and cheek (Figure 69.14c).

SURGICAL TECHNIQUES

Regardless of surgical technique, the principle is one of more or less vertically raising both the deep and superficial malar fat pads.

Lifting is known as *low malar lifting* when the tissue traction is applied to the lower part of the cheek beneath the maximal anterior project point of the pommette.

Figure 69.11 Model 1: skeletonization. The overall volume of the face becomes less than it was in young adults, lines are hollowed out, and the waves described above are pronounced. Wrinkles are often deep.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 69.12 Model 2: sagging. Overall facial volume is equivalent to that in a young adult, and the face becomes heavier with tissue sagging and imbalance of width between the upper and middle third. The waves are less pronounced.

It is known as *upper malar lifting* when the tissue traction is applied to the upper part of the pommette, above the maximal anterior project point of the pommette.

How do we define the maximum projection of the pommette? This is a segment of a line passing through the middle of the line connecting the labial commissure to the external canthus, parallel to a line connecting the labial commissure to the tragus. The three malar bolus points are located along this line (Figure 69.15).

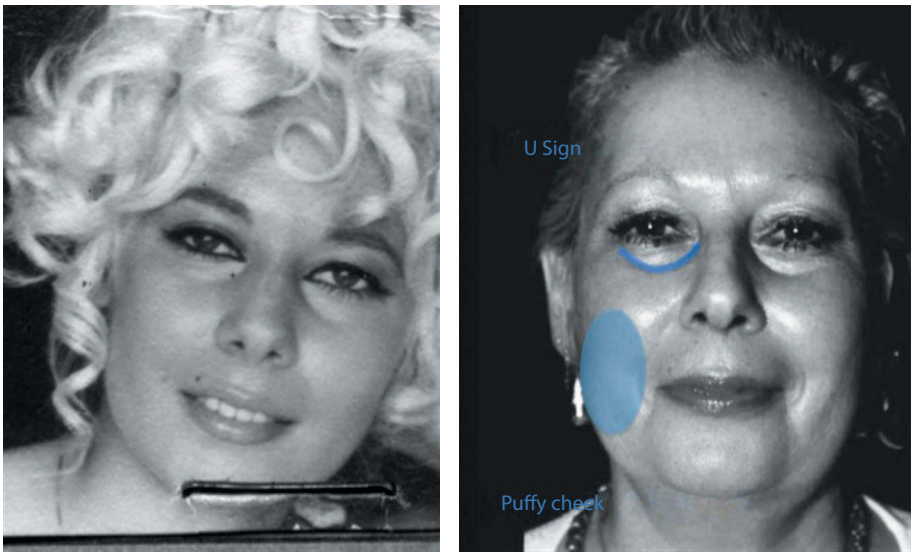
Low malar lifting raises the deep tissue, which has a limited effect on the skin, whereas high malar lifting has a greater effect on skin traction. While the former produces limited

Figure 69.13 Model 3: heaviness. The face is full and round. Wrinkles are rarer. The eyelids appear hollower because of inflation of the face.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a)

(b)



(c)

Figure 69.14 (a) Model 1: skeletonization. Clinical signs: the Y sign, deep medialized valley of tears, and hollowed-out cheeks. (b) Model 2: sagging clinical signs—the λ sign, the valley of tears, is lateralized by the malar volume, and the cheeks are full. (c) Model 3: heaviness clinical signs—the U sign due to hollowing out of the infraorbital ring and the puffy cheek.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

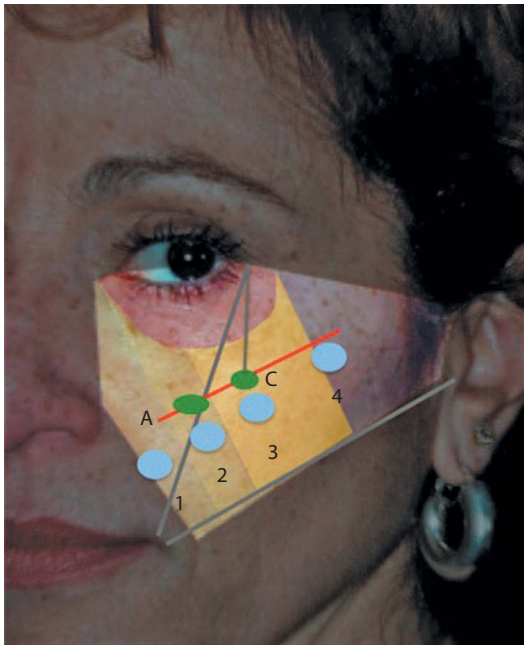


Figure 69.15 The maximum projection of the pommette. Points 1–4 design the location of the suture of the low suspension.

recruitment of the inferior palpable skin, more recruitment occurs with the latter. The amount of inferior palpable skin resection depends on this effect and is greater with a high malar lift.

Surgical Approach

There are many surgical approaches, although we will consider the two main ones: the gingival approach and the palpable approach.

Gingival Approach

This involves a vertical incision, a centimeter in length (Video 69.1), along the superior gingival sulcus next to the first premolar. It penetrates to the maxillary periosteum allowing the maxillary and zygomatic subperiosteum to be detached. It is essential to visually check the infraorbital pedicle. The detachment limits are the piriform sinus internally, the insertion of the masseter externally, and the inferior orbital border above (Video 69.2).

Palpable Approach

This allows an inferior blepharoplasty to be performed at the same time, although the approach may be limited to a centimeter incision next to the external orbital border, masked in a crow's foot line (Figure 69.16a and b).

The area of subperiosteal detachment is slightly different: the inferior and lateral edge of the orbit and zygomatic apophysis can be checked better, although detachment of the maxilla–malar belt is more difficult. This requires a curved hooked retractor to avoid fracturing the periosteum (Figure 69.16c and d).

Regardless of the surgical approach used, it is essential to release the cheek tissues, in order to allow it to be raised and effectively fixed. If it is not easy to displace it by vertical traction on the cheek with a hooked retractor, this is because the detachment is insufficient.

Implantable Medical Devices

The challenges for this technique are fixation and a long-lasting result.

Sutures

These are the prerogative of the palpable approach. The purse string sutures described by Delmar and Trepsat [21] via a gingival approach carry a high risk of superinfection, and this technique is, therefore, no longer used.

The sutures pass through a bony tunnel created in the inferior and lateral orbital border.

One or two tunnels are created, the number and site of which depend on the axis of traction, using a 1.5 drill bit or reamer, after detaching the intraorbital periosteum of the orbital floor and the lateral wall of the periosteum (Figure 69.16e and f).

Three sutures are generally used in order to lift the lower part of the nasolabial and medial malar units, the upper part of the lateral malar unit, and occasionally the orbital region (Figure 69.17a).

The axis of traction of the first two of these sutures is vertical, whereas the third is oblique, internally and upward. It differs from the description by Le Louarn [9] in that vertical rather than concentric traction is desired.

The purse string tightens the full thickness of the deep and superficial malar fatty tissues (Figure 69.17b and d).

Recommendations: Do not overcorrect; do not accept the slightest hollow or the slightest asymmetry. I, therefore, suggest that each stage of the procedure is performed bilaterally before moving to the next stage.

Specific features: The decision is taken to raise the OOM (high malar lift) if traction on the pommette skin is desired.

Inferior palpable skin resection: This resection depends on the site of the suture and traction forces involved. Greater skin resection is required with higher and tighter sutures, although postoperative morbidity is greater: slower healing, chemosis, ectropion, asymmetry, and dysfunction of the periorbital facial features.

Tension Threads and Other Implanted Medical Devices

Tension or conical threads are useful in malar lifting if the procedure is combined with subperiosteal detachment (Video 69.3). The primary approach is gingival. After completing the detachment, the gingival incision is sutured (Video 69.4). The tension threads are inserted from externally away from the detachment area into the deeper superficial malar fatty tissues. Several sutures are inserted depending on the desired traction axes (Videos 69.5 through 69.7).

Disadvantages: The tension or cone maintaining forces are insufficient if postoperative edema occurs and may lead to "detachments" and poor results. Alternatively, the cones may be resorbed and lose their effect.

The length of the result relies on healing of the bone periosteum: when the tissues become loose, the malar lift loosens secondarily.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

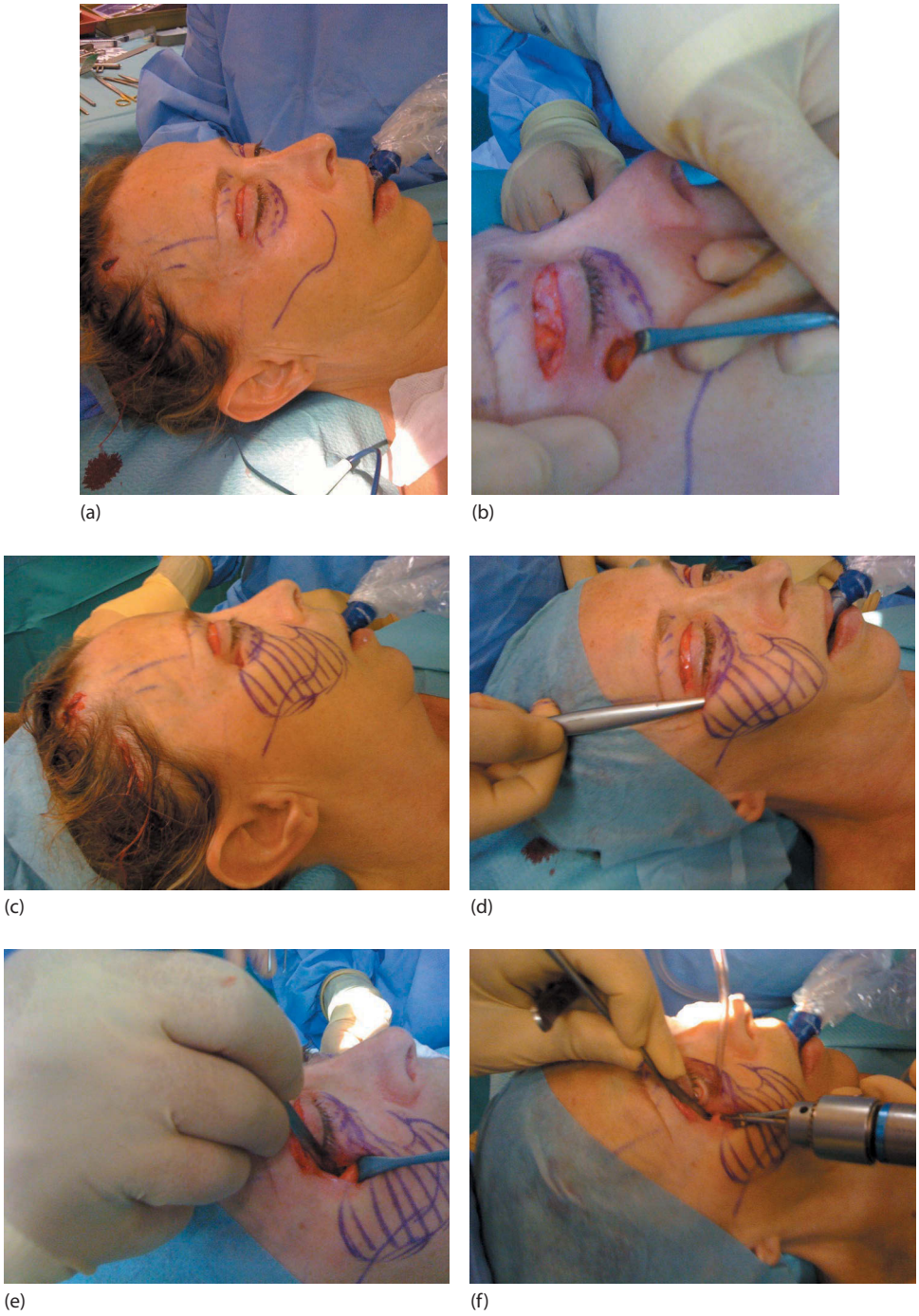


Figure 69.16 Technique of high malar suspension. (a) Marks, (b) incisions and incision of the OOM, (c) marks of subperiostal dissection, (d) complete maxillozygomatic subperiostal dissection, (e) infraorbital rim dissection, and (f) bone tunnel.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

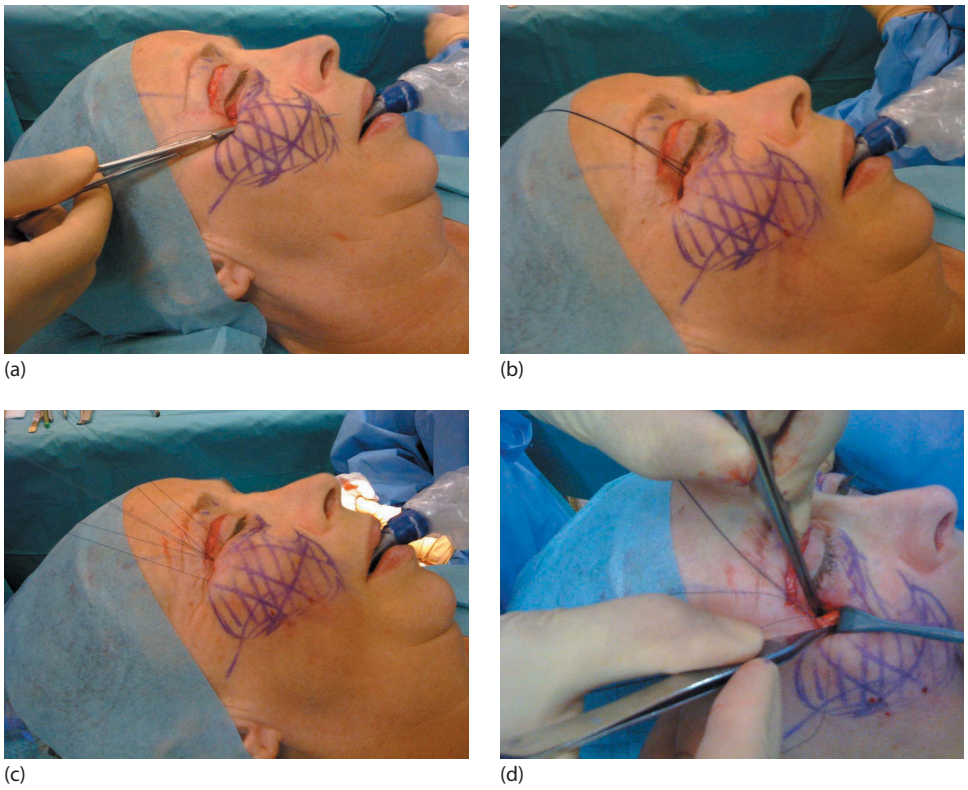


Figure 69.17 Fixation of high malar suspension. (a) Nasolabial groove suspension, (b) 3 threads, (c) + OOM suspension, and (d) fixation to the tunnels.

INDICATIONS

Thanks to the model of morphological aging process, a program of treatment is proposed:

- *Model 1: Skeletonization*. The full-face lipofeeling combined with a face and neck lift is advisable.
- *Model 2: Sagging*. In this model, the midface lift finds its major indication. This suspension can be combined with a face and neck lift and sometime with a partial lipofeeling.
- *Model 3: Heaviness*. Malar suspension can be advised if the middle third of the face is ptotic.

SIDE EFFECTS AND COMPLICATIONS

The postoperative course depends on how aggressive the procedure has been, with respect to the anatomical planes, and the traction force applied to the tissues.

Periorbital edema, chemosis, and static palpable problems depend on the clinical situation and operation plane (Figure 69.18).

The clinical situation depends on the malar vector, frontal and transverse loosening of the inferior tarsus, history of eyelid surgery, and abnormalities of tear secretion.

Postoperative problems can be more frequent and serious if the procedure involves dissection of the septal bundle of the OOM, mobilizes the lateral canthus, or creates tension and with lifts of the lateral canthal MMO.

Asymmetries are due to preexisting asymmetries in the patient and liftings along their axes and their positioning and traction.

The following complications were found from a retrospective a study of 643 patients between 1993 and 2012:

- Hematomas were extremely rare (1 case out of 643 patients).
- Infections (2 cases out of 643 patients). Superinfection of lifting sutures using the gingival approach.
- The main complication was ectropion. This is very often transient (18% of cases) and is worsened by the weight of malar edema, which is contained by adhesive bands. Persistent ectropion raises the problem of repair. Eleven cases of scleral show and ectropion. This complication can be avoided by patient selection and nonaggressive surgery (Figure 69.19).
- Nerve damage:
  - Loss of sensation in the upper hemi-lip as a result of dividing the infraorbital pedicle is extremely rare (1 case from the gingival approach out of 643 patients); this developed during my learning experience in 1993.
  - Zygomatic dysesthesia is occasionally reported by patients, whereas division of the temporomalar sensory nerve is very common.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 69.18 (a) Postoperative situation after 6 days and (b) after 12 days.

Figure 69.19 Skin lower eyelid resection.

DISCUSSION

Lifting of the middle third of the face redistributes the tissues of the cheek, supports the lower eyelid, and corrects the round eye by strengthening the malar pillar.

It has no effect on the inferior third. Upper malar lifting leads to accumulation of tissue in the lateral orbital region that then need work to be done on the temporal region.

It has no therapeutic equivalent. "Vertical" zygomatic lifting through the face and neck lifting approach, whether performed using a purse string or high SMAS flap, can only be done obliquely. This has no effect on the periorbital area.

Indications should take account of the model of morphological aging and malar vector.

An overview of the treatment is given in Table 69.1.

CLINICAL CASES

The clinical cases are demonstrated in Figures 69.20 through 69.29.

Table 69.1 Overview of Treatment

	Negative malar vector	0 Malar vector	Positive malar vector
Skeletalization	LS +++	LS ++	LS valley of tears
Sagging	ML + LS (depending on orbital recession)	ML	ML
Heaviness	/	/	/

Note: The infraorbital ring is not included in this treatment overview. "/" indicates "no suggestion."
Abbreviations: LS, liposculpture; ML, malar lifting.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Figure 69.20 Endoscopic brow lift + upper and lower blepharoplasties + midface lift high suspension + face and neck lift with submental plication. (a) Young (27 years; left) and aging picture (58 years; right), (b, c) before (left) and after 7 months (right).

Figure 69.21 Endoscopic brow lift + upper and lower blepharoplasties + midface lift high suspension + face and neck lift with submental plication + lipostructure. (a, b) Before (left) and after 9 months (right).

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a) (b)

Figure 69.22 Endoscopic brow lift + upper and lower blepharoplasties + midface lift high suspension + face and neck lift + lipostructure. (a, b) Before (left) and after 6 months (right).

(a) (b)

Figure 69.23 Endoscopic brow lift + upper and lower blepharoplasties + midface lift high suspension + face and neck lift + lipostructure. (a) Young (26 years; left) and aging picture (56 years; right). (b) Before (left) and after 8 months (right).

(a) (b)

Figure 69.24 Endoscopic temporal lift + upper and lower blepharoplasties (Muller resection) + midface lift high suspension + face and neck lift with submental plication +lipostructure. (a, b) Before (left) and after 8 months (right).

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a)

(b)

Figure 69.25 Endoscopic temporal lift + lower blepharoplasties + midface lift low suspension + face + lipostructure. (a, b) Before (left) and after 12 months (right). TE, temporal endoscopy; LS, lipostructure; SB, superior blepharoplasty; IB, inferior blepharoplasty.

Figure 69.26 Endoscopic temporal lift + upper blepharoplasties + midface lift low suspension + face and neck lift + lipostructure. Before (left) and after 6 months (right). LS, lipostructure; SB, superior blepharoplasty; IB, inferior blepharoplasty; FE, frontal endoscopy; face, facelift.

Figure 69.27 Endoscopic brow lift + upper and lower blepharoplasties + midface lift low suspension + face and neck lift + lipostructure. Before (left) and after 7 months (right).

Figure 69.28 Upper blepharoplasties + midface lift low suspension + face and neck lift + lipostructure. Before (left) and after 6 months (right). TE, temporal endoscopy; LS, lipostructure; SB, superior blepharoplasty.

Figure 69.29 Endoscopic brow lift + midface lift low suspension + face and neck lift + lipostructure. Before (left) and after 7 months (right).

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

CONCLUSIONS

Lifting of the middle third, malar lifting, or vertical lifting is a necessary part of the surgical armamentarium for facial rejuvenation. It positions the cheek in a higher position and distributes the periorbital tissue.

Its anatomy is subtle because of the many tissue layers that make it up and the interactive function between the eyelids and lips.

Facial aging is modeled morphologically as skeletalization, sagging, and heaviness.

Lifting of the middle third is particularly appropriate in sagging.

It is a method with predictable results and low morbidity when the principles of detachment and traction are followed.

VIDEOS

Video 69.1. Buccal incision: vertical along the gingival sulcus: http://goo.gl/kpE8Al

Video 69.2. Subperiosteal dissection of the maxilla and the zygoma: http://goo.gl/BWlo18

Video 69.3. Suture of the incision: http://goo.gl/s29J2V

Video 69.4. Temporal subgaleal dissection: http://goo.gl/mCtMPN

Video 69.5. Insertion of barbed threats in malar area: http://goo.gl/TjDkiB

Video 69.6. Insertion of barbed threats: http://goo.gl/VOrQ1n

Video 69.7. Fixation of tissues to the thread: http://goo.gl/fVsajW

REFERENCES

1. Tessier P. Le lifting facial sous-périosté. *Ann Chir Plast Esthet* 1988; 34:193.
2. Krastinova D. Le lifting facial sous-périosté. *Ann Chir Plast Esthet* 1989; 34:199.
3. Pessa JE, Zadoo VP, Adrian EK, Woodwards R, Garza JR. Anatomy of a "black eye": A newly described fascial system of the lower eyelid. *Clin Anat* 1998; 11:157–161.
4. Mendelson BC, Jacobson SR. Surgical anatomy of the midcheek: Facial layers, spaces and the midcheek segments. *Clin Plast Surg* 2008; 35:395–404.
5. Bartlett SP, Grossman R, Whitaker LA. Age-related changes of the craniofacial skeleton: An anthropometric and histologic analysis. *Plast Reconstr Surg* 1992; 90:592–600.
6. Iwanami M, Tsurukiri K. Histological comparison between young and aged specimens of the oriental lower eyelid using sagittal serial sections. *Plast Reconstr Surg* 2007; 119:2061–2071.
7. Rohrich RJ, Pessa JE. The fat compartments of the face: Anatomy and clinical implications for cosmetic surgery. *Plast Reconstr Surg* 2007; 119:2219–2227.
8. Delmar H. Anatomie des plans superficiels de la face et du cou. *Ann Chir Plast Esthet* 1994; 39:527–555.
9. Le Louarn C, Buthiau D, Buis J. Rajeunissement facial et lifting malaire concentrique. La concept du Face recurve. *Ann Chir Plast Esthet* 2006; 51:99–121.
10. Lambros V. Observations on periorbital and midface aging. *Plast Reconstr Surg* 2007; 120:1367–1376.
11. Gray H, Bannister LH, Berry MM, Peter L. *Williams Gray's Anatomy: The Anatomical Basis of Medicine & Surgery*. New York: Churchill Livingstone, 1995.
12. Zadoo VP, Pessa JE. Biological arches and changes to the curvilinear form of the aging maxilla. *Plast Reconstr Surg* 2000; 106:460–466.
13. Pessa JE, Zadoo VP, Mutimer KL et al. Relative maxillary retrusion as a natural consequence of aging: Combining skeletal and soft tissue changes into an integrated model of midfacial aging. *Plast Reconstr Surg* 1998; 102:205–212.
14. Mendelson BC, Hartley W, Scott M, McNab A, Granzow JW. Age related changes of the orbit and midcheek and the implications for facial rejuvenation. *Aesthetic Plast Surg* 2007; 31:419–423.
15. Freilinger G, Gruber H, Happak W, Pechmann U. Surgical anatomy of the mimic system and facial nerve: Importance for reconstructive and aesthetic surgery. *Plast Reconstr Surg* 1987; 80:686.
16. Aiache AE, Ramirez OH. The suborbicularis oculi fat pad: An anatomic and clinical study. *Plast Reconstr Surg* 1995; 95:37.
17. Ghavami A, Pessa JE, Janis J, Khosla R, Reece EM, Rohrich RJ. The orbicularis retaining ligament of the medial orbit: Closing the circle. *Plast Reconstr Surg* 2008; 121:994–1001.
18. Rohrich RJ, Pessa JE. The retaining system of the face: Histologic evaluation of the septal boundaries of the subcutaneous fat compartments. *Plast Reconstr Surg* 2008; 121:1804–1809.
19. Furnas DW. The retaining ligaments of the cheek. *Plast Reconstr Surg* 1989; 83:11.
20. Delmar H. Model the morphological ageing of the face. Personal communication at French Society of Aesthetic Plastic Surgery (SOFCEP), Paris, France, May 2001.
21. Delmar H, Trepsat F. L'apport de la video-endoscopie dans la chirurgie du rajeunissement de la face. *Ann Chir Plast Esthet* 1994; 39:5.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Surgical rejuvenation: Autologous adipose grafting

Henry Delmar

INTRODUCTION

Fat grafting technique is performed to treat insufficient volume of facial contour, defects of silhouette, breast reconstruction, and augmentation. Nowadays, there is no limit to the medical imagination.

The outcome of scientific research on adipose stem cell (ASC) has been accumulated and led ASC to be the core element of regenerative medicine.

Platelet-rich plasma (PRP), which is not an element of regenerative medicine, is used to improve the survival rate of the grafted fat. PRP is known to have synergy effect with ASC in fat graft survival.

The combination of technical improvement of fat grafting, regenerative medicine, and PRP allows a better prediction of the quality of results with increased survival rate of the grafted fat.

FAT GRAFTING TECHNIQUE

The following are what we know:

- Lidocaine and epinephrine, which are components of tumescent solution, were proved not to give effects on fat tissues.
- The cell viability of grafted fat is not influenced by the donor site.
- Harvesting fat with large cannula and gentle negative pressure helps fat survival.
- Using 4 mm cannula rather than 2–3 mm cannula increases the survival rate of fat tissue.

Lipostructure involves suction with a 10 mL syringe to reduce any damage applied to the fat cells in fat harvesting, and removes impurities and oil through proper centrifugal filtration at 300 rpm (800 g), so it raises the density of fat cells in the same volume of material. Reinjection involves using a thin cannula (1 or 3 mL syringe), raising the possibility of revascularization from the surrounding tissue with a method of distributing the arrangement of small aliquots less than 0.1 mL equally in the recipient bed.

Many descriptions have been done using washing and straining technique and a method of putting aspirated fat on sterile towel to remove fluid and debris but were not demonstrated. Filtration was proposed by some companies as LipVage (Genesis Biosystems, Lewisville, TX), PureGraft (Cytori Therapeutics, San Diego, CA), and Viafill (Lipose Corp, Maitland, FL). These technologies seem to reduce damage of fat.

Magalon reported that in fat reinjection, the diameter of adipocyte tissue should not be increased more than 700 µm, and so the holes of cannula for harvesting should not exceed that diameter value.

REGENERATIVE MEDICINE

In the mid-1990s, plastic surgeons started to study adipose tissue dumped after body contouring surgery as liposuction in Pittsburgh University in the United States. They dissociated adipose tissue with collagenase, a histolysis enzyme, and then analyzed stromal vascular fraction obtained by centrifugal filtration of cell suspension. A new type of stromal cells similar to fibroblast was identified showing multipotent differentiation potential, and these new cells are proved to be a blend of adult stem cells through various scientific experiments.

ASC can be differentiated into various tissues such as adipocytes, cardiomyocytes, chondrocytes, endothelial cells, myocytes, neuron-like cells, and osteoblasts.

So, it is acknowledged that the utility of ASCs in regenerative medicine is very high.

PLATELET-RICH PLASMA

Another method to increase survival rate of fat grafting is the use of PRP. It is known that various cytokines released from platelets promote healing process and improve fat graft survival. The ration is around 20% of PRP.

ISSUE

With increased understandings on fat biology and accumulation of clinical experience, it becomes obvious that the survival of transplanted fat is influenced by various factors such as characteristic of patients, methods of fat processing, and condition of recipient bed; however, logical and scientific understanding about engraftment process is still insufficient.

Lately, Eto et al. published the groundbreaking result of research work about engraftment of fat. According to this result, adipocyte existing within 300 µm from the surface of transplanted adipose tissue survives, but most adipocytes located deeper in transplanted fat die within 24 hours (Figure 70.1).

At this moment, some ASCs survive in the deeper part of the transplant and play an important role to regenerate adipose tissue in transplanted fat. Transplant fat as a small drop

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

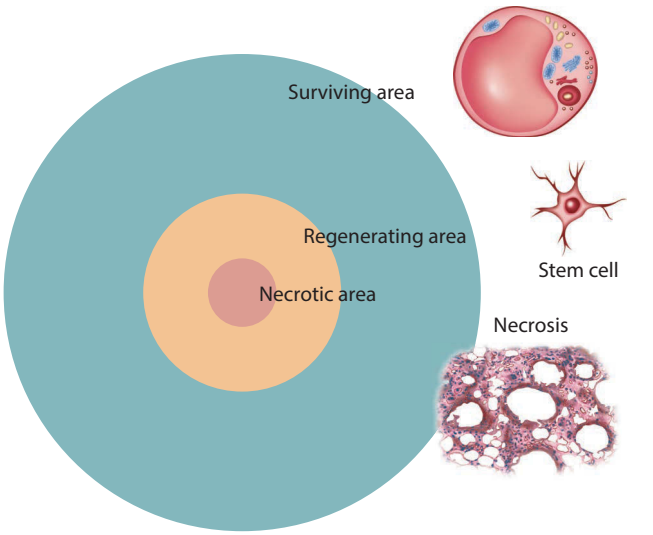


Figure 70.1 Early cell death and replacement of adipocytes, according to Eto et al. The green area where adipocytes survive is within 300 μm; the orange area represents where adipocytes are regenerating; the red area represents where adipocytes are necrotic; 90% survive for the first day, with early death and replacement at 20% around the sixth day.

increases the surface area contacting the surrounding tissue on fat grafting. Henceforward, the process of fat regeneration is progressed by ASC between 3 and 7 days, so the role of ASC is important in fat grafting.

CLINICAL APPLICATION OF FAT GRAFTING

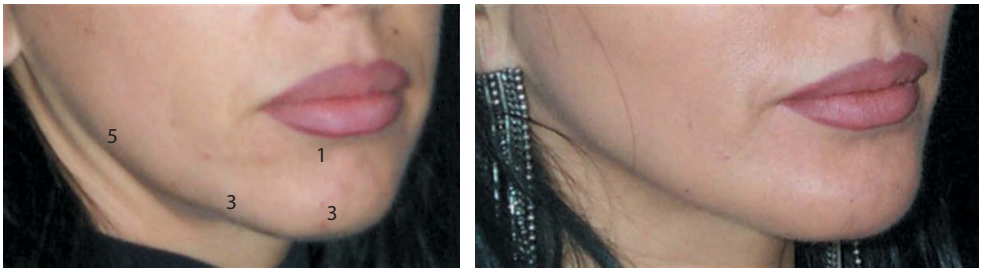
- Large volume fat grafting for the breast and buttock
- Fat transfer for burn and difficult wounds and also for scar treatment
- Volume of facial rejuvenation (Figures 70.2 through 70.6)
- Wrinkles of face

CONCLUSION

Scientific knowledge about fat and fat tissue transfer is accumulating rapidly. Fat is a unique regenerative complex comprising adult stem cells as well as high-energy resource related with tissue repair and regeneration. The regenerative potential of fat tissue led us to expand the limit of application day by day. Fat tissue is expected to be an essential component of regenerative medicine in the twenty-first century, and it is essential for plastic surgeons to understand new knowledge on fat biology to perform better and reasonable clinical practice.

Figure 70.2 Lipostructure of the inferior third of the face, involving injection of 20 mL of adipocytes (b and d show the pattern of distribution of the quantities injected). (a) Youthful appearance; (b, d) before treatment; (c, e) 6 months after treatment.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia



(a) (b)

Figure 70.3 Lipostructure of the jawline, involving injection of 24 mL of adipocytes (a shows the pattern of distribution of the quantities injected). (a) Before and (b) 9 months after treatment.

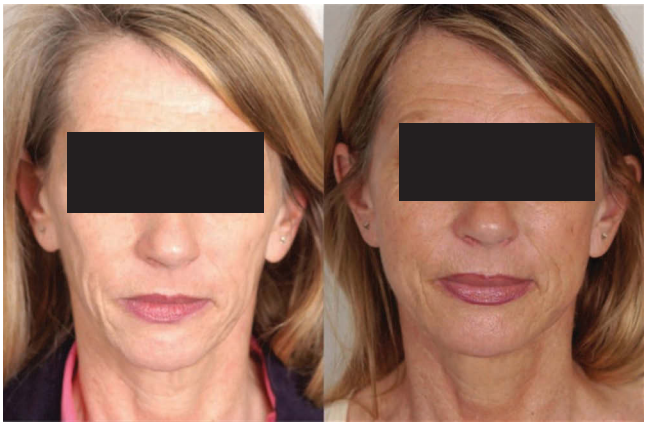
(a) (b)

(c) (d)

Figure 70.4 Lipostructure of full face. (a) Patient at 20 years old (left) and at 48 years old (right). (b) Injection of 50 mL of adipocytes: per site—orbit, 2 mL; tear trough, 1 mL; cheekbone, 8 mL; NLF, 1 mL; upper lips, 2 mL; lower lips, 3 mL; chin, 3 mL; jawline, 5 mL. (c, d) Before (left) and after 7 months (right).

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

(a)



(b)

(c)

Figure 70.5 Lipostructure of full face. (a) Injection of 54 mL of adipocytes: per site—temporal, 3 mL; orbit, 2 mL; cheekbone, 8 mL; upper lips, 2 mL; lower lips, 3 mL; chin, 3 mL; jawline, 6 mL. (b, c) Before (left) and after 6 months (right).

(a)

(b)

Figure 70.6 Lipostructure of the jawline. (a) Injection of 22 mL of adipocytes (11 mL each side, as indicated here). (b) Before (above) and after 12 months (below).

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

BIBLIOGRAPHY

1. Coleman S. Facial recontouring with lipostructure. *Clin Plast Surg* 1997;24:347–367.
2. Zuk PA, Zhu M, Mizuno H et al. Multilineage cells from human adipose tissue: Implications for cell-based therapies. *Tissue Eng* 2001;7:211–228.
4. Matsumoto D, Sato K, Gonda K et al. Cell-assisted lipotransfer: Supportive use of human adipose-derived cells for soft tissue augmentation with lipoinjection. *Tissue Eng* 2006;12:3375–3382.
5. Cervelli V, Palla L, Pascali M et al. Autologous platelet-rich plasma mixed with purified fat graft in aesthetic plastic surgery. *Aesthetic Plast Surg* 2009;33:716–721.
6. Gentile R, Orlando A, Sdoli MG et al. A comparative translational study: The combined use of enhanced stromal vascular fraction and platelet-rich plasma improves fat grafting maintenance in breast reconstruction. *Stem Cells Transl Med* 2012;1:341–351.
7. Sommeling CE, Heyneman A, Hoeksema H et al. The use of platelet-rich plasma in plastic surgery: A systematic review. *J Plast Reconstr Aesthet Surg* 2013;66:301–311.
8. Yoshimum K, Sato K, Aoi N et al. Cell-assisted lipotransfer for cosmetic breast augmentation: Supportive use of adipose-derived stem/stromal cells. *Aesthetic Plast Surg* 2008;32:48–55.
9. Willemsen IC, Lindenblatt N, Stevens HR. Results and long-term patient satisfaction after gluteal augmentation with platelet-rich plasma-enriched autologous fat. *Eur J Plast Surg* 2013;36:777–782.
10. Viard R, Bouguila I, Voulliaume D et al. Fat grafting in facial burns sequelae. *Ann Chir Plast Esthet* 2012;57:217–229.
11. Rohrich RI, Soroldn ES, Brown SA. In search of improved fat transfer viability: A quantitative analysis of the role of centrifugation and harvest site. *Plast Reconstr Surg* 2004;113:391–395; discussion 396–397.
12. Moore IH Ir, Kolaczynsld IW Morales LM et al. Viability of fat obtained by syringe suction lipectomy: Effects of local anesthesia with lidocaine. *Aesthetic Plast Surg* 1995;19:335–339.
13. Shiffman MA, Mirrafati S. Fat transfer techniques: The effect of harvest and transfer methods on adipocyte viability and review of the literature. *Dermatol Surg* 2001;27:819–826.
14. Ozsoy Z, Kd Z, Bilir A. The role of cannula diameter in improved adipocyte viability: A quantitative analysis. *Aesthet Surg J* 2006;26:287–289.
15. Magalon J, Bausset O, Magalon G et al. Characterization and comparison of 5 platelet-rich plasma preparations in a single-donor model. *Arthroscopy* 2014 May;30(5):629–638.
16. Li H, Zimmerlin L, Mana KG et al. Adipogenic potential of adipose stem cell subpopulations. *Plast Reconstr Surg* 2011;128:663–672.
17. Erdim M, Tezel E, Numanoglu A et al. The effects of the size of liposuction cannula on adipocyte survived and the optimum temperature for fat graft storage: An experimental study. *J Plast Reconstr Aesthet Surg* 2009;62:1210–1214.
18. Jeong JH. Recent advancements in autologous fat grafting. *Arch Aesthet Plast Surg* 2014;20:3–7.
19. Eto H, Kato H, Suga H et al. The fate of adipocytes after nonvascularized fat grafting: Evidence of early death and replacement of adipocytes. *Plast Reconstr* 2012;129:1081–1092.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Positive and negative aspects of face and eyelid cosmetic surgery

Thierry Besins

Any reconstruction or restoration first requires destruction (ideally transitional destruction). This is also the case for any surgical procedure and this should, of course, always be kept in mind.

NEGATIVE ASPECTS OF ANY SURGERY

Scarring is unavoidable; superficial scarring due to the incision and deep scarring due to detachments. This is also true to a lesser extent for facial lipostructure, which also entails scarring at donor sites.

Cutaneous and Neural Scarring

Unavoidable to this day, cutaneous scarring is, of course, a very negative aspect of any surgery, all the more so when the surgery in question is of a cosmetic nature. It can be of varying visibility, hypertrophic, unsightly, or even painful.

Any incision entails varying degrees of sensory nerve divisions, with extremely variable and often unpredictable consequences, sometimes resulting in severe and permanent pain (mainly in cervical and temporal scars).

Subcutaneous Detachments

They account for *major and irreversible damage* and constitute the primary negative aspect of facial surgery for various reasons.

Any detachment implies a dissection that, even if it is carried out gently, causes subcutaneous fat necrosis, as well as devascularization and denervation of the lifted flap, which is in theory temporary. Tissue thinning, neovascularization, and cutaneous stiffening are well-known occurrences after facelift and blepharoplasty and are partly to blame for what is commonly referred to as the "surgical look."

Detachments occurring under very thin skin turn into "skin grafts of varying thickness" with well-known consequences such as stiffening and retraction. A simple lower blepharoplasty with a subcutaneous detachment, even minimal, may cause a change in appearance (scleral show or ectropion) due to "unpredictable and uncontrollable" scarring reactions, even after the skin has been resected. These physiological scarring phenomena, which sometimes entail negative aesthetic consequences, are, of course, proportional to the damage caused by the surgical procedure and its aggressive actions, particularly dissection, detachments, coagulation, hematomas, and possible infections.

Lastly, the scarring process can be unpredictable, even if genetics, prior scarring, skin type, and tissue thickness are valid risk factors. Detachments are only indicated when they give access to a specific place in order to carry out a specific action that was programmed beforehand.

When it comes to facial cosmetic surgery, detachments are (unfortunately) often made necessary by the need to hide the scar as well as possible, which consequently creates a large gap between the entry scar and the zone of primary surgical interest.

All surgeons have doubts about the practical usefulness of their actions, even if they make sense from an intellectual point of view. But are they really useful or efficacious over time? Human tissue biomechanics do not appear to be superimposable over the biomechanics of "dead tissue".

Why do we carry out detachments? We carry out detachments in order to reach and observe a specific area and carry out an action there that we deem to be important and therefore indispensable and beneficial.

This action is generally a suture, a resection, or release of a normal anatomical facial ligament (the face's fixed attachment points). Generally, the action consists in moving a flap in order to redrape it, replacing it in another position, and, therefore, fixing and/or suspending it. This approach appears to be logical from an intellectual point of view but may only really be a form of justification as the whole process may be little more than an illusion.

Indeed, three fundamental questions come to mind:

1. Are detachments useful in the anatomical planes (that are usually chosen)?
2. Do tension sutures work?
3. Does the uncertainty and irreversible character of any surgery justify us in deciding to carry out "heavy" procedures that are in fact more often than not responsible for these predicaments?

Regarding the last question, we tend more and more to minimize our actions. Thanks to medical treatments and lipostructure, no unnecessary harm need now be made to the centrofacial area and around the eyes.

Detachments can and should be questioned. We know that detachments in a surgical plane and, therefore, in a plane of motion will only produce a beneficial reattachment during the healing phase, having been carried in planes that were

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

meant to move rather than to adhere. They will, however, inevitably create necrosis and tissue thinning. We are not entirely sure yet whether suspension and stitching procedures achieve a durable result when it comes to maintaining advancement flaps in place. They are definitely necessary in order to excise excess skin, such as in the neck area.

Lastly, we may legitimately question the efficacy of sutures and suspensions, even under slight tension: a single suture causes necrosis within 48 hours, and so do overcast sutures; only coaptation could prove to be efficient or barbed overcast sutures that distribute tension over each suture are self-binding and do not necessitate any tightening.

There still is a lot of work to be done in order to understand our actions and their usefulness. We are also questioning the reality of cutaneous ptoses, and it certainly seems as if we still are at the beginning of facial rejuvenation cosmetic surgery.

POSITIVE ASPECTS?

There is none should the result be disappointing or short-lived. The only acceptable positive aspect that could justify aggressive medical and surgical actions carried out on patients would be a successful identity reconstruction (even temporary) and/or a "rebirth," where the patient feels happier after the procedure than before it.

While we tend to focus on the quality of our "technical" and static results, patients tend to focus on the "psychological" result, which is of course related to the technical result, but not entirely so, and the real problem lies there.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Current and future options for the facelift

Thierry Besins

Every surgeon's dream (or secret goal) is to obtain the same results as with surgery, but without actually performing any surgery or via minimally invasive procedures. Why is that? Because any decent surgeon knows the potential harmful effects of surgery and strives to avoid them or at least to reduce them.

FUTURE DEVELOPMENTS

One can anticipate the following evolutions:

1. The increasingly important role of prevention.
2. Less open surgeries.
3. Progress in the understanding of tissue biomechanics in order to improve stitches and suspensions.
4. Progress in intravenous treatments.
5. The evolution of so-called machines (radio frequency, lasers, ultrasounds, etc.).
6. The provision of stem cells for facial aging treatment and prevention.
7. And I can't begin to imagine what genetic engineering is still to come.

It is hard to imagine an appropriate treatment of excess skin that wouldn't involve surgical resection. Consequently, surgery is still considered to be an indispensable step when it comes to treating excess skin on the upper eyelid or the neck, for instance.

Minimally invasive suture-based repositioning (and suspension) procedures are still being tested but don't seem to be yielding the expected results in terms of efficiency, sustainability, and complications.

Sustainable stitching systems that prevent one-off suture necrosis, and therefore also prevent those same sutures from giving way, should in theory be used more widely in the future (spreading out tension over several sutures in order to avoid necroses that occur when one suture is under pressure). For instance, one could mention tissue coaptation and barbed suture systems, which allow pressure absorption over important surfaces in cases of overcast seams and therefore entail less tissue trauma. Less detachments occur during facial surgeries, and consequently, there are less adverse effects following facelift procedures. Maybe the future lies in elastic suspension systems. Fixed, solid sutures may very well not be viable and may have to undergo scientific changes.

Finally, as we know, nowadays penetrating and transcutaneous systems entail long-lasting retentive scarring, unlike as observed during reattachment procedures carried out following detachments in anatomical planes of motion, and in the future, similar systems could emerge that would only entail scarring during the healing phase and be nonexistent should a second surgery be necessary.

On another note, recent clinical studies pertaining to facial aging carried out by Val Lambros tend to challenge the unilateral way we consider as skin ptosis, and consequently, its treatment is via skin traction and resection as we have been learning ever since this surgery was first introduced.

This situation is confusing, and we currently doubt the legitimacy of our actions, their indications, their unpredictability, and the fickleness of our results**.**

This compels us, on the one hand, to be extremely humble and, on the other hand, to carry out scientific research based on two major themes: understanding aging and tissue biomechanics.

Finally, we shall soon be able to consider "fully closed surgery," with skin excess "medically" redraped or removed and suspensions and stitches made transcutaneously or via minimally invasive surgery.

CONCLUSION: CURRENT OPTIONS

Surgery plays and will always play a key role in facial rejuvenation.

This can paradoxically be attributed to the rise of "competing" treatments that, far from having replaced surgery as the prevailing procedure, allowed it to move in the right direction and therefore achieve better results for several reasons:

Better indications are acknowledged to better understanding of aging. Unnecessary procedures aren't performed anymore and overall procedures have become more conservative.

Treatment plans are more complex and detailed and don't entail as heavy tissue (surgical) trauma.

Surgery, medical procedures (all cosmetic dermatology processes), and lipostructure are combined, yielding seamless and comprehensive results and ensuring every aspect is covered.

Fat autografts of all kinds even support the concept of beneficial and even preventive treatments given during the aging process. The fact that a surgical procedure can do more good than harm to tissue is revolutionary!

Facial rejuvenation surgery, thanks to the variety of surgical and nonsurgical tools we have at our disposal, has become exciting because, unlike our predecessors, we are able to believe in what we do and to obtain very gratifying results that provide us, as well as our patients, with utmost satisfaction.

Prevention will play the main role in facial rejuvenation if we well understand the mechanism of aging process.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Staying away from the sun, eating healthy foods, restraining tobacco use, minimizing alcohol intake, living a life, etc., are essential for skin preservation.

Posture education is fundamental to avoid bending and shortening of the neck. This must be taught to very young patients (straight, correct posture of the back, neck, and shoulders).

Regarding face aging, as the skin is not descending, the volumes alone must be replaced and repositioned, and the mimic muscles must be weakened (botulinum toxin).

Cheek fat pad will be repositioned with the thread technique, but through a new concept based on a thorough study of the biomechanism of tissues.

Improved ultrasound and radio-frequency machines will be used in skin, muscle, and superficial musculo aponevrotic system (SMAS) tightening.

Could the next decade's preventive treatment of the face to avoid facelift or surgeries be a few hours' session in the office, to produce a real preventive treatment for facial aging by a regimen of botulinum toxin, fillers, ultrasounds, and threads, combined together in one session and repeated every year or 2 years? And when would it begin? As aging starts around the 25th year, perhaps should that be the starting date for the first preventive treatments or consultation?

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

PART V

Other Aspects

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Training in aesthetic and cosmetic dermatology

Argyri Kapellari, Panagiota Riga, and Andreas Katsambas

> With few qualifications, our entire knowledge of our fellow creatures is based upon the appearance of their skins. This is well illustrated by our ready acceptance of a lion in a museum panorama which is, in reality, no more than a well preserved skin mounted on a matrix of old newspapers and sawdust and stiffened with an armature- no other organ of a lion could deputize for skin in this respect [1].

Youthful and healthy appearance is a major concern of people who visit dermatological practices. People crave to improve their appearance, to look better in order to feel better, and through this procedure to become even more confident and successful in their social and business environments. In this very competitive era, aesthetic and cosmetic dermatology may help expand a dermatologist's practice and attract more patients to their office. Numerous methods and procedures that already exist, as well as new emerging and constantly evolving ones, offer countless options. However, it is a common and true belief that it is not simple to perform aesthetic procedures. Multiple skills and continuous training are required (Table 73.1).

DERMATOLOGISTS CAN DO IT BETTER

Dermatologists are well aware of the basic mechanisms of cutaneous biology and pathology. Dermatologists are the specialists who can easily acknowledge the variety of skin conditions and skin requirements. They can better understand (as opposed to other medical specialists) the mechanism of every procedure they perform. Furthermore, when a side effect occurs, a dermatologist is more competent to understand the reason why it occurred and treat the condition accordingly. It should be kept in mind that most of the breakthrough methods, procedures, and devices (peels, toxins, fillers, laser- and light-source-based procedures, hair transplantation) have been invented or developed by dermatologists.

Dermatology in its current state brings us closer to ancient ideas of harmony and symmetry, whereas at the same time preserving our dedication to a natural kind of balance. The term "aesthetic" can be used by dermatologists in its classical sense.

KNOWLEDGE OF PHYSIOLOGY AND ANATOMY

Whether performing just a simple and easy procedure or a more advanced and demanding one, it is of tremendous importance to study and understand the physiology and the structure of the skin. Skin is an amazing organ with multiple functions and a specific biological role. (Understanding and respecting the physiology!) For example, for better treatment planning, it is vital to know that the complete replacement of the epidermis requires 28 days. It is of major importance to keep in mind the specific anatomy of the skin. For example, many fillers should be injected either in deep dermis or subcutaneously. It would be disastrous to inject the filler superficially as this would cause the patient and, consequently, the dermatologist great discomfort. Similar issues are emerging when working with lasers, chemicals peels, suspension threads, etc.

The adipocyte tissue molds body contour. As people age, they lose fat from the face and it is that exact volume that has to be restored in order to look younger. Also, when lipolysis is being done, the areas where fat has a cosmetic effect should be considered.

The anatomy of the treated region should be studied (face, neck, hand). Knowledge of the muscle anatomy in the treated area is mandatory when treating with toxins. Knowing the exact location of the vessels and the nerves of each area is also very important. Equally to be considered is the avoidance of trauma and the minimal possibility of bruising. Even small bruises may discourage the patients and deter them from continuing their treatment. Patients are afraid of social criticism, and their family and friends may not only criticize them but also the work of the physician. Dermatologists must be gentle and cautious as it is very important for the outcome of the treatment as well as for the patient's feeling that need to be reassured that no damage will be caused.

It is clear that everyone who wants to be an aesthetic dermatologist should be familiar with a great variety of subjects. Therefore, theoretical knowledge should cover the anatomy and physiology of the skin and its appendices; pathology of cosmetic disorders; aging of the skin; dermoendocrinology; phlebology; chemical and physical properties of filler agents, peelings, mesotherapy solutions, and interaction with the skin; lasers and tissue interactions; basic surgery procedures; minimally invasive liposuction and fat transfer techniques; Moh's surgery; handling unwanted effects; social, psychological, and psychiatric aspects of cosmetic dermatology; and legal aspects and regulations [2].

Dermatologists should never forget that these are healthy people being treated and that it is their duty and responsibility to secure the well-being and health of the patient.

LEARNING FROM THE EXPERTS

The future of cosmetic dermatology resides in the well-informed and trained community of dermatologic surgeons or aesthetic dermatologists [3]. Knowledge provides for the opportunity to excel and thrive as medical experts and revolutionize each

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Table 73.1 Training Algorithm

Knowledge of physiology and anatomy
Special fields
Deciding one's interest
Learning from the experts
Congresses
Workshops
Articles, books, Internet, DVDs
Learning how to make the assessment of the patient
Studying methods and protocols
Choosing materials
Obtaining the equipment
Becoming familiar with the procedure
Practicing the procedure
Starting from the easiest and simplest
Being cautious
Respecting the anatomy
Following the protocols
Building up on experience
Keeping records
Taking photos
Asking

Table 73.2 Aesthetic Dermatologic Societies

IACD: International Academy of Cosmetic Dermatology
ESCAD: European Society for Cosmetic And Aesthetic Dermatology
International Academy of Cosmetic Dermatology
Afro-Asian Society for Cosmetic Dermatology and Lasers
International Society for Dermatologic Surgery
European Academy of Cosmetic Surgery
Egyptian Afro-Asian Society for Cosmetic Dermatology and Laser
European Society for Dermatologic Surgery
European Society for Laser Dermatology
European Nail Society
European Hair and Scalp Society
European Society for Anti-Aging and Aesthetic Medicine
European Society for Laser Dermatology
American Academy of Dermatology
American Society for Dermatologic Surgery
American Society for Cosmetic Dermatology and Aesthetic Surgery
World Academy of Anti-Aging Medicine
International College of Aesthetic Medicine
International Society of Aesthetic Plastic Surgery

procedure. The best place to start is to learn from the experts. In the past two decades, teaching conferences for specific issues and world-known congresses have multiplied. Nowadays, data from the Internet tend to be overwhelming, so there is a need for better screening the available information and evaluating the scientific reliability of the sources. Dermatological societies (Table 73.2) can provide information about educational and training programs for residents or trained dermatologists [4]. In order to adapt to the demand of cosmetic services at a scientifically based standard, the inclusion of cosmetic procedures in basic resident training programs worldwide and the organization of fellowships for more advanced learning is required [5]. Dermatologists should seek out and certify training centers where specific regulations for training programs will be implemented. An international or national board–certified examination for special qualification in cosmetic dermatology is vital. In that manner, the dermatologist, who is more competent to provide cosmetic treatments, can better respond to the public and gain recognition [2].

Training starts from theory and the best way to learn and understand is through participation at international congresses. All the experts meet there and communicate their skills and experience. Attendees should be prepared and emphasize their weak spots and should not hesitate to ask questions in order to clarify a subject. Congresses are places of sharing knowledge, forming new ideas and meeting experts, which dermatologists may obtain the best out of them through the communication with other professionals from various countries, visits at the booths of different companies, attendance at lectures, and live-patient demonstrations. Then dermatologists can move on to special "hands on" courses or special theme seminars. In these workshops or "boot camps," one can obtain adequate and extensive knowledge of specific procedures or new techniques. Supervised "hands on training" is mandatory to master new cosmetic procedures and learn from the experience and the mistakes of experts [6]. Mentorship is a powerful tool to strengthen aesthetic dermatology as a subspecialty and proper reward and recognition should be given to these mentors.

Familiarizing oneself with the procedures is one thing, but the basic theoretical knowledge still remains the most essential part. There are excellent books and DVDs in aesthetic dermatology on which one can rely. In the convenience of personal free time and own pace, dermatologists can learn and optimize their practices. Subscription to scientific journals provides evidence-based information on special topics (*Journal of Cosmetic Dermatology*, *Dermatologic Clinic*, *Dermatologic Surgery Journal*, *Dermatologic Clinic*, *Archives of Dermatology*, *Journal of the European Academy of Dermatology and Venereology*, etc.), and also networking forums provide real-time communication with fellow colleagues [7].

A dermatologist with a strong and balanced foundation on basic dermatologic and aesthetic science will certainly be in a better position to manage a patient than someone who has a focused approach only in machines and techniques [6]. They can detect problems at the early stages and provide treatment accordingly, as well as address the aesthetic patient as a whole in a way that they can provide basic skin care, dermatological counseling, and, if needed, cosmetic therapy. A patient who suffers from rosacea can become a future candidate for facial rejuvenation and vice versa, so in a dermatological and aesthetics office, the flow of patients can regenerate itself.

ASSESSMENT OF THE PATIENT

The assessment of the patient is crucial. Acquiring a thorough medical history and asking persistently about previous aesthetic procedures is a must. Some people tend to forget or purposefully conceal such treatments. The next step would be to examine the skin carefully, ensuring that there is no skin disease or condition, which may interfere with the proposed procedure. Assessing the quality of the skin, the skin type, and the degree of aging and photoaging is also an important step. The use of the Fitzpatrick skin–type scale and the Glogau photoaging classification would be useful in this case. Observing the patient and the expressions of the face is necessary in order to identify any existing asymmetries or scars. The dermatologist should have time to discuss with their patient and understand their expectations. Patients who are dysmorphobic or have unrealistic expectations should be excluded. Each treatment should be individualized.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

MAKING DECISIONS

The dermatologist must think and decide what can be done in their practice. Is there enough room for new equipment? Is it possible to have an assistant, e.g., a nurse? Unfortunately, it is rather difficult to be instantly trained in every available aesthetic procedure. It is time-consuming and rather expensive. It is of great importance to choose something that one is able to do. Focusing on the procedures already being performed and the equipment already owned and learning how to can get the most and best out of them is helpful too. If, for example, a dermatologist wants to buy a laser device, the needs of their practice should be considered so that they purchase something that will satisfy them. Companies, which produce materials and equipment, launch new products constantly and spend enormously large amounts of money in marketing. One should be cautious and skeptical and should not hesitate to ask colleagues who already used these devices about the annual maintenance cost and the treatment outcome, as well as feedback from their patients. Calculating the cost of every procedure for their practice in making the most cost-effective choice is beneficial.

MATERIALS

Many materials are available on the market and thus it can be rather confusing to select the right one. But that choice is the most important one for the outcome and safety of each treatment. Learn the most you can about every substance you are using and its biological role. Those that have just been launched in the market should be avoided. Many new substances may cause side effects that usually are observed in the first year of use. As for fillers, biodegradable ones are recommended. Each area of the face (and body) may need different fillers and dermatologists should know that in order to optimize the result.

It is suggested to begin with substances of proven efficacy and safety. After all, patient satisfaction is the goal of each treatment, but it should not be forgotten that patient safety should be the paramount consideration.

OBTAINING THE EQUIPMENT

Before any procedure, the dermatologist should think carefully of what is needed and it should be purchased on time. Needles of various sizes, micro cannulas, antiseptic solution for the patient and the equipment, cotton pads, gauzes, ice packs, topical anesthetics, steroid creams, and an autoclave are only some of the things required. Certain procedures require specific equipment, e.g., a centrifuge for the preparation of platelet-rich plasma treatments.

STUDYING METHODS AND PROTOCOLS

Inadequate information and training regarding a procedure is the main reason for unsuccessful treatment. It should be taken into consideration that, like every medical procedure, aesthetic procedures have risks and potential side effects.

Dermatologists should learn and follow the exact protocol to optimize the result and minimize the possibility of a poor outcome.

PRACTICING THE PROCEDURE

The first "real-time" cosmetic patients for practicing outside residency can be the dermatologist's spouse, close relatives, friends, and/or themselves. They should start conservatively, and then as knowledge and experience are built upon, they can then expand their techniques. One should never be afraid of criticism; it makes everyone evolve. One can also practice injection or surgery techniques on skin models or pig skin. Documentation is also as essential as medical record, not only in order to trace an adverse event back to its origin (e.g., to know the serial number of the product we used), but also as a tool for the professional to evaluate the success of each treatment, to judge the response, to compare the results of different treatment protocols, and, last but not least, to learn and understand how to tailor the needs of every single patient. In any case, one should remember to have baseline photo documentation before each treatment. Proper equipment and standardized lighting are essential to achieve reproducibility.

Finally, it should be noted that in essence the words "aesthetic dermatologist" derive from the words *aesthetic*, meaning harmony in Greek philosophy; *derma*, meaning skin in Greek; and *logos*, meaning science and logic. Therefore, these three components should be implemented in order to perfect the services and performance of a cosmetic dermatologist.

REFERENCES

1. Billingham RE, Silvers WK. A biologist's reflections on dermatology. *J Invest Dermatol* 1971; 57:227–240.
2. Kerscher M, Williams S. Aesthetic and cosmetic dermatology. *Eur J Dermatol* 2009; 19:530–534.
3. Boh EE, Lupo MP. Training in cosmetic dermatology. *Cosmet Dermatol* 2012; 25:392–393.
4. Laban J, Zachary C. Resident training needs in aesthetic dermatology. *Pract Dermatol* 2009 August:27–29.
5. Group A, Philips R, Kelly E. Cosmetic dermatology training in residency: Results of a survey from the residents perspective. *Dermatol Surg J* 2012; 38:1975–1980.
6. Dogra S. Fate of medical dermatology in the era of cosmetic dermatology and dermatosurgery. *Indian J Dermatol Venereol* 2009; 75:4–7.
7. Goh CL, Cutan J. The need for evidence-based aesthetic dermatology practice. *Aesthet Surg* 2009; 2:65–71.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Aesthetic technician

Alexandre Ostojic and Ewa Guigne

The participation of an aesthetic technician within a firm raises many issues. And certainly not the least is the question of his training and his status according to each country's regulations. Integration in a team requires thoughtful organization taking into account the quality of care and continuous training. The various skills required for the different sectors, aesthetic laser surgery and secretariat, will be reviewed.

STATUS OF THE AESTHETIC TECHNICIAN

The status and training of an aesthetic assistant are complex issues following different points of view of people involved and the progress of legislation in different countries.

It should of course immediately oppose the aesthetic assistant who benefits from a delegation to perform the actions under a supervising physician to a physician who possess training without dermatologist or plastic surgeon skills but who has complete autonomy. So a medical assistant or a nurse with a master's level can also be opposed with a nonmedical staff receiving training as a technical assistance practitioner for aesthetic surgery and safety practice.

For the benefit of the patient and practice, these three levels may exist and achieve positive osmosis.

The employment of staff under the supervision of a doctor allows to generate valuable time that can be devoted to improving clinical expertise, conducting acts of experts, and risk management. The inclusion of an aesthetic assistant and his or her use within a firm adds real value to the firm and its development.

The transfer of skills for medical activities to paramedics is organized in several countries. Since the 1960, training has been organized at the master's level to support complex procedures for consultation at the primary level and for surgery at the secondary level. The larger experiments concern the United States and Canada. In Europe, the experience of delegation is the largest in the United Kingdom and the Netherlands but still heterogeneous.

In France, we do not find the same legal opportunities delegations, some practices are identified as anesthesia.

However, the delegation act despite legislative recommendations (HPST law) and the efforts of professional training are always a problem because the state board clearly distinguishes between a nonmedical procedure and a medical procedure that can only be performed by a doctor.

This law can, in theory, stand in opposition to the two types of training described earlier, but in reality this does not occur because the medical assistant profession is hardly represented in Europe.

The largest paramedic training in Europe leading to a master's degree is nursing practice. But few of those who graduate choose to practice under the supervision of a medical aesthetics practitioner. The US physician assistants or nurses can, in addition to a PA-level training, complete their training with training modules that confers diplomas for private aesthetic practice.

Physician assistants are highly skilled members of the health-care team who, under the supervision of a licensed physician, provide diagnostic and therapeutic patient care in a variety of medical specialties and practice settings. The typical PA program lasts about 2 full years and usually requires at least 2 years of college and significant health-care experience for admission. The Centralized Application Service for Physician Assistants is available to applicants, but currently only half of California PA programs participate (with a greater percentage in other states).

All PA programs must meet the same curriculum standards, but programs do follow different models and award a variety of credentials. Students should check current admission requirements at each school before they apply. Some PA programs award an associate's, bachelor's, or master's degree as well as a certificate of completion, but such a degree is not required to be a licensed physician assistant. PA programs are under the control of the National Commission on Certification of Physician Assistants. The latest issue of *Accreditation Standards for Physician Assistant Education,* fourth edition, is available online on the ARC-PA's website. In this formation, delegation acts are more likely to succeed. The assistant has a status of an employee, or else he can choose to be an independent contractor in some states.

In Europe and, especially, in France, the concept of assistant covers a very different career field with a vocational nonacademic training and, for nontitled employees, taking an equivalent of 5 years of vocational training in alternation. The qualification gives a professional but nonacademic title and remains a legal problem in the delegation acts.

MANAGEMENT OF TEAMS WITH AN AESTHETIC TECHNICIAN

As you decide to create a team with an aesthetic technician, you need a new approach based on supervision. Spontaneously, your habit is to engage yourself in a quality improvement process.

The wheel of quality is a simplistic illustration for the purpose of management (Figure 74.1). Supervision with a

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

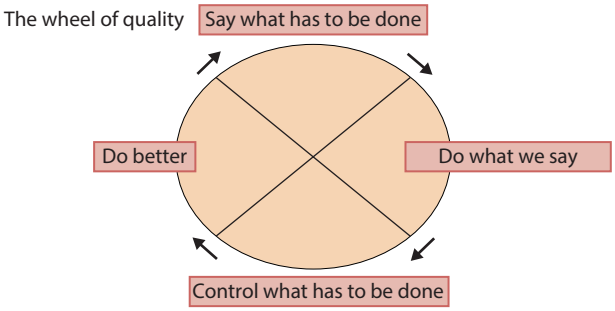


Figure 74.1 Care quality and safety.

rational approach needs more investment with time and training. The main goal is improving care.

The employment of an aesthetic technician can drive the development of the firm but with strengths and weaknesses. The increase of activity is to be balanced with the time devoted to the coordination for safety, quality, and communication. The transition to the delegation of aesthetic acts has to be assumed fully.

The consultation team must be organized and the integration of new members must be guaranteed. The boundaries questions and answers collection must be standardized with pre-established forms. Multiplying acts and diverse activities introduces the risk of disparate methodologies and risk of miscommunication.

All protocols are defined and drafted as a reference for the whole team. Internal scientific meetings are helpful for technical and scientific watch. They are fully part of tutorials for assistants. They are also essential for defining common goals and discussing the monitoring of good practices. These meetings are also efficient for defining common goals.

Actions to raise overall satisfaction or consideration of pain would be discussed (Figure 74.2). The data gathering will lead to better management of complications and find quality indicators. The protocol of use and maintenance of the equipment and facilities has to be drafted. Conducting annual meetings is essential for optimizing human resources.

The challenges of teaching need to organize the schedule for outdoor education and internship with training sequences. Monitoring all these practices is the duty of a supervisor.

In a larger team, the supervisor has to think of the organization beyond his or her personal practice. Improving the practice with an assistant is to be taken as a common goal of the team on a scientific basis. It is essential to formalize leadership and education.

EDUCATION AND SKILLS

Reception and Secretarial

Telephone Reception

Helpline is of prime importance. It is the first contact with the firm. It makes the patient confident. The first 15 seconds of a phone call is enough to get a first impression of the caller, and this impression will be directly related to the image of the firm. The patient must feel assured speaking to a concerned and courteous professional.

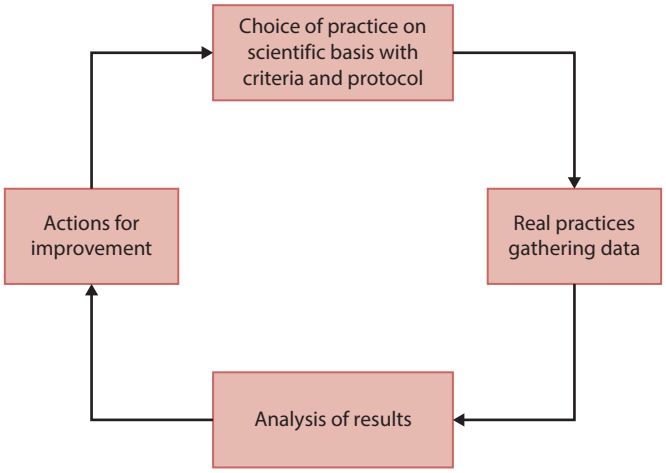


Figure 74.2 Consultation process.

Hosting

The physical welcome of the patient through verbal language but also by body language (smile, eye contact, gestures, tone of voice) is should not be neglected.

The assistant can, of course, give an appointment but listen, inform, reassure, make the link with the doctor, and manage side effects posttreatment. The assistant must be able to provide basic information on the updated procedures performed in the office. He must know the possible complications of practical interventions and determine the urgency of a problem. He must know how to take a message and convey clearly to the doctor. These help to reinforce the impression of confidence and availability of the firm.

Aesthetic Technician

The aesthetic patient is not sick, but he seeks to improve his appearance. He can easily seek advice from an assistant for a second opinion, which will strengthen the discourses of the doctor. "Will that technique match well to my problem? Will I be better than before?"

The assistant's skills become useful if he is aware of

- The basis of performing a procedure and indication for injectable products: botulinum toxin, hyaluronic acid, and other fillers
- Know the different toxins and is an expertise in dilutions
- Know the side effects and postinjection complications
- Assemble a needle or cannula to a syringe (appropriate diameter depending on the viscosity of the product)
- Know how to clean the skin
- Perform a superficial peel
- Know the method and posteffects of a medium peel (TCA)

The assistant will be a help for

- Preparing the skin for injections (cleansing, disinfection, preparation gloves, Easter ice)
- Preparing products (dilutions of toxin)
- Gathering product labels and record number lots for product traceability
- Making up the patient after injection

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

The aesthetic assistant has multiple missions. He is a great help for all interventional dermatology, laser dermatology, dermatologic surgery, and minor cosmetic dermatology.

He is a time saver for doctors, who can fully devote themselves to the intervention.

The patient comfort is improved. Before the arrival of the doctor, the patient has a specific person who will make him comfortable and reassure and explain again the procedure that follows. After surgery, the assistant, through posttreatment care, will also explain the precautionary measures. He helps communicate the messages from the physician better.

The assistant reflects the professionalism of the firm, as well as the clean, tastefully decorated rooms.

He can also inform the patients of the other techniques used in the office and contribute to the loyalty of patients. The assistant is an additional cost to the firm of which one must study the risk–benefit ratio. The more interventional dermatology the doctor can perform, the more there are obvious financial incentives to take on an assistant. The assistant can work part-time or only on interventional days or share his time between several doctors.

Assistant Laserist

The assistant laserist has two distinct tasks: ensuring the laser performs as delegated by the physician and helping the doctor while performing laser procedures. He must have received specialized training to perform laser techniques. This training is essential in order to appropriately inform the patient, assist the physician in his practice, and comply with safety regulations. This training can be done by the doctor himself.

The assistant must

- Know the basic principles of laser proceedings.
- Know the different types of lasers and their indications.
- Be able to explain the expected side effects of lasers and reassure the patient that these effects are normal and will disappear. If the patient calls, the assistant needs to recognize the unexpected side effects and report to the doctor.
- Know how to give recommendations, explain the precautions (avoiding the sun) and postlaser treatment such as healing creams and protective clothing, and give makeup tips to hide postlaser traces.
- Know the concepts of laser maintenance (cleaning lenses, changing canisters).
- Know the specific safety precautions with regard to the use of laser (glasses for everyone in the room, doors closed, opaque windows, use of a smoke vacuum cleaner if necessary, wear gloves and masks if skin is broken and projections).

Delegated Acts

Delegated acts have different legislation in different countries. The delegated acts mainly concern depilatory lasers, flash lamps, and light-emitting diodes. This is generally a simple act of hand, easily reproducible with a low level of technology and rather time-consuming part.

The assistant performs itself a laser act under the responsibility of the doctor and his physical presence in the place the doctor may, meanwhile, engage in another activity.

The doctor himself is responsible for the act performed by his assistant. The insurance must cover the doctor for the acts, and the delegated assistant must himself have his own insurance.

The doctor must teach the assistant with his own expertise and monitor him regarding the devices he his working with. Each doctor has his therapeutic strategies and thereby the assistant should be modeled on that of the doctor he works under. Each machine is different and the settings are not the same.

The delegation of tasks may be gradual following the achievements of the assistant. Initially it may require the presence of the physician to set the machine and determine the areas to be treated. Progressively, the physician may delegate completely simple care and intervene in cases of only complicated procedures. Mutual trust between the physician and his assistant is essential. The assistant should evaluate his purview and seek the doctor's advice in case of difficulty.

Role of Assistant for Laser Procedures Performed by the Doctor

Before the procedure

- Positioning the patient, removal, skin disinfection in the case of a laser with breaking the skin barrier act, application of anesthetic cream, application of conductive gel, setting up glasses, material preparation, verbal contact with the patient, reassure, explain the procedure that will follow

During the procedure

- Installation and servicing of the vacuum cleaner and the anesthetic chiller

After the procedure

- Heavy daily wound dressings after laser resurfacing, care after laser skin break, chill spreading, spreading of healing cream, and makeup if possible
- *Verbal contact*: information of postact care, precautions (avoiding exposure to the sun), and determining control appointments

Surgical Assistant

The training program of a technical assistant for conducting surgical procedures includes fundamental information on the conditions for carrying out a procedure. Teaching should include the characteristics of skin and anatomical areas and their critical relations with nerves and blood vessels. Knowledge of material and various stages of intervention dermatologic surgery should be provided.

The local organization must be controlled including clean areas and evacuation zones for managing septic waste. The circuit of sterile instruments and equipment must not cross contaminated material. The hygienic care of the premises must be understood, and the use of water points and evacuation for the surgery should be distinct from that for the public and the practice.

Fire safety procedures (with fire extinguisher maintenance, evacuation plan) will require training.

Antiseptic liquid soap, alcohol gel, and disposable paper towels have to be verified. Bags and containers for soiled items and the pedal bin should be checked. The waste collection company has to be monitored, and slips disposal and incineration should be collected.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

The concept of hemostasis by a scalpel with monopolar or bipolar function (pacemaker) should be known. The list of basic perishable equipment should be known. This should be displayed at the storage place. The list should be checked and expiry dates examined.

The instrumentation used should be known with a set of lists established. (sterile pencil demographic, sterile fields, Kocher forceps, scalpel handle, blade nos. 15 and 11, Adson forceps-type needle holder with tungsten jaws, curved blunt scissors to take off (Metzenblum style), a pair of scissors for cutting suture material, Gillis hooks, Halstead artery forceps). Sterilization of reusable equipment must be perfectly mastered. The process of decontamination and cleansing should be understood. Decontamination, cleaning, the use of ultrasonic cleaners, rinsing, and drying should be done well. The packaging has to be appropriate.

The establishment of integrators to control the physicochemical parameters of the sterilization should be known. Autoclaving has to be mastered and batch sterilizations have to be monitored by date. The disposable equipment has to be monitored for their expiration dates. Knowledge of toxicities of xylocaine and adrenaline should be known.

BIBLIOGRAPHY

Cipher DJ, Hooker RS, Sekscenski E. Are older patients satisfied with physician assistants and nurse practitioners? *JAAPA* 2006; 19:36–44.

Department of Health/National Health Service. The competence and curriculum framework for the physician assistant. Department of Health/National Health Service, London, U.K., 2006.

Dhuper S, Choksi S. Replacing an academic internal medicine residency with a physician assistant hospitalist model: A comparative analysis study. *Am J Med Qual* 2009; 24:132–139.

Drennan V, Levenson R, Halter M, Tye C. Physician assistants in English general practice: A qualitative study of employers' viewpoints. *J Health Serv Res Policy* 2011; 16:75–80.

Farmer J, Currie M, West C et al. Evaluation of physician assistants to NHS Scotland. UHI Millennium Institute, Inverness, U.K., 2009.

Frossard LA, Liebich G, Hooker RS et al. Introducing physician assistants into new roles: International experiences. *Med J Aust* 2008; 188:199–201.

Gladwell M. *Outliers: The Story of Success.* New York: Little Brown and Co., 2008.

Hooker RS, Cawley JF, Everett CM. Predictive modelling the physician assistant supply: 2010–2025. *Public Health Rep* 2011; 126:708–716.

Hooker RS, Kuilman L. Physician assistant education: Five countries. *J Physician Assist Educ* 2011; 22:53–58.

Merkle F, Ritsema TS, Bauer S, Kuilman L. The physician assistant: Shifting the Paradigm of European medical practice? *HSR Proc Intensive Care Cardiovasc Anesth* 2011; 3(4):255–262.

Ouzonakis P, Chalkias T. The confidentiality of medical secrets of patients by nursing staff. *Int J Caring Sci* 2010 January–April; 3(1):1–2.

Ritsema TS, Paterson KE. Physician assistants in the United Kingdom: An initial profile of the profession. *JAAPA* 2011; 24:60.

Spenkelink-Schut G, ten Cate OTJ, Kort HSM, Fahringer D. Training the physician assistant in the Netherlands. *J Phys Assist Educ* 2008; 19:46–53.

Zwijnenberg NC, Bours G. Nurse practitioners and physician assistants in Dutch hospitals: Their role, extent of substitution and facilitators and barriers experienced in the reallocation of tasks. *J Adv Nurs* 2012; 68(6):1235–1246.

ONLINE RESOURCES

American Academy of Physician Assistants. Quick facts regarding the PA profession. http://www.aapa.org/the_pa_profession/quick_facts.aspx. Accessed November 21, 2011.

American Society for Aesthetic Plastic Surgery. 2008 cosmetic surgery National Data Bank statistics. http://www.surgery.org/download/2008stats.pdf. Accessed July 6, 2009.

Brahmavar SM, Hetzel F. *Medical Lasers: Quality Control, Safety Standards and Regulation*. October 2001. Medical Physics Publishing, Madison, WI. http://www.aapm.org/pubs/reports/rpt_73.pdf.

Bureau of Labor Statistics, U.S. Department of Labor. *Occupational Outlook Handbook*, 2012–2013 ed., Physician Assistants. http://www.bls.gov/ooh/healthcare/physician-assistants.htm. Visited March 28, 2013.

Central Application Service for Physician Assistants (CASPA). www.caspaonline.org.

Ministry of Health, Welfare and Sport, the Netherlands. Ontwerpbesluit tijdelijke zelfstandige bevoegdheid physician assistant. 2011. http://www.rijksoverheid.nl/documenten-en-publicaties/besluiten/2011/04/27/ontwerpbesluit-tijdelijke-zelfstandige-bevoegdheid-physician-assistant.html. Accessed November 22, 2011; Lennox P. Krystie physician assistants for aesthetic surgery practices: Friend or foe? *Med Aesthet Arch* 2009; 2(3), www.plasticsurgerypulsenews.com.

Netherlands Association of Physician Assistants. Specialisms physician assistant. http://napa.artsennet.nl/Kwaliteit/Specialismen.htm.; Lennox, KP. Physician assistants for aesthetic surgery practices: Friend or foe? *Med Aesthet Arch* 17(7). http://paeaonline.org. Last updated October 12, 2009; Posted July 22, 2009.

Physician Assistant Education Association. PAEA statement on master's degree as entry-level and terminal degree for PA profession. http://www.paeaonline.org/index.php?ht=d/sp/i/212/pid/212. Accessed November 22, 2011.

Dao E. QC the professional secret, confidentiality and legal professional privilege in Europe: An update on the report Conseil des Barreaux de L'union Europeenne. Council of The Bars and Law Societies of The European Union, http://www.europarl.europa.eu/meetdocs/2009_2014/documents/libe/dv/ccbeedward_report_update_/ccbeedward_report_update_en.pdf.

United Kingdom Association of Physician Assistants FAQs. http://www.ukapa.co.uk/faq/index.html#10. Accessed November 21, 2011.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Internet and e-consultation in aesthetic and cosmetic dermatology

Leonardo Marini

Modern health-care systems are moving within increasingly complex national and international scenarios. They are continuously "fueled" by the accelerating sophistication of diagnostic and therapeutic equipment and escalation of economical and social challenges. Dermatology, and its aesthetic and cosmetic branches, certainly fits the group of most rapidly evolving medical-surgical specialties. Modern Dermatology finds its place at the very forefront of this highly challenging innovative, boundless medical environment. Quality of care and efficiency of diagnostic and therapeutic procedures require constant attention to details that might not be anymore confined to small, easily controllable local scenarios. Current and future communication technology opens the view to wider worldwide horizons. Internet was instrumental in providing a new, incredible dimension to medical communication, allowing both physicians and patients to easily and rapidly access incredibly huge sources of data and information. Dealing with this apparently limitless virtual reality is a fascinating yet challenging exercise requiring optimization of energy and time resources along with a constant attention to quality assessment and quality control of medical information. The use of the Internet to deliver medical services such as medical consultations and drug prescriptions is known as cybermedicine, a natural evolution of telemedicine. Dermatology is a "visual" specialty that heavily relies on clinical observation. For this reason, it naturally lends itself to the innovations provided by telemedicine, next-generation cybermedicine, and mobile health devices. Acquiring, transferring, and critically observing clinical images along with carefully assessing properly "filtered," protected medical data constitute the core of an efficient e-consultation in cyber-dermatology and "mobile dermhealth."

INFORMATION AND COMMUNICATION

The most important pillars on which human success is based are *information* and *communication*. Information derives from Latin *informare*, to give form to the mind, instruct, and teach, and *informatio*, concept or idea. Information perceived and interpreted by a conscious mind leads to transformation of already stored information into knowledge. Medicine as well as all other sciences are constantly called to answer an enormous number of questions, leading a growing body of information that need to be stored, safely retrieved, and professionally elaborated. Records are able to keep all consciously produced information that needs to be retained because of their value. Record management ensures that stored information integrity is properly protected and preserved for as long as data accessibility is required.

It is estimated that the world's technological capacity to store information grew from 2.6 exabytes (EBs) in 1986—the information equivalent to less than one 730 MB CD-ROM (539 MB per person)—to 295 EB in 2007 corresponding to 61 similar capacity DC-ROM per person [1]. The EB is a unit of information stored in a digital format equal to one quintillion bytes. The prefix "exa" indicates the sixth power of 1000. Therefore, 1 EB corresponds to 10^{18} bytes equal to 1,000,000,000 GB or 1,000,000 TB. Durability of digitally stored information is an important issue since conventional miniaturized data storage solutions can presently guarantee a lifespan of 30 years. Recently, Hitachi (2012) proposed and presented an innovative glass medium data storage solution that could guarantee 1000 years durability.

Communication derives also from Latin *communis*: to share. Communication is the activity of conveying information through the exchange of thoughts and messages as by speech, visuals, signals, writing, or behavior. Communication requires a *sender*, a *message*, and a *recipient*. The recipient does not necessarily need to be really present at the very time of message delivery nor to be aware of the sender's intention to communicate. Communication can therefore occur across vast distances in time and space but requires that communicating parties share a proper area of communicative communality. The communication process can be considered effectively completed only when the receiver has entirely understood the message of the sender.

Human communication progressively evolved through the establishment of oral and written languages oftentimes supported by pictograms. Fundamental innovations like the printing process, telephone, radio, television, personal computers, mobile smartphones, and digital imaging strongly contributed to increase the bulk, speed, and spatial sphere of modern communication. Technological miniaturization definitely helped the portability and diffusion of communication devices, further contributing to improve communication to the point that being constantly "connected" to information channels is considered indispensable for any kind of profession today.

E-REVOLUTION AND E-HEALTH

During the 1990s, as the Internet was gaining ground into public consciousness, an increasing number of e-terms begun to appear and rapidly proliferate. E-mail and e-commerce were natural precursors to e-health. E-health came into use in 1999 with the aim of providing an innovative scenario on which the world of medical information and advanced communication technologies could synergistically perform at their best.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

E-health focuses its attention to improve patient-centered care, implementing *share decision making*; computer-assisted diagnosis and therapy delivered through telemedicine, e-consultations, remote multidisciplinary second-opinion diagnosis; advanced information systems through the scheduling of electronic medical appointments and medical prescriptions; and virtually limitless storage of medical information and its fast, efficient retrieval. E-health aims at reducing medical costs, reducing medical errors, and improving quality of care. Its main instruments are electronic medical records (EMRs), advanced clinical decision support systems, and secure private medical information exchange. E-health is already playing a major role in the extremely complex medical world, providing advanced information platforms; rapid and efficient transfer of clinical, laboratory, and digital imaging data; and avoiding unnecessary duplication of expensive efforts.

TELEMEDICINE

The practice of medicine when patients and doctors are geographically separated is possible today thanks to innovations in computing and telecommunications. The American Medical Association has defined telemedicine as "medical practice across distance via telecommunications and interactive video technology." The European Commission defines telemedicine as "the provision of health-care services, through the use of ICT, in situations where health professional and patient (or two health professionals) are not in the same location. It involves secure transmission of medical data and information through text, sound, images, or other forms needed for the prevention, diagnosis, treatment, and follow-up of patients" [2]. Unfortunately, there is no universal consensus on what telemedicine really is.

Telemedicine is a complex, multifactorial process of delivering health-care services. It combines conventional medical care with the innovative efficiency of current and future telecommunication technologies to deliver high-level health care beyond any geographical bounds. Recent studies confirmed the high level of patient satisfaction provided by telemedicine services [3], while others still favor the diagnostic accuracy provided by conventional consultations particularly when dealing with pigmented and nonpigmented neoplasms [4,5].

The simplest method adopted by telemedicine is the universally known, time-honored *telephone consultation*. From this extremely effective, but limited form of medical communication, we progressively moved to advanced telemedicine, not anymore a science fiction issue sporadically used in special situations such as with space exploration or deep sea navigation. Presently in less developed countries or in complex military scenarios, where distance from efficient and experienced health-care centers is really a matter of life and death, telemedicine allows filling the gap [6,7]. Due to significant reduction of costs, telemedicine may offer a more "democratic" healthcare approach to members of different economic classes [8–11]. Telemedicine's greatest virtue is its ability to provide limitless access to health care. Telemedicine is commonly divided into three major categories of health delivery programs: (1) *store and forward systems*, (2) *interacting videoconferencing systems*, and (3) *remote surgical assistance.*

Store and forward systems are considered the most convenient telemedicine methods in terms of simplicity of technical devices, costs, and human resources. They account for over 80% of telemedicine encounters in use today [12]. These systems allow medical information collected in any forms to be stored and sent to medical experts who study and review it before "bouncing back" to the sender with a proper electronic diagnosis.

Interacting videoconferencing is a more sophisticated and expensive telemedicine method mostly used in case of emergencies or major disasters by emergency room specialists.

Remote surgical assistance represents the most complex and expensive scenario where advanced "video game–type technology" allows surgeons to control surgical instruments during an operation performed in another location.

Telemedicine offers quite a lot of advantages in terms of cost-effectiveness, quality of care improvement, advanced educational opportunities for health-care providers, and significant potential for interesting economic growth.

Teleconsulting between general practitioners and specialists, specialists of different medical branches, nurses, and specialists is an opportunity that has been successfully experimented in different fields of medicine such as cardiology, dermatology, ophthalmology, orthopedics, and psychiatry.

MOBILE HEALTH (M-HEALTH) AND MEDICAL DATA SECURITY

The widespread use of rapidly evolving *mobile communication technology* has further provided new innovative platforms for a ubiquitous, faster access to medical information [13]. The continuous development of smartphones, tablet personal computers, wireless medical devices, and wireless networks along with a growing number of inexpensive, easily downloaded medical apps has raised new concerns for data integrity and security. The global smartphone mobile health application market increased by a factor of 7 from 2010 to 2011 [14]. *Personal privacy protection* (*PPP*) is regulated differently in different countries. Security threats may occur during the whole process of data management: *data at rest*, *data in use*, *and data in transit*. Secure mobile health systems must also allow for a proper storage and transfer of multimedia content like audio, video, and file sharing [15]. In the United States, secure handling of medical data is regulated by the Health Information Portability and Accountability Act of 1966 (HIPAA) [16]. In Europe, PPP is regulated by Article 8 of the European Convention of Human Rights (Table 75.1) and by the Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data approved by the European Council in 1981 [17]. Canada regulates PPP through the Personal Information Protection and Electronic Documents Act that came into effect on January 2001 [18]. Modern *E-health* and *M-health* communication allows both synchronous and asynchronous interactions. The American Telemedicine Association has provided effective guidelines for synchronous communication systems regarding PPP [19]. According to these guidelines, synchronous audiovisual medical sessions should be properly protected by the use of a private, point-to-point circuit able to host an *advanced encryption standard* (AES) to allow a proper encryption of data or a *virtual private network* (VPN) for Internet transmission. The guidelines also call for network and software security protocols, authentication and accessibility protocols, and for adequate measures to protect medical and personal data against intentional and unintentional corruption. Protecting electronic patient data needs to follow standardized methods mostly based on encryption modalities. Data transferred through the Internet are secured by *transport layer security*, by using asymmetric cryptography

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Table 75.1 European Convention on Human Rights: European Court of Human Rights - Council of Europe - 01 June 2010

Article 8
Right to respect for private and family life 1. Everyone has the right to respect for his private and family life, his home, and his correspondence. 2. There shall be no interference by a public authority with the exercise of this right except such as is in accordance with the law and is necessary in a democratic society in the interests of national security, public safety or the economic well-being of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others.

Source: Council of Europe, F-67077 Strasbourg, cedex www.echr.coe.int

with 128-bit or 256-bit encryption methods. HIPAA requires 128-bit encryption of electronic protected medical information. AES is also used by commercial companies like Skype™ (256-bit AES).

VPNs are another option for transmitting voice, video, or data using the Internet. They provide a secure way of connecting to a private local area network at a remote location, using the Internet or any public network to transport encrypted data packets. *Mobile VPNs* can be used in settings where the end point of the VPN is not limited to a single Internet protocol address but roams across different networks from cellular carriers between multiple Wi-Fi access points. The main concern with wireless technology is that unencrypted data can be monitored or recorded by third parties much easier than on a VPN or traditional wired networks [20]. Electronic data encryption needs to be completed before data transmission to allow proper protection in wireless environments. Current security standards are *Wi-Fi protected access* (*WPA and WPA2*) and need to be implemented by end users. Unfortunately, there is no guarantee that these standards are brought into operation within in-home or public environments. Data security related to mobile device apps is typically based on an application security model where the developer verifies the integrity of the application itself before making it available for download. Security standards must support interoperability among different systems. *Interoperability* can be defined as the ability of two or more systems to interact with one another exchanging information with the aim of achieving predictable communication results.

Mobile-health authentication is another important step to properly defend data integrity and security. The minimum acceptable authentication level should be based on two interlinked factors: *personal identification number* and password. Biometrics, such voice printing, facial recognition, fingerprints, and retinal scans, can add extra security to the authentication process [21]. Presently, the lack of standardization in data security management does not allow interoperability of mobile devices to reach their full capabilities, but next-generation technology will certainly provide effective and affordable solutions to break this barrier.

INFORMED CONSENT IN TELEMEDICINE

Informed consent may be defined as a duty to outline the risks, benefits, and possible acceptable methods of treatment as well as the implications of not having proposed treatment performed. *Failure to obtain consent before a medical treatment is considered an unauthorized trespass against patients' bodily autonomy*. In telemedicine, all standard approaches to informed consent should be applied. In particular, telemedicine requires that patients approve the electronic transfer of telemedical encounters and be provided with a list of parties being involved in the treatment at all ends of the transmission [2,22,23]. Patients should also informed about potential risks involved in the use of telehealth equipment such as *interception, misuse, and misappropriation*. Disclosures of all measures taken to preserve the integrity of medical data (encryption, physical access key devices, possible bioidentification devices) should be also provided. A statement regarding the possibility of inaccurate diagnosis and consequent treatment as a result of improper/faulty data transmission should be included. Patients should have access to all information transmitted during a teleconsultation with the opportunity to withdraw/withhold their consent at any time without affecting the right to future care or treatment. Patients can also decide to limit the presence of medical students and/or doctors in training during their telemedicine consultation if they so desire. All documents recorded during a telemedicine consultation will be given the same level of protection as medical records against proper disclosure. In some countries, a mandatory written informed consent is to be signed by patients prior to any telemedical procedure. Informed consent will be stored in the patient's medical record, and a copy will be sent to the consulting doctor before the actual consultation takes place.

CONVENTIONAL AND ELECTRONIC MEDICAL RECORDS

Medical records are the most valuable sources of patient-centered medical information. They are indispensable tools for a good medical practice since they structurally collect all relevant medical information important to reach a proper diagnosis and plan efficient treatment strategies. Medical records are dynamic since they need to be periodically updated and should be easily readable by all physicians and medical staff to efficiently and rapidly retrieve all necessary information. Conventional medical records are paper-based and hand written and require quite a lot of protected space for their storage. Duplicating them to protect extremely valuable medical information from major risks like water and fire as well as natural deterioration of ink, paper, and folders is not an easy task. They are nevertheless quite popular among doctors because they are relatively inexpensive, portable, and easily written without any restrictions concerning formats and drawings, but they are not easy to decipher due to endless types of handwriting styles. EMRs are computer-based, require a proper standardization of medical data entry, allow unlimited portability of medical data, and provide an indispensable ground on which to base peer-to-peer or multidisciplinary e-consultations. The extreme portability and duplicability of EMR raises the question of how to properly protect medical data from being inadvertently disclosed to third parties violating patient privacy. The risks of unauthorized access to and subsequent misuse of confidential medical information are always present. A confidential computer file containing the names of 4000 HIV-positive patients was illegally accessed in Pinellas County (FL, USA) in 1997 [24], and in Italy, computer vandals deleted 10 years' worth of AIDS research [25]. Extremely efficient data protection management should therefore be implemented when working with EMR.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

CONSUMERS' ACCESS TO HEALTH-CARE INFORMATION

Consumers have always been interested in knowing more about medical issues as part of their legitimate attitude to establish a more balanced relationship with their doctors. In the past, this sort of information was quite difficult to obtain since the cost and diffusion of medical books were quite discouraging obstacles for the general population. Patients consulted with doctors taking back all information they could collect from their experience and keep it jealously to be used to the benefit of family members and friends in case of future needs. Medical advice was easily passed from patient to patient, most of the time with some personal interpretation added to the original version, variably modifying the medical information obtained from doctors. Medical consultations were quite expensive, and people wanted to take maximum advantage out of each of them. Consulting with another doctor to get a second opinion was obviously possible but not for everybody's pocket. Doctors' life was much easier then, since consumer-centered medical information was too scarce and difficult to obtain.

With the advent of modern communication systems, medical information started to be available to increasingly vast sectors of the population, providing a source of *consumer medical education*, which progressively lost full doctors' control. Medical encyclopedias, medical debates, and therapeutic challenges on newspapers and magazines were, and still are, quite popular. But the true revolution began with personal computer technology, the Internet, and mobile smartphones [26]. Time is a major issue today, and fast access to relevant information is crucial to succeed in modern life. More and more consumers and patients alike spend an increasing amount of time to consult with Internet-available medical information trying to get multiple and faster answers to their medical problems. Modern conventional consultations are quite challenging for doctors today since patients come already with enough medical information to confront them with diagnosis, treatment plans, and interventional advices. Doctors can be divided into two main categories regarding their attitude to react to this kind of interactive confrontation. Part of them react *defensively*, partially refusing to properly consider what patients bring up to the discussion. This attitude can jeopardize two major pillars of the patient–physician relationship—trust and communication—potentially leading to a failure in establishing a fruitful, mutually beneficial patient–physician cooperation. *Deliberative–collaborative* doctors behave quite differently helping patients to properly select medical information pertinent to their specific cases. This kind of physicians act as "facilitators" toward retrieving medical information through accredited sources providing a "guiding professional advice" to select most beneficial data found on the Internet. This attitude can instill trust in patient–physician communication, potentially leading to a reinforcement of modern patient–physician medical alliance [27,28].

E-MEDICAL CONSULTATION AND E-MEDICAL ADVICE IN AESTHETIC AND COSMETIC DERMATOLOGY

Cosmetic and aesthetic dermatology is an advancing branch of dermatology that is not only involved in beautifying the skin and its adnexa but also in correcting congenital and acquired skin defects to restore an harmonic and balanced social message. Antiaging and age-preventive strategies are integral parts of cosmetic and aesthetic dermatology. Cosmetic and aesthetic therapies and procedures are always based on a proper diagnosis that involves a thorough general and specific anamnesis similarly to what happens in conventional general dermatology. The major difference between general dermatology and cosmetic and aesthetic dermatology consists in patients' perception of their skin alterations. Most patients tend to amplify the personal perception of their skin defects due to the social impact they think their defects induce.

Dealing with cosmetic-oriented patients is not easy and requires a very balanced, trustworthy professional approach. As all medical–surgical disciplines, cosmetic and aesthetic dermatology is based on a strong patient–physician relationship, leading to a well-structured problem-solving approach. Initial consultation; medical, cosmeceutical, and nutraceutical prescriptions; invasive and noninvasive procedures; and long-term follow-up visits commonly take place in doctors' offices or more advanced medical–surgical facilities. Face-to-face or in-person visits are, without any doubts, the gold standard in medical profession because of the immediate, direct access to all relevant clinical, psychological, pathological information necessary to reach a proper diagnosis from doctors' point of view and because of the unrestrained communication advantage that this sort of interaction offers to patients. Unfortunately, conventional consultations imply a considerable investment of time to reach doctor offices, wait in waiting rooms before they actually see the doctor, and being actually involved in the medical procedure itself. Time investment is inevitably dilated when doctors are located far away from patients' place of living—in another city or even in another country. Occasionally, face-to-face dermatologic consultations might also subtend psychological embarrassment for patients suffering from cosmetic and aesthetic unbalance in personal perception of their external image, inducing them to look for other forms of communication. Time, space, and psychological barriers have progressively dissolved with the advent of *E-health* and *M-health*. Today, it is quite common for a dermatologist to receive spontaneous, unstructured e-mail messages from patients regarding their cosmetic and aesthetic conditions. This form of communication is not regulated by any rules and is usually offered at no charge in doctors' websites. Most of messages come from patients motivated to really solve their problems, but a minority of e-mails just focus on curiosity in specific techniques, technologies, and procedures. Answering to this kind of e-mail messages is a professional courtesy that can potentially contribute to increase the patient portfolio of any dermatological practice (Table 75.2). Motivated

Table 75.2 Most Common Requests Coming from Patients Concerned about Cosmetic–Aesthetic Issues

Diagnostic information
Focused cosmetic problem: clinical evolution—potential interactions with specific anatomical functions
Extended cosmetic problems: clinical evolution—potential interactions with full body functions
Second opinion on specific diagnosis and treatment options
Information on treatment options
Specific treatment proposed by patient after reading through Internet-available medical information
Multiple treatment options proposed by the patient after reading through the Internet and consulting with other health-care professionals
Specific treatment advice to further improve clinical results obtained after already performed procedures

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

patients might also spontaneously provide some digital images of their skin alterations, laboratory exams, pathology reports, previous consultations, but this is not a common scenario. Most of the time spontaneous motivated patient e-mails require a two-step approach involving an initial exchange of information based on a specific interpretation of the message received by the doctor and a second exchange of information once specific digital images and relevant medical documents are requested and received. When physicians request further information to patients who spontaneously come in touch with their practices, an informed consent stating that all received relevant clinical data will be protected under the PPP rules valid in the country where the practitioner is located and licensed to practice needs to be signed. Quite unfortunately, the quality of digital images sent by patients varies widely, and their interpretation could be extremely challenging. Patients should be properly instructed to use a consumer-grade digital camera with a recommended 800×600 pixel (480,000) resolution when taking clinical images. In difficult-to-interpret cases, it is always better to invite patients to schedule a conventional face-to-face appointment. When involved in this kind of e-communication activities, any physician should consider the potential medico-legal implications that an "innocent," free of charge medical advice could bear. A simple statement saying that no responsibility can be taken for the clinical interpretation of a dermatologic condition when given on a patient's spontaneous description and associated, uncertified digital images should be usually enough. The statement should also state that a free e-medical advice is not a properly structured e-medical consultation regulated by telemedicine laws.

The American Academy of Dermatology Position Statement on Telemedicine approved by the Board of Directors on February 22, 2002, and amended by May 22, 2004, supports the use of telemedicine to deliver dermatologic expertise to populations who would not otherwise have access to dermatologists [29]. The statement urges practitioners wishing to integrate teledermatology in their practices to choose between two fundamental different platforms of care delivery: *store and forward* vs. *live interactive*.

Live interactive teledermatology takes advantage of video-conferencing as its core technology. Participants are separated by distance, but interactive in time. Video-conferencing systems work optimally when a connection speed of a minimum of 384 kbps is used. Practitioners who render care using live/interactive systems are subject to credentialing and privileging at the distant site when they are providing direct care to patients. Credentialing is provided by the *Joint Commission for Accreditation of Health Care Organizations* (*JCAHO*). Appropriate medical records should be available by the consulting dermatologist prior to or at the real time of the telemedicine encounter. A copy of the updated record generated by telemedicine consultation should be subsequently available at both consultant and referral sites. All practitioners who practice telemedicine should insure compliance with the PPP rules. Transmissions should be encrypted when running over the public Internet. Interactive telemedicine requires all equivalent safety measures of direct patient contacts. In the United States, teledermatology using interactive technologies is restricted to jurisdiction where the provider is licensed. In the case of a direct patient care model (provider to patient) without any providers at the referring site, the liability rests entirely on the dermatologist. Diagnostic and therapeutic recommendations rendered are used solely on information provided. Therefore, liability should be based on the information available at the time the consult was answered.

Store and forward teledermatology refers to a method of providing diagnostic advice, usually to another provider. A dermatologic history and a set of images are collected at the point of care (POC) and subsequently transmitted for review by the consulted dermatologist. In turn, the consulted dermatologist provides a written report back to the POC [30–34]. Practitioners who render care using store and forward systems are viewed by JCAHO as "consultants" and are not required to be credentialed at the originating site. Most store and forward systems work as "de facto" EMRs. The record of the specific medical care is typically available electronically to both the consultant and the referring provider. PPP compliance is largely a matter of informing patients that their medical information will be traveling by electronic means to another site for consultation. This should be noted in the consent form at the POC. All electronic transmission of medical data should be encrypted, and reasonable care should be taken to authenticate those providers who have electronic access to the records. Store and forward providers should take particular care regarding direct prescribing to patients via electronic communication. Most states in the United States have regulations that discourage or prohibit practitioners from prescribing drugs to patients that they have not seen face to face. Since most of the store and forward providers are working in collaboration with a provider at the POC, this issue should not inhibit patient care. The dermatologist should therefore recommend, as opposed to prescribe, specific drug regimens. In the consultative mode (provider to provider), the referring provider ultimately manages the patient with the aid of the recommendations from the consultant. The referring provider may accept the recommendations in part or whole or none at all. The liability in this specific scenario will be shared between the referring provider and the consultant based on the extent to which the recommendations were followed by the referring provider.

Most of the aesthetic and cosmetic dermatologic consultations are based on a store and forward type of care delivery platform. Two kinds of consultations can be described: a *direct patient–provider medical consultation* (*cyber-consultation*) and an *indirect referring provider–distant consultant medical consultation* (telemedicine consultation). In the first case, patients consult directly with dermatologists after being properly instructed about all necessary steps required for a properly controlled teledermatologic consultation, signing an appropriate informed consent, and a limited liability statement. Cybermedicine consultations could be considered unethical or even illegal should an initial conventional face-to-face consultation not be properly documented in the patient's EMRs. All relevant documents, reports, and digital images will be kept by the dermatologist within properly protected medical records along with a copy of teledermatology report issued at the end of the e-consultation. In the referring provider–distant consultant teledermatologic scenario, AAD Position Statement rules should be implemented.

When teledermatology and cyberdermatology are practiced, cross-border special attention should be given to finance and taxation systems. According to the European law, the member state of treatment (member state where the service provider is established) must ensure that health care is provided in accordance with its legislation [2].

Another growing form of cosmetic and aesthetic e-consultation is centered on advanced management of postoperative complications. Dermatologists and practitioners performing cosmetic and aesthetic procedure need inevitably to

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

confront with potentially challenging postoperative complications. Taking fast and properly diligent actions to solve these kinds of medical problems can make the difference between a satisfied patient and a medico-legal litigation. Consulting with world-known experts in specific fields of cosmetic and aesthetic dermatology is possible through a simple store and forward teledermatology communication platform. Expert advice can provide extremely useful information about how to deal with all different aspects of specific postoperative complications, speeding up recovery time and lowering the risk for permanent skin alterations. Patients involved in these kinds of unfortunate events feel more comfortable when expert doctors are consulted to deal with their problems. These reassuring scenarios can surely add to the diligent behavior of the first operator. Expert advice can be requested periodically by operators during the healing and maturation phases of skin repair. In the unfortunate case of a malpractice claim, the involved practitioner might also rely on a teledermatologic expert witness consultation to support his or her position in front of the court.

MEDICAL LIABILITY IN CYBERSPACE

While the use of computers, the Internet, and mobile communication devices in health care has exploded over the past decade, producing new innovative efficiencies and improvement in advanced communication, patient education, medical record management, billing, and access to specialty care, practitioners employing these tools in their practices has been exposed to novel medico-legal risks and liability that did not exist a generation ago. *Telemedicine*, in contrast to traditional health care, is a medical practice involving an on-site attending physician and a "remote teleconsultant" who provides a service such as interpretation of clinical images or consultation for the benefit of selected patients. Telemedicine may have several benefits, including elevating standard of care, improving access to highly specialized care, and potentially reducing costs.

Cybermedicine, on the other hand, is quite different from telemedicine. In cybermedicine, there is no face-to-face contact between practitioners and patients; diagnosis and treatment are rendered by potentially unknown physicians to unknown patients, or care is given to an already established patient but only through electronic communication. A series of important issues must be considered when engaging in telemedicine. Specific medical license, standard of care, specific physician–patient relationship, medical liability limitation and coverage, specific informed consent, and confidentiality of electronic communication should be all properly implemented.

Privacy and Confidentiality

It must be remembered that since Hippocratic times, confidentiality has been the hearth of medical ethics as it has been further stressed by the International Code of Medical Ethics in more recent times stating that a doctor must preserve "absolute confidentiality in all he/she knows about his/her patient" even after the patient's death. The British General Medical Council is quite explicit in defining patients' rights: "patients have the right to expect that you will not disclose any personal information which you learn during the course of your professional duties, unless they give permission. Without assurances about confidentiality, patients may be reluctant to give doctors the information they need in order to provide good care." Telepractitioners, health-care facilities, and telecommunication service providers might face legal action where confidential medical information is sent to persons not within the ambit of a patient's consent.

Licensure and Liability Coverage

Usually, medical boards mandate that physicians providing diagnosis and treatment to patients within a state's geographical borders must have full, unrestricted medical license in that particular state. Any physician willing to provide telemedicine or cybermedicine services to patients in any particular state must query their state's medical board about licensure requirements. Physicians must notify their medical liability insurance carriers of the specific locations where patients receive their telemedicine or cybermedicine care. Failure to comply may result in disciplinary actions for practicing medicine without a valid license in a given state, as well as denial of medical liability coverage in the event of a lawsuit. In the EU, medical qualifications awarded by one member state are valid in all other EU member states; however, there is not an automatic right to registration. Cross-border medical practice in the EU requires the recognition of the doctor's registration to practice in countries other than that in which doctors are living and practicing and the completion of formal registration requirements in all those "host" countries in which the doctor intends to provide his or her own medical services to patients (even if he or she may never be physically present) [2].

Most countries nevertheless consider cybermedicine unethical unless physicians have already performed a conventional face-to-face consultation with their patients (Table 75.3).

Physician–Patient Relationship and Standard of Care

Performing telemedicine consultation a properly licensed physician, meeting appropriate insurance requirements, would be protected if standards of care are met. Cybermedicine practice could be considered unethical, illegal, and not covered by liability insurance unless practitioners have already established a solid patient–physician relationship.

Privacy and Informed Consent

PPP rules and confidentiality may be more difficult to be properly implemented in a cyberspace scenario. Unintentional corruption or release of information to unknown recipients may become a major legal problem. Security of PPP is almost

Table 75.3 Main Five Issues to Be Considered before Entering the Complex Field of Telemedicine

Licensing
Do telemedicine providers also need to be licensed/registered in the state(s) where patients reside?
Data protection
What are the conditions for the legitimate processing of personal health data?
Reimbursement
Will cross-border telemedicine service be reimbursed and what will be the pertinent applicable taxation?
Liability
What is the liability regime applicable in case damage arises?
Relevant jurisdiction and applicable law
What are the relevant jurisdiction and the law applicable in case damage arises?

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

impossible to manage once sensible personal data are sent over the Internet. An important step to reduce the liability potentially associated with telemedicine, or Internet communication is to make patients properly aware of the known and potentially unknown risks that are inevitably beyond physicians' control. Physicians sending electronic information to a patient or to another consultant should always request an acknowledgement of receipt besides encrypting all data before its transmission. Diligence in these matters will prove that physicians made every possible effort to protect patients' personal health data. Additionally, a consultant may be liable for the ultimate treatment undertaken by the referring practitioner especially if the consultant failed to independently inform the patient of their findings (negligent supervision).

Malpractice due to Equipment Failure

Many medico-legal experts foresee that the provider will be responsible not only for the opinion rendered but also for the proper transmission of information. Failure of a properly accurate data transmission and its potential impact on the final clinical results should be communicated to the patient. Transmitting clinical images need a specific consideration since they can be altered by the technologies used to acquire, transmit, and decode. This poses the question of who will guarantee that images sent are identical to the received ones. Health care provided might be sued for equipment failure or malfunction should these functional alteration result in a direct or indirect injury to the patient. Equipment manufacturer, hardware and software distributors, and utility and equipment service companies could be joined in a claim for equipment malfunction and could be held responsible for problems associated with their products under the product liability of the EU Directives on Medical Devices. Therefore, the liability of technological failures seems to be shared out among all involved parties. Practitioners might be found potentially liable for failing to inspect equipment for obvious defects as well as the medical facility where the telemedicine equipment was provided. Manufacturers and distributors of hardware, software, and peripherals may also face an increased exposure to claims linked with their specific activities. In Europe, medical products, equipment, and devices have to be registered with the *Medical Devices Agency* (MDA) since 1994. This agency ensures that all approved medical devices meet the requirements of standard of safety, quality, and performance set by the unified statutory system of European Union Directives (1993, 1995, and 1997). The MDA strongly recommends that purchasers and providers of medical devices develop and implement effective procedures for the properly and correct use of devices for the purposes they were designed for, for assessing the proper training of end users regarding their operations, and for proper maintenance protocols.

Medical liability scenarios in cyberspace medicine are constantly evolving. All practitioners involved in telemedicine, cybermedicine, or electronic patient communication should carefully monitor specific medico-legal issues regarding this expanding branch of modern medicine. Failure to keep up with latest issues and lack of knowledge could not provide an acceptable defense in case of a medical malpractice lawsuit.

Insurance Policies

The growing number of potentially difficult to manage medical-legal issues involved in telemedicine would force providers of telecommunication services to take out expensive insurance policies that would inevitably be transferred on telemedicine providers bearing a more than potential risk of discouraging further developments of this highly innovative approach to medical care.

SUMMARY

Teledermatology can easily open its horizons to the world of cosmetic and aesthetic dermatology. A store and forward telecommunication system seems to be ideal to the task allowing patients to get access to expert advice before and after planning cosmetic–aesthetic procedures suitable to solve their skin problems. Due to the high complexity of cosmetic and aesthetic alterations, multiple expert opinions are usually sought by many patients in order to find a concordance in diagnosis and possible treatment options. Teledermatology can provide an easily accessible communication platform where many experienced dermatologists can share their expert opinions, satisfying even the most demanding of patients. Many cosmetic and aesthetic procedures may need considerably numerous postoperative follow-ups to monitor the evolution of repair and remodeling processes. E-follow-up procedures allow patients to be periodically evaluated without the need for conventional face-to-face appointments provided a good quality, protected imaging, and data transfer be implemented. Interexpert e-consultations can help dermatologists facing difficult to manage complications deal with them in a much more efficient and rapid way, potentially limiting possible medico-legal implications. Teledermatology might therefore represent an interesting and innovative communication system for an advanced patient-centered cosmetic and aesthetic care provided all necessary organizational and protective steps are properly implemented [34].

REFERENCES

1. Hilbert M, Lopez P. The world's technological capacity to store, communicate and compute information. *Science* 2011 April; 332(6025):60–65.
2. European Commission. Commission Staff Working Document on the applicability of existing EU legal framework to telemedicine services. E Health action plan 2012–2020. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=SWD:2012:0414/Fin:EN:PDF. Accessed December 7, 2012.
3. Whited JD, Hall RP, Foy ME, Marbrey LE, Grambow SC, Dudley TK, Datta SK, Simel DL, Oddone EZ. Patient and clinician satisfaction with a store-and-forward teledermatology consult system. *Telemed J E Health* 2004; 10:422–431.
4. Warshaw EM, Lederle FA, Grill JP et al. Accuracy of teledermatology for pigmented neoplasms. *J Am Acad Dermatol* 2009 November; 61(5):753–765.
5. Warshaw EM, Lederle FA, Grill JP et al. Accuracy of teledermatology for non pigmented neoplasms. *J Am Acad Dermatol* 2009 April; 60(4):579–588.
6. Balas EA, Jaffrey F, Kuperman GJ, Boren SA, Brown GD, Pinciroli F, Mitchell JA. Electronic communication with patients: Evaluation of distance medicine technology. *JAMA* 1997; 278:152–159.
7. Levin YS, Warshaw EM. Teledermatology: A review of reliability and accuracy of diagnosis and management. *Dermatol Clin* 2009 April; 27(2):163–176.
8. Armstrong AW, Dorer DJ, Lugn NE, Kvedar JC. Economic evaluation of interactive teledermatology compared with conventional care. *Telemed J E Health* 2007; 13:91–99.
9. Pak HS, Datta SK, Triplett CA, Lindquist JH, Grambow SC, Whited JD. Cost minimization analysis of a store-and-forward teledermatology consult system. *Telemed J E Health* 2009; 15:160–165.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

10. Whited JD, Datta S, Hall RP, Foy ME, Marbrey LE, Gambow SC, Dudley TK, Simel DL, Oddone EZ. An economic analysis of a store-and-forward teledermatology consult system. *Telemed J E Health* 2003; 9(4):351–360.
11. van der Heijden JP, de Keizer NF, Bos JD, Spuls PI, Witkamp L. Teledermatology applied following patient selection by general practitioners in daily practice improves efficiency and quality of care at lower costs. *Br J Dermatol* 2011 November; 165(5):1058–1065.
12. Lim AC, Egerton IB, See A, Shumack SP. Accuracy and reliability of store-and-forward teledermatology: Preliminary results from St George Teledermatology Project. *Australas J Dermatol* 2001 November; 42(4):247–251.
13. Visvanathan A, Gibb AP, Brady RRW. Increasing clinical presence of mobile communication technology: Avoiding pitfalls. *Telemed J E Health* 2011 October; 17(8):656–660.
14. Osunmuyiwa O, Ulusoy AH. Wireless security in mobile health. *Telemed J E Health* 2012 December; 18(10):810–815.
15. Luxon DD, Kail RA, Mishkind MC. mHealth data security: The need for HIPAA-compliant standardization. *Telemed J E Health* 2012; 18(4):284–288.
16. U.S. Department of Health and Human Services. Health Insurance Portability and Accountability Act of 1966 (HIPAA): Security standard. www.cms.hhs.gov/SecurityStandard Office for Civil Rights rev.05.03.
17. European Court of Human Rights - Council of Europe - 01 June 2010 and European Council. Convention for the protection of individuals with regards to automatic processing of personal data. 1981. http://conventions.coe.int/Treaty/en/Treaties/Html/108.htm.
18. Personal Information Protection and Electronic Documents Act (PIPEDA). Office of the Privacy Commissioner of Canada. 2001. http://www.priv.gc.ca/leg_c/leg_c_p_e.asp.
19. American Telemedicine Association. Practice guidelines for videoconferencing-based telemental health. October 2009. www.americantelemed.org/files/public/standards/PracticeGuidelinesforVideoconferencing.
20. Phifer L. Mobile VPN: Closing the gap. SearchMobileComputing.com. 2006. http://searchmobilecomputing.techtarget.com/tip/Mobile-VPN-Closing-the-gap.
21. Varchol P, Levicky D, Juhar J. Multimodal biometric authentication using speech and hand geometry fusion. *15th International Conference on Systems, Signals, and Image Processing, 2008* (*IWSSIP 2008*), IEEE, Bratislava, Slovakia, pp. 57–60. http://ieeexplore.ieee.org/stamp/stamp/Jsp?tp=&arnumber=4604366&isnumber=4604343.
22. Lakdawala N, Fontanella D, Grand-Kels JM. Ethical considerations in dermatologic photography. *Clin Dermatol* 2012 September; 30(5):486–491.
23. Berle I. Clinical photography and patient rights: The need for orthopraxy. *J Med Ethics* 2008 February; 34(2):89–92.
24. Privacy Rights Clearinghouse. http://www.ncbi.nlm.nih.gov/pubmed/11364080.
25. Smith RG. Telemedicine and crime. *Trends and Issues in Crime and Criminal Justice*. Australian Institute of Criminology, Canberra, Australian Capital Territory, Australia, April 1997.
26. Arican O. E-dermatology: Emails about dermatological diseases on the Internet. *J Dermatol* 2007; 43:375–380.
27. Hanson AH, Krause LK, Simmons RN, Ellis JI, Gamble RG, Jensen JD, Noble MN, Orser ML, Suarez AL, Dellavalle RP. Dermatology education and the Internet: Traditional and cutting-edge resources. *J Am Acad Dermatol* 2011 October; 65(4): 836–842.
28. Pak HS. Medical connectivity: The visual nature of dermatology is a good match for telemedicine. *Telemed J E Health* 2011 July/August; 17(6):405–408.
29. American Academy of Dermatology. Position statement on telemedicine. Approved by Board of Directors February 22, 2002. Amended by Board of Directors May 22, 2004. www.aad.org
30. Withed JD. Teledermatology research review. *Int J Dermatol* 2006 March; 45(3):220–229.
31. Oakley AM, Duffill MB, Reeve P. Practicing dermatology via telemedicine. *N Z Med J* August 14, 1998; 111(1071):269–269.
32. Whited JD, Hall RP, Foy ME, Marbrey LE, Grambow SC, Dudley TK, Datta S, Simel DL, Oddone EZ. Teledermatology's impact on time to intervention among referrals to a dermatology consult service. *Telemed J E Health* 2002; 8(3):313–321.
33. Warshaw EM, Hilmlman YJ, Greer NL, Hagel EM, MacDonald R, Rutks IR, Wilt TJ. Teledermatology for diagnosis and management of skin conditions: A systematic review. *J Am Acad Dermatol* 2011 April; 64(4):759–772.
34. WMA. WMA statement on the ethics of telemedicine. Adopted by the 58th WMA General Assembly, Copenhagen, Denmark, October 2007. World Medical Association/publications. http://www.wma.net/en/30publications/10policies/t3/

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Fundamentals of managing and marketing a cosmetic dermatology clinic in the modern world

Wendy Lewis

In the evolving digital world, consumers educate themselves long before they ever get near a waiting room of the dermatologist's clinic. Patients get stuck in a quagmire of information overload, and they often buy into the theory that they know what they want and need better than the doctor does.

Consumers are bombarded with information about medical aesthetic treatments from a wide spectrum of sources, including print, electronic, and broadcast media, websites, physicians, and other specialists. Although some of the information obtained from these sources may be educational and helpful, some of it can be misleading and inaccurate in terms of possible outcomes, while minimizing risks and downtime. The plethora of websites devoted to aesthetic treatment overload consumers with information promoting one procedure over another. It is a daunting task for consumers to sort through the conflicting claims and to locate a properly trained and qualified dermatologist.

The average consumer does not have the knowledge or expertise to comb through all the material to make an informed decision. The more conflicting information they get, the more confused they become, which can result in the patient doing nothing. The responsibility lies with the dermatologist to educate the patient by presenting the facts in an unbiased manner. Ultimately, patients need to place their trust in the dermatologist's professional recommendations. Trust lies at the cornerstone of the doctor–patient relationship.

Cosmetic dermatologists are not selling a product; they are providing a service and one that is personal and customized to each patient. It is a high-end service that encompasses the entire patient experience. This experience begins with the initial point of contact. In the past, that would have been a telephone inquiry. However, in the digital world of modern practice, it may be a Google ad, a review or rating online, or the clinic website. The patient's experience then progresses through encounters with the clinic receptionist, nurse, or physician's assistant, other patients in the waiting room, and up to the dermatologist, thus hopefully culminating in a treatment plan and, finally, the treatment. The ultimate success of the overall experience is dependent on the dermatologist's skill, expertise, bedside manner, and good judgment. However, there are many other factors to consider, including location, accessibility, the image of the brand, the staff, services offered, and the service culture of the clinic.

WELL-APPOINTED CLINIC

Basic information about the clinic and a synopsis of the main procedures offered may be readily available on the clinic website, and maps with directions to the clinic should be of sufficient detail so patients can find you easily. The clinic should ideally be convenient to some public transport, and parking instructions should be detailed on the website.

It is important to distinguish a cosmetic dermatology clinic from the bog-standard GP's rooms that may consist of a reception desk, shared waiting area, and one or two consult rooms. Patients seeking cosmetic procedures are looking for something more modern. They want to be reassured that they have come to the right place and that their choice of practitioner is spot on.

Most practitioners tend not to realize how outdated and dreary their clinics may look; however, cosmetic patients do notice. They look at every detail with a very critical eye. For this reason, the reception desk should be clean and tidy and patient areas should be maintained, appealing to the eye, and with an ambiance of professionalism and comfort. The physical environment your clinic embodies has a direct impact on your brand image. Having a facility that you can be proud of will increase your ability to attract new patients, retain existing patients, and operate efficiently. If your clinic doesn't look good, patients may vote with their feet.

To maintain an aesthetically appealing clinic environment, do a walk-through to determine what is in dire need of updating. Start with the exterior and assess the curb appeal. Enter through the doorway that patients use, and survey your space for anything that is shabby, broken, or soiled. Assign a staff member to look after daily upkeep, such as making sure washrooms have toilet paper and towels, brochure racks are filled, and reading material is current. Every small detail can affect your brand image.

Strive to create an environment that is welcoming and comfortable for patients while maintaining an air of a proper medical clinic. Although dark colors can hide dirt, warm and lighter colors make a clinic look brighter, more open, and larger. There is nothing worse than stained or frayed carpets in a medical clinic. It sends the message to patients that you lack attention to detail. Invest in quality furnishings and flooring that are stain resistant and designed for areas with high foot traffic. Generally, carpeted areas and large upholstered pieces should be cleaned every year, hardwood floors should be refinished every 3–5 years, and a fresh coat of paint may be needed every 2 years to maintain the clinic's polished image. The artwork you choose for patient areas also impacts the mood. If you highlight magazine clippings and diplomas, they should be professionally matted and framed in a consistent way. If your clinic looks like it is stuck in a time warp, it is worth the investment to modernize.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Pivotal Role of Clinic Staff

The front desk serves as mission control for every clinic and having the right staff at the helm is essential. Unfortunately, in many clinics, the lowest paid employee is the person who has been charged with answering the phone, scheduling appointments, and greeting patients. If these individuals are effective, they can greatly affect the bottom line of a cosmetic clinic. However, if they are curt, inefficient, or disinterested in helping patients, they can damage your brand, which in turn can wreak havoc to your bottom line.

One of the best investments you can make in your cosmetic clinic is to get the right staff on board. In general, it is important to hire nice people from the outset. Most reasonably intelligent people can be properly trained to function in a medical aesthetics clinic; however, you cannot train people to be nice. By nice, I mean that they should be naturally people loving, affable, and nurturing. Cosmetic patients, who are paying out of their own pocket, are known to be much more demanding than general dermatology patients, who may be seeing the doctor for dermatitis that is covered by health insurance.

An accommodating administrative and medical staff in your clinic will ensure a better patient experience that encourages referrals and repeat visits. The first phone call patients made to your clinic may be the deciding factor as to whether they will actually schedule a consultation. This point of contact leaves an indelible impression with the patient. If the experience is unpleasant or mishandled, the patient may decide against making an appointment or fail to keep it. Effective telephone etiquette is of utmost importance. The phone should be answered after a maximum of three rings, and the voice that greets the caller should be friendly and helpful, announcing the name of the clinic and preferably the name of the person answering. For example, *Chester Cosmetic Laser Clinic, this is Sandra, may I help you?* is a good standard to set for staff answering the clinic phone lines. Whenever possible, having the receptionist or scheduler use his or her first name is more personal and inviting than just an anonymous voice on the phone. A favorable first encounter will leave the caller with a positive impression. Conversely, the wrong impression can be created when the phone is answered in a rushed or unprofessional manner.

The scheduler needs to understand the importance of flexibility, even for busy dermatologists who are fortunate enough to have a long waiting list for new patients. It may sound impressive to inform a patient that the dermatologist is fully booked for several months, but in most cases, this will only encourage him or her to look elsewhere. Most people are not able to schedule appointments way out because plans can change and things come up. Patients value their time as much as practitioners do, and long lead times to schedule treatments or unreasonable waiting times are a deterrent. A clinic should be open and the doctors should be available when patients want to be treated, otherwise they will seek their fillers and peels with someone else.

A reasonable lead time for a new patient visit falls within a 3–4-week window and preferably shorter. It is not uncommon for someone wishing to have a neurotoxin treatment to be seen within a day or two. Most patients are unwilling to wait weeks or months for repetitive treatments, such as neurotoxins, dermal fillers, peels, laser hair removal, or IPL treatments. However, they may schedule larger procedures well in advance, like ablative resurfacing or hair restoration, where there will be some downtime to plan for.

More and more clinics are now offering evening and Saturday appointments to accommodate patients' busy schedules more rapidly. New patients should be asked how soon they would like to schedule the appointment, and an effort should be made to schedule an appointment as soon as possible. The receptionist should also be trained to record the caller's name, address, and contact information and inquire about the reason for the consultation. Some patients may be reluctant to disclose this information over the phone, but it is reasonable to ask to help with scheduling. Patients seeking removal of a skin lesion may not require as much time at the initial visit as someone seeking a full facial rejuvenation consultation.

Having enough staff and having the right staff are both important considerations. Depending on the patient flow in your clinic, there should be at least one front desk person and one assistant in the clinic when patients are scheduled. It is unreasonable to expect a sole secretary to handle several busy phone lines, computerize check-in, collect payments and billing, and deal with patients appropriately. Cosmetic patients are particularly attuned to this. An overworked staff means that they are more inclined to be in a rush and irritable.

Another thing to consider is having the right technology in place, which shows patients that you run an efficient and modern clinic. Patients don't want to see open files of paper charts crowding up the reception area. As more practitioners are using automated technologies to perform routine tasks, like billing, submitting claims electronically, and using electronic medical records to document notes, lab results, prescription information, and other patient information, technology will play an even more important role in clinic management.

COSMETIC CONSULTATION

Even though the patient may be looking forward to it, this initial consultation can be a stressful event. The decision to seek an aesthetic treatment is usually not a spontaneous one. Most likely, the patient has been contemplating this possibility for months, if not years, before searching for a cosmetic dermatologist. Most patients will do extensive research about the procedures they are interested in and dermatologists' credentials and check out many clinics before they ever schedule a consultation appointment. They will look online, follow trends in the media, and may rely on adverts to guide them in locating a dermatologist. Others may act on the recommendations of friends, family, colleagues, beauty professionals, and other practitioners for guidance.

With this in mind, the initial consultation in your clinic may be a big step for patients, and they may have anxiety about meeting the doctor. The first encounter with a new patient may last from 30 to 60 minutes in some cases. It is not really feasible to do a proper consultation about skin resurfacing or facial injectables in less than 30 minutes anymore. Few patients have only one thing in mind when they make an appointment. Rather, it is more common for them to come to your clinic with a long list of questions about multiple procedures of the face and body, as well as pages printed off the Internet or from glossy magazines. In some cases, it may be prudent to schedule a second consultation to address any lingering issues or concerns that you were unable to cover sufficiently due to time constraints. There is only so much information that the average patient can absorb in a single visit. If they are overloaded with all of the options on offer, they may get too confused to make

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

any decision. Investing the time in establishing a rapport with the cosmetic patient during the first consultation can be well worth it.

Although everyone assumes that doctors are rarely on time, it is a common courtesy to see patients as close to the appointed time as possible. Obviously, this is not always feasible. It is good practice, however, to notify patients if you are running seriously late either before they arrive or upon their arrival.

The patient's first face-to-face encounter in the dermatologist's clinic is typically with the receptionist, who should look up from the desk to greet the patient upon arrival. It is disconcerting for a patient to walk into the dermatologist's office for the first time only to find that no one is there to greet her or him. Even worse is when staff members are engrossed in conversation about their weekend plans or talking on their mobile phones and the patient is ignored. Once the patient has been checked in, he or she should be told if there is a long delay and given an estimate of the waiting time. Implement a system to text or email patients in advance to warn them or offer to reschedule the appointment and allow them to log onto your Wi-Fi network so they can pass the time quickly.

The patient will then be escorted to one of the rooms where an assistant may take a medical history, record previous aesthetic treatments and skin care usage, and ask about the reason for the consultation. The dermatologist may review this information before meeting with the patient so he or she is well prepared to address their concerns in a timely manner.

Patient Screening

Throughout the consultation, the patient will be interviewing the doctor. Despite a doctor having an international reputation and a formidable CV, patients will often base their decisions on demeanor, eye contact, and how warm, attentive, and caring the doctor appears to be. The top three topics of bad reviews posted online about doctors are in this order: too long waiting times, the feeling of being sold (on a procedure or course of treatments or products), and lacking good bedside manner.

At the same time, the cosmetic dermatologist should be assessing the patient to determine whether this is someone whose goals are realistic and who will be satisfied with the results of the procedures recommended. Consider whether you have a rapport with the patient and to what degree you are comfortable treating him or her. Understanding patient motivation is an important goal of the initial consultation. The best patients are those who are seeking aesthetic treatments for self-improvement, rather than to please someone else, such as a partner or parent. With most patients, you will be able to determine what motivates them fairly early in the consultation visit.

Regrettably, not every patient who enters a dermatology clinic is an ideal candidate for a cosmetic procedure. It is important to weed out any patients who appear to be psychologically unstable. For example, patients who present with body dysmorphic behavior, display traits of a narcissistic personality disorder, and show obsessive–compulsive tendencies may not be suitable. Dissatisfied or unhappy patients who have been to many other clinics should also raise concern. These patients may be impossible to satisfy and may be looking for something that is unattainable with the tools in your armamentarium.

Similarly, you may wish to avoid treating patients who are overly demanding, noncompliant, abusive to clinic staff, or chronically late for their appointments. Patients who do not pay their bills in a timely manner must be carefully monitored. It is not uncommon for patients to run up sizeable balances for cosmetic procedures that they cannot afford. Most aesthetic clinics expect all fees to be paid in advance or on the day of treatment by personal check, cash, and credit or debit card. In some cases, payment plans and financing programs may be offered. It is advisable to have a written policy clearly visible in the clinic that all payments for cosmetic procedures are expected on the day of the visit. Consultation fees should be based on your geographic area and the positioning of the practice. If you are in a middle-income suburban area where the cost of living is lower than in central London, for example, a consultation fee may not be feasible to charge at all. However, the best compromise is often to apply the consultation fee charged to the patient's account to a treatment or product.

Most patients will consult with at least one other aesthetic clinic before making a choice, and often two or more. Getting another opinion should not be frowned upon. In fact, I would argue that it should be encouraged. A well-educated patient, who has taken the time and effort to get the information needed to move forward, has the most potential to be a satisfied patient.

Be wary of patients who have seen multiple doctors or tend to clinic shop, as in having a filler injection with one clinic and going to another clinic for peels and switching to another clinic for laser treatments, etc.

Informed Consent

It is important to discuss risks and complications with the patient during the initial consultation. All patients should be properly informed of any relevant general and specific risks, complications, and alternative treatments. Of particular note, the potential for infection, delayed healing, visible scars, hyper- and hypopigmentation, asymmetries, prolonged erythema, and ecchymosis should be explained in their entirety to avoid any misunderstandings later on. Think of it this way: if you don't tell the patient ahead of time everything that could happen from the treatment you are performing, when it does happen, they will assume it is a complication.

At the end of the consultation, the patient may spend additional time with the assistant, nurse, or receptionist, who will discuss fees, scheduling, and pre- and posttreatment instructions in detail. It is generally not advisable for a dermatologist to discuss fees with patients directly.

Patient Privacy

Many cosmetic patients do not want to receive mail, phone calls, emails, or other communications that are identified as coming from a cosmetic dermatology clinic. In the interest of patient confidentiality, the receptionist should specifically ask all patients how they wish to be contacted by the clinic, for example, home, mobile, or office phone, email, or regular mail. Some may not want to be contacted at all, and that request should be honored.

In addition, sign-in lists where the patient signs his or her name under the name of the previous patient should be avoided at all costs today. The receptionist should sit in an enclosed space and be instructed to refrain from loudly announcing the patient's name in the waiting room. If your clinic is on the high street in a small community, it is likely that patients will run into one another in your waiting room. For these instances,

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

it may be prudent to consider a separate entrance or bring patients into a consult room upon request so they can have a private visit.

Clinical Photography

In today's litigious environment, taking good clinical photography before and after procedures is imperative, as patients tend to forget what they looked like before you treated them. Proper detailed documentation in all patients' charts as well as pre- and posttreatment photographs are vital tools for cosmetic dermatologists. For example, if a PDT patient complains that she doesn't see any improvement, you have the advantage of showing her the photos you took before the laser and comparing them side by side with her postlaser photos to assess the improvement.

Although it is quite difficult to get patients to allow you to use their photographs, collecting good clinical photography of your cases goes a long way to demonstrate to patients the quality of work you can offer and results that can be achieved.

Many clinics offer tablets in the waiting room and treatment areas or electronic photoframes to display before and after photographs of popular procedures offered in the clinic. This serves as an excellent marketing strategy to encourage patients to ask questions about more of the services you feature that they may not know about.

There is no substitute for visuals when it comes to explaining what having two syringes of a hyaluronic acid filler may look like on the patient's cheeks or how much visible improvement can be achieved after a series of nonablative fractionated laser treatments. At the last resort, you can request before and after photographs from the manufacturers whose products you use as an alternative; however, these are often captioned with the name of the physician and/or the company and patients will know they are not your own photographs.

ESSENTIALS OF CLINIC MARKETING

An effective marketing program should be based on considering your clinic in terms of your patients' needs and their satisfaction, whereas selling is all about techniques to get people to buy your product or service. The inherent difference is that a marketing strategy is an integrated effort that is in line with your core business model. To maintain visibility, a cosmetic dermatology clinic should have a consistent presence across a variety of channels that are relevant to the segment of patients that it wants to reach. In essence, your clinic needs to be visible where your patients are. For example, just having a clinic website and a Facebook page is not sufficient. These are only two spokes of the marketing wheel, albeit important ones, but not the only strategies to invest in.

A strong marketing plan can increase your clinic's visibility and profile, maintain communication with existing patients on a regular basis, and encourage referrals of new patients due to the high quality of care you deliver. Before investing in a marketing program, determine whether you have the right/enough staff, if your staff needs additional training, if your location is convenient to your target audience, whether you currently have the right menu of services in place, and what needs to be added to expand your reach.

Defining Your Clinic Brand

Your brand determines your competitive advantage, and it is a vital asset that should be protected at all costs. It exemplifies your reputation among patients, colleagues, and influencers. By building brand equity, you can distinguish your aesthetics clinic from all the others in the market that offer similar services. Branding is about more than just putting up a sign with the name of your clinic, the design and colors of your logo, or the facility and location. It is about who you are as a practitioner, the reputation you have earned among your patients, your core competencies, and the type of service culture your clinic offers.

Your value proposition or unique selling point is what sets your clinic apart from the clinic across the road or the chain of clinics springing up within your postcode. This may entail your specific strengths and unique training, the quality of care you provide, hours of operation, your specialization in a particular treatment category such as body shaping, the convenience of your location, and selection of lasers, light-based systems, or dermal fillers. Your unique selling point is usually a combination of factors that you can point to as making your clinic better or at least different than the competitor.

Your existing brand depends largely on what comes to mind when your patients think about your clinic as a result of the total impressions made by encounters with your brand name, logo, website, marketing, adverts, and everything else that people see and hear about your clinic. Even the most basic things like the signage outside your clinic entrance contribute to how your brand is perceived. Every time someone walks past your clinic, sees your Google ad, meets one of your staff members, or reads about you in the paper, they form an impression about your clinic.

Looking at your clinic through a prospective patient's eyes will help you define your brand. Align everything you offer with what it actually delivers. If this does not line up, there is a gap that needs attention. For example, if you are promoting a laser lipolysis system that you are calling, "Lunchtime Lipo," and the patient being treated winces in pain and leaves with severe bruising and cannot go back to work for a few days, the trust factor of your clinic brand will suffer.

Fee Structure

Another component of branding is to determine your positioning in the marketplace. Decide if you want your clinic to be high volume and low cost or low volume and premium pricing. The former requires a fairly substantial expenditure on marketing to keep a steady stream of new patients coming in, whereas the latter may be best accomplished by investing in public relations (PR) activities and forming referral relationships with like-minded practitioners of other specialties.

Competing mainly on price is a losing proposition; there will always be someone who is willing to offer the same or similar service or product for a lower profit. It is important to determine what your competition is charging in your local community for the same or similar treatments. It is best not to offer the lowest price in your community, but rather to establish a belief among your patients that they are receiving good value from your practice. Instead of cutting prices and thereby reducing profits, offer more in terms of services, convenience, after care, and pampering. Price is just a dollar amount, but value is the relative worth or desirability of a product or service to the end user.

Inbound Marketing

Consumers are taking control of educating themselves; therefore, you need to make it easy for these patients to find you.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

This is called inbound marketing, which is defined simply as the process of helping potential patients find your clinic before they are ready to make a purchasing decision and then leveraging that early awareness of your clinic stays top of mind when they are ready to make a purchasing decision, that is, book a consultation, schedule a treatment, or purchase a product.

Website Development

Your clinic website is the marketing mothership. Having an updated and optimized website today is mandatory for a busy dermatologic clinic. Patients search for local businesses online, and your website should be created to reflect the personality and positioning of your clinic. Market your clinic in a way that highlights quality over quantity to attract a loyal patient base. The site must be optimized for search engine pick up or only people searching for you by name will find your clinic online.

You only have 3 seconds to convince visitors that your site is worth any more of their time. Therefore, the look and feel of your site should create the desired effect. The landing page should contain the words or pictures that are already on the mind of your target audience, and it should deliver on any promise your external marketing program makes for consistency. The top of the landing page—above the fold—should contain the most important details that you want the visitor to know. For example, tell visitors who you are, what you do, where you are located, and how to reach out by including a phone number, email link, and/or scheduling form.

Another component of a well-designed clinic website is a robust photo gallery of actual patients who have signed photo consents or releases. This is very often the area of the website that consumers go to first. If you do not have photographs to post, you are putting your website at a supreme disadvantage. It is also important to avoid blacked out eyes, pictures of facial regions instead of the entire face, and poor quality photos with bad lighting, inconsistent angles, or makeup. Consumers are very wise to the tricks of photo-enhancing programs, so if your photos do not ring true, they are likely to be suspicious. Descriptors are helpful to let visitors know exactly what treatment was performed and the interval between the before and after photos. Wherever possible, select photos that match the target audience you are marketing to.

Mobile Platforms

With the advent of advanced mobile devices becoming a fact of life across all demographics, mobile marketing is taking the center stage. If your website is not searchable on mobile platforms, you may be unwittingly turning visitors away. Since the screen size of a mobile phone or tablet is small, it limits the scope of content that can be displayed. Therefore, creating a mobile version of your practice website is a worthwhile investment that is relatively affordable. Drawing out content for mobile devices, whether it is text, images, or video, needs to be simpler than for desktops or laptops. At a minimum, your website should have the capability of being viewed on the small screen of a mobile device, at least the size of an iPad and preferably an iPhone or droid. Reaching out to patients on the technology they use affords a dermatology clinic many unique benefits, including lower costs, improved customization, easier tracking, and reduced staff time.

Search Engine Optimization

Web marketing involves keyword-rich page content that helps you get found by search engines. For example, using descriptive words along with your practice name will create your identity online and allow visitors to find you based on their interests. Working off a list of keywords, you will need to work closely with your web designer on page headlines, subheadlines, and opening paragraphs for each page that include these words and phrases. Another tip to make sure they find your clinic is to include the street address, postcode, phone number, and other towns or cities you attract patients from every page of your site. Create a free listing for your clinic on Google, Yahoo!, and Bing so that it shows up on a map when potential patients do a local search.

Set a reasonable budget for what you want to achieve in terms of site visitors, new patients, and increased revenue, and engage a firm that has good references and wide experience working in the medical space. Create rich, SEO words that lead search engine users to your website. Think of search terms consumers will use to find your clinic. For example, "Devon Laser Clinic," "Best Botox Windsor," or "Acne Scar Treatment." Focus on the treatments that are most profitable and that you want to promote most, rather than trying to be everywhere. For example, if someone is looking for a specific topic, such as "Cellulite Reduction," you want your site to be as high up on search engines as you can afford so patients can land there. Pay Per Click (PPCs) adverts are an integral part of a web marketing program. These are the ads you will find on the right column on Google.

Starting a Blog

The most popular blog program is WordPress, which looks more professional than some other platforms and is easier to use. It should be set up by a programmer who can install the requisite widgets and plug-ins to make your blog more interactive. Ideally, a blog should have the same look and feel as your clinic website. It can be set up to live either within your site or under a separate domain name to increase search engine rank.

The challenge for dermatologists is finding first the time to blog and then deciding what to blog about. One of the best ways to add engaging meaningful content to your practice blog is to compile interesting content that is already posted on medical websites and Facebook pages. By collating timely and relevant content, you can add your own spin to make it uniquely yours. Find good content by searching on social media platforms, medical blogs, medical portals, and ASDS and AAD websites. Another tip is to set Google alerts for key categories and topics, such as cosmetics, laser resurfacing, dermatologic surgery, skin cancer, sun protection, and acne treatments.

An average blog post should be 300–500 words and include share buttons so readers can recycle the content on their social media platforms. You can vary the posts on the blog to feature photos, videos, press clips, links, and graphics to make each post more interesting. Allowing several members of the clinic staff to post in their own voices may add another dimension to the blog.

To help with search engine visibility, posts should be optimized by including keywords in the text, such as "laser resurfacing Sydney," while keeping it readable. Blog posts

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

can usually be scheduled in advance, and frequency should be at least once weekly and preferably more to keep the momentum going.

Email Marketing

By definition, internal marketing involves promoting your practice and services to the staff as if they are the internal customers of the practice. This concept has evolved to include communications to existing patients who already know your practice. A big part of the marketing effort for any practice is an emphasis on staff training to make sure they are up to speed on what your clinic offers. Internal marketing can be facilitated in a number of ways and should be done consistently to keep your practice top of mind and instill patient loyalty.

One form of internal marketing for clinics that is a mainstay is eblasts. Distributing newsletters by email to past and present patients is a well-accepted method of keeping in contact with patients. In order to set this program in motion, you will need an up-to-date email database that your patients have opted in to. Eblasts, as these newsletters are commonly referred to, can include helpful articles, monthly specials, and information on clinic news. The goal is stay relevant and visible to your patients as their preferred aesthetics provider when they are ready to have a treatment.

Eblasts are best timed at specific intervals, but not too often as to cause the recipients to mark them as spam or opt out of your mailing list. Monthly is a safe model to follow. Many clinics also use printed newsletters that are mailed out on a quarterly basis. Clearly, print runs are more expensive, but these tend to have a longer shelf life. The content can be prepared in-house or by a marketing consultant as needed.

Open House Events

Open house events are a mainstay among successful dermatology clinics. Typically, this strategy is more effective in smaller cities and suburban areas, where there are fewer distractions than in major cities. These events can range from small and intimate gathering of people who are very motivated to have a treatment to a large group of people who have brought their friends.

Clinic seminar events are a great way for established patients to learn about different cosmetic procedures and products that your clinic offers. Evening after hours are the most popular time to host events and invite patients to come to the clinic, enjoy cocktails and canapés, or coffee and cake, and check out information on different procedures in more detail. Some clinics will offer demonstrations of treatments so patients can see how it is performed. They are given the opportunity to ask the demonstration patient questions about the procedure, pain level, and what it feels like and see photographs of actual patients' results.

Open house seminars can be developed around a seasonal theme, such as "Brighten Up Your Skin for Spring," or "Shape Up for the Holidays." In some cases, representatives from vendors may be invited to attend and support clinic events. A PowerPoint presentation is helpful for guests to learn more about what the clinic offers. Patients are then encouraged to schedule a consultation for more information, and they are given goody bags of promotional products to take home.

Patient Reward Programs

It is well accepted that word of mouth is the most trusted form of advertising because the person providing the recommendation has used the service or product and is speaking from personal experience. Generating positive word of mouth for your clinic is a constant challenge, especially in places where patients are less inclined to broadcast the fact that they have had aesthetic treatments done. Cosmetic dermatologists know that happy, satisfied customers are less likely to go public, say thank you, or write glowing reviews and endorsements. Whereas disgruntled patients tend to be more vocal, proactive, and often tell you what they don't like and expect an immediate response.

Successful marketing strategies start and end with making patients a top priority. Patient acquisition adds growth opportunity, but the mainstay of your practice's longevity comes from loyal patients. Rewarding patients for their loyalty can be a worthwhile investment. Incentivizing happy patients will show them that you appreciate their business and referrals. They can become brand ambassadors for your clinic in the local area and spread the word about you.

Patients can be very fickle because they are bombarded with a daily assault of deals for cheap laser hair removal and discounted filler injections. Rather than spending a fortune to attract new patients all the time, dermatologists are well served by doing everything possible to keep existing patients coming back. If a patient is satisfied with the experience in your office and the care they receive, they will return and will hopefully refer their friends. Recognizing and rewarding patients who refer their friends is also a good way to keep them referring more in the future.

Consider implementing a VIP card, similar to the American Express Platinum Card that comes with added benefits. For example, if you add a new laser to your clinic, invite your VIP patients to come in for a complimentary trial. Offer them an extra area of neurotoxin from time to time, or let them try a new skin care regime you are trialing for their feedback. In short, make them feel special and they will stay with you.

Social Media Platforms

Social media plays an important role in marketing for an aesthetic practice. There are not many other ways to reach thousands of potential patients all over the world without spending a fortune on advertising and PR. In the long run, social media is a more cost-effective strategy than any traditional form of advertising. Social media marketing is an effective strategy to define your brand, build your reputation, and bring in new patients.

Social media channels are new ways of talking to existing and new patients online. Think of social media as essentially a network of communication channels that can be linked together in several ways. It is an effective way to build new relationships; strengthen existing relationships with colleagues, clients, media, and vendors; and let them know about what is happening in your clinic. However, the most valuable way to use these channels is to focus your efforts on leading people toward making a purchase; for example, booking a consultation, scheduling a treatment, or purchasing a product from your clinic.

Each social channel has its unique strengths and weaknesses, and it is important to understand the best way to use these vehicles, how your patients interact with each of them,

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

and the associated costs. Putting systems in place to measure the effectiveness is an important aspect of the process. You can track where your clicks are coming from and stay on top of your social media results on a monthly basis. Analytics are readily available for most platforms so you can continually measure the response you get. Linking your website to all of your social media platforms will also expand your online presence.

Integrated marketing draws upon the power of traditional methods, such as web marketing, advertising, and PRs, and merges these with tools that include SEO, PPC ads, and social media. Integrating your marketing programs involves creating a central theme and imagery that defines your brand in a cohesive manner. For example, the look and feel of your blog should complement your Facebook page and the landing page of your website. Most updated websites and blogs have links to every other platform that the practice is engaged on, including Facebook, Twitter, LinkedIn, YouTube, Pinterest, and Google+. All content can be shared, adapted, and recycled across every other platform you participate in for maximum exposure. The key is to avoid duplicating content because that can work against you with search engines.

Facebook, Twitter, and YouTube are the most highly trafficked social media sites. Set up a profile on these as well as Google+, Pinterest, and Instagram, and then focus on those that have the highest return for your clinic. The social media sites that most of your patients are active on are the ones you should invest the most time and money in.

Begin by assigning a staff member to assist with day-to-day social media marketing activities. If someone is going to be interfacing with your patients, colleagues, and prospects, they need to understand the nuances of your clinic to be effective. It is useful to constantly link back to your website by posting your URL or domain name on Twitter, Facebook, etc., to drive people back to your website. Thus, when you are tweeting, Facebooking, or blogging, you should be continually sending people back to your website where you can capture their email address into your own database.

Facebook

With over 1.5 billion monthly users worldwide, Facebook has become an essential component of a clinic marketing program. Cosmetic dermatologists and clinics can build brand loyalty, establish the expertise of their medical staff, engage with patients on a deeper level, and drive traffic to their clinic website. For clinics just starting out in social media, Facebook is the place to begin. Your customized Facebook Business Page can feature your product and service offering, schedule appointment, highlight multiple locations and monthly specials, and grow a fan base. Your page can be promoted via eblasts, Facebook ads, promoted posts, and through your Facebook network of fans directly. Content sharing also means having share buttons on your website and blog for social media optimization purposes to encourage visitors to share your content.

A common concern of practitioners just starting to become active in social media is how to police what is posted on your Facebook Page. Facebook allows you to have as much or little control over your fan base as you select. For example, if a fan of your page posts a negative comment, the assigned Page Administrator can delete the post and block the user from ever posting again. Derogatory posts are actually less common than one would think, and at least on Facebook, there are built-in mechanisms to manage any unsavory or controversial content easily.

Twitter

Twitter is an entirely portable form of communication, even more so than Facebook, largely because the posts are only 140 characters and, therefore, simple to do on mobile devices from almost anywhere. Twitter has emerged as a strong leader among social media platforms in terms of stimulating conversations about current events, pop culture, and brands. Users turn to Twitter when looking to speak directly to a brand or find out about other people's experience with a brand.

Practitioners can benefit from using Twitter to announce milestones, such as an anniversary or adding a new laser or filler, and to promote special offers, events, and media appearances. It also drives followers to your website, Facebook page, YouTube channel, and blog when linked back to these sources. Getting started on Twitter takes literally minutes, and the options for customization allow you to brand your Twitter easily. The best strategy is to link your Twitter to your Facebook Page so that posts are automatically shared with Twitter. Thus, if you are not ready to dedicate a lot of time to tweeting, your Facebook posts will serve as content to at least keep it going until you can focus on this channel more seriously.

Twitter is like a virtual word of mouth that allows users to share their immediate thoughts on people and places, including doctors and treatments. For aesthetic practitioners, engaging via Twitter can allow positive impressions to be built and shared and brand ambassadors to be developed. By prompting users to retweet your tweets and share their favorable opinions with their followers, it may ultimately lead to an increase in traffic and revenue.

YouTube

YouTube, which is owned by Google, gets over 1 billion unique visitors monthly and is all about original video content. To get started on YouTube, you need to create a channel for your clinic and then upload video content. This content may take the form of educational videos, commentary about a procedure or treatment, footage of an actual procedure, or patient testimonials. Many practitioners tape a consultation with a patient or an open house seminar for YouTube. The video camera on your iPhone is sufficient quality for this purpose. YouTube only allows you to post original videos or ones you have the rights or permission to use, which does not usually include clips from television appearances. Uploading materials is fast and simple to do. As with other social networks, YouTube can be formatted to allow all new videos added to be posted on Twitter automatically.

Google+

Having your clinic on Google+ is more helpful for SEO value than reaching patients or engagement. Google+ is composed of "Circles," similar to networks, so that you can share various types of information to specific circles. For example, you may have circles divided into friends, family, colleagues, staff, vendors, etc. You can invite users to join your circles, although they can add you without you adding them back. Google+ serves more value as a platform to enhance a clinic's search results and for that purpose alone, it is very important to have a presence in this powerful network.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Public Relations

PR campaigns are important for brand awareness. The brand is the dermatologist and the clinic as a unit. Even though you cannot always measure the precise return on investment from PR exposure, patients remember that they saw you quoted in a magazine or on a talk show. This greatly heightens your credibility to your patient base and may be the deciding factor to transform a patient who has heard about you into scheduling a visit. If you have TV or print coverage on a specific procedure, that may give your clinic a big boost in terms of a new patient coming in.

A good PR firm that has experience working in the medical field and has current contacts across health and beauty media can give you an entre to editors, producers, bloggers, and journalists who have the clout to improve your brand. If you are not inclined to enlist a professional PR agency to represent you, you can try to manage media outreach in your local market in-house. For example, you may consider sending out press releases on newswires when you have something of interest to broadcast, such as a new technology or clinical study.

Newspapers and online magazines have a constant need for fresh content. Your staff may be able to pitch the clinic or you as a skin expert to write a column or feature articles on timely healthy skin tips or sun protection, acne, and more. National television segments are hard to come by and there is stiff competition; however, there may be opportunities in your local market. A 5 minute spot on your local news can be very compelling to patients who already know you and serves as a reinforcement that they are in the right dermatology practice. It can also drive new patients into the clinic, who are intrigued by the new treatment or device they heard about on the news.

CONCLUSION

Keep in mind that offering a high level of patient care and service as well as marketing your clinic requires a constant, 24/7, year-round effort. Most solo or small group practices will have to decide between what they are able to do themselves and what should be outsourced. For example, most busy dermatologists do not have time to blog or tweet on a regular basis. Thus, they are faced with the choice of identifying someone on staff who has the skill set to manage social media networks and web updates, hiring someone to take over the marketing functions in-house or engaging a marketing consultant. Ideally, the dermatologist and/or staff can provide the information to the consultant and let them know what is going on in the clinic and how best to promote it.

If you are not savvy about marketing and the Internet, get educated by attending courses offered at national and international conferences. For larger clinics with multiple doctors and several locations, hiring a marketing manager or clinic director can free up physician time to treat more patients and greatly increase efficiency and profits.

BIBLIOGRAPHY

Angelucci DD. Patients' reasonable expectations key to better results. *Dermatology Times* 2011 February. http://dermatologytimes.modernmedicine.com/dermatology-times/news/modernmedicine/modern-medicine-feature-articles/patients-reasonable-expectati. Accessed August 1, 2013.

Blackwell K. Business advisor: Upselling without upsetting. *Pract Dermatol* 2012 January. http://bmctoday.net/practicaldermatology/2012/01/article.asp?f=business-advisor-upselling-without-upsetting. Accessed August 1, 2013.

Donnelly S. Marketing a dermatology practice. *Dermatologist* 2013 May; 21(5):43–45.

Downie JB. Defend and build your reputation online. *Pract Dermatol* 2012 March. http://bmctoday.net/practicaldermatology/2012/03/article.asp?f=defend-and-build-your-reputation-online. Accessed August 1, 2013.

Downie JB. Ethical and effective strategies for dispensing your practice. *Pract Dermatol* 2013 July. http://bmctoday.net/practicaldermatology/2013/07/article.asp?f=ethical-and-effective-strategies-for-dispensing-in-your-practice. Accessed August 1, 2013.

Doyle B. Five online marketing tips for your aesthetic practice. *Mod Aesthet* 2013 May/June. http://modernaesthetics.com/2013/06/5-online-marketing-tips-for-your-aesthetic-practice. Accessed August 1, 2013.

Evans D. Internet marketing jargon: Decoded and demystified. *Plast Surg Pract* May 1, 2012. http://www.plasticsurgerypractice.com/news/18057-internet-marketing-jargon-decoded-and-demystified. Accessed August 1, 2013.

Flasch H. Engagement: Still key to healthcare marketing in the digital age. *Pract Dermatol* 2012 March. http://bmctoday.net/practicaldermatology/2012/03/article.asp?f=engagement-still-key-to-healthcare-marketing-in-the-digital-age. Accessed August 1, 2013.

Fried RG, Werschler WP. The key to mastering cosmetic dermatology patient selection. *Dermatologist* 2006 October; 14(10). http://www.the-dermatologist.com/article/6268. Accessed August 1, 2013.

Fried RG. The 'triangle of intimacy': The key to cosmetic patient satisfaction. *Dermatologist* 2011 February; 19(2):36–39.

Juttla B. Social media fuels increase in requests for surgery. *PRIME Int J Aesthet Anti Ageing Med* 2013 May 28. https://www.prime-journal.com/social-media-fuels-increase-in-requests-for-surgery/. Accessed August 1, 2013.

Kelz Ben-Yoseph M. A physician's guide to generating and effectively using positive PR. *PRIME Int J Aesthet Anti Ageing Med* May 18, 2013. https://www.prime-journal.com/a-physicians-guide-to-effectively-using-and-generating-positive-pr/. Accessed August 1, 2013.

Lewis W. Social media 101. *Dermatologist* 2011 May; 19(5):17–18.

Lewis W. The value of micro-site marketing. *Plast Surg Pract* 2011 May 26. http://www.plasticsurgerypractice.com/news/17934-the-value-of-microsite-marketing. Accessed August 1, 2013.

Lewis W. To tweet or not to tweet. *PRIME Int J Aesthet Anti Ageing Med* 2013 March 4. https://www.prime-journal.com/to-tweet-or-not-to-tweet/. Accessed August 1, 2013.

Lewis W. Keep calm and get optimised. *PRIME Int J Aesthet Anti Ageing Med* 2013 July 23. https://www.prime-journal.com/keep-calm-and-get-optimised/. Accessed August 1, 2013.

Morley G, Foster B. Business advisor: Capturing the online aesthetic patient. *Pract Dermatol* 2011 April. http://bmctoday.net/practicaldermatology/2011/04/article.asp?f=business-advisor-capturing-the-online-aesthetic-patient. Accessed August 1, 2013.

Munavalli G (Q&A format). Talking points: Effective patient communication at all levels of cosmetic service. *Pract Dermatol* 2010 October. http://bmctoday.net/practicaldermatology/2010/10/article.asp?f=talking-points-effective-patient-communication-at-all-levels-of-cosmetic-service. Accessed August 1, 2013.

Reisman NR. Informed consent: Protecting the patient is protecting yourself. *Mod Aesthet* 2013 May/June. http://modernaesthetics.com/2013/06/informed-consent-protecting-the-patient-is-protecting-yourself-by-neal-r-reisman-md-jd-facs-1. Accessed August 1, 2013.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Schlessinger J. Internet use and the medical office. *Cosmet Dermatol* 2010 February; 23(2):73–74.

Schlessinger J. In-office dispensing: Expert insights. *Pract Dermatol* 2011 May. http://bmctoday.net/practicaldermatology/2011/05/article.asp?f=in-office-dispensing-expert-insights. Accessed August 1, 2013.

Schlessinger J. Medical meets cosmetic in dermatology. *Pract Dermatol* 2012 November. http://bmctoday.net/practicaldermatology/2012/11/article.asp?f=medical-meets-cosmetic-in-dermatology. Accessed August 1, 2013.

Schlessinger J. Going digital: Marketing for the 21st-century. *Pract Dermatol* 2013 January. http://bmctoday.net/practicaldermatology/2013/01/article.asp?f=going-digital-marketing-for-the-21st-century. Accessed August 1, 2013.

Waldorf HA. Pricing your worth: Tips for deciding costs and promoting cosmetic procedures. *Mod Aesthet* 2013 January/February. http://modernaesthetics.com/2013/02/pricing-your-worth-tips-for-deciding-costs-and-promoting-cosmetic-procedures. Accessed August 1, 2013.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Legal considerations in aesthetic and cosmetic dermatology

David J. Goldberg

Multiple legal issues can occur in the practice of aesthetic and cosmetic dermatology. Although legal considerations can arise in the performance of any cosmetic procedure, they are increasingly seen in the field of cutaneous laser surgery because of the large numbers of energy-based devices currently being used. A full textbook on health-care law would be required to adequately cover all the legal aspects as they relate to cutaneous laser surgery. This chapter will, therefore, only deal with the most common interaction between cutaneous laser physicians and health-care law—that of negligence.

The first part of the chapter will discuss the elements of negligence and the evolution of a medical malpractice cause of action following cutaneous laser surgery. The second part of the chapter will describe various hypothetical laser surgical complications and the likelihood of a successful malpractice case evolving from such a postoperative complication.

Any analysis of physician negligence must first begin with a legal description of the elements of negligence. There are four required elements for a cause of action in negligence: duty, breach of duty, causation, and damages. The suing plaintiff must show the presence of all four elements to be successful in her claim [1].

The duty of a physician performing cutaneous laser surgery is to perform that cutaneous laser procedure in accordance with the standard of care. Although the elements of a cause of action in negligence are derived from formal legal textbooks, the standard of care is not necessarily derived from some well-known textbook. It is also not articulated by any judge. The standard of care is defined by some, as whatever an expert witness says it is, and what a jury will believe. In a case against any cutaneous laser surgeon, the specialist must have the knowledge and skill ordinarily possessed by a specialist in that field and have used the care and skill ordinarily possessed by a specialist in that field in the same or similar locality under similar circumstances. A dermatologist, plastic surgeon, or internist performing cutaneous laser surgery will all be held to an equal standard. A failure to fulfill such a duty may lead to loss of a lawsuit by the physician. If the jury accepts the suggestion that the surgeon mismanaged the case and that the negligence led to damage of the patient, then the physician will be liable. Conversely, if the jury believes an expert who testifies for the defendant doctor, then the standard of care in that particular case has been met. In this view, the standard of care is a pragmatic concept, decided case by case and based on the testimony of an expert physician. The cutaneous laser surgeon is expected to perform a laser procedure in a manner of a reasonable physician. He need not be the best in his field; he need only perform the procedure in a manner that is considered by an objective standard as reasonable.

It is important to note that where there are two or more recognized methods of diagnosing or treating the same condition, a physician does not fall below the standard of care by using any of the acceptable methods even if one method turns out to be less effective than the other method. Finally, in many jurisdictions, an unfavorable result due to an "error in judgment" by a physician is not in and of itself a violation of the standard of care if the physician acted appropriately prior to exercising his professional judgment.

Evidence of the standard of care in a specific malpractice case includes laws, regulations, and guidelines for practice, which represent a consensus among professionals on a topic involving diagnosis or treatment and the medical literature including peer-reviewed articles and authoritative texts. In addition, obviously, the view of an expert is crucial. Although the standard of care may vary from state to state, it is typically defined as a national standard by the profession at large.

Most commonly for litigation purposes, expert witnesses articulate the standard of care. The basis of the expert witness, and therefore the origin of the standard of care, is grounded in:

1. The witness's personal practice
2. The practice of others that he has observed in his experience
3. Medical literature in recognized publications
4. Statutes and/or legislative rules
5. Courses where the subject is discussed and taught in a well-defined manner

The standard of care is the way in which the majority of the physicians in a similar medical community would practice. If, in fact, the expert herself does not practice like the majority of other physicians, then the expert will have a difficult time explaining why the majority of the medical community does not practice according to her ways.

It would seem then that in the perfect world, the standard of care in every case would be a clearly definable level of care agreed on by all physicians and patients. Unfortunately, in the typical situation, the standard of care is an ephemeral concept resulting from differences and inconsistencies among the medical profession, the legal system, and the public.

At one polar extreme, the medical profession is dominant in determining the standard of care in the practice of medicine. In such a situation, recommendations, guidelines, and policies regarding varying treatment modalities for different clinical situations published by nationally recognized boards, societies, and commissions establish the appropriate standard of care. Even in some of these cases, however, factual disputes may arise because more than one such organization will publish conflicting standards concerning the same medical condition.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Adding to the confusion, local societies may publish their own rules applicable to a particular claim of malpractice.

Thus, in most situations, the standard of care is neither clearly definable nor consistently defined. It is a legal fiction to suggest that a generally accepted standard of care exists for any area of practice. At best, there are parameters within which experts will testify. Unfortunately, due to the increased reliance on laser technology by the cutaneous laser surgeon and unrealistic expectations by the public, physicians may sometimes run the risk of being held to an unrealistic and unattainable standard of care. But in the end, it is the physician community that establishes that standard of care.

American physicians have in recent years put forth substantial efforts toward standard setting, specifying treatment approaches to various conditions. Clinical practice guidelines have been developed by specialty societies such as the American Academy of Dermatology. The Institute of Medicine has defined such clinical guidelines as "systemically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances." Such guidelines represent standardized specifications for performing a procedure or managing a particular clinical problem.

Clinical guidelines raise thorny legal issues [2]. They have the potential to offer an authoritative and settled statement of what the standard of care should be for a given cutaneous laser-treatable condition. A court would have several options when such guidelines are offered as evidence. Such a guideline might be evidence of the customary practice in the medical profession. A doctor acting in accordance with the guidelines would be shielded from liability to the same extent as one who can establish that she or he followed professional customs. The guidelines could play the role of an authoritative expert witness or a well-accepted review article. Using guidelines as evidence of professional custom, however, is problematic if they are ahead of prevailing medical practice.

Clinical guidelines have already had an effect on settlement, according to surveys of malpractice lawyers. A widely accepted clinical standard may be presumptive evidence of due care, but expert testimony will still be required to introduce the standard and establish its sources and its relevancy.

Professional societies often attach disclaimers to their guidelines, thereby undercutting their defensive use in litigation. The American Medical Association (AMA), for example, calls its guidelines "parameters" instead of protocols intended to significantly impact on physician discretion. The AMA further suggests that all such guidelines contain disclaimers stating that they are not intended to displace physician discretion. Such guidelines, in such a situation, could not be treated as conclusive.

Plaintiffs usually will use their own expert, as opposed to the physician's expert to define the standard of care. Although such a plaintiff's expert may also refer to clinical practice guidelines, the physician's negligence can be established in other manners as well. These methods include (1) examination of the physician defendant's expert witness; (2) an admission by the defendant that he or she was negligent; (3) testimony by the plaintiff, in a rare case where she is a medical expert qualified to evaluate the allegedly negligent physician's conduct; and (4) common knowledge in situations where a layperson could understand the negligence without the assistance of an expert [3,4].

Some laser centers are located within either hospitals or certified ambulatory care centers. In such situations, a plaintiff may seek hospital committee proceeding minutes about the allegedly negligent physician. The plaintiff may request production of a committee's minutes or reports, set forth "interrogatories" about the committee process and/or outcome, or seek to depose committee members about committee discussions. If the plaintiff is suing the cutaneous laser surgeon, whose work was reviewed by the committee, the discovery process may seek to confirm the negligence of the professional or to uncover additional evidence substantiating the plaintiff's claims. Such "discovery" requests are often met with a claim that information that is generated within or by a hospital committee is not discoverable. Courts have ruled that the discovery protection granted hospital quality review committee records prevents the opposing party from taking advantage of a hospital's careful self-assessment [5]. The suing plaintiff must utilize his or her own experts to evaluate the facts underlying the incident. It is felt, by the courts, that such immunity of committee proceedings protects certain communications and encourages the quality review process. External access to committee investigations is argued, stifles candor, and inhibits constructive criticism to be felt necessary for a quality review process. Constructive, objective, peer criticism might not occur in an atmosphere of apprehension that one doctor's suggestion will be used as a denunciation of a colleague's conduct in a malpractice suit.

When a plaintiff seeks discovery of a facility or hospital incident report, rather than a committee proceeding, policy considerations are somewhat different. Incident reports kept in the medical records, and possibly filed by a staff member, are often more directly related to a single claim for malpractice than would general committee investigations. Courts are usually less willing to protect such incident reports.

Because the field of cutaneous laser surgery has evolved rapidly over the past decade, physicians are quick to try new innovations and experimental concepts. Such innovations partially explain the excitement of this growing field. New laser surgical procedures and the treatment of conditions that were heretofore untreatable (i.e., port-wine stains and Nevus of Ota) may fall into a regulatory gaps not covered by the strict regulations for the laser device itself. Licensing through the Food and Drug Administration (FDA) carefully regulates medical devices such as lasers [6]. Most human experimentation is governed by regulations of the Department of Health and Human Services. The regulations require that an institution sponsoring research must establish an institutional review board. Such an organization will evaluate research proposals before any experimentation begins to determine whether human subjects might be "at risk" and, if so, how to protect them.

It is not usually difficult to determine whether a new laser is being used experimentally. It is, however, very difficult to determine whether an actual given laser procedure is experimental. Laser surgeons often view themselves as artists in addition to scientists, custom tailoring a treatment for a particular condition. Such approaches can lead to a bad result with variable outcomes in the courts. A laser surgeon who chooses to use a carbon dioxide laser, rather than a scalpel, to perform a circumcision procedure, with a resultant complication leading to penile amputation would have problems, suggesting that his or her medical experimentation conformed to reasonable standard of care. However, another surgeon who chooses, after appropriate informed consent, to use the same laser, rather than a scalpel, for excision of a nevus with resultant significant scarring might be considered an innovator rather than an experimenter. Such a physician would be no more liable for straying from his

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

duty than the surgeon who might use a standard scalpel, with the same complication, for the same procedure.

In fact, most clinical innovation falls between standard practice and experimental research. Much of this innovation is unregulated by the government. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research has suggested that any "radically new" procedure should be made the object of formal research at an early stage in order to determine whether such a procedure is safe and effective. It could be argued that some of the cutaneous laser procedures that have evolved, using already FDA-cleared laser devices, might be considered radical; most clearly are not.

It is clear then that in order for the plaintiff to win his or her negligence cause of action against the cutaneous laser surgeon, he or she must establish that his or her physician had a duty of reasonable care in treating him or her and had in fact breached that duty. However, that breach must also lead to some form of damages. A mere inconvenience to the plaintiff, even in the setting of a physician's breach, will usually not lead to physician liability in a cause of action for negligence.

It is often difficult to predict, in any given malpractice cause of action, what the ultimate outcome will be. The following teaching hypotheticals are designed to be suggestive of potential malpractice cases and the likely results. Any connection between these scenarios and actual malpractice cases is fortuitous.

THE STANDARD OF CARE

JH is a 48-year-old woman with Class I rhytids and extensive solar telangiectases. She has used a variety of antirosacea medications and has undergone three sessions of electrocautery for the treatment of her telangiectases. These treatment modalities have led to minimal clinical improvement. Her niece had seen a local otolaryngologist (Dr. Nose) for a rhinoplasty procedure and was extremely happy with the cosmetic results. Because of this physician's expertise in cosmetic surgery, and her niece's recommendation, JH sought cosmetic treatment from this physician. Dr. Nose, 1 month prior to seeing JH, spent a weekend learning "laser skin resurfacing." It is his understanding that carbon dioxide lasers seal small blood vessels while leading to skin rejuvenation. He correctly assumes that this laser will thermally destroy many of the telangiectases on the face of JH. Dr. Nose discusses with JH the associated risks of cutaneous laser resurfacing, such as scarring and postinflammatory pigmentary changes following the procedure. The physician chooses to rent his laser from a local rental company. This company also rents such lasers as KTP lasers, Q-switched lasers, and "hair removal" lasers. Since Dr. Nose has only learned to use the carbon dioxide laser, he chooses to treat his patient with this laser.

The full-face procedure is undertaken without any difficulty. Because of the extensive thermal wound, JH is required to stay in her house for 10 days following the procedure. This is not terribly difficult for her since she has a home-based job and need not leave her house on a daily basis. The telangiectases respond nicely to treatment. Unfortunately, the postresurfacing erythema lasts for over 6 months. JH had marital difficulties before the laser surgery. Her husband was never supportive of her undergoing the procedure. Because of the prolonged erythema, JH is reluctant to leave her house. This reclusive behavior represents the final strain to her marriage. Her husband leaves her and ultimately files for divorce. Soon thereafter, JH finds out that her telangiectases could have been treated with a KTP laser without any significant ablative wound. There would also have been no delayed erythema following the laser procedure.

JH files a lawsuit against Dr. Nose. She claims negligence in his use of the carbon dioxide laser to treat her telangiectases. Did Dr. Nose breach the standard of care? If so, will he be liable for negligence? Dr. Nose has a duty of care to JH. His duty is no more or less than that of any dermatologist or plastic surgeon performing the identical procedure. His limited weekend training will not be an adequate defense. His lack of knowledge about KTP lasers will also support his choice of a carbon dioxide laser to treat his patient's telangiectases. Thus, it would appear that he breached his duty of care. He chose to use a laser that is not ideal for the treatment of telangiectases. Is he then liable? His liability would only result if the breach caused "damages." JH will be hard pressed to prove that her already failing marriage and resultant divorce represented damages caused by Dr. Nose's inappropriate use of the carbon dioxide laser in the treatment of telangiectases. She is not likely to win the case even though Dr. Nose chose an inappropriate laser to treat his patient.

IS A PHYSICIAN ALWAYS NEGLIGENT IF THERE IS A COMPLICATION?

Dr. Doc is a well-known dermatologist with over 5 years of experience using a variety of lasers. For the last 2 years, he has been performing laser hair removal with millisecond visible and near-infrared lasers and light sources. He has seen success with a variety of systems and has used these systems with a variety of cooling gels, cryogen sprays, and sapphire-tipped cooling systems. He evaluates a Fitzpatrick Type IV–complected individual (PC) with dark hair. He explains to her that the ideal laser hair removal patient is a dark-haired, light-skinned individual. Because of her complexion, and the potential risk of laser-induced postinflammatory pigmentary changes, Dr. Doc uses a lesser fluence and slightly longer pulse duration in treating her. He also uses a very cold gel on her skin prior to treatment. It is his understanding that such an approach is safer in darker complected individuals. He also provides PC with a laundry list of general risks such as postlaser scarring and textural changes. She is treated three times over the course of 9 months without difficulty. Unfortunately, 2 months after a fourth session, a hypertrophic scar develops at the site of an upper lip herpes simplex infection that appeared to be activated 1 week after a laser hair removal session. PC had not had a herpetic outbreak in 30 years and, when asked about such proclivity prior to the first laser procedure, she denied any history of herpes simplex infections.

PC learns from a friend that most cutaneous laser surgeons provide their cutaneous laser resurfacing patients with a course of oral antiviral agents—even if they

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

provide no personal history of herpes simplex infections. She reasons, and her attorney agrees, that the same logic should apply to other laser procedures of the skin.

Is Dr. Doc liable? It is clear that there is permanent damage to JH. If these damages resulted from the laser procedure, Dr. Doc might be liable. However, unfortunately for JH, it will be hard to prove that Dr. Doc breached the standard of care. Just because physicians routinely provide their resurfacing patients oral antiviral agents does not mean that such medications are required after all laser procedures. The fact that PC denied a history of oral herpes simplex would only bolster Dr. Doc's defense.

CAN A PHYSICIAN BE LIABLE FOR A YET TO BE REPORTED COMPLICATION?

Dr. Good is a well-trained cutaneous laser surgeon. In fact, she not only learned to use lasers during his residency training but also undertook a 1-year laser fellowship in 1993. In 1995, she began to perform cosmetic cutaneous laser resurfacing for photo-damaged skin. In her patient handouts, she describes the benefits of carbon dioxide laser resurfacing as compared to deeper peeling agents. One advantage, she suggests, is the lack of obvious phenol-induce delayed hypopigmentation seen with these deeper peels. Dr. Good provides a consent form for his patients and does mention the risk of scarring and *temporary* pigmentary changes following the laser procedure. In 1996, she performs full-face carbon dioxide laser resurfacing on a 55-year-old Fitzpatrick Type II, Class III rhytid individual. The patient, BB, follows all the appropriate wound care instructions and returns to Dr. Good's office 3 times during the 6 months after her laser resurfacing procedure. Both doctor and patient are thrilled with the results and the patient is discharged. Unfortunately, 1 year after the procedure, BB begins to notice significant loss of perioral pigmentation. This problem progressively worsens over the next year. BB can no longer go out of the house without makeup and is devastated. Soon thereafter, reports begin to appear in the medical literature about the possibility of delayed postcarbon dioxide laser–induced hypopigmentation. BB files suit against Dr. Good. BB's attorney produces Dr. Good's promotional materials suggesting the safety of this procedure, the consent form that makes no mention of delayed permanent hypopigmentation, and copies of the recent journal articles documenting this problem.

Will Dr. Good lose in this negligence cause of action? It would seem that she breached her duty by not mentioning the risk of permanent postlaser–induced hypopigmentation. Certainly, the alleged breach of her duty is the cause of the permanent damage to BB's face. However, Dr. Good can correctly defend her actions by stating that at the *time of the incident,* the standard of care was not to warn about delayed carbon dioxide laser–induced permanent hypopigmentation. Dr. Good cannot be held responsible for laser-induced complications that were not known, nor described, at the time of the laser procedure.

WAS THERE A BREACH IN THE DUTY?

Dr. Laser is well experienced in erbium:YAG laser resurfacing. He uses this laser for superficial resurfacing; all his patients reepithelialize in 5–7 days. He routinely places his patients on 1 week of oral antiviral therapy. Recently, Dr. Laser has become disenchanted with this laser's efficacy in the treatment of deeper Class III rhytids. He begins to rent a carbon dioxide laser for his more severely rhytid patients. He continues to give these patients 1 week of oral antiviral treatment despite the fact that reepithelialization usually takes 10 days in these patients. SG represents one such Class III rhytid patient. Dr. Laser performs the carbon dioxide laser procedure, provides a 7-day oral antiviral treatment to his patient, and sees her in the office at day 3 following the laser procedure. At day 3, SG appears to be doing well and Dr. Laser advises her to return 3 weeks after the procedure. At the 3-week follow-up visit, she is well healed except for four erosive areas on her lip and upper forehead. Dr. Laser reassures her and suggests that she continue to use moist dressings. Two weeks later, the erosions are still not healed and SG seeks evaluation by an expert in the field. This new physician performs a viral culture and determines that she has a herpes simplex infection. He retreats her with antiviral therapy. She eventually heals but is left with hypertrophic scarring. She files a negligence cause of action against Dr. Laser for performing a procedure that led to her scars. She admits that she signed a consent form that warned her about the risks of laser-induced scarring. When challenged in court about the positive herpes simplex infection, Dr. Laser responds by reminding the jury that he did use 7 days' worth of antiviral treatment in his patient, something he traditionally did in his erbium:YAG laser-treated patients. Unfortunately, for Dr. Laser, he is likely to lose his case. It will be argued by SG's expert that it is not the use of antiviral agents that defines the standard of care after laser resurfacing. Instead, he will contend the standard of care dictates that antiviral agents be used until full reepithelialization has occurred. Dr. Laser's duty was not to simply provide his patient with antiviral agents; his duty was to provide such agents for the full 10 days of reepithelialization. The breach in this duty leads to the scars on the face of his patient. Dr. Laser may be found culpable in a negligence malpractice cause of action.

DOES THE STANDARD OF CARE CHANGE OVER TIME?

Dr. James, a well-known and respected dermatologist, purchased an old carbon dioxide laser from his medical school roommate, a colon–rectal surgeon in the local community. Dr. James undertook extensive training in carbon dioxide laser resurfacing and had a good knowledge of facial anatomy, wound healing, and the use of several good pulsed char-free carbon dioxide lasers. His laser, purchased at a bargain basement price, was a continuous wave carbon dioxide laser. Dr. James performed 20 full-face laser-resurfacing procedures with this machine. All of his

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

patients were happy with the results. When challenged at a recent meeting about the use of such a continuous wave laser for resurfacing, Dr. James responded by suggesting that he was expert at this technique. In addition, he noted that before the use of pulsed resurfacing lasers, some physicians used such continuous lasers for facial resurfacing.

Recently, Dr. James treated his 21st patient, a 55-year-old woman with Class II rhytids and photodamage. The technique was performed in an identical manner to that of the previous procedures. Unfortunately, his patient had a protracted course of healing with resultant significant hypertrophic scarring.

The scarred plaintiff brought a lawsuit alleging malpractice by Dr. James. The plaintiff's expert, a well-respected cosmetic surgeon, testified that Dr. James' use of a continuous wave, nonpulsed carbon dioxide laser represented a deviation in the standard of care. The expert contended that a reasonable medical practitioner would not use a continuous wave laser for cosmetic laser resurfacing.

Dr. James, testifying on his own behalf, set forth numerous manuscripts from 20 years ago that such lasers could be used for such procedures. He contended that such papers proved that his practice was in accordance with the standard of care, even if such a technique was not used by most.

Dr. James' argument that he is performing within the standard of care is a fallacious one. It may be true that laser resurfacing, with a continuous wave laser, was the standard of care at the time the provided medical literature was written. However, it is uniformly accepted that the standard of care, timewise, is defined at the time a procedure is performed. Dr. James cannot claim that his procedure is in accordance within the standard of care, at the time of the procedure, simply because he may have complied with the standard established many years before the actual performance of the procedure. The scarring produced by the continuous wave laser may very well represent a breach of the standard of care. He is likely to lose in this negligence cause of action.

Cutaneous laser surgery involves the use of exciting ever-changing technology. Physicians are increasingly learning to perform a variety of laser procedures. Because such new technology is ever changing, it is important that physicians be aware of their duty of reasonable care. Should they breach that duty, they may be found liable in a medical malpractice cause of action.

REFERENCES

1. Furrow BF, Greaney TL, Johnson SH, Jost TS, Schwartz RL. *Liability in Health Care Law*, 3 ed. St. Paul, MN: West Publishing Co., 1997.
2. Hyams AL, Shapiro DW, Brennan TA. Medical practice guidelines in malpractice litigation: An early retrospective. *J Health Polit Policy Law* 1996; 21:289.
3. *Lamont v. Brookwood Health Service, Inc.*, 446 So.2d 1018 (Ala.1983).
4. *Gannon v. Elliot*, 19 Cal.App.4th 1 (1993).
5. *Coburn v. Seda*, 101 Wash.2d 270 (1984).
6. Federal Food, Drug, and Cosmetic Act, 21 U.S.C.A. s301.

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Taylor & Francis
Taylor & Francis Group
http://taylorandfrancis.com

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Index

Ablative fractional lasers, 241, 361, 364, 373, 455
Ablative laser skin resurfacing
  complications
    acneiform eruptions, 365
    anesthesia toxicity, 366
    contact dermatitis, 366
    delayed purpura, 366
    eruptive keratoacanthomas, 366
    erythema, 365–366
    heat-induced recall phenomenon, 366
    infections, 365
    pigmentary alteration, 366
    scarring, 366
  drug delivery, 366
  history, 357
  home fractionated devices, 366
  indications
    acne scar, 358
    benign lesions, 360
    dermal lesions, 360
    hypertrophic scars, 358
    melasma, 358–359
    photoaging, 358
    pigmented lesions, 359
    premalignant and malignant skin cancer, 359
    rhinophyma, 359
    traumatic scar, 358
    varicella scar, 358
  mechanism
    CO_2 laser, 357–358
    Er:YAG, 358
  patient selection, 365
  postoperative course, 365
  preoperative management and anesthesia, 365
  tattoo removal, 366
Ablative photodecomposition, *see* Photoablative effect
Abnormal scars management
  acne scars
    box scar, 242–243
    chemical peels, 241
    depigmented atrophic scar, 240, 244
    hypertrophic scar, 240, 244
    ice-pick scar, 242–243
    laser ablation, 241–242
    mechanical dermabrasion, 241
    microneedling, 241
    qualitative grading, 240
    rolling scars, 242–243
  artificial scars, 242–243
  clinical features, 233–234
  definition, 233–231
  erythematous scars, 242
  extraordinary therapeutic options, 244
  hyperpigmented scars, 242
  hypertrophic and keloid scars
    ablative lasers, 238
    algorithm, 237
    cryotherapy, 238
    excision, 239
    intralesional treatment, 238
    nonablative lasers, 238
    PDT, 238
    surgery plus compression, 239
    surgery plus 5-FU, 239
    surgery plus imiquimod, 239
    surgery plus radiation, 240
    surgical procedures plus steroid injection, 239–240
    topical treatments, 237–238
    treatment, 242
  prevention
    nonsurgical prevention strategies, 235
    NPWT, 235–236
    serial excision, 236
  risk factors, 233–234
  scar variants, 233–234
  stretching/dehiscence of scars, 236
Abrasive techniques
  anesthesia, 325
  anterior chemoabrasion, 324
  bismuth subgallate, 325
  definition, 324
  depth selection, 325
  grade II abrasion, 325
  occlusion, 325
  perform and preparation, 325
  posterior chemoabrasion, 324
  prepeel skin conditioning, 325
  sandpaper, 325
  skin preparation, 325
Acne-induced postinflammatory erythema, 363
Acne scars, 492
  box scar, 242–243
  chemical peels, 241
  depigmented atrophic and hypertrophic scar types, 240
  ice-pick scar, 242–243
  laser ablation, 241–242
  mechanical dermabrasion, 241
  microneedling, 241
  qualitative grading, 240
  rolling scars, 242–243
Acquired dermal hypermelanocytosis, 474–475
Actinic keratoses, 21–23, 512
Adipocytolysis
  clastic, 540
  phagocytic, 540–541
Adipose-derived stem cells (ASCs), 39–40, 47–49
Adipose tissue (AT)
  BAT, 43–44
  blood flow regulation, 46
  cell type heterogeneity, 47–49
  classification and distribution of, 43–44
  development of, 46–47
  fat cell precursors
    macrophages and endothelial cells, 49
    preadipocyte progenitors, 47–49
  fat deposition and fat mobilization, 49–53
  histogenesis and fine structure, 45
  productions, 53–55
  routine liposuction, 44–45
  WAT, 43–45
Adipose tissue blood flow (ATBF), 46
ADSO, *see* Advanced dermatological surgery office
Advanced dermatological surgery office (ADSO), 193
Advanced encryption standard (AES), 772
Advanced hybrid clinical-surgical units (AHCSUs), 192, 194
AES, *see* Advanced encryption standard
Aesthetic consultation
  appointment confirmation, 67
  arrival, clinic, 67
  cost, 70
  diagnosis, 69
  discontented patients
    complaining or litigious patients, 73–74
    difficult-to-please patient, 73
    prevention, 74
  doctor-patient relationship
    medical model, 71
    mutual understanding, 71
    placebo response, 71
    professionalism, 71
    trust and confidence, 70–71
  easy-to-please patient, 73
  less easy-to-please patient, 73
  managing the day, 67
  medical report or letter, 70
  meeting preparation, 67
  meeting the patient, 67–68
  patient examination, 68–69
  patient expectations, 70
  patient history, 68
  patient's direct contact, 67
  patient selection, 70
  psychological considerations
    anxiety, 72
    BDD, 72
    depressed patients, 73
    depression, 72
    OCD, 72
    patient's expression, 71
    psychiatrist or a clinical psychologist, 73
    symptoms and signs, 71
  referrals, 67
  reputation, 67
  treatment, 69–70
Aesthetic field
  burns and scars, 392
  innocuousness, 392–393
  ocular risks, 393
  pain, 391–392
  pathological scars and scar prevention, 391–392
  photodynamic photorejuvenation, 389, 391
  prolonged hyper/hypopigmentations, 392
  tattoos, 391–392
Aesthetic measure, 4
Aesthetic nail surgery
  anesthesia, 288–291
  big toenail, 290–293
  chronic paronychia, 300–301
  distal nail avulsion, 300–301
  double nail, 289–290, 292
  ingrown nails, 294–296
  laterally localized tumors, 299–300
  longitudinal melanonychia, 298–299
  myxoid pseudocyst, 298–299

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

onychopapilloma, 299
patient preparation, 287–288
patient selection, 287
postoperative care, 289
proximal nail avulsion, 301
proximal nail fold, 300
retronychia, 296–297
split nail deformity, 292–294
toenails, 295–297
tourniquet, 289
trapezoid nails, 290, 293
traumatically damaged nail, 301–302
ungual fibrokeratomas, 298
vertically implanted nail, 290, 293
viral warts, 297–298
Aesthetic suture techniques
buried sutures
buried backstitch suture, 213
butterfly suture, 213
running intradermal sutures, 213–214
simple buried stitches, 213
tacking/anchoring (pexing) sutures, 214
dressing, 216
localization, 207
needles, 208
particular wound healing characteristics, 207
percutaneous sutures
epidermal suture, 209
half-buried vertical suture, 210–211
horizontal mattress sutures, 210–211
running locked sutures, 210, 212
simple interrupted stitches, 210
simple running suture, 210, 212
vertical mattress sutures, 210
pitfalls, 217
pulley sutures, 214
skin closure tapes, 209
staples, 209
suture material and wound closure materials
absorbable sutures, 207–208
nonabsorbable sutures, 208
suture removal, 216–217
suture techniques, 209
tissue adhesives, 208
tissue-sparing techniques, 214–217
wound condition, 207
wound direction, 207
Aging
facial
prevention, 759
preventive treatment, 759
skin preservation, 760
SMAS, 760
treatment plans, 759
ultrasound and radio-frequency machines, 760
heaviness, 739–741
morphological modeling, 739
sagging, 739–741
skeletonization, 739, 741
AHCSUs, *see* Advanced hybrid clinical-surgical units
Allergic contact dermatitis, 101–103, 122, 140–141, 143, 182, 241
Allergic reactions
application and cumulative effects, 101
composition
concentration of ingredients, 99–100
purity of ingredients, 99–100
contact time, 101
cosmetic contact allergens, 101–103
cosmetic ingredients, pharmaceuticals, 100
cosmetovigilance, 103–104
cross sensitivity, 100
diagnosis, 103
frequently usage, 99
immunologic contact urticaria, 103
penetration-enhancing substances, 100
photocontact allergens, 103
sensitive skin products, 103
skin condition, 100–101
American barbed threads, continuous cosmetic suture, 677, 679
Aminolevulinic acid (ALA), 354, 504
Anal and vaginal disorders, 550–551
Androgenetic alopecia
digital phototrichogram, 257–258
female androgenetic alopecia, 259–261
male androgenetic alopecia, 257–260
multifactorial classification, 257
transsexuals, 261
Androgenic alopecia
concoction, 614
definition, 611
frequency, 614
hair life cycle, 612–614
material, 614
medicines, 614
technique of nappage, 614–615
Antiadhesive dressings
advantages, 221
disadvantages, 221
examples, 221
uses, 220
Antiaging effect, 26, 78–79, 114, 116, 406
Apocrine chromhidrosis, 550, 552
Apocrine sweat glands, 159, 163
Aptos cog (barbed) threads
continuous cosmetic suture, 677, 679
lifting of soft tissues, 677, 679
memory-retaining polypropylene, 678, 681–682
Aptos thread lifting
absorbable threads
for armoring, 678, 682
brow lifting, 688
opposite direction barbs, 678, 682
patients, soft lifting, 686, 688
Aptos Nano, 678, 682
brow lifting, 688
needleless Aptos threads and methods, 678
neocollagenesis, 678
nonabsorbable second-generation, cheekbone area lifting, 687–688
Visage sutures, 678
Aquagenic keratoderma, 552
Aquatic bicycle, 531
Arterial vascularization
deep network, internal carotid artery, 714
face's venous system, 714
internal maxillary artery, 714
ophthalmic artery, 714
superficial network, external carotid artery, 714
superficial temporal artery, 714
Artificial nails
nail gels, 147–150
preformed, 143–146
sculptured, 146–147
ASCs, *see* Adipose-derived stem cells
Astaxanthin, 114–115
AT, *see* Adipose tissue
ATBF, *see* Adipose tissue blood flow
AT expandability theory, 47
Atopic dermatitis (AD), 122, 166
Autologous adipose grafting, *see* Fat grafting technique
Axillary hyperhidrosis, 166–168
Axillary sweat gland excision, 163
"Bar code" wrinkles, 20
Basal cell carcinoma, 513
BDD, *see* Body dysmorphic disorder
Beauty, 2–5
Bichat's fat pad, 736
Big toenail, 290–293
Biodegradable products
bovine collagen, 593
human collagen
allograft, 593–594
autograft, 594
porcine collagen, 594
Biplane bayonet technique., 723
Blepharoplasty
adjunctive procedures
botox injection, 702
deep sulcus, 702
lipofilling, 702
superficial resurfacing, 702
volume injection, 702
canthopexy, 702
lower eyelid blepharoplasty, 697–701
palpebral and upper face examination, 691–692
palpebral, lower and midface examination, 691, 693, 697
upper eyelid blepharoplasty, 692–697
Blepharoptosis
correction, 582–583
of left eye, 582
Blue rubber bleb nevus syndrome, 484–485, 488
Body dysmorphic disorder (BDD), 558
aesthetic consultation, 72
causes
neurobiological, 8
neuropsychological, 7
psychoanalytic approach, 7–8
psychosocial, 8
clinical aspects, 8
diagnostic criteria, 7
epidemiology, 7
prevention, 9
prognosis, 9
psychiatric disorders, 8
treatment, 8–9
Yale Brown Obsessive Compulsive Scale Modified, 8
Body hair growth alopecia
beard and mustache, 264
eyebrows, 261, 263
eyelashes, 261, 263
pubic hairs, 264
Body piercings (BP)
complications
acute infections, 180
blood-transmitted infections, 181
edema and transient hematoma, 181
infective endocarditis, 181
nonspecific complications, 181
oral/genital piercings, 181
primary inoculation, 180
corset piercings, 179
embedded upper lip piercing, 182
epidemiology, 179
forceps/clamps, 180
healing times, 180
hypertrophic reaction, 182–183
industrial piercing, large keloids, 183–184
"intimate" piercings, 179
lip piercing, gingival recession, 183, 185
microdermal piercings, 179
navel scar, young woman, 182–183
orofacial piercings, 179
pocketing, 179
Q-switched laser, 183
site-specific complications, 183, 185–186

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

soft earlobe piercing, earlobe split, 183, 185
surface piercings, 179, 182
Bone morphogenetic proteins (BMP), 47
Botulinum (BTX) toxin
medicinal uses
anal and vaginal disorders, 550–551
apocrine chromhidrosis, 550
aquagenic keratoderma, 552
axillary hyperhidrosis, randomized controlled trials, 548–549
benign eccrine tumors and cysts, 551
in Bullous disease, 550
CNS effects, 548
cutaneous leiomyomas, 552
effects on exocrine glands, 547–548
evidence level, 552
facial flushing, 551
focal hyperhidrosis, 549
Frey's syndrome, 549
granulosis rubra nasi, 552
immune effects, 548
inflammatory disorders, 550
intertrigo, 552
itch, 548
muscular atrophy, 547
neurogenic pruritus, 551
osmidrosis, 550
pachydermoperiostosis, 551
pain relief, 548
palmar hyperhidrosis, randomized controlled trials, 549
pruritus, 548
scar management, 551
severe hyperhidrosis, 548
SNAP-25, 547
treatment
aesthetic indications, 558
aftercare, 579
Azzalure injection sites, 559
blepharoptosis, 561
brands and storage, 558
bruising minimization, 559
conventional teaching, 559
discomfort minimization, 559
facial asymmetries, 558–559
focal hyperhidrosis, 557
history, 557
license-based practice, 559
migraine, 557
M-M BTX (*see* Multi-mini botulinum)
mode of action, 557
pretreatment consultation, 558
psychological considerations, 558
skin quality, 557
stimulated nerve endings, 557
stratum corneum hydration, 557
technique controversies, 559
tension headache, 557
unit equivalence, 558–559
wrinkles and rhytids, 557–558
Botulinum toxin (BTX)-A
anesthesia, Palms after Kreyden, 169
for axillary hyperhidrosis, 166–168
BTX type-A-purified neurotoxin complex, 165
history, 165
hyperhidrosis
of anogenital, 170
of forehead, 169
sporadic sweating, 170
of submammary, 170
minor starch test, 165–166
for palmoplantar hyperhidrosis, 168–169
Bowen's disease (SCC *in situ*), 512–513
BP, *see* Body piercings
Brown adipose tissue (BAT), 43–44
Brow ptosis
aging, 583–584
BTX treatment, 582
eyelid rubbing/pulling habits, 583
facial expression muscles, 583
gravity, 583
natural progression, 583
sleeping, 583–584
Bullous disease, 550
Buried backstitch suture, 213
Buried parallel pulley suture, 214–215
Buried sutures
buried backstitch suture, 213
butterfly suture, 213
running intradermal sutures, 213–214
simple buried stitches, 213
tacking/anchoring (pexing) sutures, 214
Butterfly suture, 213

Capillary malformations (CM), 485–488
Cardiac arrhythmias, 315, 318
Cellulite
anticellulite diet, 534
assessment, 526–527
causes and mechanisms, 526
classification, 525, 608–609
clinical appearance, 526
definition, 525
diagnosis, 526
etiopathogeny, 526
evolution and monitoring, 534
fibrous, 530
food tips, 534
hydrotherapy treatments, 531
Liposcore® test, 527–528
medical treatment
cryolipolysis, 533
focused ultrasound system, 533
ice-shock lipolysis, 533
infrared lipolysis, 533
injection lipolysis, 531–532
laser lipolysis, 532–533
lipolaser, 532–533
LLLT, 533
mesotherapy, 533–534
microlipolyse, 533
radio-frequency lipolysis, 533
technical ML3, 533
morphological features, 525
paramedical treatment
Bodysculptor®, 530
Cellu-M6® device, 530
Cellusonic®, 530
electrolipolysis method, 530
electrotherapy, 531
inovo body, 530
luxopuncture, 530
manual lymphatic drainage, 530
SPA jet, 530
Starvac, 531
Technical Alice®, 530
Vacu-Step®, 530
physiopathology, 608
adipose, 525
fibrose, 525–526
lipogenesis, 525
water retention, 525
surgical treatments, 534
therapeutic protocols, 610–611
therapeutic strategy, 527, 529
treatment with mesotherapy, 608–609
visual observations, 525
water retention index, 527
Cervico-facial lift technique, 712
anatomical marks, 717
anesthesia and installation, 717–718
cervical subcutaneous detachment, 717–718
cutaneous resection and closure
fat dressing 24 hours., 720
final periauricular scar, 720
pre auricular skin resection, 719–720
and scar migration, 719–720
skin excess, 719
skin suture, silk/prolene, 719–720
sub-SMAP face lifting, 720–721
face lifting installation, 717–718
incision's outline, 717–718
mapping, landmarks and periauricular incision., 717–718
retroauricular detachment, 717
SMAP flap detachment, 717, 719
SMAP traction and suture, 718–719
subcutaneous detachment, 717
Chemical peels
abrasive techniques
anesthesia, 325
anterior chemoabrasion, 324
bismuth subgallate, 325
definition, 324
depth selection, 325
grade II abrasion, 325
occlusion, 325
perform and preparation, 325
posterior chemoabrasion, 324
prepeel skin conditioning, 325
sandpaper, 325
skin preparation, 325
AHA and TCA association
glycolic acid, 319
indication, 319
post-peel treatment, 320
TCA applications, 319–320
carbon dioxide application, 320
complications, 303–304
contraindications, 303
deep/phenol peel, 304
fillers, 319
history, 303
indications, 303
Jessner Peel association, 320–321
laser pixel peel/fraxpeel, 321–322
medium-depth peel, 304
mesotherapy, 319
microneedling pixel peel, 322–324
mosaic peel, 319
penetration enhancement combinations, 319
phases, 304
pixel peel, 319
superficial peels, 303–304
Chronic paronychia, 140, 300–301
Chronic venous insufficiency
EVLT
bruising and pain, 269
DVT, 269
indication, 267
induration and pigmentation, 268–269
materials and methods, 267–268
paresthesias, 268
pulmonary embolism, 269
foam sclerotherapy
deep venous thromboembolism, 271
follow-up, 270
materials, 270
methods, 270
neurologic events, 270
results, 270
skin necrosis, 271
skin pigmentations, 271
middle-sized and spider veins
chromated glycerin, 272
complications, 272–273

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

matting, 274–275
pigmentation, 273–274
polidocanol, 272
superficial reflux, 272
systematized and nonsystematized network, 271
tetradecyl sulfate, 272
therapeutic result, 271
procedure selection, 267
radio frequency
complications, 269
hematomas, 269
hypoesthesias, 269
indications, 269
materials and methods, 269
matting, 269–270
paresthesias, 269
pigmentation, 269
results, 269
thromboembolism, 269
therapeutic strategy, 267
Chronological aging, 17–18
Clinic management
aesthetic treatment, 779
clinic staff, roles, 780
cosmetic consultation, 780–781
information overload, 779
and marketing, 782–786
well-appointed clinic, 779
Clinic marketing
blog posts, 783–784
clinic brand, 782
Email marketing, 784
Facebook, 785
fee structure, 782
Google+, 785
high quality of care, 782
inbound marketing, 782–783
mobile platforms, 783
open house events, 784
patient reward programs, 784
PR, 786
search engine optimization, 783
social media platforms, 784–785
Twitter, 785
unique selling point, 782
value proposition, 782
website development, 783
WordPress, blog, 783–784
YouTube, 785
Closure® technique, 268
Colloid milium, 21, 127, 364
Contact dermatitis, 318
Corset piercings, 179
Cosmeceuticals
antioxidants, 81, 83
α-lipoic acid, 79
niacinamide, 79
plant materials, 79–80
vitamin C, 78–79
vitamin E, 79
cell regulators, 81, 83
growth factors, 81
polypeptides, 80–81
retinol/vitamin A and derivatives, 80
signal peptides, 81–83
Hamburg skin aging score, 84–85
innovative vehicles
DMS, 77
moisturizing creams, 78
nanodisperse systems, 78
skin aging scale, 84
treatment options, skin aging stage, 84, 86
Cosmetic botulinum
blepharoptosis, 582–583
brow ptosis, 582–584
clown sign, 584, 586
complications, 581
correction methods, 581
natural recovery, 581
strengthening exercises, 581
treatments, 581
depressor labii inferioris weakness, 588–589
dosage and antibody considerations, 581
femme fatale, 584–585
"frozen" face, 581
intraorbital fat herniation, lower eyelids, 586–588
malar festoons, 588
malar mounds, 588
Mephisto-Ascher sign, 584–585
pathogenesis, 581
playground sign, 584, 586
"puffy lower eyelids", 586–588
"puffy pommettes", 588
residual eyelid wrinkles, 586–587
scleral show, 586–587
"Tell-Tail" sign, 584–585
therapeutic ratio, 581
vacuous expression, 581–582
Cosmetic consultation
clinical photography, 782
informed consent, 781
patient privacy, 781–782
patient screening, 781
Cosmetic tattooing, *see* Permanent makeup
Cosmetovigilance, 103–104
Cross-tunneling technique, 665–666
Crumpling wrinkles, 20
Cryolipolysis
adipocytolysis, 540–541
apoptosis and necrosis, 540
clinical interaction
adverse effects, 544–545
contraindications, 544
indication, 544
late-onset pain, 545
heat extraction, 538
heat transfer
conduction (thermal conductivity), 537
convection, 537
cooling power, 538
history, 537
lipid crystallization, 541–543
lipolysis, 540
nomenclature, 537
patient expectations, 545
protocol, 545
vacuum
adverse effects, 539
coloring, 539
friction, 539
immobility, 539
pain, 539
Curcumin, 80, 116
Cushing syndrome, 109
Cybermedicine, 776

Daidzein, 116
DDSO, *see* Dermatological day surgery office
Deep peels
cardiac arrhythmias, 318
complications, 316
contact dermatitis, 318
contraindications, 315
croton oil, 313
different phenol formulas, 314
histological studies, 314
history, 313
indications, 314–315
infections, 318
occlusion, 314
paradoxical effect, 313
phenol characteristics, 313
phenol toxicity, 313
pigmentary changes, 317
post-peel, 316–317
pre-peel, 315
procedure, 315–316
prolonged erythema, 317
scarring, 317–318
septisol, 313
type IV Glogau's classification, 313–314
unoccluded Baker's formula, 314
Depilation field
medical indications of depilatory lasers, 381–382
pigmented field, 383, 385–386
three sessions, 380, 382
vascular field, 381–385
Dermabrasion
anesthesia, 328
Bell Hand Engine®, 329
Boxcar and rolling type scars, 331–332
dermabrader tips, 329
facial skin surface, 331, 333, 335
fullface wire brush dermabrasion, 330–331
full-thickness donor punches, 331, 333
full-thickness punch excision, 331, 333
history, 327
ice pick and boxcar scars, 331–332
indications, 327–328
intraoperative wire brush dermabrasion, 330
laboratory studies, 328
larger and wider full-thickness punch graft, 331, 333
NoKor needle, 330–331
patient's history, 328
postoperative considerations and adverse reactions, 331–332, 334–338
postoperative medications, 328
preoperative medications, 328
preoperative view, 329
RAM® engine, 329
revolutions per minute, 329
scientific background, 327
Dermal-epidermal junction (DEJ), 11
Derma membrane structure (DMS), 77
Dermatitis artefacta (DA), 242–243
Dermatological day surgery office (DDSO), 193
Dermatological offices
ADSO, 193
classification, 193–194
class IV laser systems, 194, 197
clean activity service functional unit, 194–195
DDSO, 193
dirty activity service functional unit, 194–195
functional units
definition, 192
main functional units, 192–193
service functional units, 192–193
size, 192
IPPL sources, 1 98, 194, 197
pre- and post-operative recovery room, 194, 196
SDSO, 193
surgical hand-washing unit, 194–195
surgical nurse station, 194, 196
Dermatoporosis, 22–23
Diet
carotenoids, 114–115
polyphenols and flavonoids, 115–116
polyunsaturated fatty acids, 116
pre- and probiotics, 116–117
vitamin B6, 114

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

vitamin C, 114
vitamin D, 115
vitamin E, 114
Direct patient-provider medical consultation, 775
Distal nail avulsion, 300–301
Double nail, 289–290, 292
Dressing systems
antiadhesive dressings
advantages, 221
disadvantages, 221
examples, 221
uses, 220
closed dressings, 220
"lunchtime" cosmetic procedures, 219
occlusive dressings
foam dressings, 222–223
hydrocolloids, 221–222
hydrogels, 222
polymer films, 221
open dressings
advantages, 219
disadvantages, 219
examples, 219
uses, 219
tapes, 223
Dynamic wrinkles, 20

Eccrine sweat glands, 157–159
E-health and M-health communication, 772
Elastotic creases, 20
Electrical energy and optical spectrum
deteriorate dichroic filter, 377, 379
flashlamp emission, 377, 379
IPL handpieces, 377–378
multipulse radiation, 377, 379
polychromatic irradiation, 377–378
typical spectral response, 377–378
Electrolipolysis method, 530
Electronic data encryption, 773
Electrotherapy, 531
Email marketing, 784
Embedded upper lip piercing, 182
E-medical consultation
antiaging and age-preventive strategies, 774
care delivery platform, 775
congenital and acquired skin defects, 774
live interactive teledermatology, 775
store and forward teledermatology, 775
Endoscopic brow lift technique, 731
Endovenous laser ablation (EVLA), 495
Endovenous laser treatment (EVLT)
bruising and pain, 269
DVT, 269
indication, 267
induration and pigmentation, 268–269
materials and methods, 267–268
paresthesias, 268
pulmonary embolism, 269
Epidermal stem cells, 38
Epidermal suture, 209
Erythrosis, 21–22
Erythrosis interfollicularis colli, *see* Poikiloderma of civatte
Estrogen
aging skin, 14
menopause-induced skin aging, 18
EVLT, *see* Endovenous laser treatment
Extracellular matrix (ECM), 11
Eye cosmetics
for eyebrow, 135–136
for eyelash
camouflaging, 135
eyeliner, 134–135
mascara, 134
for eyelids
dyspigmentation, 134
powder eye shadows, 133
texture-modifying agents, 133
Eyelid ptosis (blepharoptosis), 561

Face
pigmented lesions, 21–22
texture
colloid milium, 21
Favre and Racouchot syndrome, 20–21
kinds of wrinkles, 20
senile sebaceous hyperplasia, 21
solar elastosis, 19–20
trichostasis spinulosa, 21
vascular lesions, 21–22
Face and body epilation
beard pseudofolliculitis, 505–506
contraindications, 504–505
groin pseudofolliculitis, 505
hormone imbalances, 505
hypertrichosis, 505
indications and efficacy, 504
medical history assessment, 504
post treatment, 504–505
pretreatment hirsutism, 504–505
sunlight exposure, 505
Face and eyelid cosmetic surgery
negative aspects
cutaneous and neural scarring, 757
subcutaneous detachments, 757–758
positive aspects
identity reconstruction, 758
rebirth, patient feeling, 758
"technical" and static result quality, 758
Face and neck soft tissue lifting, 677
Facelift
age perception codes modifications, 705
age-related reconstruction, 706
excess skin treatment, 759
facial aging, 759
fat autografts, 759
identity reconstruction (restoration), 706
indications, 759
invasive suture-based repositioning, 759
medical procedures, 759
mutilating procedures, 705
patient's appearance, 705–706
posture education, 760
practical anatomy
arterial vascularization, 714
cutaneous ligaments, 713
deep aponeurotic structures, 713
dermal hypodermic aging, 708–709
dermal muscles and muscular and aponeurotic structures, 711–712
facial innervation, 714–715
fat tissue, 708–711
planes of motion, 712–713
prevention, 759
return on investment, 706
sustainable stitching systems, 759
technical quality, 706
therapeutic and non-invasive approaches, 705
treatment plans, 759
Facial fat tissue
cervicofacial region, 711
deep fat, 708
embryological origin, 711
melting and ptosis, 708
MRI view, 708–709
periorificial craniofacial region, 708
subcutaneous, 711
superficial fat, 708
Young cadaver dissection, 708–709
Facial innervation
anastomoses, 714–715
great auricular nerve, 715
live dissection, facial nerve, 714
motor, 714–715
sensory, 715
trigeminal nerve, 715
Facial redness
AD, 122
contact dermatitis, 122
eczema, 122
psoriasis, 122
rosacea, 120–121
seborrheic dermatitis, 121
sensitive skin, 119–120
skin barrier, 119
Factors Affecting the Protection Provided by Sunscreens, 92
Facultative technical equipment (FTE), 192
Fat grafting technique
adipocyte grafts, 655
adipocytes, early cell death and replacement, 751–752
autologous adipose tissue graft, 655–656
body
breasts, 660–661
buttocks, 658–660
genital organs, 660
hand, 658
breast augmentations, 655
breast hypoplasia, 655
centrifugation, 656
clinical application, 752–754
concave-shaped faces, 658
epinephrine serum infiltration, 657
harvesting, 656
indications, 657
isolated use, face
cheekbones and tear troughs, 657
chin and jawline, 658
lip, 658
nasolabial folds and marionette lines, 657
upper eyelid and temple, 657
lipostructure, 656
of full face, 752–754
jawline, 752–754
physiological description, 655–656
physiology, 656
platelet-rich plasma, 751
postinjection blindness, 657
regenerative medicine, 751
reinjection, 657
screening quality, 655
tissue engineering, 655
Fat mobilization
catecholamines, 52
and deposition
biological functions, 49–50
de novo lipogenesis, 49
hormones and factors, 49–50
human fat cell lipolysis, 49, 53
LCFAs, 49, 52
lipid deposition and lipid mobilization, 49, 51
lipoprotein lipase transfer, 49, 51
triacylglycerol (TAG), 49, 53
lipolysis, 52
Favre and Racouchot syndrome, 20–21
Field cancerization/multiple NMSC, 513
Filler
adverse side effects
acrylic hydrogel, 633–636
autologous fat, 629
autologous human collagen, 629
bioplastique, 638
CHA, 632–633

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

dextranomer beads, 632
granulomatous swelling, 632
HA, 630–631
histopathology, 638–639
mineral oil and lipid derivatives, 637
nonhuman collagens, 630
PAAG, 633–634
paraffin, 637
PMMA, 634, 637
polyalkylimide gel, 633
poly-L-lactic acid, 632
polyvinylhydroxide microspheres, 633
silicone, 637
silicone elastomer suspension, 638
classification, 627
early complications, 627
immediate reactions, 627
irreversible, 627
late complications, 627–628
long-lasting fillers, 629–630
permanent (irreversible) fillers, 629
prevention, 639
reversible, 627
soft-tissue fillers, 628–629
treatment, 639–640
Fitzpatrick skin-type scale, 764
Fluid management, 665–666
Fluorescence-activated cell sorter analysis (FACS), 49
Foam dressings, 222–223
Foam sclerotherapy
deep venous thromboembolism, 271
follow-up, 270
materials, 270
methods, 270
neurologic events, 270
results, 270
skin necrosis, 271
skin pigmentations, 271
Focal hyperhidrosis
compensatory hyperhidrosis, 171
endoscopic thoracic sympathectomy, 171
Frey Syndrome, 170
LUH, 171
primary, 156–157
Ross syndrome, 170–171
secondary, 155–156
Focal ultrasound, 518, 520
Focused ultrasound lipolysis, 533
Focused ultrasound system, 533
Follicular unit extraction (FUE)
advantages, 253–254
aspects, 253, 255
Choi implanter, 253, 256
disadvantages, 254
indications, 253
stick and place process, 253
technique, 252, 254–255
Follicular units with long hair (FUL)
advantages, 250–251
after segmentation, 250–251
disadvantages, 251
donor area, 251–252
postoperative aesthetic embarrassment, 250–251
recipient area, 252–253
Fractional ablative technology, 361
Fractional laser skin resurfacing
ablative systems, 360–361
complications
acneiform eruptions, 365
anesthesia toxicity, 366
contact dermatitis, 366
delayed purpura, 366
eruptive keratoacanthomas, 366
erythema, 365–366
heat-induced recall phenomenon, 366
infections, 365
pigmentary alteration, 366
scarring, 366
drug delivery, 366
history, 360
home fractionated devices, 366
indications
acne scarring, 362–364
photoaging, 361–362
pigmentary disorders, 364
posttraumatic scar, 364
striae distensae, 364
surgical scar, 364
vascular disorders, 364
mechanism, 360
nonablative systems, 360–361
patient selection, 365
postoperative course, 365
preoperative management and anesthesia, 365
tattoo removal, 366
Fractional nonablative lasers
density, 373–374
different types of, 373
efficacy, 373
indication, 374
irradiance, 374
tissue effects, 373
treatment strategies, 374–375
wavelength, 374
Fractional resurfacing (FR), 128
Frey's syndrome, 170, 549
FU, *see* Functional units
FUE, *see* Follicular unit extraction
FUL, *see* Follicular units with long hair
Functional units (FU)
definition, 192
main functional units, 192–193
service functional units, 192–193
size, 192

Genistein, 116
German barbed threads, Achilles tendon rupture, 677–678
Glogau classification, 21
Glogau photoaging classification, 764
Glycosaminoglycan (GAG), 11
Granuloma telangiectaticum, 490
Granulosis rubra nasi, 552
Gravitational wrinkles, 20
Groin pseudofolliculitis, 505

HA, *see* Hyaluronic acid
Hailey–Hailey disease, 550
Hair follicle bulge, 38
Hair follicle destruction
laser pulse width (exposure duration), 503–504
optimal pulse duration, 504
photochemical destruction, 504
photomechanical hair destruction, 504
photothermal destruction, 501, 503
thermal conduction, 504
Half-buried vertical suture, 210–211
Hamburg skin aging score, 84–85
Heliodermic wrinkles, 20
Hemangioma, 485
Hemorrhoidectomy, 551
Hereditary hemorrhagic telangiectasia (HHT), 490
HHT, *see* Hereditary hemorrhagic telangiectasia
HIFU, *see* High-intensity focused ultrasound
High-intensity focused ultrasound (HIFU), 427
Horizontal mattress sutures, 210–211
Hormone replacement therapy (HRT), 109
Hormones
endocrine disruptors, 110
endocrine functions, 107–108
endocrinopathies, 109
gender-independent endocrine aging, 107–108
gender-influenced endocrine aging, 108–109
HRT, 109
neuroendocrine compounds, 107–108
HRT, *see* Hormone replacement therapy
Hutchinson-Gilford progeria syndrome, 13
Hyaluronic acid (HA), 11
for body
hyaluronidase, 624
Macrolaner (galderma), 623–624
skin testing, 624
contraindications, 617–618
discovery, 617
indications, 618
injections (*see* Injections, HA)
pretreatment, 618
science of, 617
Hydrocolloids, 221–222
Hydrogels, 222
Hyperandrogenism, 18–19
Hyperpigmentary disorders
acquired pigmentations, 125–126
chemical peelings, 128
melasma, 125–126
new injection treatments, 128
physical treatments
intense pulsed light, 128
lasers, 127
topical and cosmetic treatments
arbutin/arbutoside, 127
azelaic acid, 127
hydroquinone, 127
Kojic acid (KA), 127
4-*n*-butylresorcinol, 127
retinoic acid, 127
steroids, 127
tretinoin, 127
Hyperpigmentation, 109
Hyperpigmented lesions
adverse reactions, 477
scientific basis, 473
treatment
acquired dermal hypermelanocytosis, 474–475
Becker nevus, 474
Cafe-au-lait macules, 474
dark rings, 476
Freckles, 474
giant congenital nevus, 475
ito nevus, 474
lentigines, 474
LWNH, 475–476
melasma, 476–477
nevus spilus, 474–475
ota nevus, 474
postinflammatory hyperpigmentation, 476
solar lentigines, 474
vitiligo, 477
Hypertrichosis, 505
Hypertrophic and keloid scars, 513–514
ablative lasers, 238
algorithm, 237
cryotherapy, 238
excision, 239
intralesional treatment, 238
nonablative lasers, 238

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

PDT, 238
surgery plus compression, 239
surgery plus 5-FU, 239
surgery plus imiquimod, 239
surgery plus radiation, 240
surgical procedures plus steroid injection, 239–240
topical treatments, 237–238
treatment, 242
Hypertrophic scar, 311
Hypomelanosis guttatae, 22

Ice-shock lipolysis, 533
Illouz' s wet technique, 673
Implantable medical devices
features, 742
high malar suspension fixation, 742, 744
implanted medical devices, 742
inferior palpable skin resection, 742
sutures, 742
tension/conical threads, 742
Indirect referring provider-distant consultant medical consultation, 775
Induced pluripotent stem cells, 31–32
Industrial piercing, 183–184
Inflammatory disorders, 550
Infrared light, 521
Infrared lipolysis, 533
Ingrown nails, 294–296
Injection lipolysis, 531–532
Injections, HA
crow's feet, 619
eyebrows, 619
forehead, 619
glabellar area, 619
lower face
chin remodeling, 622
jawline, 622
lip augmentation, 622
low cross-linked HA, 622
Marionette lines, 622
nasolabial crease filling procedure, 620, 622
non-cross-linked glycerol added HA, 622–623
upper lip, 622
nose, 620–621
sunken eyes, 619–620
tear trough, 620–621
temples, 619
zygomatic arch, 620
Intense polychromatic pulsed light (IPPL) sources, 194, 197–198
Intense pulsed light (IPL), 483
abralight technique, 386–387
acne, 389–390, 492
acquired vascular alterations, 485
aesthetic field
burns and scars, 392
innocuousness, 392–393
ocular risks, 393
pain, 391–392
pathological scars and scar prevention, 391–392
photodynamic photorejuvenation, 389, 391
prolonged hyper/hypopigmentations, 392
tattoos, 391–392
blue rubber bleb nevus syndrome, 488
calibration system, 378, 380
capillary malformations, 485–488
congenital lesions, 485
cooling systems, 378–380
depilation field
medical indications of depilatory lasers, 381–382
pigmented field, 383, 385–386
three sessions, 380, 382
vascular field, 381–385
devices, 483
electrical energy and optical spectrum
deteriorate dichroic filter, 377, 379
flashlamp emission, 377, 379
IPL handpieces, 377–378
multipulse radiation, 377, 379
polychromatic irradiation, 377–378
typical spectral response, 377–378
electrical pulsing stabilization, 378
granuloma telangiectaticum, 490
handpieces, 378
hemangioma, 485
HHT, 490
leg veins, 490
Nordlys system, 484
optical filters, 378, 380
patient preparation, 484–485
photodynamic therapy, 389–390
poikiloderma of civatte, 490
practical applications, 484
pulse delivery, 378
red or hypertrophic scars, 492
rejuvenation and collagen "remodeling", 387–389
rosacea, 491–492
senile angioma, 488–489
spider angioma, 490
telangiectasias, 489–490
treatment guidance, 484
venous lakes, 492
venous malformation (VM), 488
Intense pulsed lights (IPLs), 511
Internal marketing, 784
International Society for Cellular Therapy, 34
Internet and e-consultation
consumers' access, health-care information, 774
equipment failure malpractice, 777
E-revolution and E-health, 771–772
European Convention on Human Rights, 772–773
health-care systems, 771
human communication, 771
information and communication, 771
insurance policies, 777
licensure and liability coverage, 776
medical consultations, 774
medical data security, 772–773
medical records, conventional and electronic, 773
mobile health (M-health), 772–773
physician-patient relationship, 776
privacy and confidentiality, 776
privacy and informed consent, 776–777
record management, 771
standard of care, 776
telemedicine, 772
"Intimate" piercings, 179
Intrinsic skin aging, 113
IPL, *see* Intense pulsed light

Koebner phenomenon, 174

Laser-assisted lipolysis (LAL)
advantages, 675
dosimetry, 675
limited global development, 675
liposuction
LAL, 673
PAL, 673
SAL, 673
localized adiposity, 673
mathematical model of Mordon, 673–674
mechanisms of action, 675
photoacoustic effects, 675
photomechanical effects, 675
photothermal effects, 675
41-laser dermatology
absorption
Beer-Lambert law, 343–344
coefficient g, 346
energy gaps, 343
ground state, 343
human skin, 346
Jablonski diagram, 343
light, 344–346
scattering and transport mean free path, 347
singlet states, 343
tissue scattering structures, 346
triplet states, 343
electromechanical effect, 341
penetration of light, 347–349
photoablative effect, 341, 353
photochemical/photodynamic effect, 341
choice of wavelength, 354
electromechanical effect, 355
mechanisms of type I, 353
mechanisms of type II, 354
molecule and different pathways, 353
reflection
refractive index, 342
scattered, 341–342
specular, 341–342
variation, 342
thermal effect, 341
heat transfer, 350–351
light-heat conversion, 350
mechanisms of action, 349–350
tissue denaturation, 351–353
Laser epilation, 501
Laser lipolysis, 532–533
Lasers and intense pulsed light
beard removal, in men, 506
classical methods, 501
face and body epilation
beard pseudofolliculitis, 505–506
contraindications, 504–505
groin pseudofolliculitis, 505
hormone imbalances, 505
hypertrichosis, 505
indications and efficacy, 504
medical history assessment, 504
post treatment, 504–505
pretreatment hirsutism, 504–505
sunlight exposure, 505
hair follicle destruction
laser pulse width (exposure duration), 503–504
optimal pulse duration, 504
photochemical destruction, 504
photomechanical hair destruction, 504
photothermal destruction, 501, 503
thermal conduction, 504
optimal hair removal method, 501
patient expectations and outcome, 505–506
postprocedural complications, 507–508
potential risks, 507
preoperative and postoperative care, 506–507
types, 501–503
unwanted hair removal, in women, 506
Laser treatment
acne, 492
acquired vascular alterations, 485
background, 481

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

blue rubber bleb nevus syndrome, 488
blue veins, 496–498
capillary malformations, 485–488
complications, 498–499
congenital lesions, 485
cutaneous vessels treatment, 498
devices, 483
endovenous laser ablation, 495
facial telangiectasias, 493
fluence/energy level, 446
granuloma telangiectaticum, 490
hemangioma, 485
HHT, 490
history, 481
leg veins, 490
mobile macrophages, 446–447
Nordlys system, 484
patient evaluation
clinical considerations, 444
contraindications, 444
Kirby–Desai scale, 444
professional polychromatic decorative tattoo, 444–445
treatment sessions, 444
patient preparation, 484–485
perforator veins, 495
poikiloderma of civatte, 490
posttreatment, 447–448
practical applications, 484
pretreatment, 445–446
pulse width/duration, 446
red or hypertrophic scars, 492
red veins, 496–497
rosacea, 491–492
selective photothermolysis
fluence, 482–483
pulse time, 482
spot size, 483
wavelength, 481–482
senile angioma, 488–489
side effects and complications
allergic reactions, 448–449
dyspigmentation and textural changes, 448
epidermal debris, 449
ink darkening, 449
spider angioma, 490
spot size, 446–447
telangiectasias, 489–490
telangiectatic and reticular leg veins, 495–497
treatment effect, 498
treatment guidance, 484
varicose veins, of leg
causes, 494
chronic venous disease, 493–494
classic symptoms, 494
cost-effective, 494
incidence, 494
prevalence, 494
risk factors, 494
treatment options, 494–495
ultrasound examination, 494
vascular, 493–494
venous lakes, 492
venous malformation (VM), 488
wavelength, 446
Laterally localized tumors, 299–300
Leg veins, 490
Levator labii superioris and alaeque nasi, 25
Levator palpebrae superioris (LPS), 561
Light-emitting diode (LED) devices, 14, 511
Linear and whorled nevoid hypermelanosis (LWNH), 475–476
Lip cosmetics
camouflaging, 132–133
color correction, 133
lip liners, 132–133
lipstick
opaque, 131–132
polymer, 131–132
sun protection, 131–132
Lipectomy, conjunctival approach, 699–700
Lipid crystallization
contrast lipocryolysis, 543
nucleation, 541, 543
postlipocryolysis, 541
sample analysis, 541–542
structure, 541
temperature treatment patterns (TTPs), 543
Lipodystrophy, *see* Cellulite
Lipofilling techniques, 657
Lipolaser, 532–533
Lipolysis, 540
Liposcore® test, 527–528
Liposonix, 429
Liposuction
anesthesia, 665
of arms, 669
description, 663
evolution, 671
fluid management, 665–666
hip/flanks, 669
infiltration, 665
informed consent process, 664
instrumentation and current devices
cannula shaft lengths, 666
LAL, 667
mercedes-tip design liposuction cannulas, 666
power-assisted cannulas, 666
RFLAL, 667
SAL, 666
UAL, 666
knees treatment, 670
lateral gluteal fold, 669
markings, surgical marker, 664
in neck region, 667–668
operative technique, 665
patient selection, 663
pertinent anatomy, 663
physical examination, 664
positioning, 664
postoperative care, 670–671
preoperative planning, 663–664
prevention of complications, 670–671
risks and complications, 671
subcutaneous abdominal fat, 669
subcutaneous fat and skin, back, 669
thighs and buttocks, 669–670
wetting solutions, types, 665
Lip piercing, gingival recession, 183, 185
Live interactive teledermatology, 775
LLLT, *see* Low-level laser therapy
Local anesthesia (LA)
clinical use
agents, 228
nerve blocks, 229–230
perilesional infiltration, 229
topical application, 228
history, 225
iontophoresis, 228
nervous driving mechanism
anatomy, 225–226
biochemistry, 226
chemical agents, 227
cryoanesthesia, 228
mechanisms of action, 226–227
physiology, 225–226
vasoconstrictor agents, 227–228
side effects, 230
Localized unilateral hyperhidrosis (LUH), 171
Long-chain fatty acids (LCFAs), 49, 52
Longitudinal melanonychia, 298–299
Long-lasting fillers, 629–630
Lower eyelid blepharoplasty
by anterior approach
premuscular cutaneous approach, 698–699
subciliary and retromuscular approach, 697–698
with fat repositioning, infraorbital edge, 700
and hyperlaxity
full-thickness resection, eyelid's free edge, 700
lateral canthoplasty, 700–701
lipectomy
conjunctival approach, 700
skin excision, 700
and Malar bags
classic subcutaneous anterior lower blepharoplasty, 701
midface lift, 701
transconjunctival, 699–700
Lower transconjunctival blepharoplasty, 699–700
Low-level laser therapy (LLLT), 533
Lymphatic aquadrainage, 531

Makeup techniques
camouflaging cosmetics, 136–137
eyes (*see* Eye cosmetics)
facial foundation, 136–137
for lips (*see* Lip cosmetics)
pigmentation defects, 137
Malar lifting
deep fat pad, 736
dissection, 736
SOOF pad, 736
Matrix metalloproteinases (MMP), skin aging, 12
Matting
risk factors, 274–275
treatment, 275
Medium-depth peels
action, 309
body peels, 312
complications, 310–312
contraindications, 309
depressed acne scars, 308
histological aspects, 310
history, 309
melasma, 308
photoaging, 308
preparation, 309
TCA, 311
technique, 310
Melanocytic stem cells, 38
Melanotic lesions, *see* Hyperpigmented lesions
Menopause-induced skin aging
estrogenic deficiency signs, 18
hyperandrogenism, 18–19
Mesenchymal stem cells (MSCs)
adipose-derived stem cells, 37–38
bone marrow–derived MSCs, 34–36
clinical trials, 29–30
criteria, 34
dermal/adipose stem cells, 33–34, 37
MesoGlow, *see* MesoLift
MesoLift
composition, 605–606
definition, 603
epidermal mesotherapy, 603–604
equipment, 603
fine lines before/after treatment, 606
indications, 605

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

intradermal technique, 604
medicines
Papaverine, 605
Pentoxifylline, 605
meso-canulla, 605
mixture and techniques, 606
non-cross-linked hyaluronic acid, 605
oval and nasolabial fold, 606–607
oval face, 606–607
papula technique, 604
regeneration rate of skin, 606
techniques and depths of injection, 603
Mesotherapy
alopecia (*see* Androgenic alopecia)
cellulite, 608–611
description, 599
history, 599–602
hypertrophic scars and keloids, 615
indications, 602
psoriasis, 615
stretch marks, 615
viral warts, 615
Vitiligo, 615
Methyldibromo glutaronitrile, 101
Microdermal piercings, 179
Microepidermal necrotic debris (MEND), 360
Micrografts
androgenetic alopecia
digital phototrichogram, 257–258
female androgenetic alopecia, 259–261
male androgenetic alopecia, 257–260
multifactorial classification, 257
transsexuals, 261
body hair growth alopecia
beard and mustache, 264
eyebrows, 261, 263
eyelashes, 261, 263
pubic hairs, 264
preauricular alopecia, 261–262
pseudopeladic alopecia, 261
scarring alopecia, 261–262
traction alopecia, 261–262
Microlipolyse, 533
Micropigmentation, *see* Permanent makeup
Middle-sized and spider veins, sclerotherapy
chromated glycerin, 272
complications, 272–273
matting, 274–275
pigmentation, 273–274
polidocanol, 272
superficial reflux, 272
systematized and nonsystematized network, 271
tetradecyl sulfate, 272
therapeutic result, 271
Midface lift
anatomy
definition, 733–734
features, 733
malar region, 733
orbital region, 733–734
structures, 734
zygomatic region, 733
clinical cases, 746–748
descriptive anatomy, 733
functional anatomy, 733
implantable medical devices, 742, 744
indications, 744
low malar lifting, 739
modeling, aging, 733
morphology, 733
side effects and complications, 744–745
skeleton and deep muscles, 734–735
skin traction, 733
superficial planes
facial muscles, 735–736
fascia and ligaments, 737
fatty tissue planes, 736
horizontal histological section, 737–738
malar fat pad, 736
OOM, 736
surgical approaches
gingival, 742
palpable, 742–743
tissue aging, 733
tissue stratification, 734
treatment overview, 745
upper malar lifting, 740
Minor starch test, 165–167
Mobile communication technology, 772–773
Mobile-health authentication, 773
Mobile VPNs, 773
Morbus–osle syndrome, *see* Hereditary hemorrhagic telangiectasia
Multi-mini botulinum (M-M BTX)
brow elevator, 567
bunny lines, 570
corrugator
depressor supercilii complex, 566–567
insertions, 563, 565–566
origin, 563–564
at Corrugator Superciliaris, 560–561
crow's feet, 568
depressor anguli oris (DAO), 574–575
depressor septi nasi, 572–573
dilator naris, 572–573
disadvantages, 559
early jowling, 576–577
eyebrow elevation, frontalis muscle, 560
eyebrow ptosis, 561
eyebrow tail, 569
eyebrow "Tell-Tail" sign, 569
frontalis, 567
injection dose, 562
Levator Labii Superioriset Alæque Nasi, 571–572
lower eyelid margin, 570–571
lower sand point, 568
Masseter BTX, 575–576
Mentalis, 575
migraine and tension headache, 579
multiple mini-dose injections, 559
Nefertiti lift, 576
at OO, 561–562
orbicularis oculi bands, 571–572
Orbicularis Oris, 572, 574
"Owwee" point, 570–571
placement and dose, 560
platysmal bands, 576, 579
procerus, 562–563
sand point, 567–568
venus rings, 576, 578
Multiple legal issues, cosmetic procedure
clinical guidelines and innovation, 790–791
complications, physician, 791–792
cutaneous laser surgery, 789, 793
health-care law, 789
laser centers, 790
standard of care, 789, 791–793
Muscle aging
characterization, 24
neck and platysmal cords, 25–26
nose, 25
peribuccal area, 25
periorificial fronto-orbital area, 24–25
Muscular and aponeurotic structures
buccolabial region, 712
depressor supracilii muscle, 711
epicranial aponeurosis, 711
eyebrow's lowering muscular complex, 711
eyelid orbicular muscles, 711
eyelids' orbicular muscle, 711
galea aponeurotica, 711
McGregor patch, 712–713
muscular aponeurotic complex, 711
pars orbicularis, 711
pars palpebralis, 712
pyramid muscle/procerus, 711
Myxoid pseudocyst, 298–299

Nail adornment
lacquered nail resting, 150
nail piercing, 151
stick-on nail dressings, 150
Nail gels
acrylic light-cured gels, 147
allergic hazards, 150
benefits, 149
composition, 147
ethyl cyanoacrylate gels, 147
infectious hazards, 150
light-cured gel, 147–148
polymerization, 147
screening patch tests, 150
stickers, 147, 149
technical and mechanical hazards, 149
Nail lacquers
additives, 141
advantages, 142
allergic hazards, 142–143
camouflaging, 142
categorisation
base coats, 141
gel polish, 141–142
hardeners, 141
hypoallergenic, 141
ridge fillers, 141
top coats, 141
UV-curing nail lacquers, 141–142
cosmetic, 142
film formers, 140
film modifiers, 140
pigments and colorants, 141
plasticizers, 140–141
protection, 142
solvents, 141
technical and mechanical hazards
keratin granulations, 142
nail brittleness, 142
severe nail damages, 142
yellow-orange staining, 142
thinners, 141
thixotropic agents, 141
Nail manicure
allergic hazards, 140
benefits, 140
buffing, 139
chronic paronychia, 140
creams for brittle nails, 139
cuticle removers, 139
cuticle softeners, 139
cutting and filing, 139
infectious hazards, 140
mechanical hazards, 140
microtraumatisms, 140
nail lacquers, 140–143
nail polish remover, 139
Nail prosthesis, 151
Nail repair
composition, 143
nail mending, 143
Nail surgery
anatomic and physiologic considerations
arterial blood supply, 287, 289
cuticle formation, 287–288
hyponychium and nail isthmus, 287–288
matrix and nail layers, 287–288

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

nail growth, 287, 289
sagittal section, 287–288
anesthesia, 288–291
big toenail, 290–293
chronic paronychia, 300–301
distal nail avulsion, 300–301
double nail, 289–290, 292
ingrown nails, 294–296
laterally localized tumors, 299–300
longitudinal melanonychia, 298–299
myxoid pseudocyst, 298–299
onychopapilloma, 299
patient preparation, 287–288
patient selection, 287
postoperative care, 289
proximal nail avulsion, 301
proximal nail fold, 300
retronychia, 296–297
split nail deformity, 292–294
toenails, 295–297
tourniquet, 289
trapezoid nails, 290, 293
traumatically damaged nail, 301–302
ungual fibrokeratomas, 298
vertically implanted nail, 290, 293
viral warts, 297–298
Natural tattoos, *see* Traumatic tattoos
Negative-pressure wound therapy (NPWT), 235–236
Nevus araneus, *see* Spider angioma
Niacinamide, 79
Nominal scoring, skin aging, 63
Nonablative lasers
evolution, 371
fractional lasers
density, 373–374
different types of, 373
efficacy, 373
indication, 374
irradiance, 374
tissue effects, 373
treatment strategies, 374–375
wavelength, 374
remodeling lasers
aftereffects, 372
dermal remodeling, 372
fibroblast stimulation, 372
histological studies, 372
indications, 372
mechanisms, 372
platelet factors, 372
principles, 372
Nonbotulinum treatment, primary hyperhidrosis
anticholinergic medications, 161–162
antitranspirants, 161
cholinergic pathway, 161
parasympatholytics, 161–162
surgical treatments
axillary sweat gland excision, 163
minor starch test, 164
sweat gland suction and curettage, 163–164
thoracic endoscopic sympathectomy, 164
TWI, 162–163
Noncollagenic agents
calcium hydroxyapatite, 595–596
Lutrol F 127, 594–595
poly-L-lactic acid, 595
Nonsurgical fat destruction, cellulite, *see* Cellulite
Nonsurgical skin tightening
focal ultrasound, 518, 520
infrared light, 521
nonablative Er:YAG laser, 521–522
radiofrequency, 518–519
skin laxity
causes, 517
managment, 517–518
Nutricosmetic ingredient, 113–114

Obsessive-compulsive disorder (OCD), 7–9, 72
Occlusive dressings
foam dressings, 222–223
hydrocolloids, 221–222
hydrogels, 222
polymer films, 221
OCD, *see* Obsessive-compulsive disorder
Office surgery
accreditation, 192
certification, 192
facultative technical equipment, 205–206
PPP, 192
primary technical equipment
advanced clinical–surgical hybrid tables, 201–204
audio system, 205
cabinets, 204
ceiling lights, 201
electrosurgical units, 204
Mayo stands, 202
operating room tables, 201–204
photographic equipment, 205
refrigerator, 204
resuscitative equipment, 203–204
surgical carts, 202
surgical clock, 205
surgical lights, 201
surgical stools, 202
surgical suction and gases, 202
vital functions monitoring equipment, 202–203
waste disposal, 205
x-ray film viewer, 205
quality of care, 192
risk management, 192
safety, 192
surgical environment
aims and requirements, 191
definition, 191
dermatological offices, 192–196
ergonomics, 196–201
Olfactory beauty, 5
Onychopapilloma, 299
Orbicularis labii oris, 25
Orbicularis oculi muscle (OOM), 734–735
Orofacial piercings, 179
Osler–Weber–Rendu syndrome, *see* Hereditary hemorrhagic telangiectasia
Osmidrosis, 550

Palmoplantar hyperhidrosis, 168–169
Palpebral and upper face examination
dermochalasis, Caucasian woman, 691–692
eyebrow ptosis, 691–692
forehead–facial region, 691–692
medical examination record, 691–692
upper eyelid, 691–692
Palpebral, lower and midface examination
jugal (cheek) region, 691
lid/cheek junction, 691
lower eyelid, 691
standard ophthalmological assessment, 691
Papulopustular rosacea, 120
Paradoxical hypertrichosis, 507–508
Parallel pulley suture, 214–215
Partial androgen decline in the aging male (PADAM), 108–109
Participation, aesthetic technician
aesthetic patient, 768–769
assistant laserist, 769
delegated acts, 769
education and skills
hosting, 768
telephone reception, 768
instrumentation, 770
medical activities, 767
status and training, 767
surgical assistant, 769–770
team management, 767–768
Patient privacy protection (PPP), 192
PDT, *see* Photodynamic therapy
Perifollicular edema, 506
Perioral dermatitis, 311–312
Periorbital skin tightening, nonablative Er:yag laser, 521–522
Periorificial fronto-orbital area, 24–25
Permanent (irreversible) fillers, 629
Permanent makeup (PMU)
acute complications
cutaneous infections, 174–175
hypersensitivity reactions, tattoo pigments, 175
PEH, 176
sarcoidal granuloma, 175–176
skin cancers, PMU, 176
systematic sarcoidosis, 175–176
blepharopigmentation, 176
decorative tattooing, 173
fake "freckles", 174
laser treatment, 176
local legislation, 173
MRI, 176
progressive fading, eyebrow tattoos, 174
"semipermanent", 173
Permanent products
complications, 593
mineral oil injections, 591
polyacrylamide gel, 592–593
polyalkylimide gel, 593
polyethyl-methacrylate microparticles, 592
polymethyl-methacrylate microspheres, collagen, 592
polytetrafluoroethylene implant, 593
silicone injections, 591–592
Permanent vertical frontal wrinkles, 20
Personal privacy protection (PPP), 772
Phenol peels, *see* Deep peels
Phlebectomy
adverse reactions, 282–283
contraindications, 277
history, 277
indications
curettage of telangiectasias, 284
dilated veins, 284–285
posttraumatic dilatation, 284–285
Ramelet's hook, 284
superficial thrombophlebitis, 284–285
vein biopsy, 285
preoperative requisites, 278
procedure
dressing, 280–281
instruments and equipment, 279–280
local anesthesia, 278–279
operations, 279–281
postoperative course, 281–282
preoperative/peroperative sclerotherapy, 278–279
varicose veins, marking of, 278–279
results, 282–283
scientific basis, 277

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Photoablative effect, 353
Photobiomodulation (PBM)
  bystander cell theory, 402
  clinical practice, 401
  device, 401–402
  forward biased/direction, 395–396
  indications
    biofilm, 405–406
    cicatrization process, 403–406
    hair growth, 406–408, 411–412
    inflammation, 403–405
    persistent psoriasis, 404, 410
    photobiomodulable clinical forms, 406, 410
    physiopathological hypotheses, 406
    propionibacterium acnes, 404–405
    stretch marks, 404, 407, 409
  interpulse/dark period, 402
  Joules and power density, 403, 404
  light/energy absorbtion, 397
  photon energy, 395, 397
  pigmentation
    biological clock and retinohypothalamic–sympathetic pathway, 408
    melanocyte network, 411
    melasmas and postinflammatory pigmentations, 412
    postinflammatory pigmentation, 412
    visible light, 412
    visual transduction, 408
    vitiligo, 412–413
  PN and depletion zone, 395–396
  pre-injury/illness level of activity, 395
  semiconductivity
    cellular cross-talk, 396
    citric acid cycle, 399
    dermoepidermal cross-talk, 396, 398
    electron transport chain, 399
    glycolysis, 399
    inflammation, 396
    Keloid scar appearance, 396, 399
    molecular switch, 400
    proliferation, 396
    remodeling, 396
    retrograde, 399
    tiny impurities, 395
    wound healing, 396
  speaking light hypothesis, 402
Photobiomodulation rejuvenation process, 403, 405
Photochemical destruction, 504
Photodynamic therapy (PDT), 353
  actinic keratoses, 512
  adverse events, 512
  basal cell carcinoma, 513
  Bowen's disease (SCC *in situ*), 512–513
  field cancerization/multiple NMSC, 513
  hypertrophic and keloid scars, 513–514
  photorejuvenation, 514
  photosensitizing drug, 511
  topical, 511–512
Photomechanical hair destruction, 504
Photooxidative stress, 113
Photoprotection
  risk of burning, 89–90
  skin aging, 14
  solar ultraviolet index, 89–90
  sun protection
    clothing and hats, 90–91, 93
    optical filters, 91
    shade, 89–92
  sunscreens
    core ingredient, 91
    sun protection factor, 91–92, 94–96
    sunscreen–sunburn paradox, 93–94
    wavelengths of UV radiation, 93
  ultraviolet age, 96–97
Photorejuvenation, 514
Photothermal destruction, 501, 503
Physical peels, 308
Pillow wrinkles, 20
Platelet-rich plasma (PRP), 751
  aesthetic dermatology, 645
  in aesthetics
    applications, 648
    centrifugation, 649
    clinical approach, 648
    coagulation, 649
    fractional ablative CO_2 laser resurfacing, 648–649
    harvesting kits, 649
    human dermal fibroblasts, 648
    mesotherapy-like injections, 648
    platelet concentration, 649
    purity, 649
  centrifugation, 645
  controlled GF release over time, 646, 648
  definition, 645
  long-term collagen remodeling effect, 651
  lower eyelid left before therapy, 651–652
  in medicine, 647–648
  multiple modalities, skin rejuvenation, 645–646
  nasolabial left before therapy, 651–652
  protocols, 649–650
  for rejuvenation, 645
  for skin regeneration, 645
  whole face approach, 649–651
Platelets
  alpha and dense granules, 645
  growth factors, 645
  life span, 645
  in wound healing
    chemical process of, 645–646
    factors, 645, 647
    fibroblast role, 645, 647
Poikiloderma of civatte, 490
Polymer films, 221
Postinflammatory hyperpigmentation (PIH), 476
Postlaser erythema, 506
Postlaser perifollicular edema, 506–507
Power-assisted lipoplasty (PAL), 667, 673
Practical anatomy, facelifts, *see* Facelift
Preadipocyte progenitor cells, 47–49
Preauricular alopecia, 261–262
Preformed plastic nails
  composition, 143–144
  guillotine clipper, 144–145
  mechanical hazards, 147
  procedure, 144
Premuscular cutaneous approach, 698–699
Primary hyperhidrosis
  BTX-A, 165–171
  clinical appearance, 156–157
  diagnostic procedures, 157
  focal hyperhidrosis, 157–158
  of groin, 157, 159
  nonbotulinum treatment, 160–164
  sub- and intermammary hyperhidrosis, 157, 159
  therapy modality, 157
Primary technical equipment (PTE), 192
Proctalgia fugax, 551
Provoked vestibulodynia, 551
Proximal nail avulsion, 301
Proximal nail fold, 300
Pseudoepitheliomatous hyperplasia (PEH), 176
Pseudopeladic alopecia, 261
Psoriasis, 122
Public Relations (PR), 786
Pulsed dye laser (PDL), 493
  vs. NAFP, 364
  scar prevention, 236
Purse string suture, 216
Pyogenic granuloma, *see* Granuloma telangiectaticum

Q-switching, 440
Quadratus labii superioris (QLS), 734–735

Radio frequency (RF)
  acne scarring, 419, 421
  bipolar configuration, 417–418
  cellulite, 421–422
  complications, 269
  by conductivity, 417
  hair growth stimulation, 422
  hematomas, 269
  hypoesthesias, 269
  indications, 269
  lipolysis, 533
  "low-frequency" RF energy, 417
  materials and methods, 269
  matting, 269–270
  monopolar configuration, 417–418
  Nonsurgical skin tightening, 518–519
  paresthesias, 269
  pigmentation, 269
  by radiation, 417
  results, 269
  striae, 421
  surgical, 419
  thromboembolism, 269
  tissue interaction, 418
  tissue tightening and rejuvenation, 419–420
  unipolar configuration, 417
Radio frequency–assisted liposuction (RFLAL) energy, 667
Ramelet's hook technique, 284
Regenerative medicine, fat grafting technique, 751
Remodeling lasers
  aftereffects, 372
  dermal remodeling, 372
  fibroblast stimulation, 372
  histological studies, 372
  indications, 372
  mechanisms, 372
  platelet factors, 372
  principles, 372
Removal techniques
  chemical tissue destruction methods, 437–439
  mechanical methods
    dermabrasion, 436–437
    hypertrophic scarring/keloid formation, 436
    radical one-time removal, 437–438
    salabrasion, 436
    sandpaper, 436–437
    surgery, 436, 438
    surgical removal, 437
  thermal methods
    laser pulses, 439–440
    pigment molecules, 439
    QS alexandrite laser, 446
    QS Nd:YAG laser, 441–443
    QSRL, 440–441
    Q-switching, 440–442
Repigmentation essay, 408
Restorative dental bonding, 147
Resveratrol, 116
Retinol, 115
Retronychia, 296–297

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Rosacea, 120–121, 491–492
Ross syndrome, 170–171
Routine liposuction, 44–45
Running horizontal intradermal suture, 213–214
Running intradermal sutures, 213–214
Running locked sutures, 210, 212
Running spiral intradermal suture, 214

Saphenous vein insufficiency, 267
Scalp
  follicular unit transplantation
    anterior frontal line, 249–250
    automatic system, 256–257
    Choi implanter, 256
    FUE, 252–254
    FUL, 250–253
    FUT, 252
    goals, 249–250
    history, 249
    local anesthesia, 250
    Minoxidil effect, 255
    platelet growth factors (PRP), 256
    postoperative course, 254–255
    preoperative stage, 249
    principles, 249
    robotic system, 257
  micrografts
    androgenetic alopecia, 257–261
    body hair growth alopecia, 261, 263–264
    preauricular alopecia, 261–262
    pseudopeladic alopecia, 261
    scarring alopecia, 261–262
    traction alopecia, 261–262
Scarring alopecia, 261–262
Sculptured artificial nails, mechanical hazards, 147
Seborrheic dermatitis, 121
Secondary hyperhidrosis, 155–156
Selective serotonin reuptake inhibitors (SSRIs), 8–9
Senile angioma, 488–489
Senile sebaceous hyperplasia, 21
Silymarin, 116
Simple buried stitches, 213
Simple dermatological surgery office (SDSO), 193
Simple hybrid clinical–surgical units (SHCSUs), 192–193
Simple interrupted stitches, 210
Simple running suture, 210, 212
Skin aging
  biology, 59–60
  clinical scoring, 63
  environmental factors
    body, 22–23
    face, 19–22
    photoaging, 19
    smoke-induced skin aging, 23
  extrinsic factors, 24
  facial aging, 27
  factors, 59–60
  instrumentation
    dark complexion, 61–63
    elasticity decrease, 59–60
    menopause, sebaceous gland activity, 60
    rougher and anisotropic, 61–62
    transparency and dryer, 60–61
    wound healing, 60–61
  intrinsic factors
    chronological aging, 17–18
    general and psychiatric diseases, 19
    menopause-induced skin aging, 18
  nutrition and effect, 113
  pathophysiology
    aging and genomic analysis, 13
    infrared and visible radiations, 13
    matrix metalloproteinases, 12
    mtDNA, 12
    neutrophils and mast cells, 13
    reactive oxygen species, 13
    rejuvenation strategies, 13–14
    structural and functional changes, 11
    telomere shortening, 13
  prevention of, 113
  underlying structures
    bony atrophy, 26–27
    fat ptosis and atrophy, 26–27
    muscle aging, 24–26
Skin aging and wrinkles, *see* MesoLift
"Skin-Ego", 7
Skin laxity
  causes, 517
  managment, 517–518
SMAP, *see* Superficial musculoaponeurotic plane
Smoke-induced skin aging, 23
Social media, 784–785
Soft earlobe piercing, 183, 185
Soft-tissue augmentation
  autologous fat transplantation, 596
  biodegradable products, 593–594
  "lipofilling" technique, 591
  noncollagenic agents, 594–596
  permanent products, 591–593
Soft-tissue fillers, 628–629
Soft tissue lifting, suspension sutures, *see* Suture lifting technique
Solar elastosis, 19–20
Solar lentigines, 21
SPF, *see* Sun protection factor
Spider angioma, 490
Split nail deformity, 292–294
Squamous cell carcinoma *in situ*, 512–513
Status cosmeticus, 119–120
Stem cells and growth factors
  adipose-derived stem cells, 39–40
  clinical applications, 31, 33
  embryonic stem cells, 29, 31
  epidermal stem cells, 38
  follicular bulge, 29–30
  hair follicle bulge, 38
  induced pluripotent stem cells, 31–32
  melanocytic, 38
  MSCs, 29–30, 33–38
  plasticity and transdifferentiation, 29–31
  totipotent stem cells, 29
  transient amplifying cell, 29–30
Store and forward teledermatology, 775
Stroma-vascular fraction (SVF), 47
Subciliary and retromuscular approach, 697–698
Subcutaneous detachments
  major and irreversible damage, 757
  necrosis, 758
  scarring process, 757
  stiffening and retraction, 757
  tissue thinning, 758
Sublative rejuvenation, 419
Suborbicularis oculi fat (SOOF) pad, 736
Sub-SMAP face lifting
  with BTX, platysma muscle, 720–721
  and mental fat injection, 720, 722
  with submental lipoaspiration, 720–721
Suction-assisted lipoplasty (SAL), 666–667, 673
Sunpleated wrinkles, 20
Sun protection factor (SPF)
  application technique, 94
  application thickness, 94
  reapplication, 95–96
  SFP15 sunscreen, 92
  SPF30 sunscreen, 92
  sunscreen formulation, 94–95
Superficial musculoaponeurotic plane (SMAP)
  aponeurotic and muscular layer, 712
  deep aponeurotic plane, 713
  deep dissection plane, 713
  fixation, resorbable sutures, 718–719
  flap detachment, 717, 719
  McGregor patch, 713
  sub-SMAS pre parotidien dissection, 717, 719
  traction and suture, 718–719
Superficial musculoaponeurotic plane technique, *see* Cervico-facial lift technique
Superficial musculoaponeurotic system (SMAS), 518, 760
Superficial peels
  acne, 305
  AHA
    fundamentals, 307
    histology, 307
    history, 307
    indications, 307
    technique, 307–308
  definiton, 304
  melasma, 304–305
  photoaging, 304
  PIH, 305
  TCA
    histological aspects, 306
    Jessner's solution, 306–307
    Obagi Blue Peel, 306
    salicylic acid, 307
    technique, 305
    Unna paste, 306
Surface piercings, 179, 182
Surgical rejuvenation
  autologous adipose grafting (*see* Fat grafting technique)
  endoscopic brow lift, 731
  modeling, aging (*see* Midface lift)
  superficial musculoaponeurotic plane technique (*see* Cervico-facial lift technique)
  temporal lift (*see* Temporal lifting)
Suspension sutures
  flabby buccolabial fold, 677
  soft tissue lifting (*see* Suture lifting technique)
  suture lifting technique, 677
Suture lifting technique
  American barbed threads, 677, 679
  aptos cog (barbed) threads, 677, 679
  barbed thread, soft tissues without skin mobilization, 677, 680
  classic suture material, 683
  clinical considerations, 683
  contraindications, 683
  double-blind placebo-controlled investigation, 678
  double-edged needle
    barbed suture, 678, 681
    smooth suture, 678, 681
  elastic spiral Aptos threads, 677, 681–682
  by Excellence Visage, 683, 688
  face and neck soft tissue lifting, 677
  first-generation Aptos thread
    insertion needle, 677, 680
    lifting soft tissues, 677, 680
  German barbed threads, 677–678
  histological investigations, 682–683
  insertion, subcutaneous, 682–683

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

markings, mid-face-lifting, 677, 680
operative, 684–685
patent ed second-generation Aptos thread, 677, 681, 687
postoperative, 684, 688
preoperative
marking, 683–684
skin, antiseptic processing, 684–685
thread lifting procedures, 683–684
Sweat glands
apocrine, 159
eccrine, 157–159
physiology
secretory activity, 160
thermoregulation, 159–160
suction and curettage, 163–164
Swinehart's technique, 307

Tacking/anchoring (pexing) sutures, 214
Tap water iontophoresis (TWI)
description, 162
palmoplantar hyperhidrosis, 162
physical therapy, 163
side effects, 163
time-saving therapy, 162
treatment modality, 163
Tattoos
atypical mycobacteria infections, 455, 468
black tattoo, 454–455, 462–463, 466
cosmetic tattoo, 454, 460–461
eczema/granular lesions, 455, 469
elimination, 433–434
forearm decorative tattoo, 433–434
fractional resurfacing, 452
guidances, 469
history of, 433
imiquimod, 453
laser tattoo ink interaction, 453
Maghreb ritual tattoo, 454, 458
Mali ritual tattoo, 454, 458
modulated imaging technique, 450
monochromatic black, 453–454
monochromatic professional, 455, 464–465
monochromatic ritual Ethiopian, 454, 459
new tattoo inks, 453
picosecond lasers, 452
polychromatic, 454–456, 463, 466
postinflammatory hyperpigmentation risk, 455, 466–468
professional monochromic tattoo, 454, 456
professional polychromatic tattoo, 454, 457
professional tattoo, deep ink, 454–455
QS lasers, 450–451
reactive erythema and edema, 454
removal techniques
chemical tissue destruction methods, 437–439
mechanical methods, 436–438
thermal methods, 437–444
"R20" method, 449
sculpture-like tattoo, 455, 466
Senegal ritual tattoo, 454, 459–460
superficial pigment professional tattoo, 453
types of
amateur tattoos, 434
cosmetic tattoos, 434–435
medical tattoos, 435
professional tattoos, 434
random/well-structured layers, 433, 435
traumatic tattoos, 434, 436
Youlaser Quanta System, 455, 464
TCA, *see* Trichloroacetic acid
Team management, aesthetic technician
care quality and safety, 767–768
consultation process, 768
protocols, 768
Telangiectasias, 21–22, 489–490
Telemedicine
consultation, 775
remote surgical assistance, 772
store and forward systems, 772
teleconsulting, 772
telephone consultation, 772
videoconferencing systems, 772
Temporal lifting
bayonet technique, 723
biplane bayonet technique., 723
deep subperiosteal lifting, midface undermining, 723, 725–726, 729
deep/superficial, 723–724
extended deep temporal lift, 726, 728
external blepharochalasis, 726
incisions, anatomic considerations, 723, 726–727
preoperative and permanent postoperative neutralization, muscles, 727
superficial undermining (subcutaneous), 723
surgical solutions, 723
Temporary henna tattoos, 104
Textural anomalies, 311
Theory of phyllotaxis, 4
Therapeutic planning
cosmetic "problem" rectification, 707
fragile and depressed patients, 707
operative planning, 707
patient's data, 707
patient's identity, 707
patient's psychological strength, 707
psychological and physical information, 707–708
Thermal relaxation time (TRT), 377
Thermal transfer theory, 503
Thoracic endoscopic sympathectomy, 164
Thyroid disorders, 109
Tissue inhibitor of metalloproteinases (TIMP) genes, 12
Tissue-sparing sutures, 216
Tobacco-induced skin aging, 23
Toenails, 295–297
Totipotent stem cells, 29
Traction alopecia, 261–262
Training, aesthetic and cosmetic dermatology
annual maintenance cost, 765
cutaneous biology and pathology., 763
dermatological counseling, 764
dermatologic societies, 764
equipments, 765
materials, 765
medical procedure, 765
methods and procedures, 763
methods and protocols, 765
patient assessment, 764
physiology and anatomy, 763
regulations, programs, 764
skin care, 764
standardized lighting, 765
training algorithm, 763–764
treatment outcome, 765
Transitional destruction, 757
Trapezoid nails, 290, 293
Traumatically damaged nail, 301–302
Traumatic tattoos, 434, 436
Trichloroacetic acid (TCA)
atrophic acne scars, 241
chemical peelings, 128
histological aspects, 306
Jessner's solution
action, 306
contraindications, 307
indications, 306
technique, 306
Obagi Blue Peel, 306
salicylic acid, 307
technique, 305
Unna paste, 306
Trichostasis spinulosa, 21
Triple pulley suture with tissue-sparing effect, 216–217

UltraShape, 428
Ultrasound
acoustic energy, 426
body contouring
cellulite, 429–430
circumference reduction, 427–429
invasive sources, 431
light energy, 426
noninvasive
focused, 427, 430
nonfocused therapeutic, 426–427
skin tightening, 430
sources, 426
terminology and principles, 425–426
Ultrasound-assisted lipoplasty (UAL), 431, 673
Ultraviolet index (UVI), 89
Unfractionated ablative lasers, 375
Ungual fibrokeratomas, 298
Upper eyelid blepharoplasty
Dacryopexy treatment, 696
eyebrow ptosis correction, internal brow lift, 696
involutional ptosis
aponeurosis repositioning, 695
levator aponeurosis disinsertion, 695
operative technique, 695–696
lachrymal gland prolapse, 696
Lion's-wrinkle, blepharoplasty approach, 696
operative techniques
conventional blepharoplasty, 693–694
external palpebral cutaneous resection, 695
eyelid's levator aponeurosis, 695
neuroleptic analgesia, 693
skin integument, 694
skin suture, 695
palpebral fold, 692–693
palpebral fold (superior eyelid crease), 696–697
ptosis, 692–693
vertical and glabellar wrinkles treatment, 696
Upper malar lifting, 745

Varicose veins, leg
causes, 494
chronic venous disease, 493–494
classic symptoms, 494
cost-effective, 494
incidence, 494
prevalence, 494
risk factors, 494
treatment options, 494–495
ultrasound examination, 494
Venous lakes, 492
Venous malformation (VM), 488
Vertically implanted nail, 290, 293
Vertical mattress sutures, 210

Copyright Material – Provided by Taylor & Francis
Review Copy – Not for Redistribution
MEDpress-Inform Publishers, 1-3-4/H, 4 build.1, Kochnovsky proezd, RC "Aerobus", 125319 Moscow, Russia

Vertical wrinkles, 20
Vibration amplification of sound energy at resonance (VASER), 431
Viral warts, 297–298
Virtual private network (VPN), 772
Visual scoring, skin aging, 63

WAT, *see* White adipose tissue
Web marketing, 783
White adipose tissue (WAT)
  autonomic innervation, 45
  denervation and accumulation, 45
  functions, 43–44
  sensory innervation, 45
  TAG deposition, 49

Yale Brown Obsessive Compulsive Scale Modified for BDDs, 8