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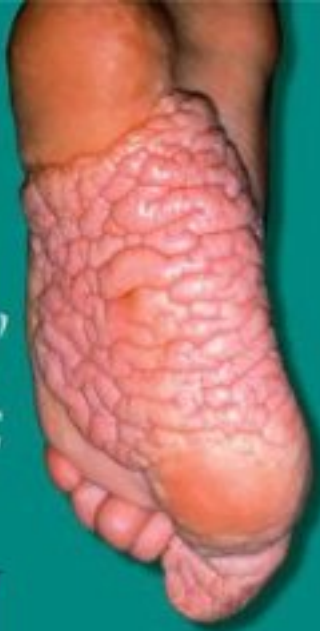

TENTH EDITION

WILLIAM D. JAMES
TIMOTHY G. BERGER
DIRK M. ELSTON

ANDREWS' DISEASES OF THE SKIN CLINICAL DERMATOLOGY

Commissioning Editors: Sue Hodgson/Karen Bowler
Project Development Manager: Melissa Dudlick
Project Managers: Cheryl Brant/Naughton Project Management
Design Manager: Jayne Jones
Illustration Manager: Mick Ruddy
Illustrator: Richard Prime
Marketing Manager(s) (UK/USA): Amy Hey/Laura Meiskey

ANDREWS' DISEASES OF THE SKIN

CLINICAL DERMATOLOGY

TENTH EDITION

WILLIAM D JAMES, MD
Paul R Gross Professor of Dermatology
Vice-Chair and Residency Program Director
University of Pennsylvania
Philadelphia, Pennsylvania

TIMOTHY G BERGER, MD
Professor of Clinical Dermatology
Executive Vice Chair and Residency Program Director
Chair in Dermatology Medical Student Education
University of California, San Francisco
San Francisco, California

DIRK M ELSTON, MD
Departments of Dermatology and Pathology
Geisinger Medical Center
Danville, Pennsylvania

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PREFACE

Andrews' remains as it was from the beginning: an authored text whose one volume is filled with clinical signs, symptoms, diagnostic tests, and therapeutic pearls. The authors have remained general clinical dermatologists in an era of subspecialists in academia. They are committed to keeping *Andrews'* as an excellent tool for anyone who needs help to diagnose a patient with a clinical conundrum or to treat a patient with a therapeutically challenging disease.

Andrews' is primarily intended for the practicing dermatologist. It is meant to be used on the desktop at his/her clinic, giving consistent, concise advice on the whole gamut of clinical situations faced in the course of a busy workday. Because of its relative brevity but complete coverage of our field, many find the text ideal for learning dermatology the first time. It has been a mainstay of the resident yearly curriculum for many programs. We are hopeful that another group of trainees will learn clinical dermatology by studying the clinical descriptions, disease classifications, and treatment insights that define *Andrews'*. We believe that students, interns, internists or other medical specialists, family practitioners, and other health professionals who desire a comprehensive dermatology textbook will find that ours meets their needs. Long-time dermatologists will hopefully discover *Andrews'* to be the needed update that satisfies their lifelong learning desires.

Many major changes have been made to this edition. Richard Odom, who was a coauthor on the last three editions, has left this revision to Bill James, Tim Berger and our newest author, Dirk Elston. The three of us have worked closely to continue to improve the quality of our text. We have tried to ensure that each entity is only discussed once, in a complete yet concise manner. In order to do this we have had to make decisions regarding the placement of disease processes in only one site. Clearly, neutrophilic eccrine hidradenitis, for example, could be presented under drug eruptions, neutrophilic reactive conditions, infection or cancer-associated disease, or with eccrine disorders. The final decisions were a team effort and made in the interest of eliminating redundancy. This allows us to present our unified philosophy in treating patients in one dense volume.

Medical science continues to progress with break-neck speed. Our understanding of the etiology of certain conditions has now led us to recategorize well-recognized disease states and dictated our addition of many newly described entities. Molecular investigative techniques, technologic breakthroughs, and designer therapeutics lead the way in providing advances in our specialty. We cover the new understanding following from such innovations by discussing the mechanisms at work in genetic diseases, covering the latest in dermatopathologic staining and analysis, adding a chapter on cosmetic surgery, and enlarging the therapeutic recommendations to include our expanded therapeutic options, such as biologic response modifiers, and biologically-engineered targeted medications. We have attempted to define the therapeutic options in a fashion that emphasizes those interventions with the highest level of evidence, but also present less critically investigated therapeutic options. To care for our patients we need a large array of options and not all are fully supported by formal evidence, yet are helpful to individual patients. Finally, a plethora of newly described conditions, infections, physical signs, and disease associations have been added.

Extensive revisions were necessary to add this wealth of new information. We also have selectively discarded older concepts. By eliminating older, not currently useful information we maintain the brief but complete one volume presentation that we and all previous authors have emphasized. Additionally, older references have been updated. The classic early works are not cited; instead we have chosen to include only new citations and let the bibliographies of the current work provide the older references as you need them. Finally, a major effort in this edition was to completely reillustrate the text with color photographs. We have looked at our own collections first. These are the result of many hours of personal effort, the generosity of our patients, and a large number of residents and faculty of the programs in which we currently work or have worked in the past. Additionally, friends and colleagues from all parts of the globe have allowed us to utilize their photographs. They have given their permission for use of these wonderful educational photos to enhance your understanding of dermatology and how these diseases affect our patients. We cannot thank them enough.

The surgical chapters continue to be coauthored by Roy Grekin. His colleague in this edition is Isaac Neuhaus, and we thank them for their efforts to expand the procedural portion of our textbook. Since the past edition was brought to print WB Saunders and Mosby have become part of a larger enterprise, Elsevier. We are proud to be a part of this team and have such professionals as Sue Hodgson, Karen Bowler, Sam Gear and Melissa Dudlick supporting us every step of the way.

We hope you enjoy this 10th edition of *Andrews'*.

William D James MD
Timothy G Berger MD
Dirk M Elston MD

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Ann, my loving wife, and my children Dan and Becca make me happy and proud. They have supported me over the years with love and patience. I cannot thank them enough for being my companions on this joyous ride. The faculty, residents, and patients of Walter Reed were indispensable to my development, and those of the University of Pennsylvania continue to teach me daily. Tim Berger and Dirk Elston provide me with examples to emulate and friendships to savor. Thank you all.

Bill D James

My wife Jessica and my daughter Olivia, "the girls," give me the joy and strength to undertake such a task. Their patience in this process was saintly. Bill and Dirk have been profoundly professional. I have learned all I know from other teachers, residents, and students. To them I owe an eternal debt of gratitude.

Tim G Berger

My wife Kathy is my support, my confidant and my best friend. Her contributions are immeasurable. Our children, Carly and Nate, are a source of joy and inspiration. Bill James and Tim Berger have been partners, friends, and mentors during this endeavor. For my worth as a clinician, I must thank the faculty, residents, and patients at Walter Reed, Ft Eustis, the Cleveland Clinic, Brooke, Wilford Hall and Geisinger. Thank you.

Dirk M Elston

CONTRIBUTORS

ROY C GREKIN, MD
Clinical Professor
Co-Director, Dermatologic Surgery and Laser Center
University of California, San Francisco
San Francisco, California

ISAAC M NEUHAUS, MD
Clinical Instructor
Dermatologic Surgery and Laser Center
University of California, San Francisco
San Francisco, California

MARIA L WEI, MD PHD
Assistant Professor
University of California, San Francisco
San Francisco, California

CHAPTER

1 Skin: Basic Structure and Function

Skin is composed of three layers: epidermis, dermis, and subcutaneous tissue (panniculus) (Fig. 1-1). The epidermis, the outermost layer, is formed by an ordered arrangement of cells called *keratinocytes*, whose basic function is to synthesize keratin, a filamentous protein that serves a protective function. The dermis is the middle layer. Its principal constituent is the fibrillar structural protein collagen. The dermis lies on the panniculus, which is composed of lobules of lipocytes.

There is considerable regional variation in the relative thickness of these layers. The epidermis is thickest on the palms and soles, measuring approximately 1.5 mm. It is very thin on the eyelid, where it measures less than 0.1 mm. The dermis is thickest on the back, where it is 30 to 40 times as thick as the overlying epidermis. The amount of subcutaneous fat is generous on the abdomen and buttocks compared with the nose and sternum, where it is meager.

EPIDERMIS AND ADNEXAE

During the first weeks of life, the fetus is covered by a layer of nonkeratinizing cuboidal cells called the periderm (Fig. 1-2). Later, the periderm is replaced by a multilayered epidermis. Adnexal structures, particularly follicles and eccrine sweat units, originate during the third month of fetal life as downgrowths from the developing epidermis. Later, apocrine sweat units develop from the upper portion of the follicular epithelium and sebaceous glands from the midregion of the follicle. Adnexal structures appear first in the cephalic portion of the fetus and later in the caudal portions.

The adult epidermis is composed of three basic cell types: keratinocytes, melanocytes, and Langerhans cells (Fig. 1-3). An additional cell, the Merkel cell, can be found in the

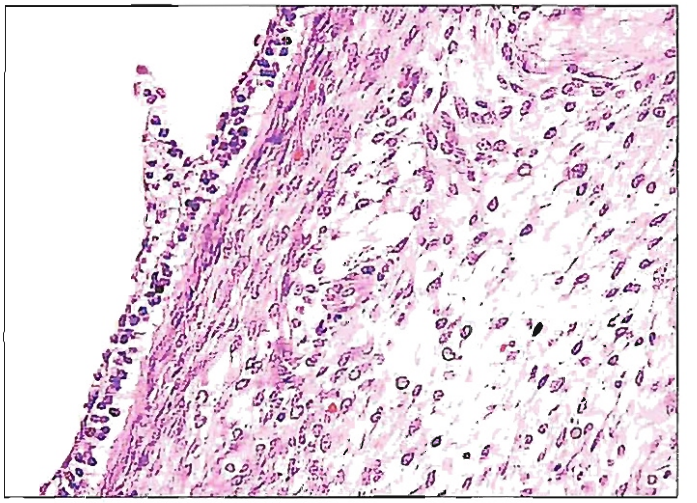

Fig. 1-2 Fetal periderm covering fetal mesenchyme.

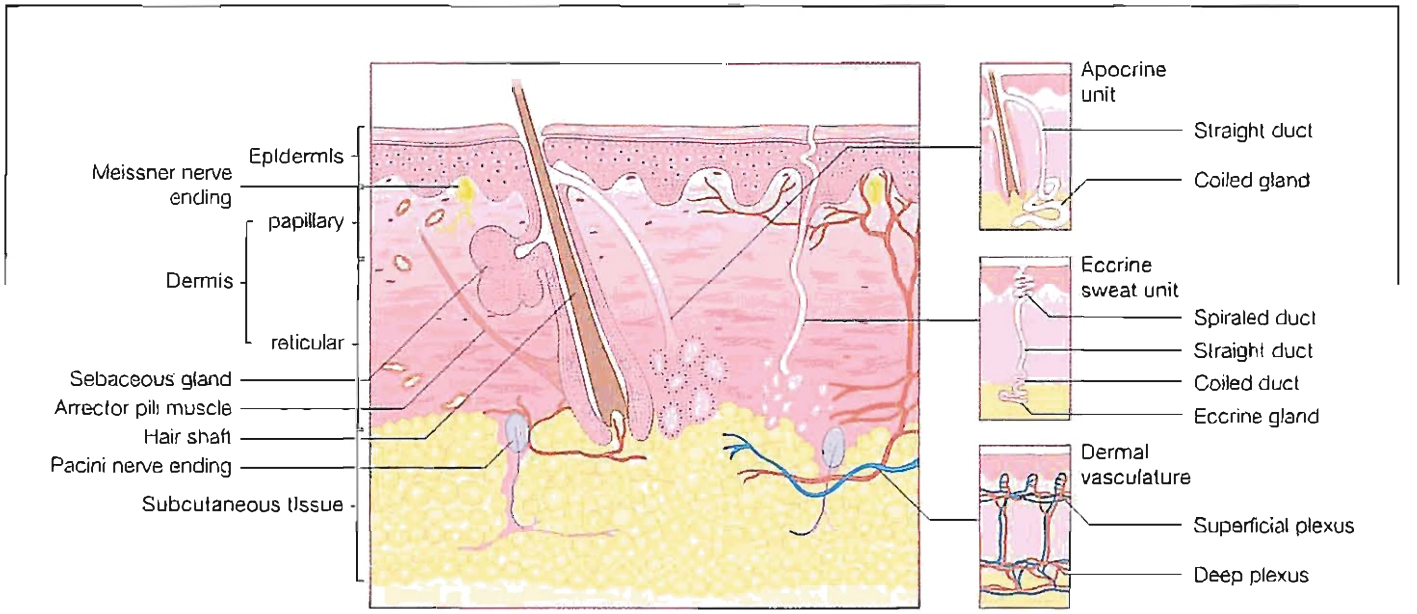

Fig. 1-1 Diagrammatic cross-section of the skin and panniculus.

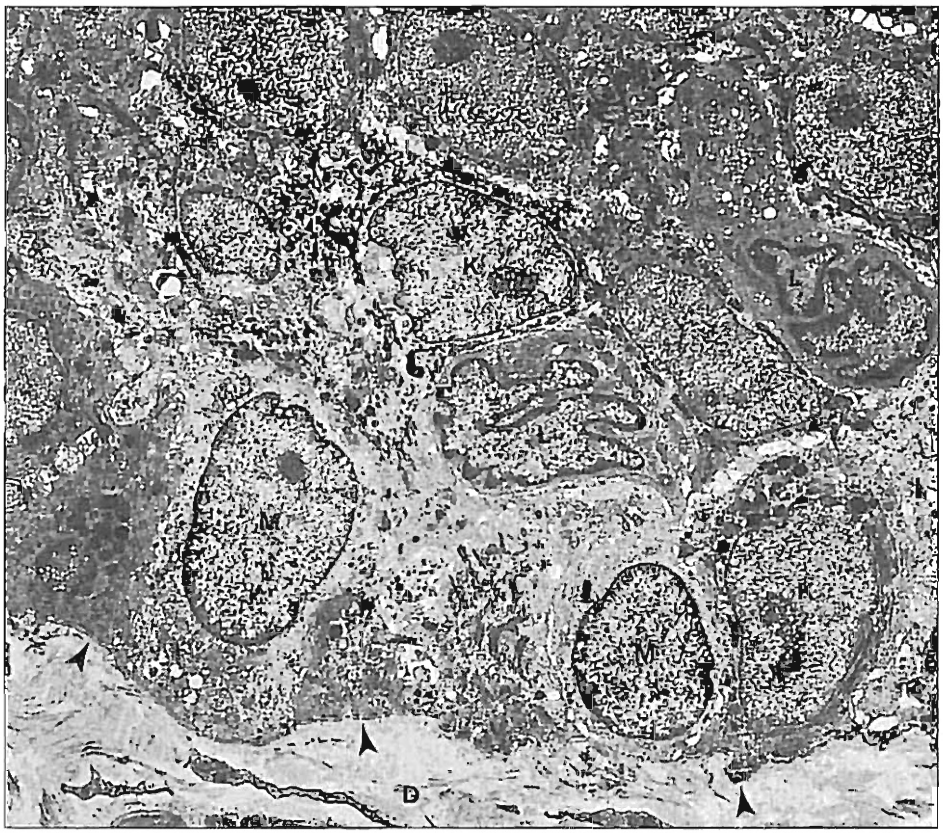

Fig. 1-3 Electron micrograph illustrating the three basic cell types in the epidermis and their relationships. Most of the cells are keratinocytes (prickle cells and basal cells), some labeled (*K*). Langerhans cells (*L*) with their characteristic cribriform nuclei are distributed among the keratinocytes in the malpighian layer. Melanocytes (*M*) are located in the basal layer of the epidermis, which is separated from (and attached to) the dermis (*D*) by the basement membrane zone (*arrowheads*).

basal layer of the palms and soles, oral and genital mucosa, nailbed, and follicular infundibula. Merkel cells, located directly above the basement membrane zone, contain intracytoplasmic dense-core neurosecretory-like granules, and, through their association with neurites, act as slow adapting touch receptors. They have direct connections with adjacent keratinocytes by desmosomes and contain a paranuclear whorl of intermediate keratin filaments. Both polyclonal keratin immunostains and monoclonal immunostaining for keratin 20 stain this whorl of keratin filaments in a characteristic paranuclear dot pattern. Merkel cells also label for neuroendocrine markers such as chromogranin and synaptophysin.

Keratinocytes

Keratinocytes, or squamous cells, are the principal cells of the epidermis. They are of ectodermal origin and have the specialized function of producing keratin, a complex filamentous protein that not only forms the surface coat (stratum corneum) of the epidermis but also is the structural protein of hair and nails. Multiple distinct keratin genes have been identified and consist of two subfamilies, acidic and basic. The product of one basic and one acidic keratin gene combines to form the multiple keratins that occur in many tissues. The presence of various keratin types is used as a marker for the type and degree of differentiation of a population of keratinocytes. Keratins are critical for normal functioning of the epidermis and keratin mutations are recognized causes of skin disease. Mutations in the genes for keratins 5 and 14 are associated with epidermolysis bullosa simplex. Keratin 1 and 10 mutations are associated with epidermolytic hyperkeratosis. Mild forms of this disorder may represent localized or widespread expressions of mosaicism for these gene mutations.

The epidermis may be divided into the following zones, beginning with the innermost layer: basal layer (stratum germinativum), malpighian or prickle layer (stratum spinosum), granular layer (stratum granulosum), and horny layer (stratum corneum). On the palms and soles a pale clear to pink layer, the stratum lucidum, is noted just above the granular layer. When the skin in other sites is scratched or rubbed, the malpighian and granular layers thicken, a stratum lucidum forms, and the stratum corneum becomes thick and compact.

Slow cycling stem cells provide a reservoir for regeneration of the epidermis. Sites rich in stem cells include the deepest portions of the rete, especially on palmoplantar skin. Stem cells divide infrequently in normal skin, but in cell culture they form active growing colonies. They can be identified by their high expression of β1-integrins and lack of terminal differentiation markers. Stem cells can also be identified by their low levels of desmosomal proteins, such as desmoglein 3. The basal cells divide and as their progeny move upward, they flatten and their nucleus disappears. Abnormal keratinization can manifest as parakeratosis (retained nuclei), as corps ronds (round, clear to pink, abnormally keratinized cells) or as grains (elongated, basophilic, abnormally keratinized cells).

During keratinization, the keratinocyte first passes through a synthetic and then a degradative phase on its way to becoming a horn cell. In the synthetic phase, the keratinocyte accumulates within its cytoplasm intermediate filaments composed of a fibrous protein, keratin, arranged in an α-helical coiled-coil pattern. These tonofilaments are

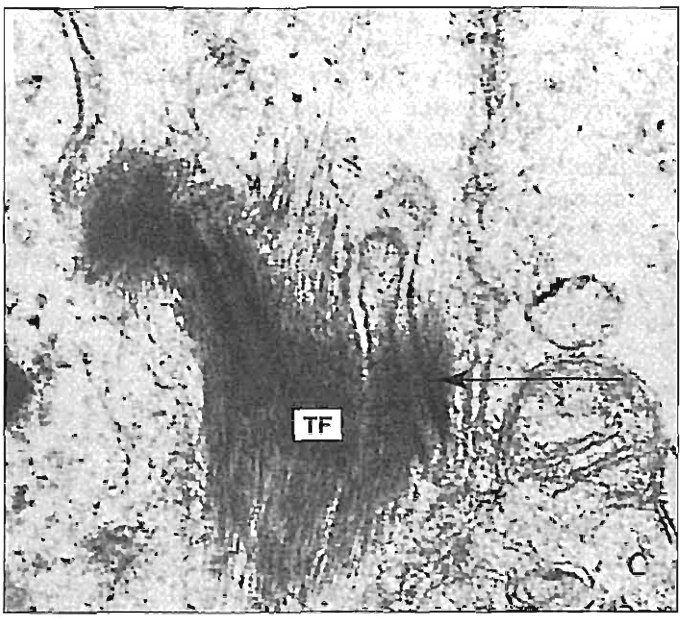

Fig. 1-4 Ultrastructral appearance of the desmosome (*arrow*), specialized attachment plate between adjacent keratinocytes. Tonofilaments (*TF*) within the cytoplasm of adjacent keratinocytes verge on the plasma membrane of each cell, where they condense to form an electron-dense one.

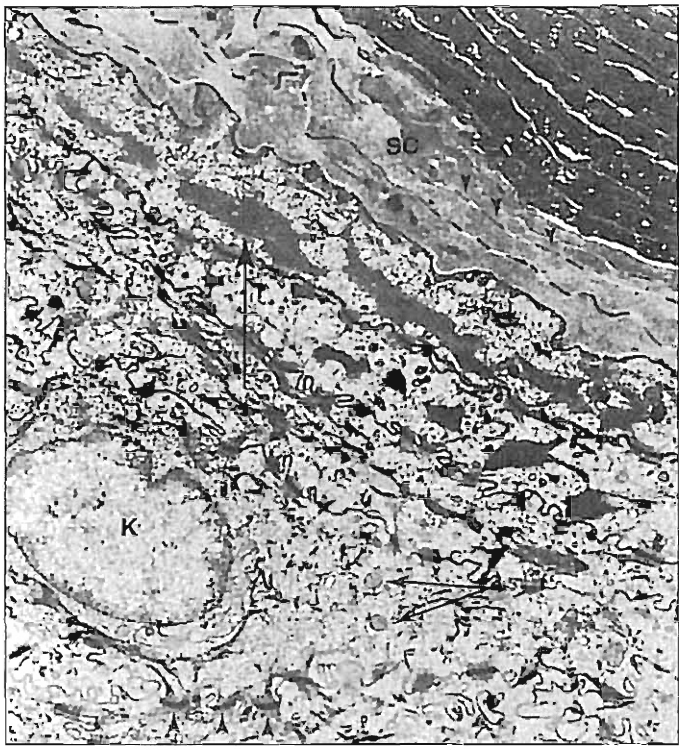

Fig. 1-5 Upper portion of the epidermis. Keratinocytes (*K*) are flatter than those of the lower portion (see Fig. 1-3), and contain keratinosomes (*thin arrows*). Desmosomes (*bottom arrowheads*) become more obvious as the ratio of nucleus-to-cytoplasm increases. Keratinocytes of the granular layer have developed keratohyalin granules (*broad, long arrow*). The stratum corneum (*SC*) is composed of horny plates that retain only filaments and amorphous material enveloped in a thickened cell membrane. Horny cells, like other keratinocytes, are joined by desmosomes (*top arrowheads*).

fashioned into bundles, which converge on and terminate at the plasma membrane, where they end in specialized attachment plates called *desmosomes* (Fig. 1-4). The degradative phase of keratinization is characterized by the disappearance of cell organelles and the consolidation of all contents into a mixture of filaments and amorphous cell envelopes. This programmed process of maturation resulting in death of the cell is termed terminal differentiation. Terminal differentiation is also seen in the involuting stage of *keratoacanthomas*, where the initial phase of proliferation gives way to terminal keratinization and involution.

Premature programmed cell death, or apoptosis, appears in hematoxylin and eosin (H&E)-stained sections as the presence of scattered bright red cells, some of which may contain small black pyknotic nuclei. These cells are present at various levels of the epidermis, as this form of cell death does not represent part of the normal process of maturation. Widespread apoptosis is noted in the verrucous phase of incontinentia pigmenti. It is also a prominent finding in catagen hairs, where apoptosis results in the involution of the inferior segment of the hair follicle.

In normal skin, the plasma membranes of adjacent cells are separated by an intercellular space. Electron microscopic histochemical studies have shown that this interspace contains glycoproteins and lipids. Lamellar granules (Odland bodies or membrane-coating granules) appear in this space, primarily at the interface between the granular and cornified cell layers (Fig. 1-5). Lamellar granules contribute to skin cohesion and impermeability. Conditions such as lamellar ichthyosis and Flegel's hyperkeratosis demonstrate abnormal lamellar granules.

Keratinocytes of the granular zone contain, in addition to the keratin filament system, keratohyaline granules, composed of amorphous particulate material of high sulfur–protein content. This material, called profilaggrin, is a precursor to filaggrin, so named because it is thought to be responsible for keratin filament aggregation. Conversion to filaggrin takes place in the granular layer, and this forms the electron-dense interfilamentous protein matrix of mature epidermal keratin. Keratohyaline is hygroscopic, and repeated cycles of hydration and dehydration contribute to normal desquamation of the stratum corneum. Ichthyosis vulgaris is characterized by a diminished or absent granular layer, contributing to the retention hyperkeratosis noted in this disorder. Keratohyalin results in the formation of soft, flexible keratin. Keratin that forms in the absence of keratohyaline granules is typically hard and rigid. Hair fibers and nails are composed of hard keratin.

Keratinocytes play an active role in the immune function of the skin. In conditions such as allergic contact dermatitis they participate in the induction of the immune response, rather than acting as passive victims. Keratinocytes secrete a wide array of cytokines and inflammatory mediators, including tumor necrosis factor (TNF)-α. They also can express molecules on their surface, such as intercellular adhesion molecule-1 (ICAM-1) and major histocompatibility complex (MHC) class II molecules, which demonstrates that keratinocytes actively respond to immune effector signals.

Melanocytes

Melanocytes are the pigment-producing cells of the epidermis. They are derived from the neural crest and by the eighth week of development can be found within the fetal

epidermis. In normal, sun-protected, trunk epidermis, melanocytes reside in the basal layer at a frequency of approximately 1 in every 10 basal keratinocytes. Areas such as the face, shins, and genitalia have a greater density of melanocytes, and in heavily sun-damaged facial skin, Mart-1 immunostaining can demonstrate ratios of melanocytes-to-basal keratinocytes that approach 1:1. Recognition of the variation in melanoctye-to-keratinocyte ratio is critical in the interpretation of biopsies of suspected lentigo maligna (malignant melanoma in situ) on sun-damaged skin.

Racial differences in skin color are not caused by differences in the number of melanocytes. It is the number, size, and distribution of the melanosomes or pigment granules within keratinocytes that determine differences in skin color (Fig. 1-6). Pale skin has fewer melanosomes and these are smaller and packaged within membrane-bound complexes. Dark skin has more melanosomes, and these tend to be larger and singly dispersed. Chronic sun exposure can stimulate melanocytes to produce larger melanosomes, thereby making the distribution of melanosomes within keratinocytes resemble the pattern seen in dark-skinned individuals.

In histologic sections of skin routinely stained by H&E, the melanocyte appears as a cell with ample amphophilic cytoplasm, or as a clear cell in the basal layer of the epidermis. The apparent halo is an artifact formed during fixation of the specimen. This occurs because the melanocyte, lacking tonofilaments, cannot form desmosomal attachments with keratinocytes. Keratinocytes also frequently demonstrate clear spaces, but can be differentiated from melanocytes because they demonstrate cell–cell junctions and a layer of cytoplasm peripheral to the clear space.

The melanocyte is a dendritic cell. Its dendrites extend for long distances within the epidermis and any one melanocyte is therefore in contact with a great number of keratinocytes; together they form the so-called epidermal melanin unit. Keratinocytes actively ingest the tips of the melanocytic dendrites, thus imbibing the melanosomes (Fig. 1-7).

Melanosomes are synthesized in the Golgi zone of the cell and pass through a series of stages in which the enzyme tyrosinase acts on melanin precursors to produce the densely pigmented granules. Melanoctyes in red-heads tend to be rounder and produce more phaeomelanin. The melanocortin 1 receptor (MC1R) is important in the regulation of melanin production. Loss-of-function mutations in the MC1R gene produce a change from eumelanin to phaeomelanin production, whereas activating gene mutations can enhance eumelanin synthesis. Most red-heads are compound heterozygotes or homozygotes for a variety of loss-of-function mutations in this gene. Eumelanin production is optimal at pH 6.8 and changes in cellular pH also result in alterations of melanin production and the eumelanin-to-phaeomelanin ratio. Within keratinocytes, melanin typically forms a cap over the nucleus, where it presumably functions principally in a photoprotective role. Evidence of keratinocyte photodamage in the form of thymidine dimer formation can be assessed using gas chromatography–mass spectrometry or enzyme-linked immunosorbent assays. Pigment within

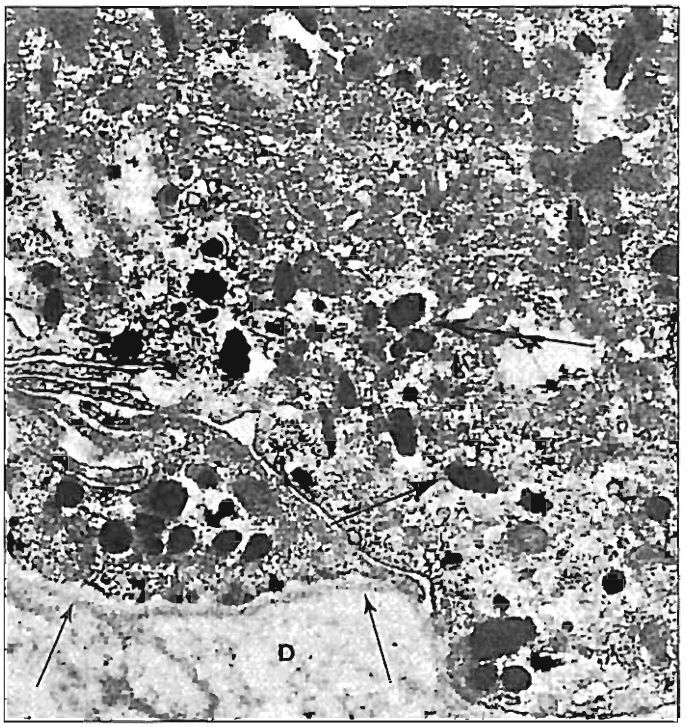

Fig. 1-6 Portion of a melanocyte from dark skin, illustrating melanosomes (*broad arrows*) at various stages of development. Basement membrane zone (*thin arrow*) and dermis (*D*) are also seen.

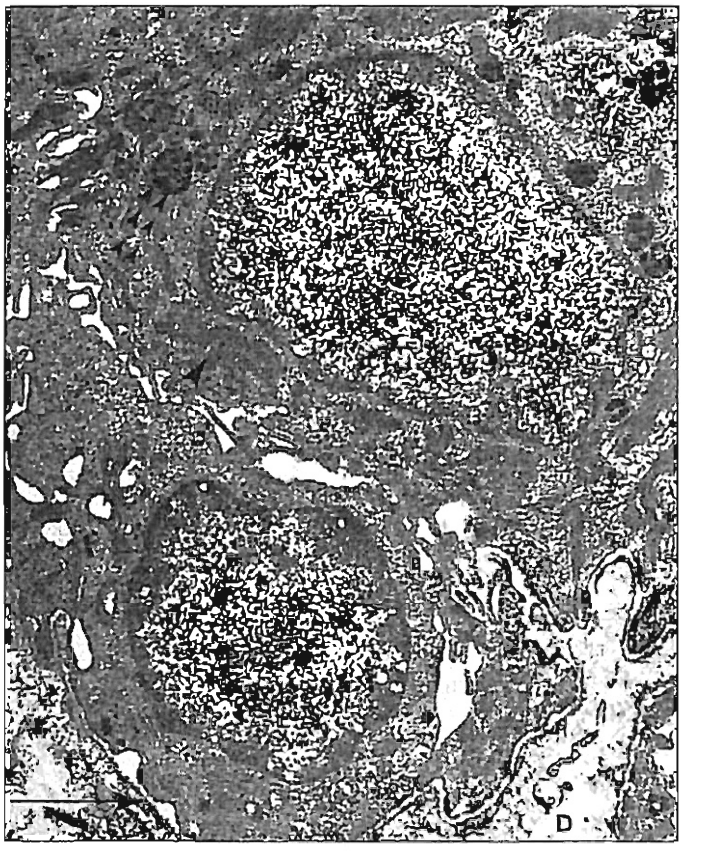

Fig. 1-7 Relationship between melanocytes (*M*) and basal keratinocytes (*K*) in light skin. Melanocytes synthesize pigment granules (melanosomes), which are transferred to keratinocytes, where they are contained within membrane-bound melanosome complexes (*small arrowheads*). Bundles of tonofilaments (*broad arrowhead*) identify the cell as a keratinocyte. The basement membrane zone (*arrow*) separates epidermis from dermis (*D*).

melanocytes also serves to protect the melanocytes themselves against photodamage, such as ultraviolet (UV) A-induced membrane damage.

Areas of leukoderma or whitening of skin can be caused by very different phenomena. In vitiligo, the affected skin becomes white because of destruction of melanocytes. In albinism, the number of melanocytes is normal, but they are unable to synthesize fully pigmented melanosomes because of defects in the enzymatic formation of melanin. Local areas of increased pigmentation can result from a variety of causes. The typical freckle results from a localized increase in production of pigment by a near-normal number of melanocytes. Black "sunburn" or "ink spot" lentigines demonstrate basilar hyperpigmentation and prominent melanin within the stratum corneum. Nevi are benign proliferations of melanocytes. Melanomas are their malignant counterpart.

Langerhans Cells

Langerhans cells are normally found scattered among keratinocytes of the stratum spinosum (Fig. 1-8). They constitute 3% to 5% of the cells in this layer. Like melanocytes, they are not connected to adjacent keratinocytes by the desmosomes. At the light-microscopic level, Langerhans cells are difficult to detect in routinely stained sections; however, they appear as dendritic cells in sections impregnated with gold chloride, a stain specific for Langerhans cells. They can also be stained with CD1a or S-100 immunostains. Ultrastructurally they are characterized by a folded nucleus and distinct intracytoplasmic organelles called *Langerhans* or *Birbeck granules*. In their fully developed form, the organelles are rod shaped with a vacuole at one end and they resemble a tennis racquet. The vacuole is an artifact of processing.

Functionally, Langerhans cells are of the monocyte–macrophage lineage and originate in bone marrow. They function primarily in the afferent limb of the immune response by providing for the recognition, uptake, processing, and presentation of antigens to sensitized T-lymphocytes, and are important in the induction of delayed-type sensitivity. Once an antigen is presented, Langerhans cells migrate to the lymph nodes. Hyaluronan (hyaluronic acid) plays a critical role in Langerhans cell maturation and migration. If skin is depleted of Langerhans cells by exposure to UV radiation, it loses the ability to be sensitized until its population of Langerhans cell is replenished. Macrophages that present antigen in Langerhans cell-depleted skin can induce immune tolerance. In contrast to Langerhans cells, which make interleukin (IL)-12, the macrophages found in the epidermis 72 h after UVB irradiation produce IL-10, resulting in downregulation of the immune response. At least in mice, viral immunity appears to require priming by CD8α+ dendritic cells, rather than Langerhans cells, suggesting a complex pattern of antigen presentation in cutaneous immunity.

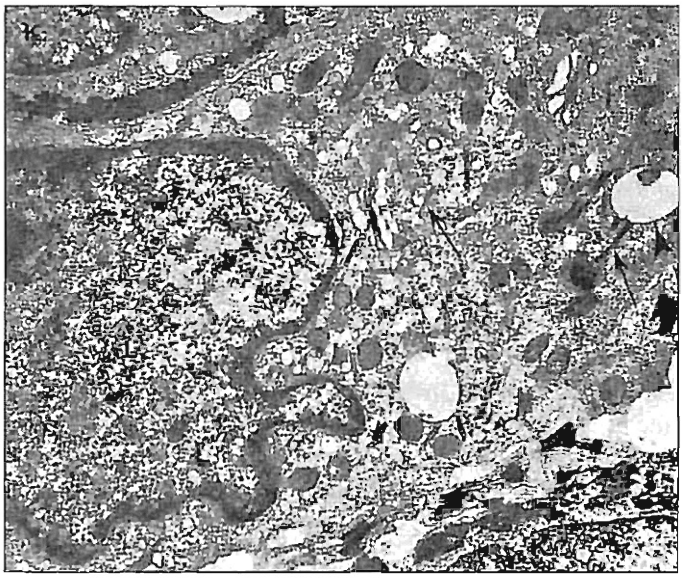

Fig. 1-8 Ultrastructural appearance of the Langerhans cell (*L*). The characteristic intracytoplasmic Langerhans (Birbeck) granules have a rod-shaped handle (*arrows*) and a wide head (*arrowhead*). The Langerhans cell is not connected to adjacent keratinocytes (*K*) by desmosomes.

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DERMOEPIDERMAL JUNCTION

The junction of the epidermis and dermis is formed by the basement membrane zone (Fig. 1-9). Ultrastructurally, this zone is composed of four components: the plasma membranes of the basal cells with the specialized attachment plates (hemidesmosomes); an electron-lucent zone called the lamina lucida; the lamina densa (basal lamina); and the fibrous components associated with the basal lamina, including anchoring fibrils, dermal microfibrils, and collagen fibers. At the light-microscopic level, the so-called periodic acid-Schiff (PAS)-positive basement membrane is composed of the fibrous components. The basal lamina is synthesized by the

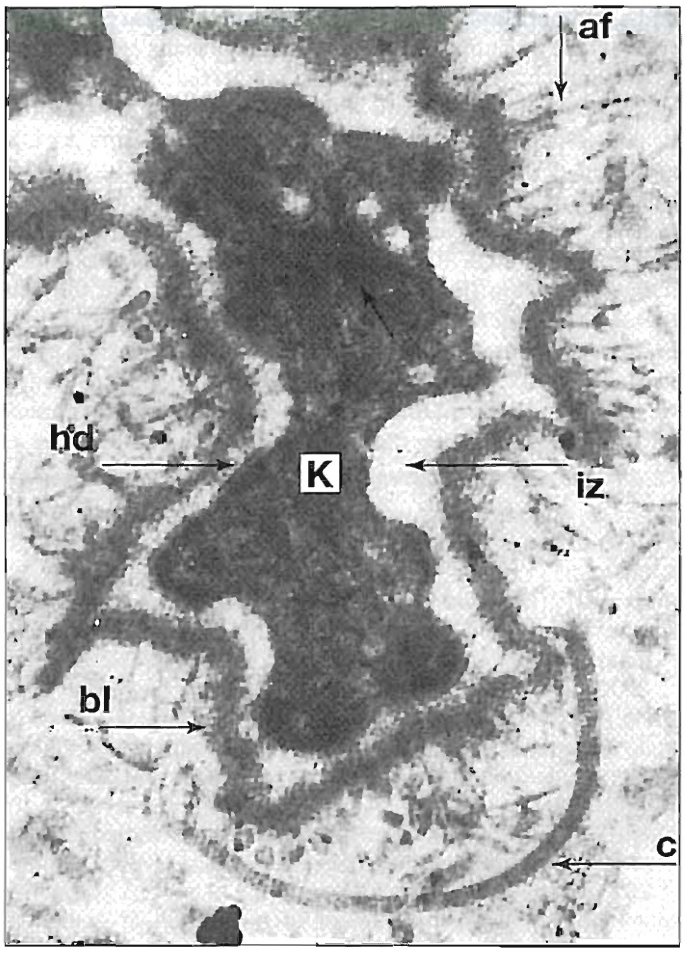

Fig. 1-9 Ultrastructural appearance of the basement membrane zone at the junction of the epidermis and dermis. The zone comprises four layers: plasma membrane of basal keratinocytes (K) with their specialized attachment plates, hemidesmosomes (hd); clear lamina lucida or intermembranous space (iz); basal lamina (bl); and dermal fibrous components, including anchoring fibrils (af) and collagen fibers (c).

basal cells of the epidermis. Type IV collagen is the major component of the basal lamina. Type VII collagen is the major component of anchoring fibrils. The two major hemidesmosomal proteins are the BP230 (bullous pemphigoid antigen 1) and BP180 (bullous pemphigoid antigen 2, type XVII collagen).

The basement membrane zone (BMZ) is considered to be a porous semipermeable filter, which permits exchange of cells and fluid between the epidermis and dermis. It further serves as a structural support for the epidermis and holds the epidermis and dermis together. The BMZ serves the same functions for the skin appendages. In the upper permanent portion of the anagen follicle, plectin, BP230, BP180, α6β4-integrin, laminin 5, and type VII collagen show essentially the same expression as that found in the interfollicular epidermis. Staining in the lower, transient portion of the hair follicle, however, is different. All BMZ components diminish and may become discontinuous in the inferior segment of the follicle. Hemidesmosomes are also not apparent in the BMZ of the hair bulb. The lack of hemidesmosomes in the deep portions of the follicle may relate to the transient nature of the inferior segment, while abundant hemidesmosomes stabilize the upper portion of the follicle.

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EPIDERMAL APPENDAGES: ADNEXA

Eccrine and apocrine glands, ducts, and pilosebaceous units constitute the skin adnexa. Embryologically they originate as downgrowths from the epidermis and are therefore ectodermal in origin. While the various adnexal structures serve specific functions, they all can function as reserve epidermis in that reepithelialization after injury to the surface epidermis occurs principally by virtue of the migration of keratinocytes from the adnexal epithelium to the skin surface. It is not surprising, therefore, that skin sites such as the face or scalp, which contain pilosebaceous units in abundance, reepithelialize more rapidly than do skin sites such as the back, where adnexa of all types are comparatively scarce. Once a wound has reepithelialized, granulation tissue is no longer produced. Deep saucerized biopsies in an area with few adnexae will slowly fill with granulation tissue until they are flush with the surrounding skin. In contrast, areas rich in adnexae will quickly be covered with epithelium. No more granulation tissue will form and the contour defect created by the saucerization will persist.

Pseudoepitheliomatous hyperplasia, noted in infections and inflammatory conditions, consists almost exclusively of adnexal epithelium. Areas of thin intervening epidermis are generally evident between areas of massively hypertrophic adnexal epithelium.

Eccrine Sweat Units

The eccrine sweat unit is composed of three sections that are modified from the basic tubular structure that formed during embryogenesis as a downgrowth of surface epidermis. The intraepidermal spiral duct, which opens directly onto the skin surface, is called the acrosyringium. It is derived from dermal duct cells through mitosis and upward migration. The acrosyringium is composed of small polygonal cells with a central round nucleus surrounded by ample pink cytoplasm. Cornification takes place within the duct and the horn cells become part of the stratum corneum of the epidermis. In the

stratum corneum overlying an actinic keratosis, the lamellar spiral acrosyringeal keratin often stands out prominently against the compact red parakeratotic keratin produced by the actinic keratosis.

The straight dermal portion of the duct is composed of a double layer of cuboidal epithelial cells and is lined by an eosinophilic cuticle on its luminal side. The coiled secretory acinar portion of the eccrine sweat gland may be found within the superficial panniculus. In areas of skin, such as the back, that possess a thick dermis, the eccrine coil is found in the deep dermis, surrounded by an extension of fat that extends from the underlying panniculus. An inner layer of epithelial cells, the secretory portion of the gland, is surrounded by a layer of flattened myoepithelial cells. The secretory cells are of two types: glycogen-rich, large pale cells; and smaller, darker-staining cells. The pale glycogen-rich cells are thought to initiate the formation of sweat. The darker cells may function in a manner similar to that of cells of the dermal duct, which actively reabsorb sodium, thereby modifying sweat from a basically isotonic solution to a hypotonic one by the time it reaches the skin surface. Sweat is similar in composition to plasma, containing the same electrolytes, though in a more dilute concentration. Physical conditioning in a hot environment results in production of larger amounts of extremely hypotonic sweat in response to a thermal stimulus. This adaptive response allows greater cooling with conservation of sodium.

In humans, eccrine sweat units are found at virtually all skin sites. Other mammals have both apocrine and eccrine glands, but the apocrine gland is the major sweat gland, and eccrine glands are generally restricted to areas such as the footpad. Ringtailed lemurs have an antebrachial organ rich in sweat glands with hybrid characteristics of eccrine and apocrine glands. In humans, eccrine glands are abundant and serve a thermoregulatory function. They are most abundant on the palms, soles, forehead, and axillae. Some eccrine glands in the axillae, especially in patients with hyperhidrosis, may have widely dilated secretary coils that contain apocrine-appearing cells. These findings suggest the presence of hybrid glands in humans. On friction surfaces, such as the palms and soles, eccrine secretion is thought to assist tactile sensibility and improve adhesion.

Physiologic secretion of sweat occurs as a result of many factors and is mediated by cholinergic innervation. Heat is a prime stimulus to increased sweating, but other physiologic stimuli, including emotional stress, are important as well. During early development, there is a switch between adrenergic and cholinergic innervation of sweat glands. Some responsiveness to both cholinergic and adrenergic stimuli persists. Cholinergic sweating involves a biphasic response, with initial hyperpolarization and secondary depolarization mediated by the activation of calcium and chloride ion conductance. Adrenergic secretion involves monophasic depolarization and is dependent on cystic fibrosis transmembrane conductance regulator-GCl. Cells from patients with cystic fibrosis demonstrate no adrenergic secretion. Vasoactive intestinal polypeptide may also play a role in stimulating eccrine secretion.

Apocrine Units

Apocrine units develop as outgrowths, not of the surface epidermis, but of the infundibular or upper portion of the hair follicle. Although immature apocrine units are found covering the entire skin surface of the human fetus, these regress and are absent by the time the fetus reaches term. The straight excretory portion of the duct, which opens into the infundibular portion of the hair follicle, is composed of a double layer of cuboidal epithelial cells. Hidrocystomas may show focal secretory cells, but are generally composed of cuboidal cells resembling the straight portion of the apocrine duct. Various benign cutaneous tumors demonstrate differentiation resembling apocrine duct cells, including hidroacanthoma simplex, poroma, dermal duct tumor, and nodular hidradenoma. Although some of these tumors were formerly classified as "eccrine" in differentiation, each may demonstrate focal apocrine decapitation secretion, suggesting apocrine differentiation.

The coiled secretory gland is located at the junction of the dermis and subcutaneous fat. It is lined by a single layer of cells, which vary in appearance from columnar to cuboidal. This layer of cells is surrounded by a layer of myoepithelial cells. Apocrine coils appear more widely dilated than eccrine coils, and apocrine sweat stains more deeply red in H&E sections, contrasting with the pale pink of eccrine sweat.

The apexes of the columnar cells project into the lumen of the gland and in histologic cross-section appear as if they are being extruded (decapitation secretion). Controversy exists about the mode of secretion in apocrine secretory cells, whether merocrine, apocrine, holocrine, or all three. The composition of the product of secretion is only partially understood. Protein, carbohydrate, ammonia, lipid, and iron are all found in apocrine secretion. It appears milky white, although lipofuscin pigment may rarely produce dark shades of brown and gray–blue (apocrine chromhidrosis). Apocrine sweat is odorless until it reaches the skin surface, where it is altered by bacteria, which makes it odoriferous. Apocrine secretion is mediated by adrenergic innervation and by circulating catecholamines of adrenomedullary origin. Vasoactive intestinal polypeptide may also play a role in stimulating aprocrine secretion. Apocrine excretion is episodic, although the actual secretion of the gland is continuous. Apocrine gland secretion in humans serves no known function. In other species it has a protective as well as a sexual function, and in some species it is important in thermoregulation as well.

Although occasionally found in an ectopic location, apocrine units of the human body are generally confined to the following sites: axillae, areolae, anogenital region, external auditory canal (ceruminous glands), and eyelids (glands of Moll). They are also generally prominent in the stroma of nevus sebaceous of Jadassohn. Apocrine glands do not begin to function until puberty.

Hair Follicles

During embryogenesis, mesenchymal cells in the fetal dermis collect immediately below the basal layer of the epidermis. Epidermal buds grow down into the dermis at these sites. The developing follicle forms at an angle to the skin surface and continues its downward growth. At this base, the column of cells widens forming the bulb and surrounds small collections of mesenchymal cells. These papillary mesenchymal bodies contain mesenchymal stem cells with broad functionality. At least in mice, they demonstrate extramedullary hematopoietic stem cell activity, and represent a

potential therapeutic source of hematopoietic stem cells and a possible source of extramedullary hematopoiesis in vivo.

Along one side of the fetal follicle, two buds are formed: an upper, which develops into the sebaceous gland, and a lower, which becomes the attachment for the arrector pili muscle. A third epithelial bud develops from the opposite side of the follicle above the level of the sebaceous gland anlage, and gives rise to the apocrine gland. The uppermost portion of the follicle, which extends from its surface opening to the entrance of the sebaceous duct, is called the infundibular segment. It resembles the surface epidermis and its keratinocytes may be of epidermal origin. The portion of the follicle between the sebaceous duct and the insertion of the arrector pili muscle is the isthmus. The inner root sheath fully keratinizes and sheds within this isthmic portion. The inferior portion includes the lowermost part of the follicle and the hair bulb. Throughout life, the inferior portion undergoes cycles of involution and regeneration.

Hair follicles develop sequentially in rows of three. Primary follicles are surrounded by the appearance of two secondary follicles; other secondary follicles subsequently develop around the principal units. The density of pilosebaceous units decreases throughout life, possibly because of drop out of the secondary follicles. In mouse models, signaling by molecules designated as ectodysplasin A and noggin is essential for the development of primary hair follicles and induction of secondary follicles. Arrector pili muscles contained within the follicular unit interconnect at the level of the isthmus.

The actual hair shaft, as well as an inner and outer root sheath, are produced by the matrix portion of the hair bulb (Fig. 1-10). The sheaths and contained hair form concentric cylindrical layers. The hair shaft and inner root sheath move together as the hair grows upwards until the fully keratinized inner root sheath sheds at the level of the isthmus. The epidermis of the upper part of the follicular canal is contiguous with the outer root sheath. The upper two portions of the follicle (infundibulum and isthmus) are permanent; the inferior segment is completely replaced with each new cycle of hair growth. On the scalp, anagen, the active growth phase, lasts about 3 to 5 years. Normally, approximately 85% to 90% of all scalp hairs are in the anagen phase, a figure that decreases with age and decreases faster in individuals with male-pattern baldness (as the length of anagen decreases dramatically). Scalp anagen hairs grow at a rate of about 0.37 mm/day. Catagen, or involution, lasts about 2 weeks. Telogen, the resting phase, lasts about 3 to 5 months. Most sites on the body have a much shorter anagen phase and much longer telogen, resulting in short hairs that stay in place for long periods of time without growing longer. Prolongation of the anagen phase results in long eyelashes in patients with acquired immunodeficiency syndrome (AIDS).

Human hair growth is cyclical, but each follicle functions as an independent unit (Fig. 1-11). Therefore, humans do not

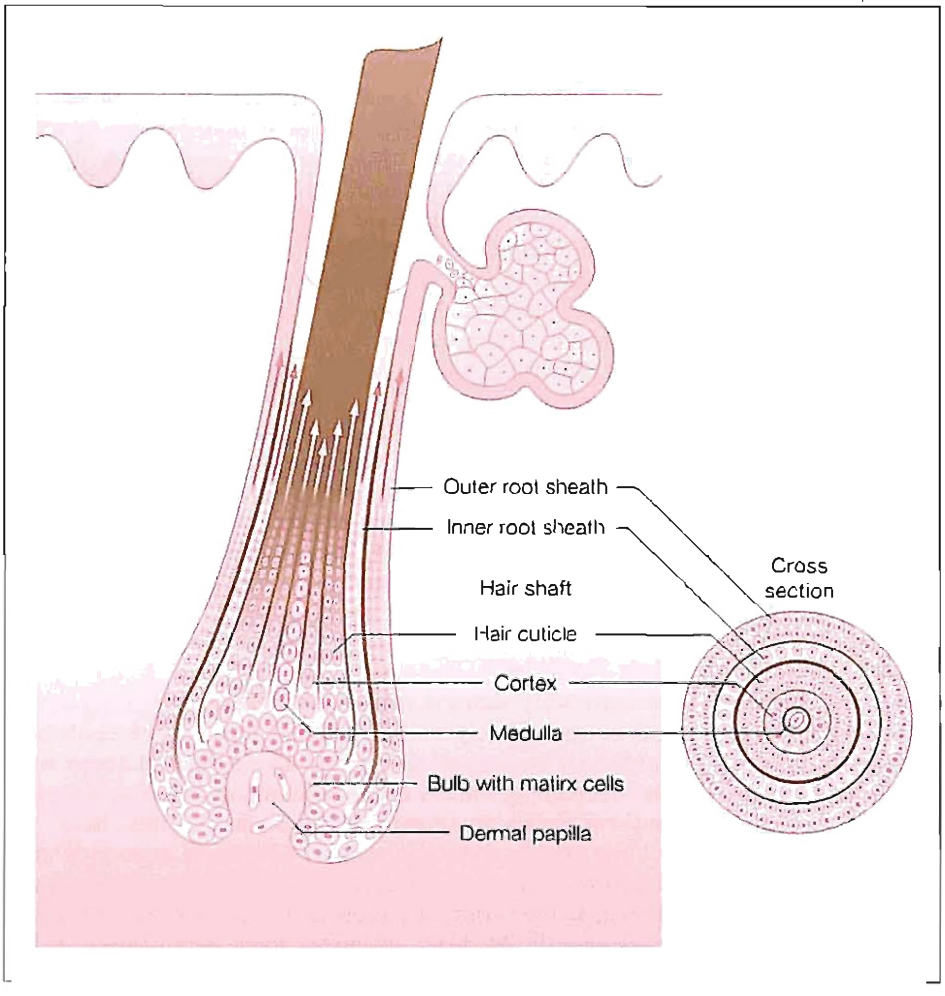

Fig. 1-10 Anatomy of the hair follicle.

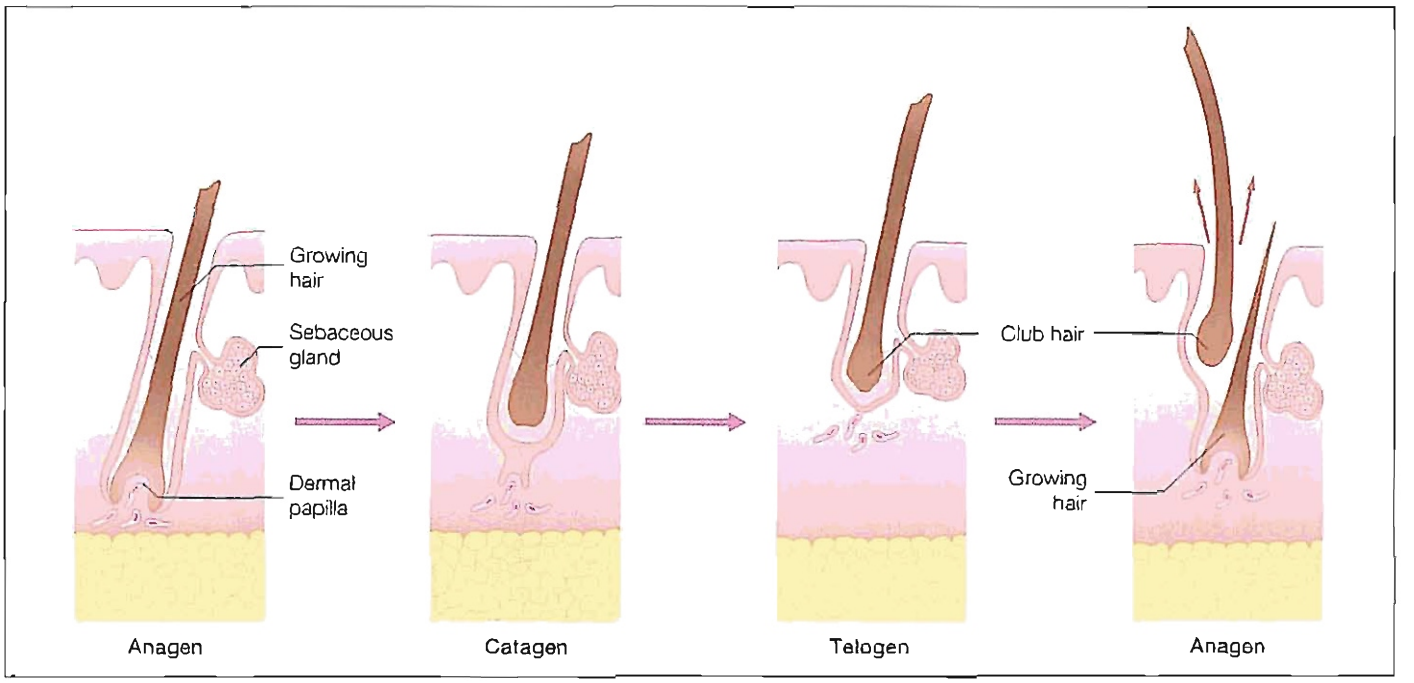

Fig. 1-11 Phases of the growth cycle of a hair.

shed hair synchronously, as most animals do. Each hair follicle undergoes intermittent stages of activity and quiescence. Synchronous termination of anagen or telogen results in telogen effluvium. Most commonly, telogen effluvium is the result of early release from anagen, such as that induced by a febrile illness, surgery or weight loss.

Various exogenous and endogenous physiologic factors can modulate the hair cycle. An example is pregnancy, which is often accompanied by retention of an increased number of scalp hairs in the anagen phase, as well as a prolongation of telogen. Soon after delivery, telogen loss can be detected as abnormally prolonged telogen hairs are released. At the same time, abnormally prolonged anagen hairs are converted synchronously to telogen. Three to 5 months later, a more profound effluvium is noted. Patients on chemotherapy often have hair loss because the drugs interfere with the mitotic activity of the hair matrix, leading to the formation of a tapered fracture. Only anagen hairs are affected, leaving a sparse coat of telogen hairs on the scalp. As the matrix recovers, anagen hairs resume growth without having to cycle through catagen and telogen. The hair papilla and the connective tissue sheath form a communicating network through gap junctions. This network may play a role in controlling hair cycling.

The growing anagen hair is characterized by a pigmented bulb (Fig. 1-12), and inner root sheath (Fig. 1-13). Histologically, catagen hairs are best identified by the presence of many apoptotic cells in the outer root sheath (Fig. 1-14). Telogen club hairs have a nonpigmented bulb with a shaggy lower border. The presence of bright red trichilemmal keratin bordering the club hair results in a flame-thrower–like appearance in vertical H&E sections (Fig. 1-15). As the new anagen hair grows, the old telogen hair is shed.

The scalp hair of white people is round; pubic hair, beard hair, and eyelashes are oval. The scalp hair of black people is also oval, and it is this, plus a curvature of the follicle just above the bulb, that causes black hair to be curly. Uncombable hair is triangular with a central canal.

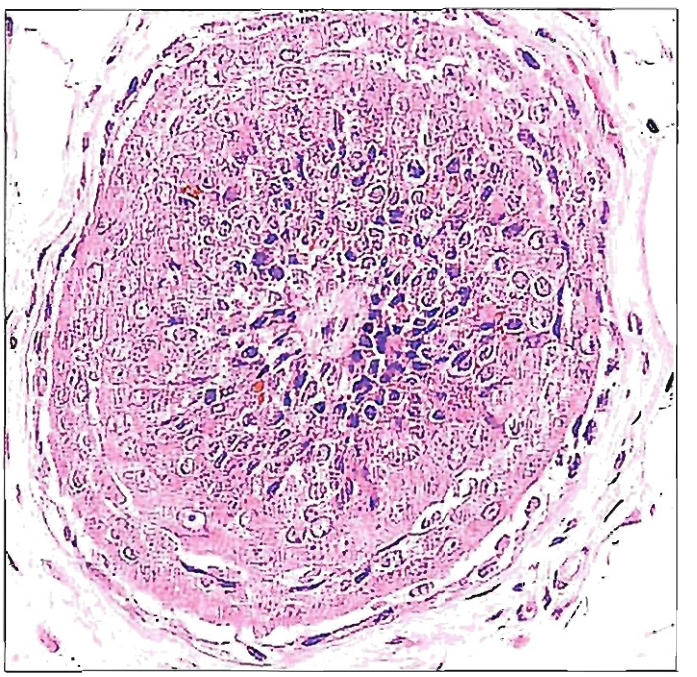

Fig. 1-12 Cross-section of anagen bulb demonstrating pigment within matrix.

Hair color depends on the degree of melanization and distribution of melanosomes within the hair shaft. Melanocytes of the hair bulb synthesize melanosomes and transfer them to the keratinocytes of the bulb matrix. Larger melanosomes are found in the hair of black persons; smaller melanosomes, which are aggregated within membrane-bound complexes, are found in the hair of white persons. Red hair is characterized by spherical melanosomes. Graying

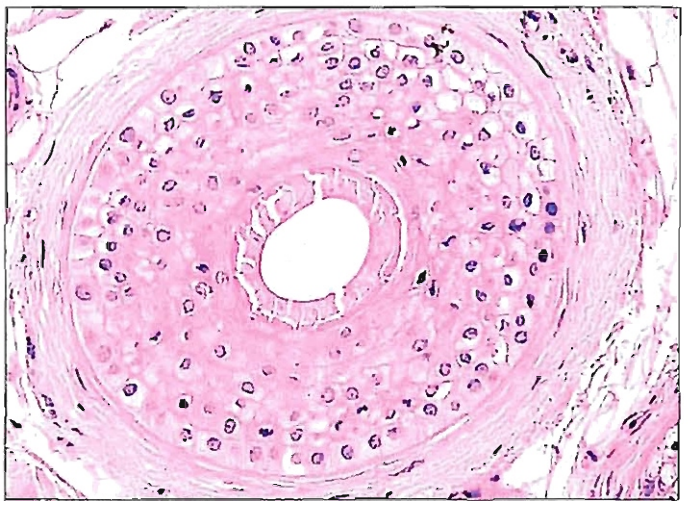

Fig. 1-13 Cross-section of isthmus of anagen follicle demonstrating glycogenated outer root sheath and keratinized inner root sheath.

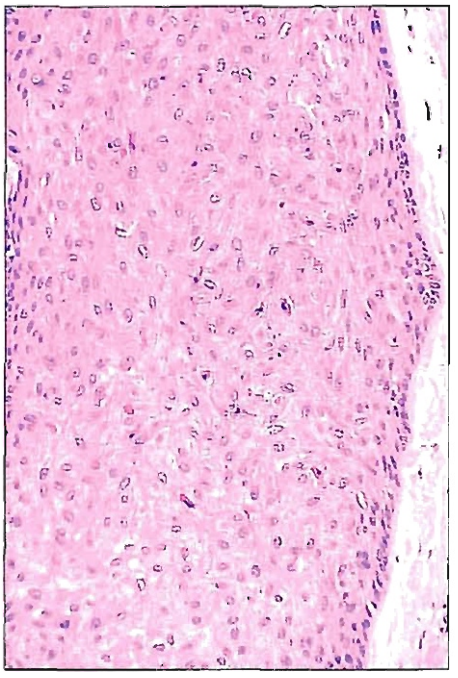

Fig. 1-14 Catagen hair with many apoptotic keratinocytes within the outer root sheath.

of hair is a result of a decreased number of melanocytes, which produce fewer melanosomes. Lerner has likened the pathogenesis of graying of the hair to that of vitiligo. Both conditions show a decreased number of melanocytes in affected sites.

Sebaceous Glands

Sebaceous glands are formed embryologically as an outgrowth from the upper portion of the hair follicle. They are composed of lobules of pale-staining cells with abundant lipid droplets in their cytoplasm. At the periphery of the lobules basaloid germinative cells are noted. These germinative cells give rise to the lipid-filled pale cells, which are continuously being extruded through the short sebaceous duct into the infundibular portion of the hair follicle. The sebaceous duct is lined by a red cuticle that undulates sharply in a pattern resembling shark's teeth. This same undulating cuticle is seen in steatocystoma and some dermoid cysts.

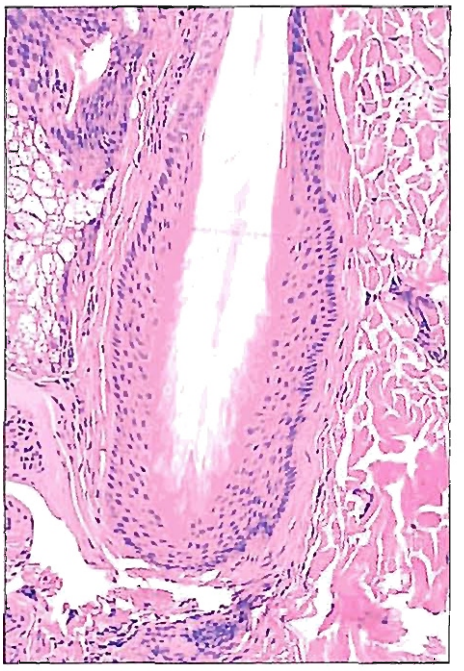

Fig. 1-15 Vertical section of telogen hair demonstrating "flame thrower" appearance of club hair.

Sebaceous glands are found in greatest abundance on the face and scalp, though they are distributed throughout all skin sites except the palms and soles. They are always associated with hair follicles except at the following sites: tarsal plate of the eyelids (meibomian glands), buccal mucosa and vermilion border of the lip (Fordyce spots), prepuce and mucosa lateral to the penile frenulum (Tyson glands), labia minora, and female areola (Montgomery tubercles).

Although sebaceous glands are independent miniorgans in their own right, they are anatomically and functionally related to the hair follicle. Cutaneous disorders attributed to sebaceous glands, such as acne vulgaris, are really disorders of the entire pilosebaceous unit. The clinical manifestations of acne, namely the comedo, papule, pustule, and cyst, would not form, regardless of increased sebaceous gland activity, as long as the sebaceous duct and infundibular portion of the hair follicle remained patent, and lipid and cell debris (sebum) were able to reach the skin surface.

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NAILS

Nails act to assist in grasping small objects and in protecting the fingertip from trauma. Matrix keratinization leads to the formation of the nail plate. The keratin types found in the nail are a mixture of epidermal and hair types, with the hair types predominating. Fingernails grow an average of 0.1 mm/day, requiring about 4 to 6 months to replace a complete nail plate. The growth rate is much slower for toenails, with 12 to 18 months required to replace the great toenail. Abnormalities of the nail may serve as important clues to cutaneous and systemic disease and may provide the astute clinician with information about disease or toxic exposures that occurred several months in the past.

Whereas most of the skin is characterized by rete pegs that resemble an egg crate, the nailbed has true parallel rete ridges. These ridges result in the formation of splinter hemorrhages when small quantities of extravasated red cells mark their path. The nail cuticle is formed by keratinocytes of the proximal nailfold, whereas the nail plate is formed by matrix keratinocytes. Endogenous pigments tend to follow the contour of the lunula (the distal portion of the matrix), whereas exogenous pigments tend to follow the contour of the cuticle. The dorsal nail plate is formed by the proximal matrix and the ventral nail plate is formed by the distal matrix with some contribution from the nailbed. The location of a melanocytic lesion within the matrix can be assessed by the presence of pigment within the dorsal or ventral nail plate.

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DERMIS

The constituents of the dermis are mesodermal in origin except for nerves, which, like melanocytes, derive from the neural crest. Until the sixth week of fetal life, the dermis is merely a pool of acid-mucopolysaccharide–containing, scattered dendritic-shaped cells, which are the precursors of fibroblasts. By the 12th week, fibroblasts are actively synthesizing reticulum fibers, elastic fibers, and collagen. A vascular network develops, and by the 24th week, fat cells have appeared beneath the dermis. Infant dermis is composed of small collagen bundles that stain deeply red. Many fibroblasts are present. In adult dermis, few fibroblasts persist, and collagen bundles are thick and stain pale red.

Two populations of dermal dendritic cells are noted in the adult dermis. Factor XIIIa-positive dermal dendrocytes appear to give rise to dermatofibromas, angiofibromas, acquired digital fibrokeratomas, pleomorphic fibromas, and fibrous papules. CD34+ dermal dendroctyes are accentuated around hair follicles, but exist throughout the dermis. They disappear from the dermis early in the course of morphea. Their loss can be diagnostic in subtle cases. CD34+ dermal dendrocytes reappear in the dermis when morphea responds to UVA1 light treatment.

The principal component of the dermis is collagen, a family of fibrous proteins comprising at least 15 genetically distinct types in human skin. Collagen serves as the major structural protein for the entire body; it is found in tendons, ligaments, and the lining of bones, as well as in the dermis. It represents 70% of the dry weight of skin.

The fibroblast synthesizes the procollagen molecule, a helical arrangement of specific polypeptide chains that are subsequently secreted by the cell and assembled into collagen fibrils. Collagen is rich in the amino acids hydroxyproline, hydroxylysine, and glycine. The fibrillar collagens are the major group found in the skin. Type I collagen is the major component of the dermis. The structure of type I collagen is uniform in width and each fiber displays characteristic cross striations with a periodicity of 68 nm. Collagen fibers are loosely arranged in the papillary and adventitial (periadnexal) dermis. Large collagen bundles are noted in the reticular dermis (the dermis below the level of the postcapillary venule). Type IV collagen is found in the BMZ. Type VII collagen is the major structural component of anchoring fibrils and is produced predominately by keratinocytes. Abnormalities in type VII collagen are seen in dystrophic epidermolysis bullosa and autoantibodies to this collagen type characterize acquired epidermolysis bullosa. Collagen fibers are continuously being degraded by proteolytic enzymes called spare collagenases, and replaced by newly synthesized fibers. Additional information on collagen types and diseases can be found in Chapter 25.

The fibroblast also synthesizes elastic fibers and the ground substance of the dermis, which is composed of glycosaminoglycans or acid mucopolysaccharides. Elastic fibers differ both structurally and chemically from collagen. They consist of aggregates of two components: protein filaments and elastin, an amorphous protein. The amino acids desmosine and isodesmosine are unique to elastic fibers. Elastic fibers in the papillary dermis are fine, whereas those in the reticular dermis are coarse. The extracellular matrix or ground substance of the dermis is composed of sulfated acid mucopolysaccharide, principally chondroitin sulfate and dermatan sulfate, neutral mucopolysaccharides, and electrolytes. Sulfated acid mucopolysacharrhides stain with colloidal iron and with alcian blue at both pH 2.5 and 0.5. They stain metachromatically with toluidine blue at both pH 3.0 and 1.5. Hyaluronan (hyaluronic acid) is a minor component of normal dermis, but is the major mucopolysaccharide that accumulates in pathologic states. It stains with colloidal iron, and with both alcian blue and toludine blue (metachromatically), but only at the higher pH for each stain.

Collagen is the major stress-resistant material of the skin. Elastic fibers contribute very little to resisting deformation and tearing of skin, but have a role in maintaining elasticity. *Connective tissue disease* is a term generally used to refer to

a clinically heterogeneous group of autoimmune diseases, including lupus erythematosus, scleroderma, and dermatomyositis. Scleroderma involves the most visible collagen abnormalities, as collagen bundles become hyalinized and the space between collagen bundles diminishes. Both lupus and dermatomyositis produce increased dermal mucin, mostly hyaluronic acid. Bullous lupus has autoantibodies directed against type VII collagen.

Defects in collagen synthesis have been described in a number of inheritable diseases, including Ehlers-Danlos syndrome, X-linked cutis laxa, and osteogenesis imperfecta. Defects in elastic tissue are seen in another group of hereditary diseases such as Marfan syndrome and pseudoxanthoma elasticum.

Vasculature

The dermal vasculature consists principally of two important intercommunicating plexuses: the subpapillary plexus, or upper horizontal network, contains the post-capillary venules and courses at the junction of the papillary and reticular dermis. This plexus furnishes a rich supply of capillaries, end arterioles, and venules to the dermal papillae. The deeper, lower horizontal plexus is found at the dermal–subcutaneous *interface and is composed of larger blood vessels than those* of the superficial plexus. Nodular lymphoid infiltrates surrounding this lower plexus are typical of early inflammatory morphea. The vasculature of the dermis is particularly well developed at sites of adnexal structures. Associated with the vascular plexus are dermal lymphatics and nerves.

Muscles

Smooth muscle occurs in the skin as arrectores pilorum (erectors of the hairs), as the tunica dartos (or dartos) of the scrotum, and in the areolas around the nipples. The presence of scattered smooth muscle throughout the dermis is typical of anogenital skin. The arrectores pilorum are attached to the hair follicles below the sebaceous glands and, in contracting, *pull the hair follicle upward, producing gooseflesh.*

Smooth muscle also comprises the muscularis of dermal and subcutaneous blood vessels. The muscularis of veins is composed of small bundles of smooth muscle that criss-cross at right angles. Arterial smooth muscle forms a concentric wreath-like ring. Specialized aggregates of smooth muscle cells (glomus bodies) are found between arterioles and venules, and are especially prominent on the digits and at the lateral margins of the palms and soles. Glomus bodies serve to shunt blood and regulate temperature.

Striated (voluntary) muscle occurs in the skin of the neck as the platysma muscle and in the skin of the face as the muscles of expression. This complex network of striated muscle, fascia, and aponeuroses is known as the superficial *muscular aponeurotic system (SMAS).*

Nerves

The dermis is rich in nerves. In the dermis, nerve bundles are found together with arterioles and venules as part of the neurovascular bundle. In the deep dermis, nerves travel parallel to the surface, and the presence of long sausage-like granulomas following this path is characteristic of leprosy.

Touch and pressure are mediated by Meissner corpuscles found in the dermal papillae, particularly on the digits, palms, and soles, and by Vater-Pacini corpuscles located in the deeper portion of the dermis of weight-bearing surfaces and genitalia. Mucocutaneous end organs are found in the papillary dermis of modified hairless skin at the mucocutaneous junctions, namely, the glans, prepuce, clitoris, labia minora, perianal region, and vermilion border of the lips. Temperature, pain, and itch sensation are transmitted by unmyelinated nerve fibers which terminate in the papillary dermis and around hair follicles. Impulses pass to the central nervous system by way of the dorsal root ganglia. Histamine-evoked itch is transmitted by slow-conducting unmyelinated C-polymodal neurons.

Postganglionic adrenergic fibers of the autonomic nervous system regulate vasoconstriction, apocrine gland secretions, and contraction of arrector pili muscles of hair follicles. Cholinergic fibers mediate eccrine sweat secretion.

Mast Cells

An important cellular constituent of the dermis is the mast cell. Six to 12 μm in diameter, with ample amphophilic cytoplasm and a small round central nucleus, normal mast cells resemble fried eggs in histologic sections. In telangiectasia macularis eruptive perstans (TMEP mastocytosis), they are spindle shaped and hyperchromatic, resembling large dark fibroblasts. Mast cells are distinguished by containing up to 1000 granules, each measuring 0.6 to 0.7 μm in diameter. Coarse particulate granules, crystalline granules, and granules containing scrolls may be seen. On the cell's surface are 100,000 to 500,000 glycoprotein receptor sites for *immunoglobulin E (IgE). There is heterogeneity to mast* cells with type I or connective tissue mast cells found in the dermis and submucosa, and type II or mucosal mast cells found in the bowel and respiratory tract mucosa.

Mast cell granules stain metachromatically with toluidine blue and methylene blue (in the Geimsa stain) because of their high content of heparin. They also contain histamine, neutrophil chemotactic factor, eosinophil chemotactic factor of anaphylaxis, tryptase, kininogenase, and β-glucosaminidase. Slow-reacting substance of anaphylaxis (leukotrienes C4 and D4), leukotriene B4, platelet activating factor, and prostaglandin D2 are formed only after IgE-mediated release of granules. Mast cells stain reliably with Leder ASD-chloracetase esterase stain. Because this stain does not rely *on the presence of mast cell granules, it is particularly useful* in situations when mast cells have degranulated. In forensic medicine, fluorescent labeling of mast cells with antibodies to the mast cell enzymes chymase and tryptase is useful in determining the timing of skin lesions in regard to death. Lesions sustained while living show an initial increase, then decline in mast cells. Lesions sustained postmortem demonstrate few mast cells.

Cutaneous mast cells respond to environmental changes. Dry environments result in an increase in mast cell number and cutaneous histamine content. In mastocytosis, mast cells accumulate in skin because of abnormal proliferation, migration, and failure of apoptosis. The terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate-biotin nick *end labeling (TUNEL) method is commonly used to assess* apoptosis, and demonstrates decreased staining in mastocytomas. Proliferation is usually only moderately enhanced.

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SUBCUTANEOUS TISSUE (FAT)

Beneath the dermis lies the panniculus, lobules of fat cells or lipocytes separated by fibrous septa composed of collagen and large blood vessels. The collagen in the septa is continuous with the collagen in the dermis. Just as the epidermis and dermis vary in thickness according to skin site, so does the subcutaneous tissue. The panniculus provides buoyancy, and functions as a repository of energy and an endocrine organ. The panniculus is an important site of hormone conversions, such as the conversion of androstenedione into estrone by aromatase. Leptin, a hormone that regulates body weight via the hypothalamus, is produced in lipocytes. It also influences how we react to flavors in food. Abnormal fat distribution and insulin resistance are seen in Cushing syndrome and as a result of antiretroviral therapy. In obese children and adolescents developing diabetes, severe peripheral insulin resistance is associated with intramyocellular and intra-abdominal lipocyte lipid accumulation.

Certain inflammatory dermatoses, known as the panniculitides, principally affect this level of the skin, producing subcutaneous nodules. The pattern of the inflammation, specifically whether it primarily affects the septa or the fat lobules themselves, serves to distinguish various conditions which clinically may resemble one another. The inflammation in septal panniculitis will regularly spill over into the fat lobule, but the lobule remains intact. In lobular panniculitis, the lobule becomes necrotic. The necrotic lobule is usually visible as large and small round aggregates of coalescing fat. When the necrotic lipocyte membranes are calcified (as in pancreatic panniculitis), the fat cannot coalesce into larger aggregates. This is also true when the intracellular lipid crystallizes (as in sclerema neonatorum, subcutaneous fat necrosis of the newborn or steroid fat necrosis).

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CHAPTER

2 Cutaneous Signs and Diagnosis

In some cases, the appearance of skin lesions may be so distinctive that the diagnosis is clear at a glance. In other cases, subjective symptoms and clinical signs in themselves are inadequate, and a complete history and laboratory examinations, including a biopsy, are essential to arrive at a diagnosis.

The same disease may show variations under different conditions and in different individuals. The appearance of the lesions may have been modified by previous treatment or obscured by extraneous influences, such as scratching or secondary infection. Subjective symptoms may be the only evidence of a disease, as in pruritus, and the skin appearance may be generally unremarkable. Although history is important, in dermatology, the diagnosis is most frequently made based on the objective physical characteristics and location or distribution of one or more lesions that can be seen or felt. Therefore, careful physical examination of the skin is paramount in dermatologic diagnosis.

CUTANEOUS SIGNS

Typically, most skin diseases produce or present with lesions with more or less distinct characteristics. They may be uniform or diverse in size, shape, and color, and may be in different stages of evolution or involution. The original lesions are known as the *primary lesions*, and identification of such lesions is the most important aspect of the dermatologic physical examination. They may continue to full development or be modified by regression, trauma, or other extraneous factors, producing *secondary lesions*.

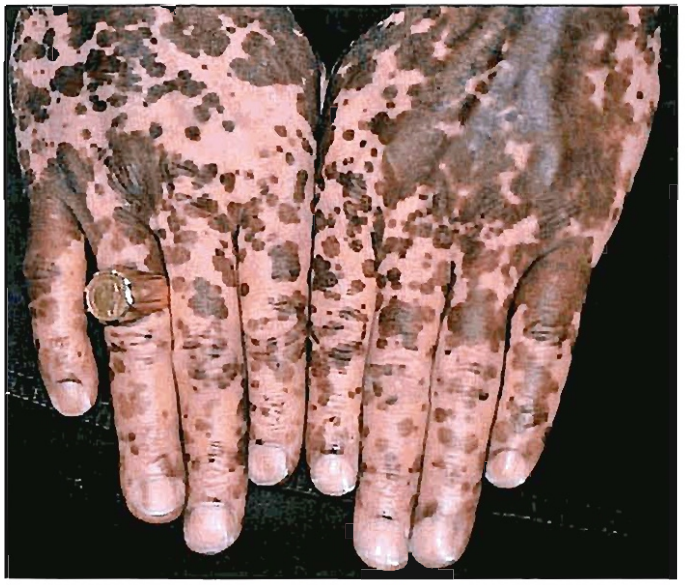

Fig. 2-1 Macular depigmentation, vitiligo.

Primary Lesions

Primary lesions are of the following forms—macules (or patches), papules (or plaques), nodules, tumors, wheals, vesicles, bullae, and pustules.

Macules (Maculae, Spots)

Macules are variously sized, circumscribed changes in skin color, without elevation or depression (nonpalpable) (Fig. 2-1). They may be circular, oval or irregular, and may be distinct in outline or fade into the surrounding skin. Macules may constitute the whole or part of the eruption, or may be merely an early phase. If the lesions become slightly raised, they are then designated papules, or sometimes, morbilliform eruptions.

Patches

A patch is a large macule, 1 cm or greater in diameter, as may be seen in nevus flammeus or vitiligo.

Papules

Papules are circumscribed, solid elevations with no visible fluid, varying in size from a pinhead to 1 cm (Fig. 2-2). They may be acuminate, rounded, conical, flat topped, or umbilicated, and may appear white (as in milium), red (as in eczema), yellowish (as in xanthoma), or black (as in melanoma).

Papules are generally centered in the dermis and may be concentrated at the orifices of the sweat ducts or at the hair follicles. They may be of soft or firm consistency. The surface may be smooth or rough. If capped by scales, they are known as *squamous papules*, and the eruption is called *papulosquamous*.

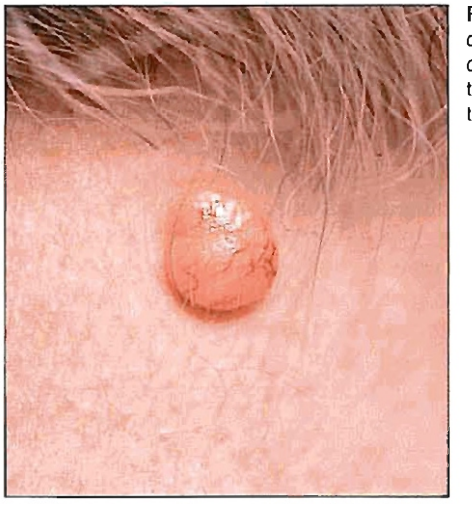

Fig. 2-2 Skin-colored papule with overlying telangiectasias, trichoepithelioma.

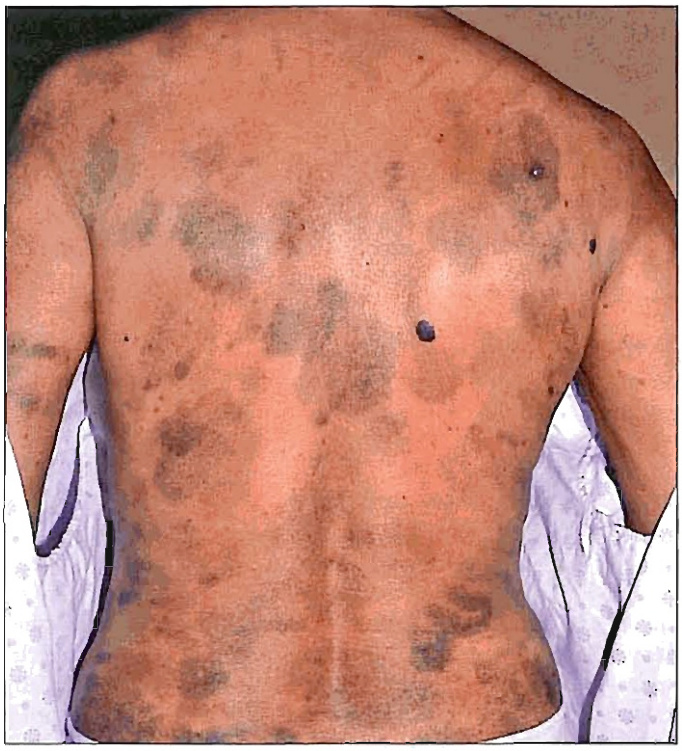

Fig. 2-3 Multiple hyperpigmented patches and plaques, cutaneous T-cell lymphoma.

Some papules are discrete and irregularly distributed, as in papular urticaria, whereas others are grouped, as in lichen nitidus. Some persist as papules, whereas those of the inflammatory type may progress to vesicles and even to pustules, or may erode or ulcerate before regression takes place.

The term *maculopapular* should not be used. There is no such thing as a maculopapule, but there may be both macules and papules in an eruption. Most typically such eruptions are morbilliform.

Plaques

A plaque is a broad papule (or confluence of papules), 1 cm or more in diameter (Fig. 2-3). It is generally flat, but may be centrally depressed. The center of a plaque may be normal skin.

Nodules

Nodules are morphologically similar to papules, but they are larger than 1 cm in diameter. They most frequently are centered in the dermis or subcutaneous fat.

Tumors

Tumors are soft or firm and freely movable or fixed masses of various sizes and shapes (but in general greater than 2 cm in diameter). General usage dictates that the word "tumor" means a neoplasm. They may be elevated or deep seated, and in some instances are pedunculated (fibromas). Tumors have a tendency to be rounded. Their consistency depends on the constituents of the lesion. Some tumors remain stationary indefinitely, whereas others increase in size or break down.

Wheals (Hives)

Wheals are evanescent, edematous, plateau-like elevations of various sizes (Fig. 2-4). They are usually oval or of arcuate

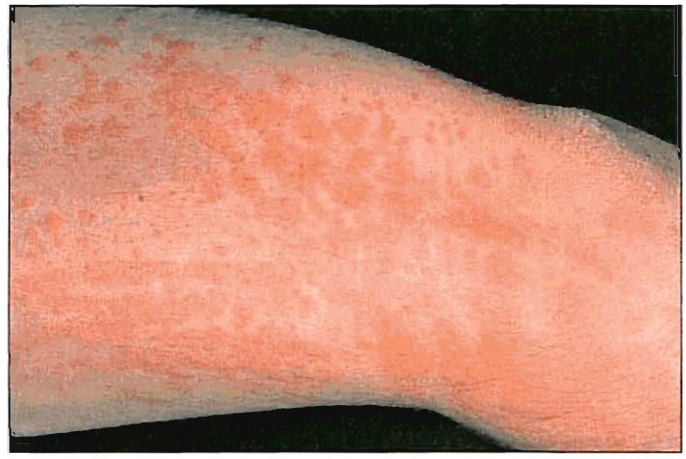

Fig. 2-4 Multiple wheals and dermatographism, urticarial vasculitis.

contours, pink to red, and surrounded by a "flare" of macular erythema. They may be discrete or may coalesce. These lesions often develop quickly. Because the wheal is the prototypic lesion of urticaria, diseases in which wheals are prominent are frequently described as "urticarial" (e.g. urticarial vasculitis). Dermographism, or pressure-induced whealing, may be evident.

Vesicles (Blisters)

Vesicles are circumscribed, fluid-containing, epidermal elevations, 1 to 10 mm in size. They may be pale or yellow from serous exudate, or red from serum mixed with blood. The apex may be rounded, acuminate, or umbilicated as in eczema herpeticum. Vesicles may be discrete, irregularly scattered, grouped as in herpes zoster, or linear as in allergic contact dermatitis from urushiol (poison ivy/oak). Vesicles may arise directly or from a macule or papule, and generally lose their identity in a short time, breaking spontaneously or developing into bullae through coalescence or enlargement, or developing into pustules. When the contents are of a seropurulent character, the lesions are known as *vesicopustules*. Vesicles consist of either a single cavity (unilocular) or of several compartments (multilocular) containing fluid.

Bullae

Bullae are rounded or irregularly shaped blisters containing serous or seropurulent fluid. They differ from vesicles only in size, being larger than 1 cm. They are usually unilocular but may be multilocular. Bullae may be located superficially in the epidermis, so that their walls are flaccid and thin and subject to rupture spontaneously or from slight injury. After rupture, remnants of the thin walls may persist and, together with the exudate, may dry to form a thin crust; or the broken bleb may leave a raw and moist base, which may be covered with seropurulent or purulent exudate. More rarely, irregular vegetations may appear on the base (as in pemphigus vegetans). When the bullae are subepidermal, they are tense, and ulceration and scarring may result.

Nikolsky's sign refers to the diagnostic maneuver of putting lateral pressure on unblistered skin in a bullous eruption and having the epithelium shear off. Asboe-Hansen's sign refers to the extension of a blister to adjacent unblistered skin when pressure is put on the top of the blister. Both of

these signs demonstrate the principle that in some diseases the extent of microscopic vesiculation is more than is evident by simple inspection. These findings are useful in evaluating the severity of pemphigus vulgaris and severe bullous drug reactions. Hemorrhagic bullae are common in pemphigus, herpes zoster, severe bullous drug reactions, and lichen sclerosus et atrophicus. The cellular contents of bullae may be useful in cytologically confirming the diagnosis of pemphigus, herpes zoster, and herpes simplex.

Pustules

Pustules are small elevations of the skin containing purulent material (usually necrotic inflammatory cells) (Fig. 2-5). They are similar to vesicles in shape and usually have an inflammatory areola. They are usually white or yellow centrally, but may be red if they also contain blood. They may originate as pustules or may develop from papules or vesicles, passing through transitory early stages, during which they are known as *papulopustules* or *vesicopustules*.

Secondary Lesions

Secondary lesions are of many kinds; the most important are scales, crusts, erosions, ulcers, fissures, and scars.

Scales (Exfoliation)

Scales are dry or greasy laminated masses of keratin. The body ordinarily is constantly shedding imperceptible tiny, thin fragments of stratum corneum. When the formation of epidermal cells is rapid or the process of normal keratinization is interfered with, pathologic exfoliation results, producing scales. These vary in size, some being fine, delicate, and branny, as in tinea versicolor, others being coarser, as in eczema and ichthyosis, while still others are stratified, as in psoriasis. Large sheets of desquamated epidermis are seen in toxic epidermal necrolysis, staphylococcal scalded skin syndrome, and infection-associated (toxin-medicated) desquamations, such as scarlet fever. Scales vary in color from white–gray to yellow or brown from the admixture of dirt or melanin. Occasionally, they have a silvery sheen from trapping of air between their layers: these are micaceous scales, characteristic of psoriasis. When scaling occurs, it usually implies that there is some pathologic process in the epidermis, and parakeratosis is often present histologically.

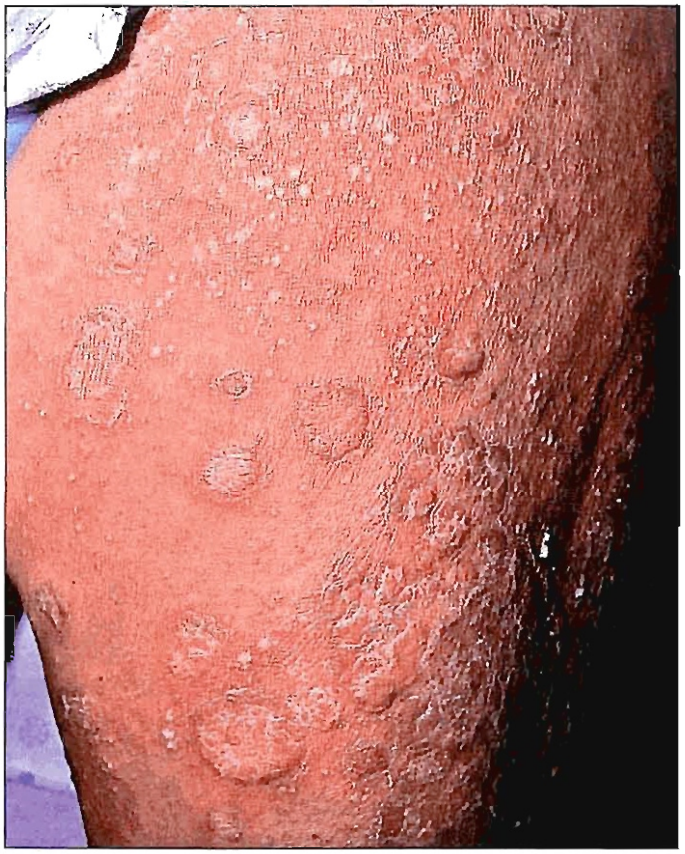

Fig. 2-5 Erythematous plaques studded with sheets of pustules, pustular psoriasis.

Crusts (Scabs)

Crusts are dried serum, pus, or blood, usually mixed with epithelial and sometimes bacterial debris. They vary greatly in size, thickness, shape, and color, according to their origin, composition, and volume. They may be dry, golden yellow, soft, friable, and superficial, as in impetigo; yellowish, as in favus; thick, hard, and tough as in third-degree burns; or lamellated, elevated, brown, black, or green masses, as in late syphilis. The latter have been described as oyster-shell (ostraceous) crusts and are known as *rupia*. When crusts become detached, the base may be dry or red and moist.

Excoriations and Abrasions (Scratch Marks)

An excoriation is a punctate or linear abrasion produced by mechanical means, usually involving only the epidermis but not uncommonly reaching the papillary layer of the dermis. Excoriations are caused by scratching with the fingernails in an effort to relieve itching in a variety of diseases. If the skin damage is the result of mechanical trauma or constant friction, the term *abrasion* may be used. Frequently there is an inflammatory areola around the excoriation or a covering of yellowish dried serum or red dried blood. Excoriations may provide access for pyogenic microorganisms and the formation of crusts, pustules, or cellulitis, occasionally associated with enlargement of the neighboring lymphatic glands. In general, the longer and deeper excoriations are, the more severe was the pruritus that provoked them. Lichen planus is an exception, however, in which pruritus is severe, but excoriations are rare.

Fissures (Cracks, Clefts)

A fissure is a linear cleft through the epidermis or into the dermis. These lesions may be single or multiple and vary from microscopic to clefts several centimeters in length with sharply defined margins. They may be dry or moist, red, straight, curved, irregular, or branching. They occur most commonly when the skin is thickened and inelastic from inflammation and dryness, especially in regions subjected to frequent movement. Such areas are the tips and flexural creases of the thumbs, fingers, and palms; the edges of the heels; the clefts between the fingers and toes; at the angles of the mouth; the lips; and about the nares, auricles, and anus. When the skin is dry, exposure to cold, wind, water, and cleaning products (soap, detergents) may produce a stinging, burning sensation, indicating microscopic fissuring is present. This may be referred to as *chapping*, as in "chapped lips." When fissuring is present, pain is often produced by movement of the parts, which opens or deepens the fissures or forms new ones.

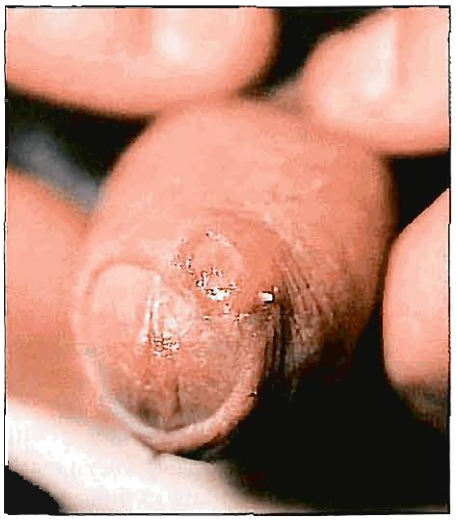

Fig. 2-6 Penile ulcer with a purulent base, chancroid.

Erosions

Loss of all or portions of the epidermis alone, as in impetigo or herpes zoster or simplex after vesicles rupture, produces an erosion. It may or may not become crusted, but it heals without a scar.

Ulcers

Ulcers are rounded or irregularly shaped excavations that result from complete loss of the epidermis plus some portion of the dermis. They vary in diameter from a few millimeters to several centimetres (Fig. 2-6). They may be shallow, involving little beyond the epidermis, as in dystrophic epidermolysis bullosa, the base being formed by the papillary layer, or they may extend deep into the dermis, subcutaneous tissues or deeper, as with leg ulcers. They heal with scarring.

Scars

Scars are composed of new connective tissue that replaced lost substance in the dermis or deeper parts as a result of injury or disease, as part of the normal reparative process. Their size and shape are determined by the form of the previous destruction. Scarring is characteristic of certain inflammatory processes and is therefore of diagnostic value. The pattern of scarring may be characteristic of a particular disease. Lichen planus and discoid lupus erythematosus, for example, have inflammation that is in relatively the same area anatomically, yet discoid lupus characteristically causes scarring as it resolves, whereas lichen planus rarely results in scarring of the skin. Both processes, however, cause scarring of the hair follicles when they occur on the scalp. Scars may be thin and atrophic, or the fibrous elements may develop into neoplastic overgrowths, as in keloids. Some individuals and some areas of the body, such as the anterior chest, are especially prone to scarring. Scars may be smooth or rough, pliable or firm, and tend at first to be pink or violaceous, later becoming white, glistening, and rarely, hyperpigmented.

Scars are persistent but tend to become less noticeable in the course of time. At times, and especially in certain anatomic locations (central chest), they grow thick, tough, and corded, forming a hypertrophic scar or keloid.

GENERAL DIAGNOSIS

Interpretation of the clinical picture may be difficult, because identical manifestations may result from widely different causes. Moreover, the same etiologic factors may give rise to a great diversity of eruptions. There is one great advantage in dermatology, namely, that of dealing with an organ that can be seen and felt. Smears and cultures may be readily made for bacteria and fungi. Biopsy and histologic examination of skin lesions are usually very minor procedures, making histopathology an important component of the evaluation in many clinical situations. Given the ease of histologic confirmation of diagnoses in skin diseases, the threshold for biopsy should be low. This is especially true of inflammatory dermatoses, potentially infectious conditions, and skin disorders in immunosuppressed hosts where clinical morphology may be atypical. Once therapy is begun empirically, histologic features may be altered by the treatment, making pathologic diagnosis more difficult.

History

Knowledge of the patient's age, health, occupation, hobbies, living conditions, and the onset, duration, and course of the disease, and its response to previous treatment are important. The family history of similar disorders and other related diseases may be useful.

A complete drug history is one of the most important aspects of a thorough history. This includes prescription and over-the-counter medications, supplements, and herbal products. Drug reactions are frequently seen and may simulate many different diseases. Anti-inflammatory agents (steroidal or nonsteroidal), antibiotics, antihypertensives, antiarrhythmics, cholesterol lowering agents, antiepileptics, and antidepressants may all produce cutaneous disorders. All may simulate entities not usually attributed to drugs. It is equally important to inquire about topical agents that have been applied to the skin and mucous membranes for medicinal or cosmetic purposes, for these agents may cause cutaneous or systemic reactions.

Other illnesses, travel abroad, the patient's environment at home and at work, seasonal occurrences and recurrences of the disease, and the temperature, humidity, and weather exposure of the patient are all important items in a dermatologic history. Habitation in certain parts of the world predisposes to distinctive diseases for that particular geographic locale. San Joaquin Valley fever (coccidioidomycosis), leprosy, leishmaniasis, and histoplasmosis are examples. Sexual orientation and practices may be relevant, as in genital ulcer diseases, human immunodeficiency virus (HIV) infection, and infestations (e.g. scabies, pubic lice).

Examination

Examination should be conducted in a well-lit room. Natural sunlight is the ideal illumination. Fluorescent bulbs that produce wavelengths of light closer to natural sunlight than standard fluorescent bulbs are commercially available. Abnormalities of melanin pigmentation, e.g. vitiligo and melasma, are more clearly visible under ultraviolet (UV) light. A Wood's light (365 nm) is most commonly used and is also valuable for the diagnosis of some types of tinea capitis, tinea versicolor, and erythrasma.

A magnifying lens is of inestimable value in examining small lesions. It may be necessary to palpate the lesion for

firmness and fluctuation; rubbing will elucidate the nature of scales; scraping will reveal the nature of the lesion's base. Pigmented lesions, especially in infants, should be rubbed in an attempt to elicit Darier's sign (whealing), as seen in urticaria pigmentosa.

The entire eruption must be seen to evaluate distribution and configuration. This is optimally done by having the patient completely undress and viewing him/her from a distance to take in the whole eruption at once. "Peek-a-boo" examination, by having the patient expose one anatomic area after another while remaining clothed, is not optimal, because the examination of the skin will be incomplete and the overall distribution is hard to determine. After the patient is viewed at a distance, individual lesions are examined to identify primary lesions and to determine the evolution of the eruption and the presence of secondary lesions.

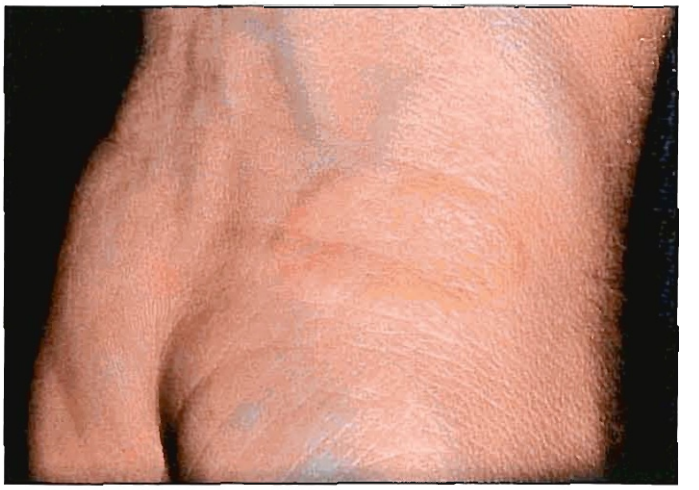

Fig. 2-7 Erythematous papules in an annular configuration, granuloma annulare.

Diagnostic Details of Lesions

Distribution

Lesions may be few or numerous, and in arrangement they may be discrete or may coalesce to form patches of peculiar configuration. They may appear over the entire body, or follow the lines of cleavage (pityriasis rosea), dermatomes (herpes zoster), or lines of Blaschko (epidermal nevi). Lesions may form groups, rings, crescents, or unusual linear patterns. A remarkable degree of bilateral symmetry is characteristic of certain diseases such as dermatitis herpetiformis, vitiligo, and psoriasis.

Evolution

Some lesions appear fully evolved. Others develop from smaller lesions, then may remain the same during their entire existence (e.g. warts). When lesions succeed one another in a series of crops, as they do in varicella and dermatitis herpetiformis, a polymorphous eruption results with lesions in various stages of development or involution all present at the same time.

Involution

Certain lesions disappear completely, whereas others leave characteristic residual pigmentation or scarring. Residual dyspigmentation, although a significant cosmetic issue, is not considered a scar. The pattern in which lesions involute may be useful in diagnosis, e.g. the typical keratotic papule of pityriasis lichenoides varioliformis acuta.

Grouping

Grouping is a characteristic of dermatitis herpetiformis, herpes simplex, and herpes zoster. Small lesions arranged around a large one are said to be in a *corymbose* arrangement. Concentric annular lesions are typical of borderline leprosy and erythema multiforme. These are sometimes said to be in a *cockade* pattern, like the tricolor cockade hats worn by French revolutionists. Flea and other arthropod bites are usually grouped and linear (breakfast-lunch-and-dinner sign). Grouped lesions of various sizes may be termed agminated.

Configuration

Certain terms are used to describe the configuration that an eruption assumes either primarily or by enlargement or coalescence. Lesions in a line are called *linear*, and they may be confluent or discrete. Lesions may form a complete circle (*annular*) (Fig. 2-7), a portion of a circle (*arcuate*), or may be composed of several intersecting portions of circles (*polycyclic*). If the eruption is not straight but does not form parts of circles, it may be *serpiginous*. Round lesions may be small, like drops, called *guttate*; or larger, like a coin, called *nummular*. Unusual configurations that do not correspond to these patterns or to normal anatomic or embryonic patterns should raise the possibility of an exogenous dermatosis or factitia.

Color

The color of the skin is determined by melanin, oxyhemoglobin, reduced hemoglobin, and carotene. Not only do the proportions of these components affect the color, but their depth within the skin, the thickness of the epidermis, and hydration also play a role. The Tyndall effect modifies the color of skin and of lesions by the selective scattering of light waves of different wavelengths. The blue nevus and mongolian spots are examples of this light dispersion effect, in which brown melanin in the dermis appears blue–gray (Fig. 2-8).

It is not advisable to place too much reliance on the color of lesions as a diagnostic factor, because it is difficult to describe colors, and they appear differently in different individuals; but color may at least serve as a corroborative aid. Interface reactions such as lichen planus or lupus erythematosus are described as *violaceous*. Lipid-containing lesions are yellow, as in xanthomas or steatocystoma multiplex. The orange–red (salmon) color of pityriasis rubra pilaris is characteristic.

Patches lighter in color than the normal skin may be completely depigmented or have lost only part of their pigment (hypopigmented). This is an important distinction, since certain conditions are or may be hypopigmented, such as tinea versicolor, nevus anemicus, leprosy, hypomelanotic macules of tuberous sclerosis, hypomelanosis of Ito, seborrheic dermatitis, and idiopathic guttate hypomelanosis. True depigmentation should be distinguished from this; it suggests vitiligo, nevus depigmentosus, halo nevus, scleroderma, morphea, or lichen sclerosus et atrophicus.

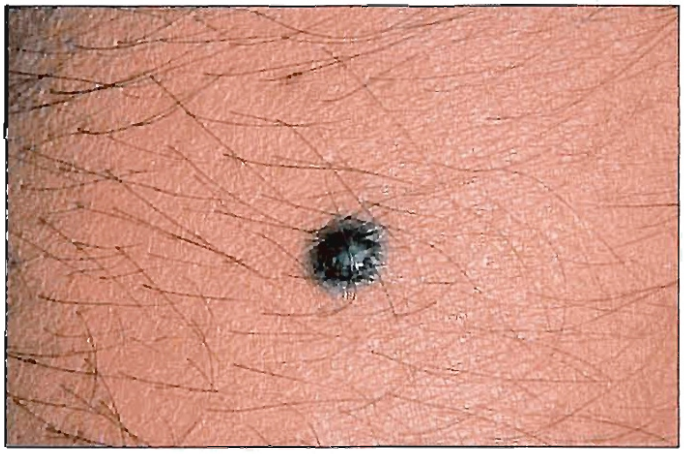

Fig. 2-8 Acral small blue papule, blue nevus.

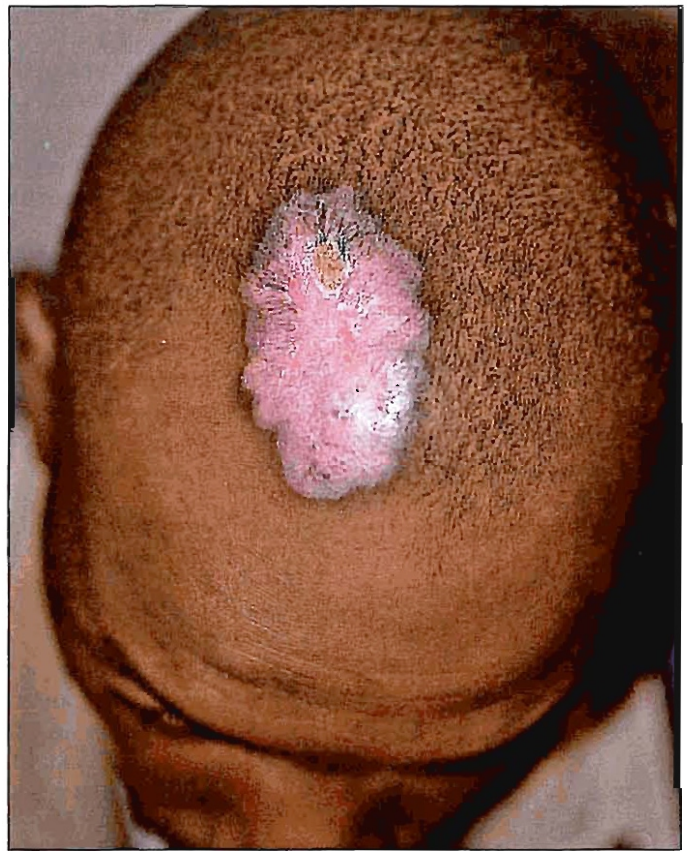

Fig. 2-9 Scalp plaque with scarring alopecia hyperpigmentation and depigmentation, discoid lupus erythematosus.

Hyperpigmentation may result from epidermal or dermal causes. It may be related either to increased melanin or deposition of other substances. Epidermal hyperpigmentation occurs in nevi, melanoma, café-au-lait spots, melasma, and lentigines. These lesions are accentuated when examined with a Wood's light. Dermal pigmentation occurs subsequent to many inflammatory conditions (postinflammatory hyperpigmentation) or from deposition of metals, medications, medication–melanin complexes, or degenerated dermal material (ochronosis). These conditions are not enhanced when examined by a Wood's light. The hyperpigmentation following inflammation is most commonly the result of dermal melanin deposition, but in some conditions, such as lichen aureus, is caused by iron. Dermal iron deposition appears more yellow–brown or golden than dermal melanin.

Consistency

Palpation is an essential part of the physical examination of lesions. Does the lesion blanch on pressure? If not, it may be purpuric. Is it fluctuant? If so, it may have free fluid in it. Is it cold or hot? If there is a nodule or tumor, does it sink through a ring into the panniculus, like a neurofibroma? Is it hard enough for calcification to be suspected, or merely very firm, like a keloid or dermatofibroma? Or brawny, like scleredema?

Hyperesthesia/Anesthesia

Certain conditions may be associated with increased or decreased sensation. For example, the skin lesions of borderline and tuberculoid Hansen's disease typically are anesthetic in their centers.

Hair, Nails, and Oral Mucosa

Involvement of hair-bearing areas by certain skin disorders cause characteristic lesions. Discoid lupus, for example, causes scarring alopecia with characteristic dyspigmentation (Fig. 2-9). On the skin the lesions may be much less characteristic. Diffuse hair loss may be seen in certain conditions such as acrodermatitis enteropathica, and may be a clue to the diagnosis. In addition, loss of hair within a skin lesion may be suggestive of the correct diagnosis, e.g. the alopecia seen in the tumid plaques of follicular mucinosis.

Some skin disorders cause characteristic changes of the nails, even when the periungual tissue is not involved. The pitting seen in psoriasis and alopecia areata may be useful in confirming these diagnoses when other findings are not characteristic. In addition, the nails and adjacent structures may be the sole site of pathology, as in candidal paronychia.

The complete skin examination includes examination of the oral mucosa. Oral lesions are characteristically found in viral syndromes (enanthems), lichen planus, HIV-associated Kaposi sarcoma, and autoimmune bullous diseases (pemphigus vulgaris).

CHAPTER

3 Dermatoses Resulting from Physical Factors

The body requires a certain amount of heat, but beyond definite limits, insufficient or excessive amounts are injurious. The local action of excessive heat causes burns or scalds; on the other hand, undue cold causes chilblains, frostbite, and congelation. Thresholds of tolerance exist in all body structures sensitive to electromagnetic wave radiation of varying frequencies, such as x-rays and ultraviolet (UV) rays. The skin, which is exposed to so many external physical forces, is more subject to injuries caused by them than is any other organ.

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HEAT INJURIES

Thermal Burns

Injury of varying intensity may be caused by the action of excessive heat on the skin. If this heat is extreme, the skin and underlying tissue may be destroyed. The changes in the skin resulting from dry heat or scalding are classified in four degrees.

A *first-degree burn* of the skin results merely in an active congestion of the superficial blood vessels, causing erythema that may be followed by epidermal desquamation (peeling). Ordinary sunburn is the most common example of a first-degree burn. The pain and increased surface heat may be severe, and it is not rare to have some constitutional reaction if the involved area is large.

Second-degree burns are subdivided into superficial and deep forms. In the superficial type there is a transudation of serum from the capillaries, which causes edema of the superficial tissues. Vesicles and blebs are formed by the serum gathering beneath the outer layers of the epidermis (Fig. 3-1). Complete recovery without scarring is usual in burns of this kind. The deep second-degree burn is pale and anesthetic. Injury to the reticular dermis compromises blood flow and destroys appendages, so that healing takes over 1 month to occur and results in scarring.

In *third-degree burns* loss of tissue of the full thickness of the skin, and often some of the subcutaneous tissues, occurs. Since the skin appendages are destroyed, there is no epithelium available for regeneration of the skin. An ulcerating wound is produced, which in healing leaves a scar.

Fourth-degree burns are the destruction of the entire skin and subcutaneous fat with any underlying tendons. Both third- and fourth-degree burns require grafting for closure. All third- and fourth-degree burns are followed by constitutional symptoms of varied gravity, their severity depending on the size of the involved surface, the depth of the burn, and particularly the location of the burned surface. It appears that the more vascular the involved area, the more severe the symptoms.

Symptoms of shock may appear within 24 h after a burn injury, followed by symptoms of toxemia from absorption of destroyed tissue on the surface of the wound. Then symptoms from wound infection may develop as a result of contamination with pyogenic organisms. The symptoms of these three conditions may merge so that differentiation is difficult.

The prognosis is poor for any patient in whom a large area of skin surface is involved, particularly if more than two-thirds of the body surface has been burned. In addition to infection of the wound and surrounding tissue (cellulitis), sepsis, with seeding of internal organs, such as the meninges, lungs, or kidneys, may occur. Irregularities in electrolytes and fluid balance and loss of serum proteins can further complicate the patient's condition.

Excessive scarring, with either keloid-like scars or flat scars with contractures, may produce deformities and dysfunctions of the joints, as well as chronic ulcerations due to impairment of local circulation. Delayed post-burn blistering occurs in partial-thickness wounds and skin-graft donor sites, is most common on the lower extremities, and is self-limited. Burn scars may be the site of development of carcinoma or sarcoma. With modern reconstructive surgery these unfortunate end results can be minimized.

Treatment

Immediate first aid for minor thermal burns consists of prompt cold applications (ice water, or cold tap water if no ice is at hand) continued until pain does not return on stopping them.

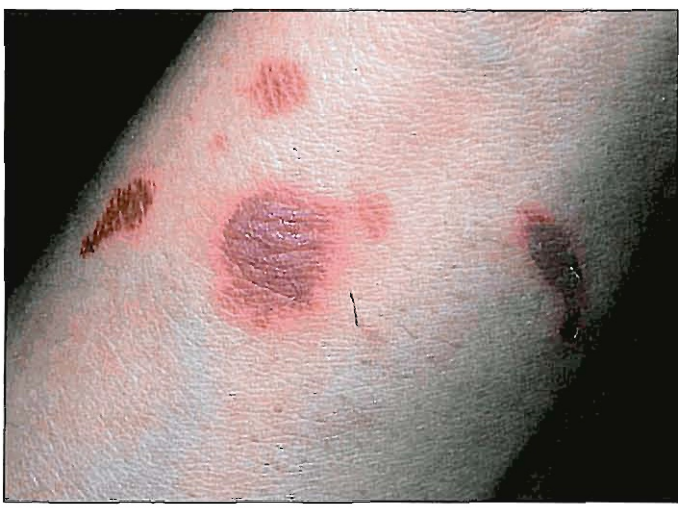

Fig. 3-1 Hot coffee burn.

The vesicles or blebs of second-degree burns should not be opened but should be protected from injury, since they form a natural barrier against contamination by microorganisms. If they become tense and unduly painful, the fluid may be evacuated under strictly aseptic conditions by puncturing the wall with a sterile needle, allowing the blister to collapse onto the underlying wound. Silver sulfadiazine (Silvadene) ointment has been found effective in the control of burn wound infections, but sulfa allergies and leukopenia may complicate the use of Silvadene. For these reasons, 0.05% silver nitrate solution or silver-impregnated dressings are often preferred in burn units. In severe deep burns, when char is present, Sulfamylon is often used. Recently developed skin substitutes that employ collagen–synthetic bilaminate membranes are enjoying increasing use in coverage of these wounds. In many centers, cultured epidermal grafts, both autologous and allogeneic, are being used with promising results.

Morbidity and mortality following severe burns are often caused by bacterial and fungal infection; therefore, treatment should be directed against this complication. Definitive therapy consists of antishock measures, debridement of loose skin and dirt, and the application of silver sulfadiazine ointment. Antibiotics and fluid and electrolyte support are given, and good nutrition is maintained with supplemental vitamins.

Expedient primary excision of deep dermal and full-thickness burn wounds with subsequent grafting is the standard of care. Severe second- and third-degree burns, especially those involving over 15% of the body surface area, require specialized teams of physicians working together in burn units to provide the most effective treatment.

Electrical Burns Electrical burns may occur from contact or as a flash exposure. A contact burn is small but deep, causing some necrosis of the underlying tissues. Low-voltage injuries usually occur in the home, are treated conservatively, and generally heal well. The oral commissure burns may require reconstructive procedures (Fig. 3-2). High-voltage burns are often occupational, internal damage may be masked by little surface skin change, and be complicated by subtle and slowly developing sequelae (Fig. 3-3). Early surgical intervention to improve circulation and repair vital tissues is helpful in limiting loss of the extremity.

Flash burns usually cover a large area and, being similar to any surface burn, are treated as such. Lightning may cause burns after a direct strike (Fig. 3-4), where an entrance and exist wound are visible. This is the most lethal type of strike, and cardiac arrest or other internal injuries may occur. Other types of strikes are indirect and result in burns that are either linear in areas on which sweat was present; are in a feathery or arborescent pattern, which is believed to be pathognomonic; are punctate with multiple, deep, circular lesions; or are thermal burns from ignited clothing or heated metal.

Hot Tar Burns Polyoxyethylene sorbitan in Neosporin ointment or sunflower oil are excellent dispersing agents that facilitate the removal of hot tar from burns.

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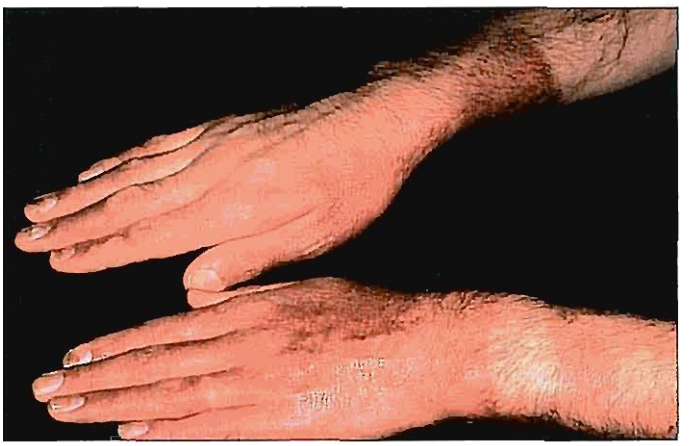

Fig. 3-3 Electrical burn.

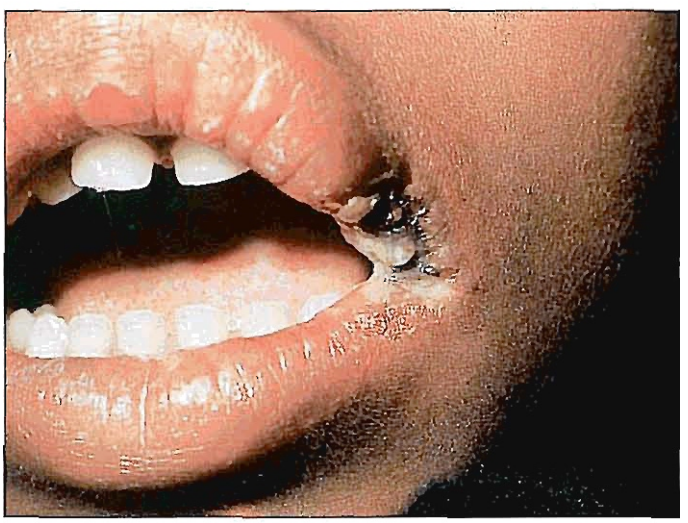

Fig. 3-2 Electrical burn from biting on a cord.

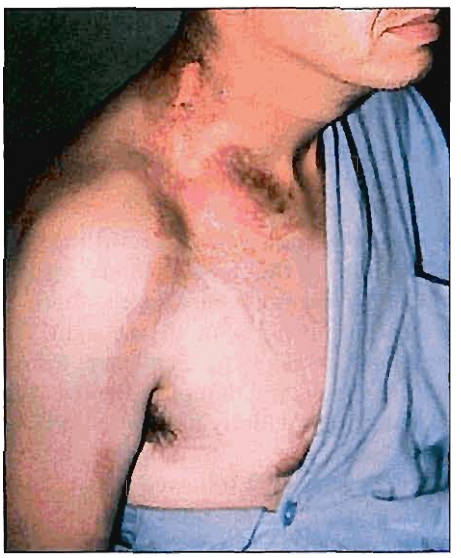

Fig. 3-4 Lightening strike. (Courtesy of J Fitzpatrick, MD)

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Phillips TJ, et al: Burn scar carcinoma. Dermatol Surg 1998; 24:561.
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Miliaria

Miliaria, the retention of sweat as a result of occlusion of eccrine sweat ducts, produces an eruption that is common in hot, humid climates, such as the tropics and during the hot summer months in temperate climates. Mowad et al showed that *Staphylococcus epidermidis*, which produces an extracellular polysaccharide substance, could induce miliaria in an experimental setting. They hypothesized that it is this polysaccharide substance that obstructs the delivery of sweat to the skin surface. The occlusion prevents normal secretion from the sweat glands, and eventually the backed-up pressure causes rupture of the sweat gland or duct at different levels. The escape of sweat into the adjacent tissue produces miliaria. Depending on the level of the injury to the sweat gland or duct, several different forms are recognized.

Miliaria Crystalline (Sudamina) Miliaria crystalline (Fig. 3-5) is characterized by small, clear, and very superficial vesicles with no inflammatory reaction. It appears in bedridden patients in whom fever produces increased perspiration or in situations in which clothing prevents dissipation of heat and moisture, as in bundled children. The lesions are asymptomatic and their duration is short lived because they tend to rupture at the slightest trauma. The lesions are self-limited; no treatment is required.

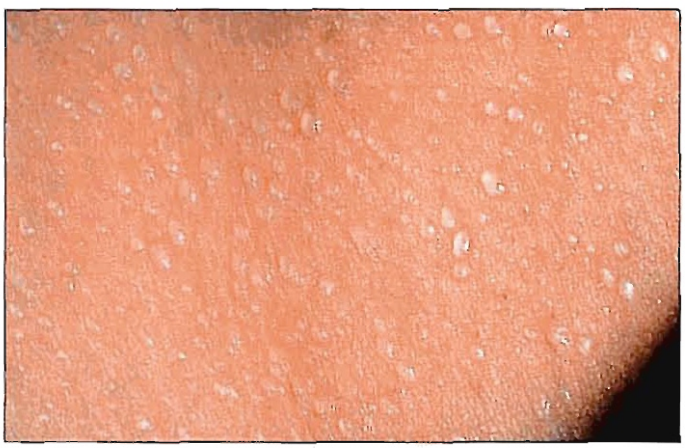

Fig. 3-5 Miliaria crytalline.

Miliaria Rubra (Prickly Heat) The lesions of miliaria rubra (Fig. 3-6) appear as discrete, extremely pruritic, erythematous papulovesicles accompanied by a sensation of prickling, burning, or tingling. They later may become confluent on a bed of erythema. The sites most frequently affected are the antecubital and popliteal fossae, trunk, inframammary areas (especially under pendulous breasts), abdomen (especially at the waistline), and inguinal regions; these sites frequently become macerated because evaporation of moisture has been impeded. The site of injury and sweat escape is in the prickle cell layer, where spongiosis is produced.

Miliaria Pustulosa Miliaria pustulosa (Fig. 3-7) is preceded by another dermatitis that has produced injury, destruction, or blocking of the sweat duct. The pustules are

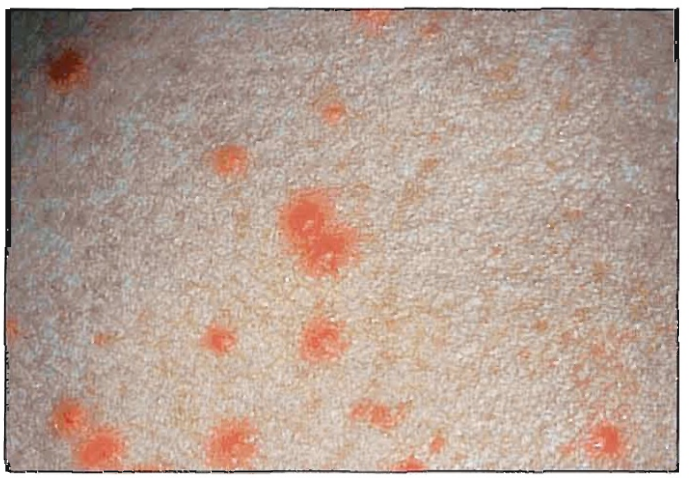

Fig. 3-6 Milliaria rubra.

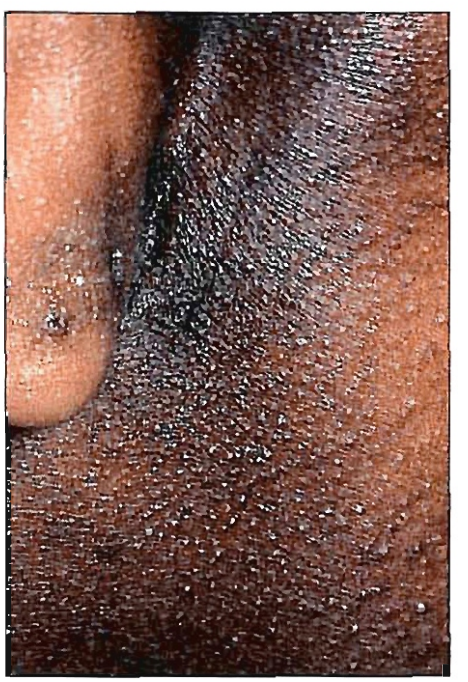

Fig. 3-7 Miliaria pustulosa. (Courtesy of C Samlaska, MD)

distinct, superficial, and independent of the hair follicle. The pruritic pustules occur most frequently on the intertriginous areas, flexure surfaces of the extremities, scrotum, and back of bedridden patients. Contact dermatitis, lichen simplex chronicus, and intertrigo are some of the associated diseases, although pustular miliaria may occur several weeks after these diseases have subsided. Recurrent episodes may be a sign of type I pseudohypoaldosteronism, as salt-losing crises may precipitate miliaria pustulosa or rubra, with resolution after stabilization.

Miliaria Profunda Non-pruritic, flesh-colored, deep-seated, whitish papules characterize this form of miliaria. It is asymptomatic, usually lasts only 1 h after overheating has ended, and is concentrated on the trunk and extremities. Except for the face, axillae, hands, and feet, where there may be compensatory hyperhidrosis, all the sweat glands are nonfunctional. The occlusion is in the upper dermis. This form is observed only in the tropics and usually follows a severe bout of miliaria rubra.

Postmiliarial Hypohidrosis Postmiliarial hypohidrosis results from occlusion of sweat ducts and pores, and may be severe enough to impair an individual's ability to perform sustained work in a hot environment. Affected persons may show decreasing efficiency, irritability, anorexia, drowsiness, vertigo, and headache; they may wander in a daze.

It has been shown that hypohidrosis invariably follows miliaria, and that the duration and severity of the hypohidrosis are related to the severity of the miliaria. Further, sweating may be depressed to half the normal amount for as long as 3 weeks following miliaria.

Tropical Anhidrotic Asthenia This is a rare form of miliaria with long-lasting poral occlusion, which produces anhidrosis and heat retention.

Occlusion Miliaria Miliaria may be produced with accompanying anhidrosis and increased heat-stress susceptibility after the application of extensive polyethylene film occlusion for 48 h or longer.

Treatment

The most effective treatment for miliaria is to place the patient in a cool environment. Even a single night in an air-conditioned room helps to alleviate the discomfort. Next best is the use of circulating air fans to cool the skin. Anhydrous lanolin resolves the occlusion of pores and may help to restore normal sweat secretions. Hydrophilic ointment also helps to dissolve keratinous plugs and facilitates the normal flow of sweat. Soothing, cooling baths containing Aveeno colloidal oatmeal or cornstarch are beneficial if used in moderation. Mild cases may respond to dusting powders, such as cornstarch or baby talcum powder.

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Erythema Ab Igne

Erythema ab igne, or *"toasted skin" syndrome*, is a persistent erythema—or the coarsely reticulated residual pigmentation resulting from it—that is usually produced by long exposure to excessive heat without the production of a burn (Fig. 3-8). It begins as a mottling caused by local hemostasis and becomes a reticulated erythema, leaving pigmentation. Multiple colors are simultaneously present in an active patch, varying from pale pink to old rose or dark purplish-brown. After the cause is removed, the affection tends to disappear gradually, but sometimes the pigmentation is permanent.

Histologically, an increased amount of elastic tissue in the dermis is noted. The changes in erythema ab igne are similar to those of actinic elastosis, and it has been suggested these changes be called *thermal elastosis*.

Erythema ab igne is most common on the legs of women as a result of habitually warming them in front of open fireplaces or space heaters. Similar changes may be produced with an electric heating pad, laptop computer, or a car heater. The condition occurs also in cooks, silversmiths, and others exposed over long periods to direct moderate heat. Epithelial atypia, which may lead to Bowen's disease and squamous cell carcinoma, has rarely been reported to occur overlying erythema ab igne. Treatment with 5-fluorouracil (5-FU) cream may be effective in reversing this epidermal alteration.

The use of emollients containing α-hydroxy acids or a cream containing fluocinolone acetonide 0.01%, hydroquinone 4%, and tretinoin 0.05% may help reduce the unsightly pigmentation.

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Meffert JJ, et al: Furniture-induced erythema ab igne. J Am Acad Dermatol 1996;34:516.

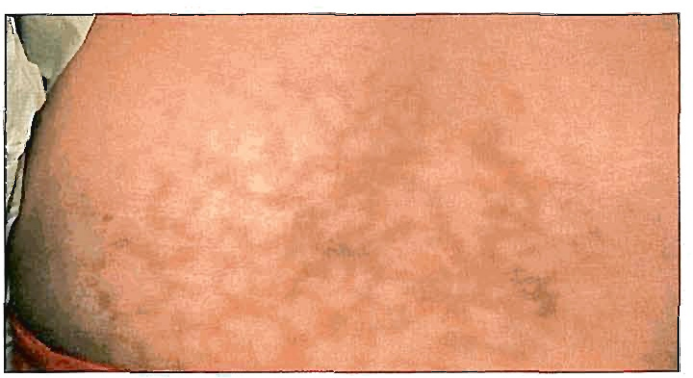

Fig. 3-8 Erythema ab igne.

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COLD INJURIES

Exposure to cold damages the skin by at least three mechanisms. Reduced temperature simply damages the tissue as in frostbite and cold immersion foot. Vasospasm of vessels perfusing the skin induced by cold temperatures prevents adequate perfusion of the tissue and causes vascular injury and consequent tissue injury (pernio, acrocyanosis, and frostbite). In unusual circumstances, adipose tissue is predisposed to damage by cold temperatures due to fat composition or location (cold panniculitis, see Chapter 23). Outdoor workers and recreationalists, the armed forces, and the homeless are particularly likely to suffer cold injuries.

Acrocyanosis

Acrocyanosis is a persistent blue discoloration of the entire hand or foot worsened by cold exposure. The hands and feet may be hyperhidrotic (Fig. 3-9). It occurs chiefly in young women. Cyanosis increases as the temperature decreases and changes to erythema with elevation of the dependent part. The cause is unknown. Smoking should be avoided. Acrocyanosis is distinguished from Raynaud syndrome by its persistent nature (as opposed to the episodic nature of Raynaud), and lack of tissue damage (ulceration, distal finger tip resorption).

Acrocyanosis with swelling of the nose, ears, and dorsal hands may occur after inhalation of butyl nitrite. Interferon-α 2a may induce it. Patients with anorexia nervosa frequently manifest acrocyanosis and it may improve with weight gain.

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Chilblains (Pernio)

Chilblains is a localized erythema and swelling caused by exposure to cold. Blistering and ulcerations may develop in severe cases. In people predisposed by poor peripheral circulation, even moderate exposure to cold may produce chilblains. Cryoglobulins, cryofibrinogens or cold agglutinins may be present and pathogenic. Chilblain-like lesions may occur in discoid and systemic lupus erythematosus (chilblain lupus). Acute chilblains is the mildest form of cold injury. This occurs chiefly on the hands, feet, ears, and face, especially in children; onset is enhanced by dampness (Fig. 3-10). A variant occurs on the lateral thighs in women equestrians who ride on cold damp days (equestrian perniosis). Wading across cold streams may produce similar lesions. *Erythrocyanosis crurum* has been used to describe similar cases. Lesions of cold injury of the lateral thighs can be nodular.

Patients with chilblains are often unaware of the cold injury when it is occurring, but later burning, itching, and redness call it to their attention. The affected areas are bluish-red, the color partially or totally disappearing on pressure, and are decidedly cool to the touch. Sometimes the extremities are clammy because of excessive sweating. As long as the damp/cold exposure continues, new lesions will continue to appear and lesions may resolve slowly. An investigation of an underlying cause should be undertaken in cases which are recurrent, chronic, extending into warm seasons or poorly responsive to treatment.

Perniosis histologically demonstrates a lymphocytic vasculitis. There is dermal edema, and a superficial and deep perivascular, tightly cuffed, lymphocytic infiltrate. The infiltrate involves the vessel walls, but fibrin may or may not be present in the vessel walls. The presence of inflammation affecting sweat glands suggests idiopathic chilblains over chilblains lupus.

Treatment

The affected parts should be protected against further exposure to cold or dampness. If the feet are affected, woolen socks should be worn at all times during the cold months. Because the patient is often not conscious of the cold exposure that triggers the lesions, appropriate dress must be stressed, even if the patient says he/she does not sense

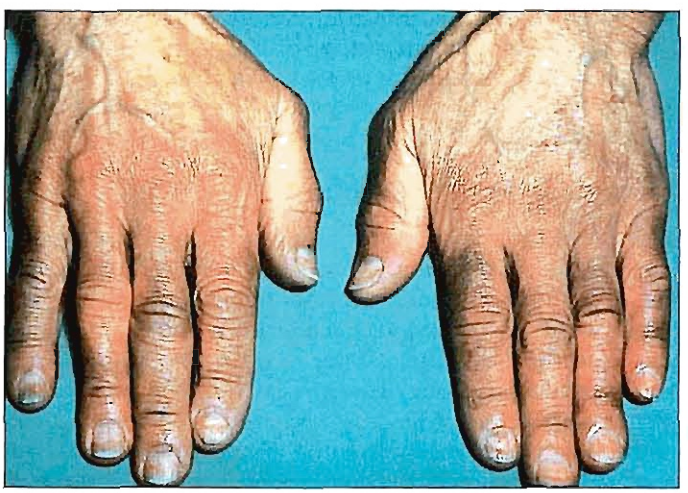

Fig. 3-9 Acrocyanosis.

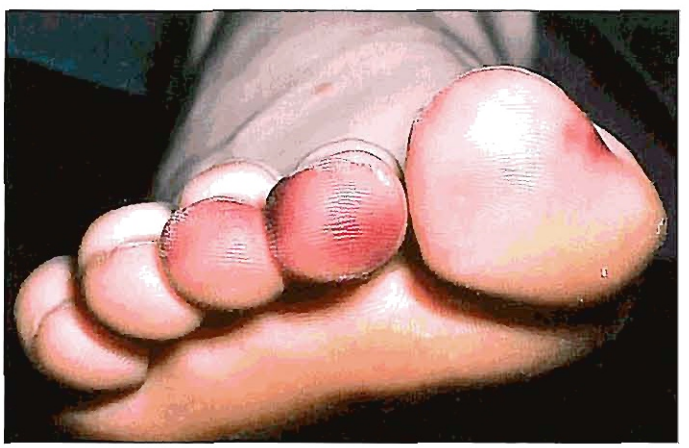

Fig 3-10 Pernio.

being cold. Since central cooling triggers peripheral vasoconstriction, keeping the whole body (not just the affected extremity) warm is critical. Heating pads may be used judiciously to warm the parts. Smoking is strongly discouraged.

Nifedipine, 20 mg three times a day, has been shown to be effective. Vasodilators such as nicotinamide, 500 mg three times a day, or dipyridamole, 25 mg three times a day, are used to improve circulation. Pentoxifylline may be effective. Spontaneous resolution occurs without treatment in 1 to 3 weeks. Systemic corticoid therapy is useful in chilblain lupus erythematosus.

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Price RD, Murdoch DR: Perniosis (chilblains) of the thigh: report of five cases, including four following river crossings. High Alt Med Biol. 2001;2:535.

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Frostbite

When soft tissue is frozen and locally deprived of blood supply, the damage is called *frostbite*. The ears, nose, cheeks, fingers, and toes are most often affected. The frozen part painlessly becomes pale and waxy. Various degrees of tissue destruction similar to those caused by burns are encountered. These are erythema and edema, vesicles and bullae, superficial gangrene, deep gangrene, and injury to muscles, tendons, periosteum, and nerves (Fig. 3-11). The degree of injury is directly related to the temperature and duration of freezing. African Americans are at increased risk of frostbite.

Treatment

Early treatment of frostbite before swelling develops should consist of covering the part with clothing or with a warm hand or other body surface to maintain a slightly warm temperature so that adequate blood circulation can be maintained. Rapid rewarming in a water bath between 37 and 43° C (100–110° F) is the treatment of choice for all forms of frostbite. Rewarming should be delayed until the patient has been removed to an area where there is no risk of refreezing. Slow thawing results in more extensive tissue damage. Analgesics, unless contraindicated, should be

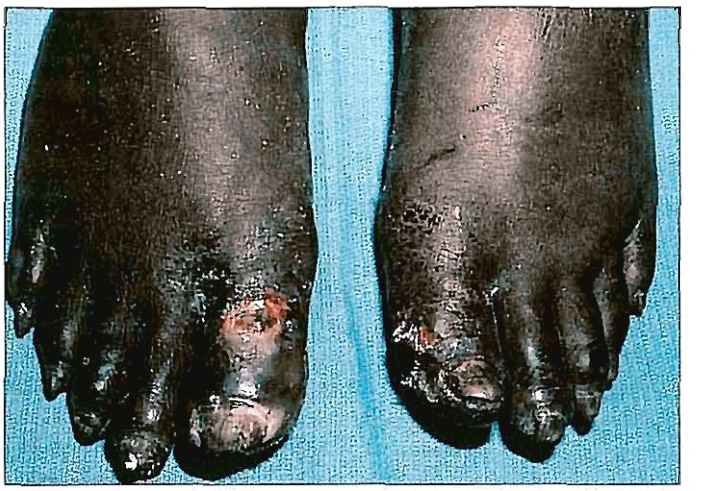

Fig. 3-11 Frostbite in a homeless person.

administered because of the considerable pain experienced with rapid thawing. When the skin flushes and is pliable, thawing is complete. Supportive measures such as bed rest, a high-protein/high-calorie diet, wound care, and avoidance of trauma are imperative. Any rubbing of the affected part should be avoided, but gentle massage of proximal portions of the extremity that are not numb may be helpful.

After swelling and hyperemia have developed, the patient should be kept in bed with the affected limb slightly flexed, elevated, and at rest. Exposing the affected limb to air at room temperature relieves pain and helps prevent tissue damage. Protection by a heat cradle may be desirable.

The use of anticoagulants to prevent thrombosis and gangrene has been advocated. Pentoxyphilline, ibuprofen, and aspirin may be useful adjuncts. Antibiotics should be given as a prophylactic measure against infection and tetanus immunization should be updated. Recovery may take many months. Injuries that affect the proximal phalanx or the carpal or tarsal area, especially when accompanied by a lack of radiotracer uptake on bone scan, have a high likelihood of requiring amputation. Whereas prior cold injury is a major risk factor for recurrent disease, sympathectomy may be preventative against repeated episodes.

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Murphy JV, et al: Frostbite: pathogenesis and treatment. J Trauma 2000;48:171.

Immersion Foot Syndromes

Trench Foot Trench foot results from prolonged exposure to cold, wet conditions without immersion or actual freezing. The term is derived from trench warfare in World War I, when soldiers stood, sometimes for hours, in trenches with a few inches of cold water in them. The lack of circulation produces edema, paresthesias, and damage to the blood vessels. Gangrene may occur in severe cases. Treatment consists of removal from the causal environment, bed rest, and restoration of the circulation. Other measures, such as those used in the treatment of frostbite, should be employed.

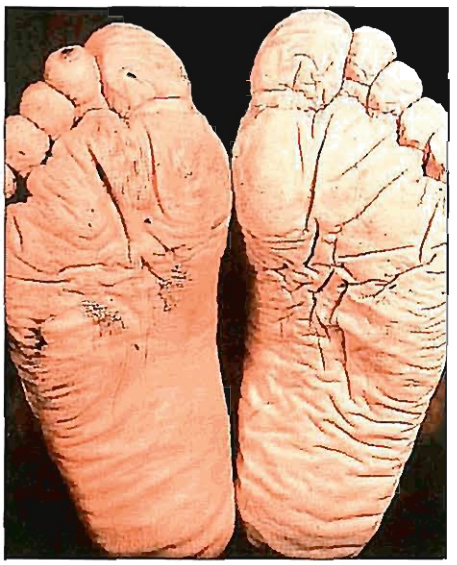

Fig. 3-12 Warm water immersion foot. (Courtesy of James WD (ed) Textbook of Military Medicine, Office of the Surgeon General, United States Army, 1994.)

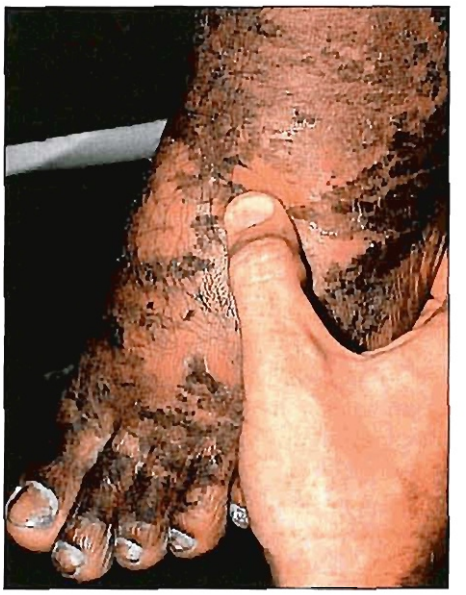

Fig. 3-13 Tropical immersion foot. (Courtesy of James WD (ed) Textbook of Military Medicine, Office of the Surgeon General, United States Army, 1994.)

Warm Water Immersion Foot Exposure of the feet to warm, wet conditions for 48 h or more may produce a syndrome characterized by maceration, blanching, and wrinkling of the soles and sides of the feet (Fig. 3-12). Itching and burning with swelling may persist a few days after removal of the cause, but disability is temporary. It was commonly seen in military service members in Vietnam but has also been seen in persons wearing insulated boots.

This condition should be differentiated from tropical immersion foot, seen after continuous immersion of the feet in water or mud of temperatures above 22° C (71.6° F) for 2 to 10 days. This was known as "paddy foot" in Vietnam. This involves erythema, edema, and pain of the dorsal feet, as well as fever and adenopathy (Fig. 3-13). Resolution occurs 3 to 7 days after the feet have been dried.

Warm water immersion foot can be prevented by allowing the feet to dry for a few hours in every 24 or by greasing the soles with a silicone grease once a day. Recovery is usually rapid if the feet are thoroughly dry for a few hours.

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ACTINIC INJURY

Sunburn and Solar Erythema

The solar spectrum has been divided into different regions by wavelength. The parts of the solar spectrum important in photomedicine include UV radiation (below 400 nm), visible light (400–760 nm), and infrared radiation (beyond 760 nm). Visible light has limited biologic activity, except for stimulating the retina. Infrared radiation is experienced as radiant heat. Below 400 nm is the UV spectrum, divided into three bands: UVA, 320 to 400 nm; UVB, 280 to 320 nm; and UVC, 200 to 280 nm. UVA is divided into two subcategories: UVA I (340–400 nm) and UVA II (320–340 nm). Virtually no UVC reaches the earth's surface, because it is absorbed by the ozone layer above the earth.

The minimal amount of a particular wavelength of light capable of inducing erythema on an individual's skin is called the *minimal erythema dose* (MED). Since MED varies with skin type and methodology (see below), the *standard erythema dose* (SED) is frequently used to express the quantity of effective erythemal UV exposure. One SED equals about 100 J/m^2. Although the amount of UVA radiation is 100 times greater than UVB radiation during midday hours, since UVB is up to 1000 times more erythemogenic than UVA, essentially all solar erythema is caused by UVB. The most biologically effective wavelength of radiation from the sun for sunburn is 308 nm. (Biologic effect is a combination of ambient amount of radiation and its inherent biologic activity.) Although UVA does not play a significant role in solar erythema and sunburn, in the case of drug-induced photosensitivity, UVA is of major importance.

The amount of UV exposure increases at higher altitudes, is substantially greater in temperate climates in the summer months, and is greater in tropical regions. UVA may be reflected somewhat more than UVB from sand, snow, ice, and water. Cloud cover, although blocking substantial amounts of visible light, is a poor UV absorber. During the middle 4 to 6 h of the day, the intensity of UVB is two to four times greater than in the early morning and late afternoon.

Clinical Signs and Symptoms

Sunburn is the normal cutaneous reaction to sunlight in excess of an erythema dose. This is equivalent to 4 SED on unacclimated white skin. UVB erythema starts at around 6 h and peaks at 12 to 24 h after exposure, but the onset is sooner and the severity greater with increased exposure. The erythema is followed by tenderness, and in severe cases, blistering, which may become confluent. Discomfort may be severe; edema commonly occurs in the extremities and face; chills, fever, nausea, tachycardia, and hypotension may be present. In severe cases such symptoms may last for as long as a week. Desquamation is common about a week after sunburn, even in areas that have not blistered.

After UV exposure, skin pigment undergoes two changes: immediate pigment darkening (IPD, Meirowsky phenomenon) and delayed melanogenesis. IPD is maximal within

hours after sun exposure and results from metabolic changes and redistribution of the melanin already in the skin. It occurs after exposure to long-wave UVB, UVA, and visible light. With large doses of UVA, the initial darkening is prolonged and may blend into the delayed melanogenesis. IPD is not photoprotective. Delayed tanning is induced by the same wavelengths of UVB that induce erythema, begins 2 to 3 days after exposure, and lasts 10 to 14 days. Delayed melanogenesis by UVB is mediated through the production of DNA damage and the formation of cyclobutane pyrimidine dimers (CPD). Therefore, although UVB-induced delayed tanning does provide some protection from further solar injury, it is at the expense of damage to the epidermis and dermis. Hence, tanning is not recommended for sun protection. Commercial sunbed-induced tanning, while increasing skin pigment, does *not* increase UVB MED, and is therefore not protective for UVB damage. An individual's inherent baseline pigmentation, ability to tan, and the ease with which they burn are described as his/her "skin type." Skin type (Table 3-1) is used to determine starting doses of phototherapy and sunscreen recommendations, and reflects the risk of development of skin cancer and photoaging.

Exposure to UVB and UVA causes an increase in the thickness of the epidermis, especially the stratum corneum. This increased epidermal thickness leads to increased tolerance to further solar radiation. Patients with vitiligo may increase their UV exposure without burning by this mechanism.

Treatment

Once redness and other symptoms are present, treatment of sunburn has limited efficacy. The damage is done and the inflammatory cascades triggered. Prostaglandins, especially of the E series, are important mediators. Aspirin (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDs), including indomethacin, have been studied, as well as topical and systemic steroids. Medium potency (class II) topical steroids applied 6 h after the exposure (when erythema first appears) give about a 10% to 20% reduction in signs and symptoms. Since oral NSAIDs and systemic steroids have been tested primarily prior to or immediately after sun exposure, there is insufficient evidence to recommend their routine use, except immediately after solar over-exposure. The addition of the leukotriene inhibitor, mizolastine (blocks 5-lipoxygenase), to ASA treatment can reduce solar erythema and, potentially, sunburn. Topical green tea polyphenols may also prevent the adverse effects of solar radiation. Until these new approaches have been more extensively tested, treatment of sunburn should be supportive, with pain management (using acetaminophen, ASA, or NSAIDs), plus soothing topical emollients or corticosteroid lotions. In general, a sunburn victim experiences at least 1 or 2 days of discomfort and even pain before much relief occurs. It is not uncommon for sunburn victims to miss work.

Table 3-1 Skin types (phototypes)

Skin type	Baseline skin color	Sunburn and tanning history
I	White	Always burns, never tans
II	White	Always burns, tans minimally
III	White	Burns moderately, tans gradually
IV	Olive	Minimal burning, tans well
V	Brown	Rarely burns, tans darkly
VI	Dark brown	Never burns, tans darkly black

Prophylaxis

Sunburn is best prevented. Use of the UV index, published daily by the National Weather Service for many US cities and found in newspapers, facilitates taking adequate precautions to prevent solar injury. Numerous educational programs have been developed to make the public aware of the hazards of sun exposure. Despite this, sunburn and excessive sun exposure continue to occur in the US and Western Europe, especially in white persons under the age of 30, among whom more than 50% report at least one sunburn per year. Sun protection programs have four messages: 1) avoid midday sun; 2) seek shade; 3) wear protective clothing; and 4) apply a sunscreen. The period of highest UVB intensity, between 9 AM and 3 to 4 PM, accounts for the vast majority of potentially hazardous UV exposure. This is the time when the angle of the sun is less than 45° or when a person's shadow is shorter than his/her height. In temperate latitudes it is almost impossible to burn if these hours of sun exposure are avoided. Trees and artificial shade provide substantial protection from UVB. Foliage in trees provides the equivalent of sun protection factor (SPF) 4 to 50, depending on the density of the greenery. Clothing can be rated by its ability to block UVB radiation. The scale of measure is the UV protection factor (UPF) (analogous to SPF in sunscreens). Although it is an in vitro measurement, as with SPF, it correlates well with the actual protection the product provides in vivo. In general, denser weaves, older, washed clothing, and loose-fitting clothing screen UVB more effectively. Wetting a fabric may substantially reduce its UPF. Laundering a fabric in a Tinosorb-containing material (SunGuard) will add substantially to the UPF of the fabric. Hats with at least a 3-inch brim all around are recommended.

A sunscreen's efficacy in blocking the UVB (sunburn inducing) radiation is expressed as an SPF. This is the ratio of the number of MEDs of radiation required to induce erythema through a thin film of sunscreen (2 mg/cm^2), compared with unprotected skin. Most persons apply sunscreens in too thin a film, so the actual "applied SPF" is about half that on the label. Sunscreening agents include UV-absorbing chemicals (chemical sunscreens) and UV-scattering or -blocking agents (physical sunscreens). Available sunscreens, especially those of high SPFs (>30) usually contain both chemical sunscreens (such as *p*-aminobenzoic acid [PABA], PABA esters, cinnamates, salicylates, anthranilates, benzophenones, benzylidene camphors [Mexoryl], dibenzoylmethanes [Parsol 1789], and Tinosorb S/M) and physical agents (zinc oxide or titanium dioxide). They are available in numerous formulations, including sprays, gels, emollient creams, and wax sticks. Sunscreens may be water resistant (maintaining their SPF after 40 min of water immersion) or waterproof (maintaining their SPF after 80 min of water immersion).

For skin types I to III (see Table 3-1), daily application of a sunscreen with an SPF of 15 in a facial moisturizer, foundation, or aftershave is recommended. For outdoor exposure, a sunscreen of SPF 15 or higher is recommended for regular

use. In persons with severe photosensitivity and at times of high sun exposure, high-intensity sunscreens of SPF 30+ with inorganic blocking agents may be required. Application of the sunscreen at least 20 min before and 30 min after sun exposure has begun is recommended. This dual application approach will reduce the amount of skin exposure by two- to three-fold over a single application. Sunscreen should be reapplied after swimming or vigorous activity or toweling. Sunscreen failure occurs mostly in men, due to failure to apply it to all the sun-exposed skin, or failure to reapply sunscreen after swimming. Sunscreens may be applied to babies (under 6 months) on limited areas. Vitamin D supplementation may be recommended with the most stringent sun-protection practices.

Photoaging and cutaneous immunosuppression are mediated by UVA as well as UVB. For this reason, sunscreens with improved UVA coverage have been developed (Parsol 1789, Mexoryl, Tinosorb). The UVA protection does not exactly parallel the SPF on the label. If UVA protection is sought, a combination sunscreen with inorganic agents and UVA organic sunscreens (identified by name in the list of ingredients) is recommended.

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Ephelis (Freckle) and Lentigo

Freckles are small (< 0.5 cm) brown macules that occur in profusion on the sun-exposed skin of the face, neck, shoulders, and backs of the hands. They become prominent during the summer when exposed to sunlight and subside, sometimes completely, during the winter when there is no exposure. Blonds and red-heads with blue eyes and of Celtic origin (skin types I or II) are especially susceptible. Ephelides may be genetically determined and may recur in successive generations in similar locations and patterns. They usually appear around age 5.

Ephelis must be differentiated from *lentigo simplex*. The lentigo is a benign discrete hyperpigmented macule appearing at any age and on any part of the body, including the mucosa. The intensity of the color is not dependent on sun exposure. The solar lentigo (frequently misnamed "liver spot") appears at a later age, mostly in persons with long-term sun exposure. The backs of the hands and face (especially the forehead) are favored sites.

Histologically, the ephelis shows increased production of melanin pigment by a normal number of melanocytes. Otherwise, the epidermis is normal, whereas the lentigo has elongated rete ridges that appear to be club shaped.

Freckles and lentigenes are best prevented by appropriate sun protection. Cryotherapy, topical tretinoin, and adapalene are effective in the treatment of solar lentigenes.

Photoaging (Dermatoheliosis)

The characteristic changes induced by chronic sun exposure are called *photoaging* or *dermatoheliosis*. An individual's risk for developing these changes correlates with his/her skin type (see Table 3-1). Risk for melanoma and nonmelanoma skin cancer is also related to skin type. The most susceptible to the deleterious effects of sunlight are those of skin type I—blue-eyed, fair-complexioned persons who do not tan. They are frequently of Irish or other Celtic or Anglo-Saxon descent. Individuals who have developed photoaging have the genetic susceptibility and have had sufficient actinic damage to develop skin cancer, and therefore require more frequent and careful cutaneous examinations.

Chronic sun exposure and chronologic aging may lead to skin changes by similar mechanisms, and hence may be additive. In addition, cigarette smoking is especially important in the development of skin wrinkles, again by identical biochemical mechanisms, hence the inability of observers to distinguish accurately solar- versus smoking-induced skin aging. The areas primarily affected by photoaging are those regularly exposed to the sun: the V area of the neck and chest, back and sides of the neck, face, backs

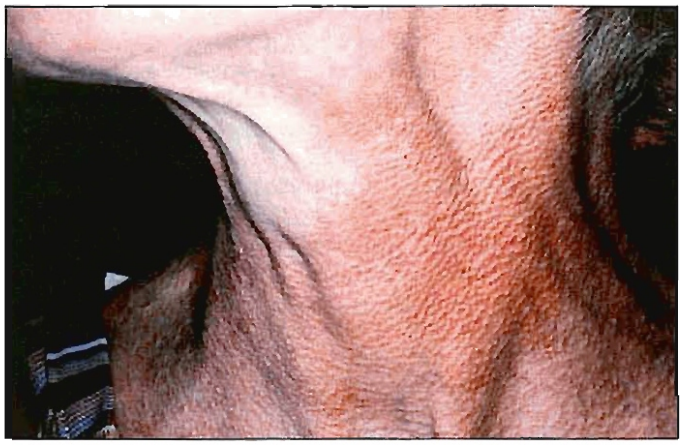

Fig. 3-14 Poikiloderma of Civatte.

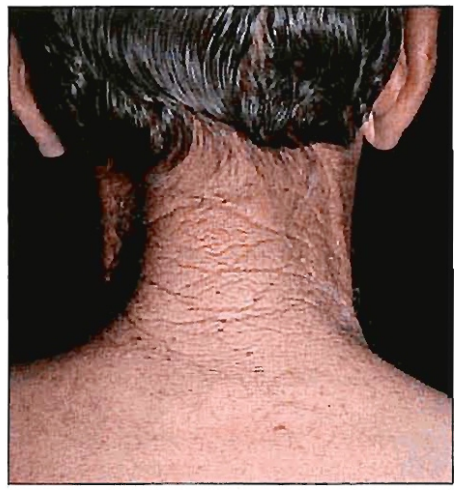

Fig. 3-15 Cutis rhomboidalis nuchae.

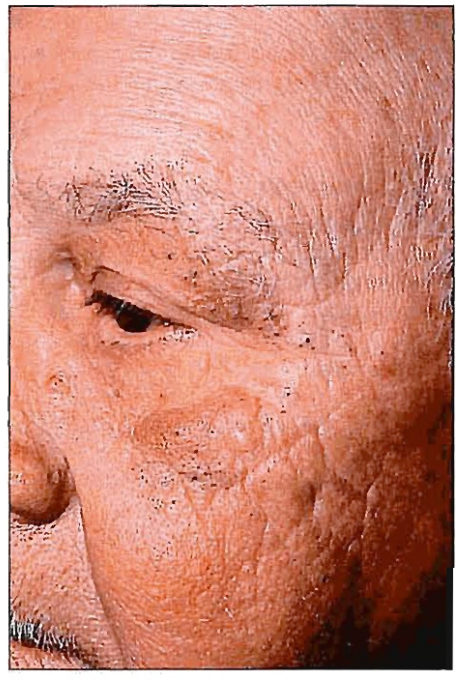

Fig. 3-16 Favre-Racouchot syndrome (nodular elasstoidosis with cysts and comedones).

of the hands and extensor arms, and in women the skin between the knees and ankles. The skin becomes atrophic, scaly, wrinkled, inelastic, or leathery with a yellow hue (Milian citrine skin). In some persons of Celtic ancestry, dermatoheliosis produces profound epidermal atrophy without wrinkling, resulting in an almost translucent appearance of the skin through which hyperplastic sebaceous glands and prominent telangiectasias are seen. These persons appear to be at high risk for nonmelanoma skin cancer. Pigmentation is uneven, with a mixture of poorly demarcated hyperpigmented and white atrophic macules observed. The photodamaged skin appears generally darker because of these irregularities of pigmentation, plus dermal hemosiderosis from actinic purpura (see below). Solar lentigines occur on the face and dorsa of the hands.

Many of the textural and tinctorial changes in sun-damaged skin are caused by alterations in the upper dermal elastic tissue and collagen. This process is called *solar (actinic) elastosis*, which imparts a yellow color to the skin. Many clinical variants of solar elastosis have been described, and an affected individual may simultaneously have many of these changes. Small yellowish papules and plaques may develop along the sides of the neck. They have been variably named *striated beaded lines* (the result of sebaceous hyperplasia) or *fibroelastolytic papulosis* of the neck (pseudoxanthoma elasticum-like papillary dermal elastolysis), which is caused by solar elastosis. At times, usually on the face or chest, this elastosis may form a macroscopic, translucent papule with a pearly color that may closely resemble a basal cell carcinoma (Dubreuilh elastoma, actinic elastotic plaque). Similar plaques may occur on the helix or antihelix of the ear (elastotic nodules of the ear). *Poikiloderma of Civatte* refers to reticulate hyperpigmentation with telangiectasia, and slight atrophy of the sides of the neck, lower anterior neck, and V of the chest. The submental area, shaded by the chin, is spared (Fig. 3-14). Poikiloderma of Civatte frequently presents in fair-skinned men and women in their mid-to-late 30s or early 40s. *Cutis rhomboidalis nuchae* (sailor's or farmer's neck) is characteristic of long-term, chronic sun exposure (Fig. 3-15). The skin on the back of the neck becomes thickened, tough, and leathery, and the normal skin markings are exaggerated. Nodular elastoidosis with cysts and comedones occurs on the inferior periorbital and malar skin (*Favre-Racouchot syndrome*) (Fig. 3-16) on the forearms (actinic comedonal plaque) or helix of the ear. These lesions appear as thickened yellow plaques studded with comedones and keratinous cysts.

Telangiectasias over the cheeks, ears, and sides of the neck may develop. Because of the damage to the connective tissue of the dermis, skin fragility is prominent, and patients note skin tearing from trivial injuries. Most commonly, patients complain that even minimal trauma to their extensor arms leads to an ecchymosis, a phenomenon called *actinic purpura*. As the ecchymoses resolve, dusky brown macules remain for months, increasing the mottled appearance of the skin. White *stellate pseudoscars* on the forearms are a frequent complication of this enhanced skin fragility (Fig. 3-17). In some patients, soft, flesh-colored to yellow papules and nodules coalesce on the forearms to form a cordlike band extending from the dorsal to the flexural surfaces (*solar elastotic bands*).

UVB and UVA radiation induce reactive oxygen species (ROS) and hydrogen peroxide. Acting through AP-1, transcription of various matrix-degrading enzymes is

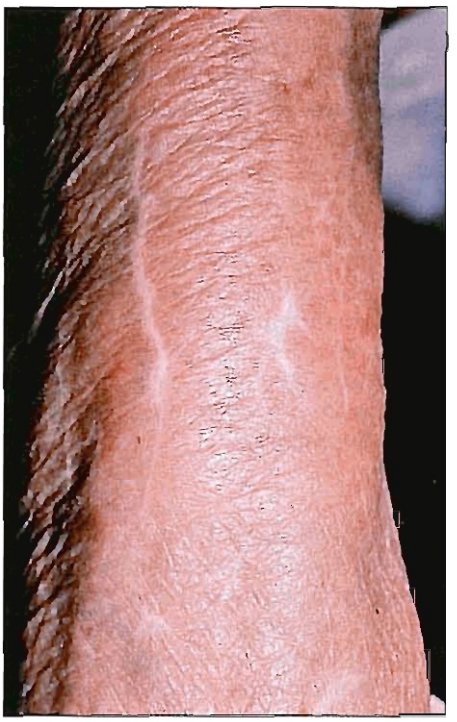

Fig 3-17 Stellate pseudoscars.

upregulated, specifically MMP-1 (collagenase), MMP-3 (stromelysin 1), and MMP-9 (gelatinase). MMP-1 cleaves a critical site on collagens types I and III, creating collagen fragments which are further degraded by MMP-3 and -9. Collagen fragments plus downregulation of procollagen promoters through AP-1 both lead to a marked decrease in new collagen formation in UV-exposed skin. In darkly pigmented persons, UV exposure does not activate MMP-1, in part explaining the protective effect of skin pigmentation against photoaging. In chronologically aged skin, due perhaps to ROS generation, MMP-1 levels are also increased through AP-1 and collagen fragments are increased four-fold. Thus, chronologic aging and photoaging may be mediated through an identical biochemical mechanism.

Histologically, chronically sun-exposed skin demonstrates homogenization and a faint blue color of the connective tissue of the upper reticular dermis, so-called *solar elastosis*. This "elastotic" material is derived largely from elastic fibers, stains with histochemical stains for elastic fibers, and demonstrates marked increased deposition of fibulin-2 and its breakdown products. Types I and III collagen are decreased. Characteristically, there is a zone of normal connective tissue immediately below the epidermis and above the elastotic material.

Colloid Milium There are two forms of colloid milium: adult and juvenile. Cases of "nodular" colloid degeneration or "paracolloid" may represent severe presentations of adult colloid milium or cases of nodular amyloidosis, but these cases are few in number and reports of them occurred prior to technologies that could have better elucidated their etiology. Pigmented forms of colloid milium associated with hydroquinone use represent ochronosis-like pigmentation. In both the adult and juvenile forms of colloid milium, the primary skin lesion is a translucent, flesh-colored, or slightly yellow 1- to 5-mm papule. Minimal trauma may lead to purpura due to vascular fragility. Histologically the colloid consists of intradermal, amorphous fissured eosinophilic material. In adult colloid milium lesions appear in the sun-exposed areas of the hands, face, neck, forearms, and ears in middle-aged and older adults, usually men. Lesions often coalesce into plaques, and may rarely be verrucous. Petrochemical exposures have been associated with adult colloid milium. Lesions have been induced by sunbed exposure, and can be unilateral, usually in commercial drivers. Adult colloid milium may be considered a papular variant of solar elastosis. The colloid material is derived from elastic fibers, and solar elastosis is found adjacent to the areas of colloid degeneration histologically. Juvenile colloid milium is much rarer. It develops before puberty and there may be a family history. The lesions are similar to the adult form, but appear initially on the face, later extending to the neck and hands. Sun exposure also appears to be important in inducing lesions of juvenile colloid milium. Juvenile colloid milium, ligneous conjunctivitis, and ligneous periodontitis may appear in the same patient and are probably of similar pathogenesis. Histologically, juvenile colloid milium can be distinguished from adult colloid milium by the finding of keratinocyte apoptosis in the overlying epidermis. The colloid material in juvenile colloid milium is derived from the apoptotic keratinocytes and stains for cytokeratin.

Prevention and Treatment

Since both UVB and UVA are capable of inducing the tissue-destructive biochemical pathways implicated in photoaging, sun protection against both portions of the UV spectrum is required to prevent photoaging. Because photoaging, like other forms of radiation damage, appears to be cumulative, reducing the total lifetime UV exposure is the goal. The guidelines outlined above for sunburn prophylaxis should be followed.

The regular use of emollients or moisturizing creams to the areas of sun damage will reduce scaling and may improve fragility by making the skin more pliable. α-Hydroxy acids may improve skin texture when used in lower, nonirritating concentrations. Topical tretinoin, adapalene, and tazarotene can improve the changes of photoaging. Changes are slow and irritation may occur. The surgical and laser treatments of photoaging are discussed in Chapter 37.

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PHOTOSENSITIVITY

Photosensitivity disorders include cutaneous reactions that are chemically induced (from an exogenous source), metabolic (inborn errors such as the porphyrias, resulting in the production of endogenous photosensitizers), idiopathic, and light-exacerbated disorders (genetic and acquired). Drug-induced photosensitivity and photoallergic contact dermatitis are discussed in Chapter 6.

Chemically-Induced Photosensitivity

A number of substances known as *photosensitizers* may induce an abnormal reaction in skin exposed to sunlight or its equivalent. These substances may be delivered to the skin externally (by contact) or internally by enteral or parenteral administration. The result may be a markedly increased sunburn response without prior allergic sensitization called *phototoxicity*. Phototoxicity may occur from both externally applied (phytophotodermatitis and berloque dermatitis) or internally administered chemicals (phototoxic drug reaction). In contrast, *photoallergic* reactions are true allergic sensitizations triggered by sunlight, produced by either internal administration (photoallergic drug reaction) or by external contact (photoallergic contact dermatitis). Chemicals capable of inducing phototoxic reactions may also produce photoallergic reactions.

In the case of external contactants, the distinction between phototoxicity and photoallergy is usually straightforward: the former occurs on initial exposure, has an onset of less than 48 h, occurs in the vast majority of persons exposed to the phototoxic substance and sunlight, and shows a histologic pattern similar to sunburn. By contrast, photoallergy occurs only in sensitized persons, may have a delayed onset (up to 14 days—a period of sensitization), and shows histologic features of contact dermatitis.

Action Spectrum

Chemicals known to cause photosensitivity (photosensitizers) are usually resonating compounds with a molecular weight of less than 500. Absorption of radiant energy (sunlight) by the photosensitizer produces an excited state, which in returning to a lower energy state gives off energy through fluorescence, phosphorescence, charge transfer, heat, or formation of free radicals. Each photosensitizing substance absorbs only specific wavelengths of light, called its *absorption spectrum*. The specific wavelengths of light that evoke a photosensitive reaction are called the *action spectrum*. The action spectrum is included in the absorption spectrum of the photosensitizing chemical. The action spectrum for photoallergy is mostly in the long ultraviolet (UVA) region and may extend into the visible light region (320–425 nm).

Photosensitivity reactions occur only when there is sufficient concentration of the photosensitizer in the skin, and the skin is exposed to a sufficient intensity and duration of light in the action spectrum of that photosensitizer. The intensity of the photosensitivity reaction is, in general, dose dependent and is worse with a greater dose of photosensitizer and greater light exposure.

Phototoxic Reactions

A phototoxic reaction is a nonimmunologic reaction that develops after exposure to a specific wavelength and intensity of light in the presence of a photosensitizing substance. It is a sunburn-type reaction, with erythema, tenderness, and even blistering occurring only on the sun-exposed parts. This type of reaction can be elicited in many persons who have no previous history of exposure or sensitivity to that particular substance, but individual susceptibility varies widely. In general, to elicit a phototoxic reaction, a considerably greater amount of the photosensitizing substance is necessary than to induce a photoallergic reaction. The erythema begins (like any sunburn) within 2 to 6 h but worsens for 48 to 96 h before beginning to subside. Exposure of the nailbed may lead to onycholysis, called *photo-onycholysis*. Phototoxic reactions, especially from topically applied photosensitizers, may cause marked hyperpigmentation, even without significant preceding erythema. The action spectrum for most phototoxic reactions is in the UVA range.

Phototoxic Tar Dermatitis Coal tar, creosote, crude coal tar, or pitch, in conjunction with sunlight exposure, may induce a sunburn reaction associated with a severe burning sensation (tar "smarts" or "flashes"). Since these volatile hydrocarbons may be airborne, the patient may give no history of touching tar products. The burning and erythema may continue for 1 to 3 days. While up to 70% of white persons exposed to such a combination develop this reaction, persons with type V and VI skin are protected by their constitutive skin pigmentation. Following the acute reaction, hyperpigmentation occurs, which may persist for years. Coal tar or its derivatives may be found in cosmetics, drugs, dyes, insecticides, and disinfectants.

Phytophotodermatitis (Berloque Dermatitis) Furocoumarins in many plants may cause a phototoxic reaction when they come in contact with moist skin that is then exposed to UVA light. This is called *phytophotodermatitis*. Several hours after exposure, a burning erythema occurs, followed by edema and the development of vesicles or bullae. An intense residual hyperpigmentation results that may persist for weeks or months. The intensity of the initial phototoxic reaction may be mild and may not be recalled by the patient despite significant hyperpigmentation. This has been referred to as Berloque dermatitis. The addition of oil of Bergamot containing 5-methoxypsoralen to commercial

products is restricted in Europe. However, "Florida Water" and "Kanagna Water," popular colognes in the Hispanic, African American, and Caribbean communities, contain this potent photosensitizer.

Most phototoxic plants are in the families *Umbelliferae*, *Rutaceae* (rue), *Compositae*, and *Moraceae*. Incriminated plants include agrimony, angelica, atrillal, bavachi, blin weed, buttercup, common rice, cowslip, dill, fennel, fig, garden and wild carrot, garden and wild parsnip, gas plant, goose foot, zabon, lime and Persian lime, lime bergamot, masterwort, mustard, parsley, St John's wort, and yarrow. In Hawaii the anise-scented mokihana berry (*Pelea anisata*) was known to natives for its phototoxic properties (the mokihana burn). Like the lime, it is a member of the rue family. Aromatherapy containing bergamot oils or home tanning solutions containing fig leaves can produce phytophotodermatitis. These may be widespread and severe enough to require burn unit management.

Occupational disability from exposure to the pink rot fungus (*Sclerotinia sclerotiorum*) present on celery roots occurred in celery farmers in upper Michigan and Florida. In addition, disease-resistant celery contains furanocoumarins and was the probable source of phytophotodermatitis in grocery workers. Celery ingestion has led to a severe phototoxic eruption.

Dermatitis bullosa striata pratensis (grass or meadow dermatitis) is a phytophotodermatitis caused by contact not with grass, but with yellow-flowered meadow parsnip or a wild, yellow-flowered herb of the rose family. The eruption consists of streaks and bizarre configurations with vesicles and bullae that heal with residual hyperpigmentation. The usual cause is sunbathing in fields containing the phototoxic plants. Similarly, tourists in the tropics will sometimes rinse their hair with lime juice outdoors and streaky hyperpigmentation of the arms and back will result where the lime juice runs down (Fig. 3-18).

Blistering phytophotodermatitis must be differentiated from *rhus dermatitis*. The vesicles and bullae of rhus are not necessarily limited to the sun-exposed areas, and itching is the most prominent symptom. Lesions continue to occur in rhus dermatitis for a week or more. In phytophotodermatitis the reaction is limited to sun-exposed sites, a burning pain appears within 48 h, and marked hyperpigmentation results. The asymmetry, atypical shapes, and streaking of the lesions is most helpful in suspecting the diagnosis.

Treatment of a severe, acute reaction is similar to the management of a sunburn, with cool compresses, mild analgesics if required, and topical emollients. The hyperpigmentation is best managed by "tincture of time." Use of topical steroids and strict sun avoidance immediately following the injury may protect against the hyperpigmentation.

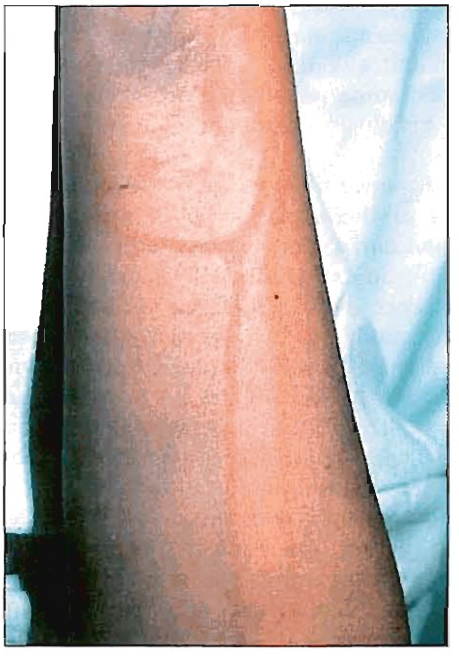

Fig. 3-18
Phytophotodermatitis, the patient had rinsed her hair with lime juice in Mexico.

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Idiopathic Photosensitivity Disorders

This group includes the photosensitivity diseases for which no cause is known. They are not associated with external photosensitizers (except for some cases of chronic actinic dermatitis) or inborn errors of metabolism.

Polymorphous Light Eruption Polymorphous light eruption (PLE, PMLE) is the most common form of photosensitivity. In various studies among Northern European white persons, a history of PLE can be elicited in between 5% and 20% of the adult population. It represents about one-quarter of all photosensitive patients in referral centers. All races and skin types can be affected. The onset is typically in the first three decades of life and females outnumber males by 2 or 3: 1. The pathogenesis is unknown, but a family history may be elicited in between 10% and 50% of patients. It has been reported by some investigators that 10% to 20% of patients with PLE may have positive antinuclear antigens (ANAs), and a family history of lupus erythematosus. Photosensitive systemic lupus erythematosus (SLE) patients may give a history of PLE-like eruptions for years before the diagnosis of SLE is made. PLE patients should be followed for the development of symptoms of SLE.

Clinically, the eruption may have several different morphologies, although in the individual patient the morphology is usually constant. The papular (or erythematopapular) variant is the most common, but papulovesicular, eczematous, erythematous, and plaque-like lesions also occur (Fig. 3-19). Plaque-like lesions are more common in elderly patients and may closely simulate lupus erythematosus, with indurated, erythematous, fixed, scaling lesions. In African Americans, a pinpoint papular variant has been observed, closely simulating lichen nitidus, but showing spongiotic

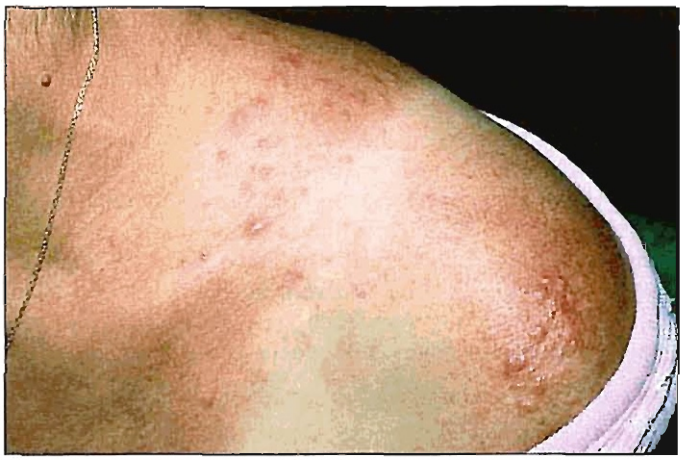

Fig. 3-19 Polymorphous light eruption, papulovesicular variant.

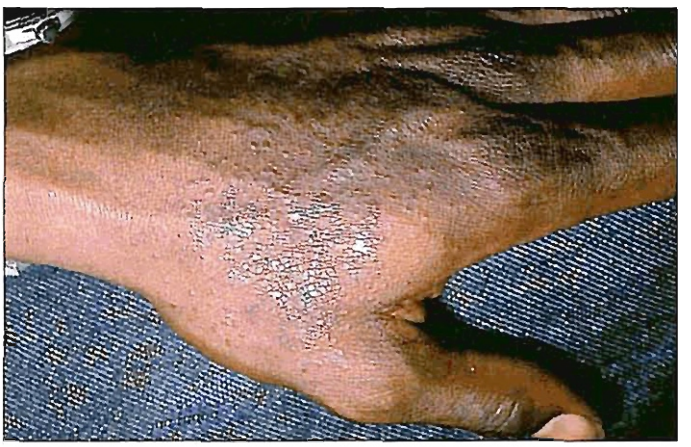

Fig. 3-20 Polymorphous light eruption, micropapular variant resembling lichen nitidus.

dermatitis histologically (Fig. 3-20). Scarring and atrophy do not occur; however, in darkly pigmented races, marked postinflammatory hyper- or hypo-pigmentation may occur. In some patients, pruritus only without an eruption may be reported (PLE sine eruption). Some of these patients will develop typical PLE later in life.

The lesions of PLE appear most typically 1 to 4 days after exposure to sunlight. Patients may report itching and erythema during sun exposure, and development of lesions within the first 24 h. A change in the amount of sun exposure appears to be more critical than the absolute amount of radiation. Patients living in tropical climates may be free of eruption, only to develop disease when they move to temperate zones, where there is more marked seasonal variation in UV intensity. Areas of involvement include the face, the V area of the chest, neck, and arms. In general, for each individual certain areas are predisposed. However, typically areas protected during the winter, such as the extensor forearms, are particularly affected, whereas areas exposed all year (face and dorsa of hands) may be relatively spared. The eruption appears most commonly in the spring. Often the eruption improves with continued sun exposure (hardening) so that patients may be clear of the condition in the summer or autumn.

The reported action spectrum of PLE varies, possibly depending on the different ethnic backgrounds of reported

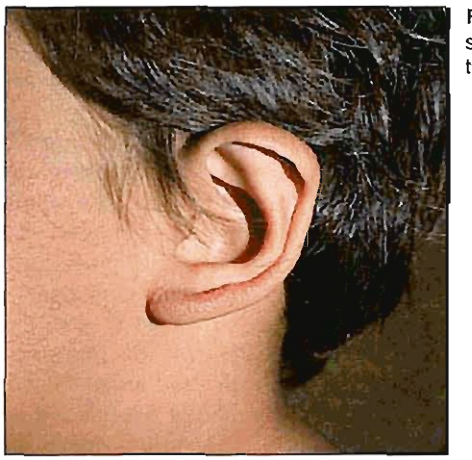

Fig. 3-21 Juvenile spring eruption of the ear.

populations. In European white persons, phototesting gives normal results in one-third, a reduced MED to UVA and UVB in one-third, and a reduced MED to UVA alone in one-third. In the US, UVB-positive phototesting may be more common, but still a substantial portion of patients have negative phototesting. Patients often report eruptions following sun exposure through window glass. Visible light sensitivity can also occur, albeit, very rarely. Women more commonly than men are sensitive to UVA only, and men are more commonly sensitive to visible light. Men, although the minority of PLE patients, tend to have more severe PLE and broader wavelengths of sensitivity. If an abnormal response occurs during phototesting, it is in general only erythema, and MED testing does not generally reproduce the eruption. Provocation testing with repeated exposures may be required. Most patients react more in affected sites, and in some, lesions can only be induced in affected areas. IgE levels may be elevated.

An unusual variant of PLE is *juvenile spring eruption of the ears* (Fig. 3-21). This occurs most commonly in boys aged 5 to 12 years, but may occur in young adult males. It presents in the spring, often after sun exposure on cold but sunny days. Large outbreaks may occur in boys' schools. The typical lesions are grouped small papules or papulovesicles on the helices. Lesions may form visible vesicles and crusting. It is self-limited and does not scar. UVA is the inducing spectrum, and some patients also have lesions of PLE elsewhere. The histologic picture is identical to that of PLE.

In the differential diagnosis of PLE, the following should be considered: lupus erythematosus, photosensitive drug eruption, prurigo nodularis, and photoallergic contact dermatitis. Histopathologic examination, ANA testing, and direct immunofluorescence (DIF) are helpful in distinguishing these diseases. Differentiation from lupus erythematosus of the subacute type may be difficult. Serologic testing alone may not distinguish PLE from SLE, due to the possibility of positive ANA tests in PLE patients. Lupus erythematosus may present initially with photosensitivity before other features of lupus erythematosus occur.

Therapeutically, most patients with mild disease can be managed by avoiding the sun and using barrier protection and high SPF broad-spectrum sunscreens. It is critical that the sunblocks contain specific absorbers of long-wave UVA (Parsol 1789, Mexoryl, zinc oxide, and titanium dioxide).

Sunblocks containing more than one of these agents may be more effective (Anthelios L60). Since UVA is the most common triggering wavelength, good UVA coverage is critical. Most patients do not apply an adequate amount of sunscreen for it to be optimally effective. These measures of photoprotection are critical for all patients, since they are free of toxicity and reduce the amount and duration of other therapies required. Patient education is very important in the management of this disease, and phototesting may be required to convince the patient that he/she is UV sensitive. It will also determine the action spectrum. The use of topical steroids, frequently of super or high potency, in several daily to weekly pulses is successful in controlling the pruritus and clearing the eruption. Antihistamines (hydroxyzine, diphenhydramine, or doxepin [Sinequan]) may be used for pruritus. Systemic corticosteroids in short courses may be necessary, especially in the spring. In patients whose condition is not controlled by the above measures, hardening in the spring with UVB, narrow-band UVB, or PUVA can dramatically increase the sun sensitivity of patients with PLE, and up to 80% of patients can be controlled with phototherapy. In the most sensitive patients, systemic steroids may be needed at the inception of the phototherapy. Systemic hydroxychloroquine sulfate (Plaquenil), 200 to 400 mg/day, may be used. It has a delayed onset and is best instituted in the late winter to prevent spring outbreaks. Chloroquine or quinacrine may be effective if hydroxychloroquine is not, but in general antimalarials are inferior to phototherapy. In the most severe patients, management with azathioprine, cyclosporin, thalidomide, or mycophenolate mofetil may be considered. If these agents are used in a patient considered to have PLE, an evaluation for chronic actinic dermatitis should be performed, as patients with PLE rarely require these agents.

Actinic Prurigo Actinic prurigo probably represents a variant of PLE; it is most commonly seen in Native Americans of North and Central America and Columbia. The incidence in Mexico has been reported to be between 1.5% and 3.5%. It has been reported in Europe, Australia, and Japan as well. The female-to-male ratio is 2 to 6:1. Actinic prurigo in Native Americans in the US begins before age 10 in 45% of cases and before age 20 in 72%. Up to 75% of cases have a positive family history (hereditary PLE of Native Americans). In Europe, 80% of cases occur before age 10. In the Inuit Canadian population onset is later and frequently in adulthood.

In childhood, lesions begin as small papules or papulovesicles that crust and become impetiginized. They are intensely pruritic and frequently excoriated. In children, the cheeks, distal nose, ears, and lower lip are typically involved (Fig. 3-22). Cheilitis may be the initial and only feature for years. Conjunctivitis is seen in 10% to 20% of patients (limbal-type vernal catarrah). Lesions of the arms and legs are also common and usually exhibit a prurigo nodule-like configuration (Fig. 3-23). The eruption may extend to involve sun-protected areas, especially the buttocks, but lesions in these areas are always less severe. In adults, chronic, dry papules and plaques are most typical, and cheilitis and crusting occur less frequently. Skin lesions tend to persist throughout the year in the tropics, although they are clearly worse during periods of increased sun exposure. In temperate and high-latitude regions, lesions occur from March through the summer and substantially remit in the winter. Hardening as seen with PLE does not occur. In up to 60% of patients with actinic prurigo that presents before the age of 20, the condition improves or resolves within 5 years, whereas adults usually have the disease throughout life.

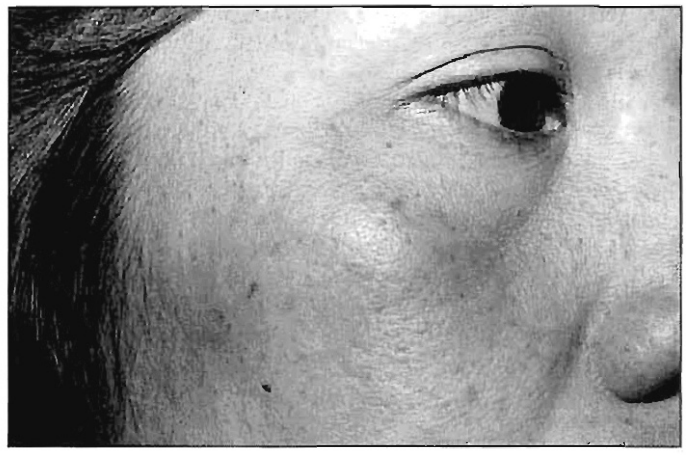

Fig. 3-22 Actinic prurigo.

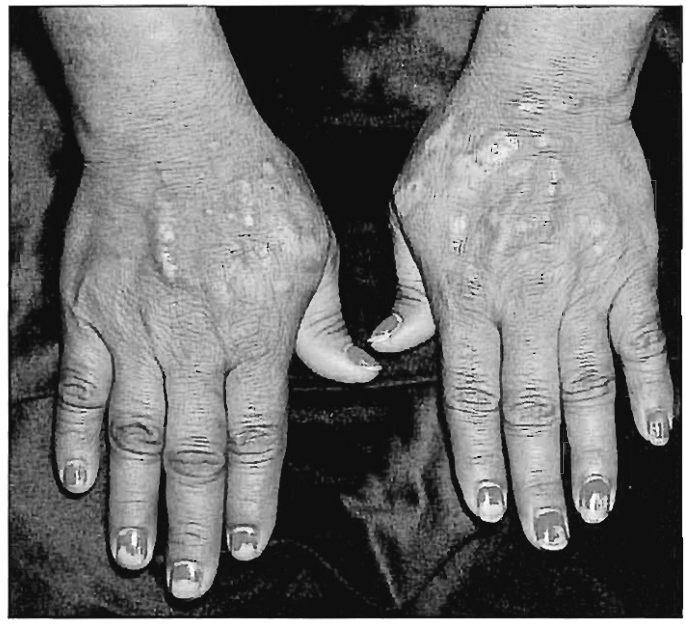

Fig. 3-23 Actinic prurigo, prurigo nodularis-like lesions.

Initial therapy is identical to that for PLE. Thalidomide has been used effectively and safely over many years in this condition. In cases refractory to or intolerant of thalidomide, cyclosporin A can be very effective. Topical cyclosporin A 2% was effective in controlling limbal lesions in one case of actinic prurigo-associated conjunctivitis.

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Brachioradial Pruritus PLE may present initially and only on the brachioradial area. This type of brachioradial eruption was the initial pattern of brachioradial pruritus described and was termed *solar pruritus* (Fig. 3-24). The majority of cases of brachioradial pruritus, and especially those characterized by severe, refractory, intractable pruritus and secondary severe lichenification are now felt to represent a form of neuropathic pruritus, related to cervical spine disease (see Chapter 4). Sunlight may be considered an eliciting factor and cervical spine disease a predisposing factor in patients with brachioradial pruritus. To identify those patients in whom photosensitivity plays a prominent role, a high SPF (UVA/UVB) sunscreen should be applied to one arm only for several weeks. In cases of PLE this usually leads to improvement of that one arm, as compared to the contralateral unprotected arm. In patients with primarily neuropathic disease, sunscreen application leads to minimal improvement.

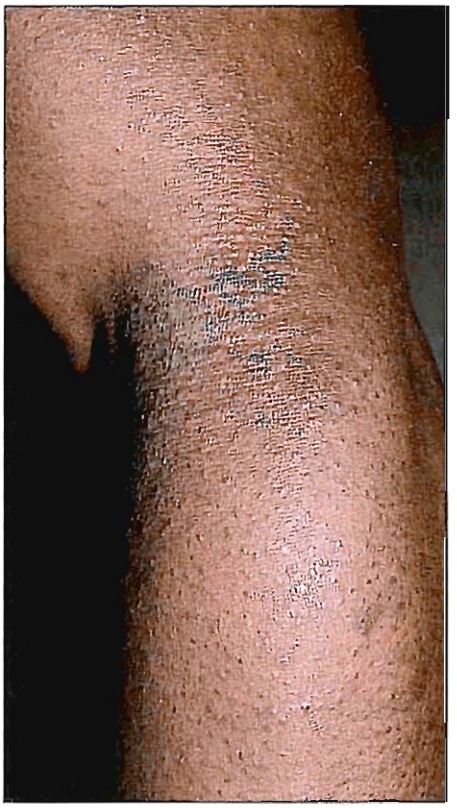

Fig. 3-24
Polymorphous light eruption, brachioradial distribution.

Solar Urticaria Solar urticaria is most common in females aged 20 to 40 years. Within seconds to minutes after light exposure, typical urticarial lesions appear and resolve in 1 to 2 h, rarely lasting more than 24 h. Delayed reactions rarely occur. Chronically exposed sites may have some reduced sensitivity. In severe attacks, syncope, bronchospasm, and anaphylaxis may occur.

Patients with solar urticaria may be sensitive to wavelengths over a broad spectrum. The wavelengths of sensitivity and the minimal urticarial doses may vary with anatomic site and over time within the same patient. UVA sensitivity is the most common, but visible light sensitivity is also frequently reported. The photosensitivity can be passively transferred, and irradiation of the patient's serum with the activating wavelength and reinjection will create a wheal in the patient, but not in an unaffected patient. This suggests the presence of a circulating photoinducible allergen to which the individual patient with solar urticaria is sensitive.

Solar uriticaria is virtually always idiopathic. Rarely, medications including tetracycline (but not minocycline), chlorpromazine, progestational agents, and repirinast have been reported to induce solar urticaria. Erythropoetic protoporphyria and very rarely prophyria cutanea tarda may present with lesions simulating solar urticaria. There are rare reports of solar urticaria in lupus erythematosus.

Histologically, early lesions contain eosinophils and neutrophils. Mast cell degranulation occurs and elevated levels of histamine are present in vessels draining lesions. Large amounts of eosinophil major basic protein are deposited in affected sites.

The diagnosis of solar urticaria is usually straightforward from the history. Phototesting is useful in solar urticaria to

determine the wavelengths of sensitivity, and to determine the minimal urticarial dose (MUD) if UVA desensitization is being considered.

Because many patients have sensitivity in the UVA or even visible range, standard sunscreens are of limited benefit. Antihistamines, especially the nonsedating H_1 agents loratadine, cetirizine HCl, and fexofenadine may increase the minimal urticarial dose 10-fold or more. Higher doses, twice or more than those standardly recommended, may be required (e.g. 180 mg of fexofenadine twice a day). These plus sun avoidance are the first-line therapy. PUVA or increasing UVA exposures are effective in more difficult cases, the former having greater efficacy. Rush hardening may induce UVA tolerance, allowing patients to begin PUVA therapy. PUVA is effective, even if the patient is not sensitive to UVA. Cyclosporin A (4.5 mg/kg/day) and intravenous immunoglobulin (IVIG; 0.4 g/kg/day for 5 days repeated monthly) have been anecdotally reported as effective. For the most difficult cases, plasmapheresis may be used to remove the circulating photoallergen, allowing PUVA to be given leading to remission.

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Hydroa Vacciniforme Hydroa vacciniforme is a very rare, chronic photodermatosis with onset in childhood. Boys and girls are equally represented, but boys present earlier and have disease on average for a longer time. There is a bimodal onset (between ages 1 and 7 and between 12 and 16). The natural history of the disorder is for it to spontaneously remit before age 20, but rare cases in young adults do occur. Lesions tend to appear in crops with disease-free intervals. The ears, nose, cheeks, and extensor arms and hands are affected. Subungual hemorrhage may occur. Within 6 h of exposure stinging begins. At 24 h or sooner erythema and edema appear, followed by the characteristic 2- to 4-mm vesicles. Over the next few days these lesions rupture, become centrally necrotic, and heal with a smallpox-like scar.

Histologically, early lesions show intraepidermal vesiculation and dermal edema that evolves into a subepidermal blister. Necrotic lesions show reticular degeneration of keratinocytes, with epidermal necrosis flanked by spongiosis with a dense perivascular infiltrate of neutrophils and lymphocytes. Dermal vessels may be thrombosed, simulating vasculitis. Lesions may be reproduced by repetitive UVA, with the action spectrum in the 330 to 360 nm range.

The differential diagnosis includes PLE, actinic prurigo, and erythropoietic protoporphyria. Porphyrin levels are normal in hydroa vacciniforme. In erythropoietic protoporphyria the burning typically begins within minutes of sun exposure, and over time patients develop diffuse, thickened, waxlike scarring, rather than the smallpox-like scars of hydroa vacciniforme. Histologic evaluation is useful in distinguishing these two conditions. Treatment is principally to avoid sunlight exposure and to use broad-spectrum or barrier sunscreens that block in the UVA range. Prophylactic narrow-band UVB phototherapy in the early spring may be effective.

A subset of children and less commonly adults with photosensitive, hydroa vacciniforme-like skin lesions will have latent Epstein-Barr virus infection. The infiltrate in their skin may be frankly lymphomatous, or the patient may have coexistent Hodgkin's disease or non-Hodgkin's lymphoma. The hydroa vacciniforme-like skin lesions may precede the diagnosis of the lymphoma by up to a decade. Treatment of the lymphoma may lead to clearing of these lesions.

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Chronic Actinic Dermatitis Chronic actinic dermatitis represents the end stage of progressive photosensitivity in some patients. It has replaced the terms *persistent light reactivity*, *actinic reticuloid*, *photosensitive eczema*, and *chronic photosensitivity dermatitis*. The basic components of this disease are: 1) a persistent, chronic, eczematous eruption in the absence of exposure to known photosensitizers;

2) usually broad-spectrum photosensitivity with decreased MED to UVA and/or UVB, and at times visible light; and 3) histology consistent with a chronic dermatitis with or without features of lymphoma.

Clinically, the disease predominantly affects middle-aged or elderly men. In the US, patients with skin types V and VI may be disproportionately affected. Skin lesions consist of edematous, scaling, thickened patches and plaques that tend to be confluent. Lesions occur primarily or most severely on the exposed skin and may spare the upper eyelids, behind the ears, and the bottoms of wrinkles (Fig. 3-25). Involvement of unexposed sites often occurs, progressing to erythroderma in the most severe cases. Marked depigmentation resembling vitiligo may result. Patients may not realize their condition is exacerbated by exposure to light. It may persist in all seasons.

The pathogenesis of this syndrome is unknown. In some patients a preceding topical or oral photosensitizer may be implicated, but the condition fails to improve with discontinuation of the inciting agent. In about one-third of patients, photopatch testing yields a positive response to previously applied agents, especially musk ambrette, sunscreen ingredients, and hexachlorophene. Patch testing to standard agents may have a positive result in about 30% of patients, but no particular relevance is found. However, in up to 85% of cases, *sesquiterpene lactone* contact sensitivity from *Compositae* has been identified in Europe. In addition, more than 75% of men over the age of 60 with sesquiterpene lactone sensitivity have abnormal phototesting results. CD8 (suppressor/cytotoxic) T-cells are disproportionately represented in the cutaneous infiltrates in the majority of cases, and less commonly, in the peripheral blood. IgE levels may be elevated.

The diagnosis of chronic actinic dermatitis is established by histologic evaluation and phototesting. Phototesting often reproduces the lesions. Sixty-five percent of patients are sensitive to UVA and B and visible light, 22% to UVA and B, and 5% to UVB or UVA only. The finding of photosensitivity to UVA and UVB helps to differentiate chronic actinic dermatitis from drug-induced photosensitivity which usually exhibits only UVA photosentivity. PLE, photoallergic contact dermatitis, airborne contact dermatitis, and mycosis fungoides or Sézary syndrome must be excluded. PLE is excluded by the broad-spectrum reduced MED in chronic actinic dermatitis, although some patients may begin with a PLE-like disease that later meets the criteria for chronic actinic dermatitis. Contact dermatitis is excluded by patch and photopatch testing. Mycosis fungoides may be difficult to differentiate from chronic actinic dermatitis in cases with atypical histology. Phototesting is critical in these cases. Mycosis fungoides should have a T-cell receptor rearrangement in lesional skin or peripheral blood and usually shows a CD4 (helper) T-cell predominance in the lesions, and in peripheral blood in the case of Sézary syndrome.

Therapy for chronic actinic dermatitis is difficult. Possible topical photosensitizers should be identified by photopatch testing and scrupulously avoided. Maximum sun avoidance and broad-spectrum sunscreens are essential. Topical and systemic steroids are effective in some cases, but chronic toxicity of systemic steroids limits chronic usage. Topical tacrolimus may be useful in some patients. Azathioprine, 50 to 200 mg/day, is the most reproducibly effective treatment and may be required annually during periods of increased sun intensity. Low-dose PUVA can be attempted, but is often not tolerated, even when used with topical and systemic steroids. Hydroxyurea, 500 mg twice a day, benefited one patient. Cyclosporin A and mycophenolate mofetil may be used in the most refractory patients. The use of immunosuppressives may allow patients to tolerate PUVA therapy. With careful management about 1 in 10 patients will lose their photosensitivity within 5 years, 1 in 5 by 10 years, and half of patients by 15 years.

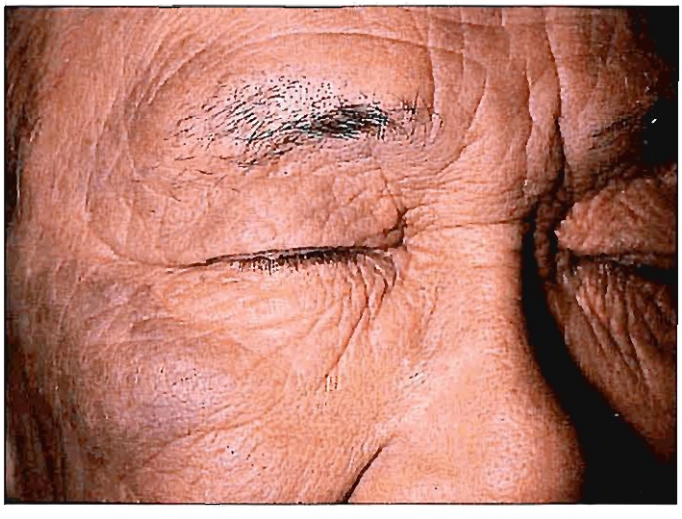

Fig. 3-25 Chronic actinic dermatitis.

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Thomson MA, et al: Chronic actinic dermatitis treated with mycophenolate mofetil. Br J Dermatol 2005;152:784.

Photosensitivity and HIV Infection Photosensitivity resembling PLE, actinic prurigo, or chronic actinic dermatitis is seen in about 5% of human immunodeficiency virus (HIV)-infected persons. In general, photosensitivity is seen when the CD4 count is below 200 (often below 50), except in persons with a genetic predisposition (Native Americans). Photosensitivity may be the initial manifestation of HIV disease. African American patients are disproportionately represented among patients with HIV photosensitivity. Photosensitivity may be associated with ingestion of a

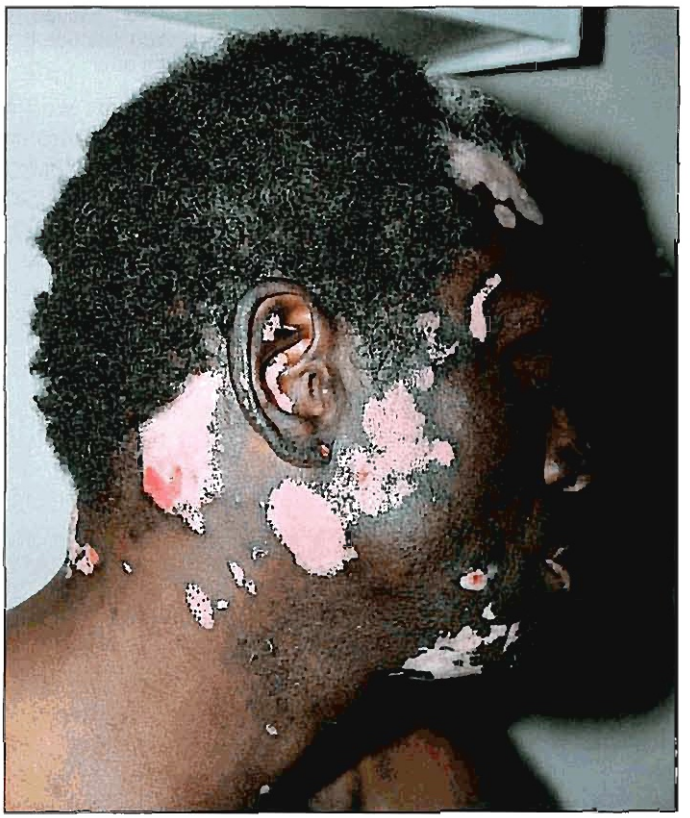

Fig. 3-26 HIV photodermatitis, marked depigmentation resembling vitiligo.

photosensitizing medication, especially NSAIDs or trimethoprim–sulfamethoxazole, but the skin eruption often does not improve even when the medication is discontinued. Histologically, the lesions may show subacute or chronic dermatitis often with a dense dermal infiltrate with many eosinophils. Histology identical to PLE, lichen planus or lichen nitidus may also occur. When the CD4 count is below 50, especially in black patients, chronic actinic dermatitis with features of actinic prurigo is typical. Widespread vitiliginous lesions may develop (Fig. 3-26). Therapy is difficult, but thalidomide may be beneficial.

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RADIODERMATITIS

The major target within the cell by which radiation damage occurs is the DNA. The effects of ionizing radiation on the cells depend on the amount of radiation, its intensity (exposure rate), and the characteristics of the individual cell.

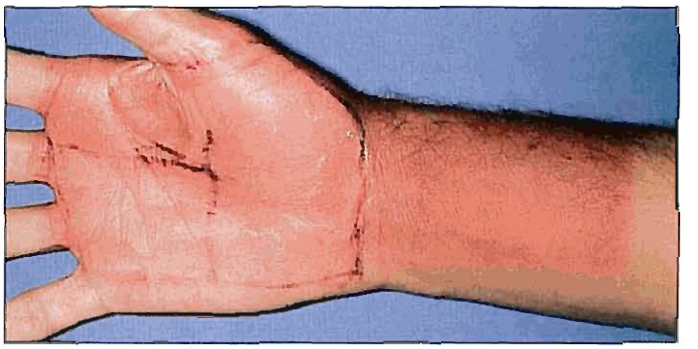

Fig. 3-27 Acute radiation burn during treatment of epitheliod sarcoma.

Rapidly dividing cells and anaplastic cells in general have increased radiosensitivity when compared with normal tissue. When radiation therapy is delivered, it is frequently fractionated—divided into small doses called fractions. This allows the normal cells to recover between doses.

In small amounts, the effect is insidious and cumulative. When the dose is large, cell death results. When it is sublethal, many changes occur. Mitosis is arrested temporarily, with consequent retardation of growth. The exposure rate affects the number of chromosome breaks. The more rapid the delivery of a certain amount of radiation, the greater the number of chromosome breaks. The number of breaks is increased also by the presence of oxygen.

Acute Radiodermatitis When an "erythema dose" of ionizing radiation is given to the skin, there is a latent period of up to 24 h before visible erythema appears. This initial erythema lasts 2 to 3 days but may be followed by a second phase beginning up to 1 week after the exposure and lasting up to 1 month. When the skin is exposed to a large amount of ionizing radiation, an acute reaction develops, the extent of which will depend on the amount, quality, and duration of exposure. Such radiation reaction occurs in the treatment of malignancy and in accidental overexposure. The reaction is manifested by initial erythema, followed by a second phase of erythema at 3 to 6 days (Fig. 3-27). Vesiculation, edema, and erosion or ulceration may occur, accompanied by pain. The skin develops a dark color that may be mistaken for hyperpigmentation, but that desquamates. This type of radiation injury may subside in several weeks to several months, again depending on the amount of radiation exposure. Skin that receives a large amount of radiation will never return to normal. It will lack adnexal structures, be dry, atrophic, and smooth, and be hypopigmented or depigmented.

Eosinophilic, Polymorphic, and Pruritic Eruption Associated with Radiotherapy Rueda et al reported that 17% of women receiving cobalt radiotherapy for internal cancer developed a pruritic eruption that favored the extremities. Acral excoriations, erythematous papules, vesicles, and bullae occurred. Histologically, a superficial and deep perivascular lymphohistiocytic infiltrate with eosinophils was present.

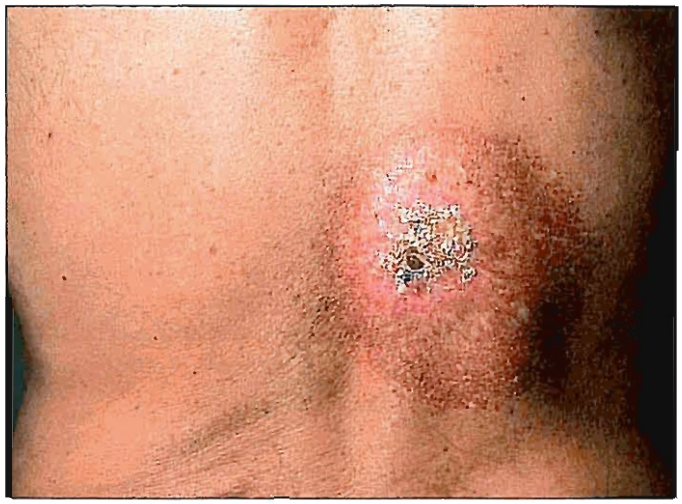

Fig. 3-28 Chronic radiodermatitis after fluoroscopy.

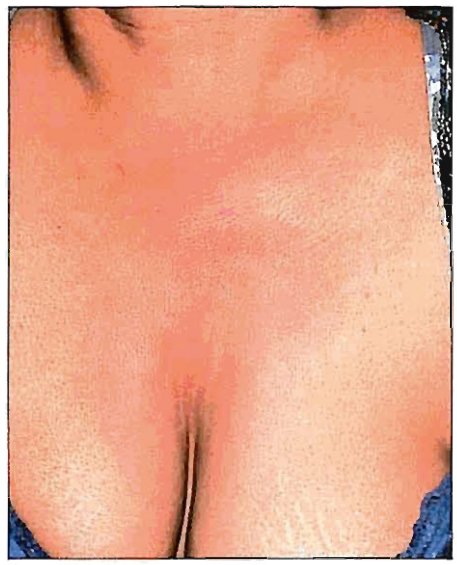

Fig. 3-30 Delayed radiation reaction 8 months after therapy.

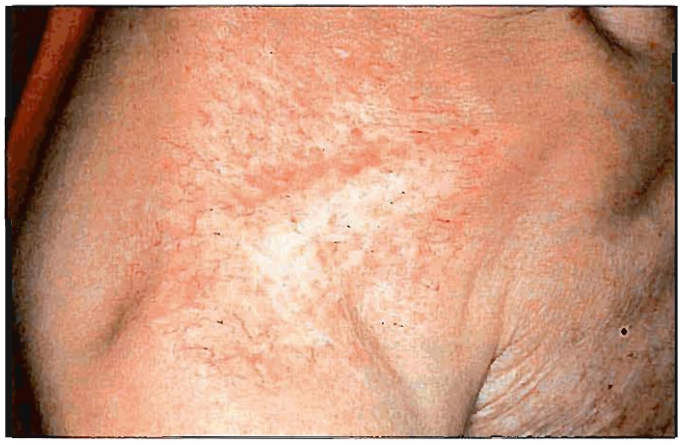

Fig. 3-29 Chronic radiodermatitis.

Chronic Radiodermatitis Chronic exposure to "suberythema" doses of ionizing radiation over a prolonged period will produce varying degrees of damage to the skin and its underlying parts after a variable latent period of from several months to several decades. In the past this type of radiation reaction occurred most frequently in radiologists and radiation technicians who were constantly exposed to ionizing radiation. It may also occur through overtreatment of various dermatoses with ionizing radiation and through excessive use of fluoroscopy and roentgenography for diagnostic purposes (Fig. 3-28).

Telangiectasia, atrophy, and hypopigmentation with residual focal increased pigment (freckling) may appear (Fig. 3-29). The skin becomes dry, thin, smooth, and shiny. Subcutaneous fibrosis, thickening and binding of the surface layers to deep tissues may present as tender, erythematous plaques 6 to 12 months after radiation therapy (Fig. 3-30). It may resemble erysipelas or inflammatory metastases. The nails may become striated, brittle, and fragmented. The capacity to repair injury is substantially reduced, resulting in ulceration from minor trauma. The hair becomes brittle and sparse. In more severe cases these chronic changes may be followed by radiation keratoses and carcinoma.

Radiation Cancer After a latent period averaging 20 to 40 years, various malignancies may develop. Most frequent are basal cell carcinoma (BCC), followed by squamous cell carcinoma (SCC). These may appear in sites of prior radiation, even if there is no evidence of chronic radiation damage. Sun damage may be additive to radiation therapy, increasing the appearance of nonmelanoma skin cancers. SCCs arising in sites of radiation therapy metastasize more frequently than purely sun-induced SCCs. In some patients, either type of tumor may predominate. Location plays some role; SCCs are more common on the arms and hands, whereas BCCs are seen on the head and neck and lumbosacral area. Other radiation-induced cancers include angiosarcoma (Fig. 3-31), malignant fibrous histiocytoma, sarcomas, and thyroid carcinoma. The incidence of malignant neoplasms increases with the passage of time.

Treatment

Acute radiodermatitis may be reduced with a topical corticosteroid cream combined with an emollient cream applied twice a day and instituted at the onset of therapeutic radiotherapy. Chronic radiodermatitis without carcinoma requires little or no attention except protection from sunlight and the extremes of heat and cold. Careful cleansing with mild soap and water, the use of emollients, and, on occasion hydrocortisone ointment, are the only requirements for good care.

The early removal of precancerous keratoses and ulcerations is helpful in preventing the development of cancers. For radiation keratoses treatment with cryosurgery, 5-FU, imiquimod cream, or topical 5-aminolaevulinic acid–photodynamic therapy may be sufficient. If the keratosis feels infiltrated, a biopsy is indicated. Radiation ulcerations should be studied by excisional or incisional biopsy if they have been present for 3 or more months. Complete removal by excision is frequently required to obtain healing and exclude focal carcinoma in the ulceration. Radiation-induced nonmelanoma skin cancers are managed by standard methods. The higher risk of metastasis from radiation-induced SCCs mandates careful follow-up and regular regional lymph node evaluation.

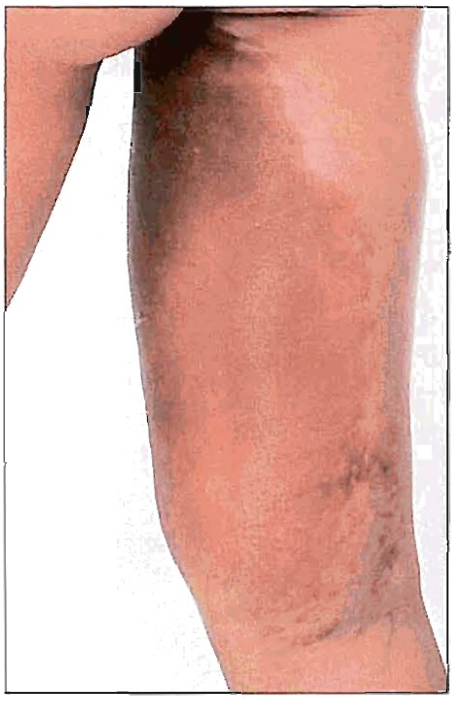

Fig. 3-31 Angioscarcoma years after radiation therapy.

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MECHANICAL INJURIES

Mechanical factors may induce distinctive skin changes. Pressure, friction, and the introduction of foreign substances (such as by injection) are some of the means by which skin injuries may occur.

Callus

Callus is a nonpenetrating, circumscribed hyperkeratosis produced by pressure. It occurs on parts of the body subject to intermittent pressure, particularly the palms and soles, and especially the bony prominences of the joints. Those engaged in various sports, certain occupations, or other repetitive activity develop callosities of distinctive size and location as stigmata. Examples of these are surfer's nodules, boxer's knuckle pads, jogger's toe, rower's rump, tennis toe (Fig. 3-32), jogger's nipple, prayer callous (Fig. 3-33), neck callosities of violinists, bowler's hand, and Russell's sign. The latter are calluses, small lacerations or abrasions on the dorsum of the hand overlying the metacarpophalangeal and interphalangeal joints, and are seen as a clue to the diagnosis of bulimia nervosa.

The callus differs from the clavus in that it has no penetrating central core and it is a more diffuse thickening. It tends to disappear spontaneously when the pressure is removed. Most problems are encountered with calluses on the soles. Ill-fitting shoes, orthopedic problems of the foot caused by aging or a deformity of the foot exerting abnormal pressure, and high activity level are some of the etiologic factors to be considered in painful callosities of the feet.

Padding to relieve the pressure, paring of the thickened callus, and the use of keratolytics, such as 40% salicylic acid plasters, are some of the effective means of relieving painful callosities. Twelve percent ammonium lactate lotion (Lac-Hydrin) is often helpful. Calluses may also be softened by moistening them nightly with two parts propylene glycol to one part water under snug plastic occlusion (a plastic baggie and a sock will do). This is especially effective with fissured calluses of the heels.

Clavus (Corns)

Corns are circumscribed, horny, conical thickenings with the base on the surface and the apex pointing inward and

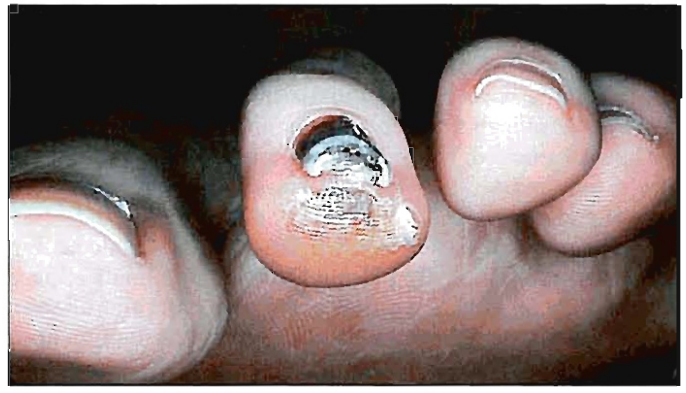

Fig. 3-32 Tennis toe.

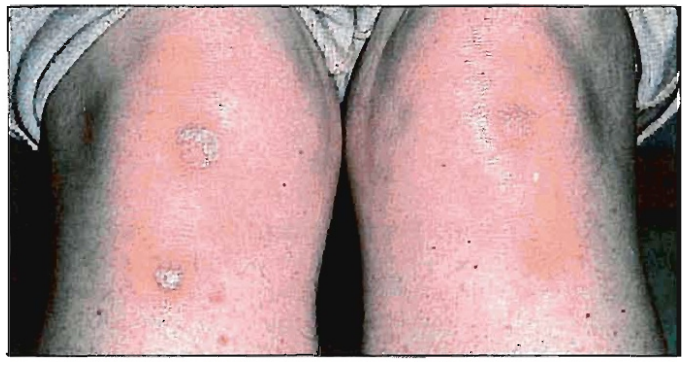

Fig. 3-33 Prayer callouses.

pressing on subjacent structures. There are two varieties: the hard corns, which occur on the dorsa of the toes or on the soles, and the soft corns, which occur between the toes and are softened by the macerating action of sweat. In a hard corn, the surface is shiny and polished and, when the upper layers are shaved off, a core is noted in the densest part of the lesion. It is this core that causes a dull/boring or sharp/lancinating pain by pressing on the underlying sensory nerves. Corns arise at sites of friction or pressure, and when these causative factors are removed, they may spontaneously disappear. Frequently a bony spur or exostosis is present beneath both hard and soft corns of long duration, and unless this exostosis is removed cure is unlikely. The soft interdigital corn usually occurs in the fourth interdigital space of the foot. Frequently, there is an exostosis at the metatarsal–phalangeal joint that causes pressure on the adjacent toe. These are soft, soggy, and macerated so that they appear white. Treatment by simple excision may be effective.

Plantar corns must be differentiated from plantar warts, and in most cases this can be done with confidence only by paring off the surface keratin until either the pathognomonic elongated dermal papillae of the wart with its blood vessels, or the clear horny core of the corn, can be clearly seen. Additionally, porokeratosis plantaris discreta is a sharply marginated, cone-shaped, rubbery lesion that commonly occurs beneath the metatarsal heads. Multiple lesions may occur. It has a 3:1 female predominance, is painful, and is frequently confused with a plantar wart or corn. Keratosis punctata of the creases may be seen in the creases of the digits of the feet where it may be mistaken for a corn.

The relief of pressure or friction by corrective footwear or padding is of primary importance; however, this step alone may not cure the lesions. Salicylic acid and dichloroacetic acid have been favorite methods of treatment, and are successful when carefully and diligently used. After careful paring of the corn with emphasis on removing the center core, 40% salicylic acid plaster is applied. After 48 h the plaster is removed, the white macerated skin is rubbed off, and a new plaster is reapplied. This is continued until the corn is gone.

Sometimes it is easier to use a salicylic acid–lactic acid in collodion rather than the plaster. The collodion medication is carefully painted on the pared site of the corn and allowed to dry each day until cure. Soaking the foot for half an hour before reapplying the medication enhances the effect. This treatment is especially effective for interdigital soft corns.

Soaking the feet in hot water and paring the surface by means of a scalpel blade or pumice stone leads to symptomatic improvement. The application of a ring of soft felt wadding around the region of the corn will often bring a good result. It should be stressed that removal of any underlying bony abnormality, if present, is often necessary to effect a cure.

Pseudoverrucous Papules and Nodules

These striking 2- to 8-mm, shiny, smooth, red, moist, flat-topped, round lesions in the perianal area of children are considered to be a result of encopresis or urinary incontinence. There is a similarity to lesions affecting urostomy patients. Protection of the skin will help eliminate them.

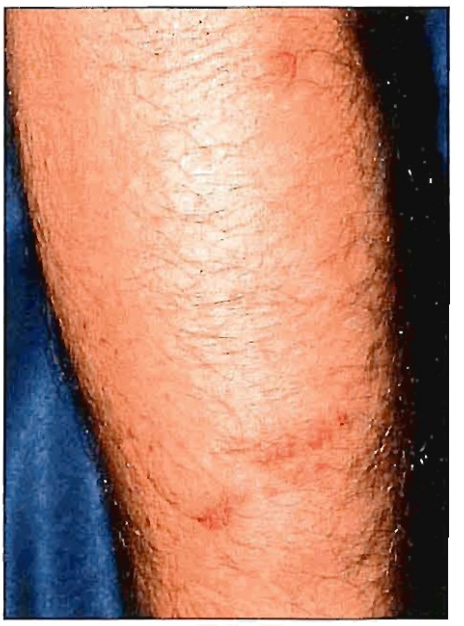

Fig. 3-34 *Fire coral stings.* (Courtesy of J Fitzpatrick, MD)

Coral Cuts

A severe type of skin injury may occur from the cuts of coral skeletons (Fig. 3-34). The abrasions and cuts are painful, and local therapy may sometimes provide little or no relief. Healing may take months. As a rule, if secondary infection is guarded against, such cuts heal as well as any others. The possibility of *Mycobacterium marinum* infection must be considered in persistent lesions.

Pressure Ulcers (Decubitus)

The bedsore, or decubitus, is a pressure ulcer produced anywhere on the body by prolonged pressure. The pressure sore is caused by ischemia of the underlying structures of the skin, fat, and muscles as a result of sustained and constant pressure. Usually it occurs in chronically debilitated persons who are unable to change position in bed. The bony prominences of the body are the most frequently affected sites. Ninety-five percent of all pressure ulcers develop on the lower body, with 65% in the pelvic area and 30% on the legs. The ulcer usually begins with erythema at the pressure point; in a short time a "punched-out" ulcer develops. Necrosis with a grayish pseudomembrane is seen, especially in the untreated ulcer. Potential complications of pressure ulcers include sepsis, local infection, osteomyelitis, fistulas, and SCC.

Over 100 risk factors have been identified with diabetes mellitus, peripheral vascular disease, cerebrovascular disease, sepsis, and hypotension being prominent. Pressure ulcers are graded according to a four-stage system, with the earliest being recognized by changes in one or more of the following: skin temperature, tissue consistency, and/or sensation. The lesion appears as an area of persistent redness. Stage II is a superficial ulcer involving the epidermis and/or dermis, with the deeper stage III ulcers damaging the subcutaneous fat, and in stage IV, the muscle, bone, tendon or joint capsule.

Prevention is to redistribute pressure at a minimum interval of 2 h. Treatment consists of relief of the pressure on the affected parts by frequent change of position, meticulous

nursing care, and the use of air-filled products, liquid-filled flotation devices, or foam products. Other measures include ulcer care, managing bacterial colonization and infection, operative repair if necessary, continual education, ensuring adequate nutrition, managing pain, and providing psychosocial support.

Ulcer care is critical. Debridement may be accomplished by sharp, mechanical, enzymatic, and/or autolytic measures. In some cases operative care will be required. Stable heel ulcers are an exception; they do not need debridement if only a dry eschar is present. Wounds should be cleaned initially and each dressing changed by a nontraumatic technique. Normal saline rather than peroxide or povidone–iodine is best. Selection of a dressing should ensure that the ulcer tissue remains moist and the surrounding skin dry.

Occlusive dressings include over 300 marketed products. They are generally classified as film, alginates, foams, hydrogels, hydrofibers, and hydrocolloid dressings. Transparent films are only used for stage II ulcers as they only provide light drainage, while hydrofibers are utilized only for full-thickness stage III and IV ulcers. Surgical debridement with reconstructive procedures may be necessary. Adjuvant therapies such as ultrasound, laser, UV, hyperbaric oxygen, electrical stimulation, radiant heat, the application of growth factors, cultured keratinocyte grafts, skin substitutes, and miscellaneous topical and oral agents are being investigated to determine their place in the treatment of these ulcers.

At times anaerobic organisms colonize these ulcers and cause a putrid odor. The topical application of metronidazole eliminates this odor within 36 h.

Friction Blisters

The formation of vesicles or bullae may occur at sites of combined pressure and friction, and may be enhanced by heat and moisture. The feet of military recruits in training, the palms of oarsmen who have not yet developed protective calluses, and beginning drummers ("drummer's digits") are examples of those at risk. The size of the bulla depends on the site of the trauma. If the skin is tense and uncomfortable, the blister should be drained, but the roof should not be completely removed as it may act as its own dressing.

In studies focusing on the prevention of friction blister of the feet in long distance runners and soldiers, acrylic fiber socks with drying action and of specific thickness have been found to be effective. Additionally, pretreatment with a 20% solution of aluminum chloride hexahydrate for at least 3 days has been shown to significantly reduce foot blisters after prolonged hiking.

Fracture Blisters

These blisters overlie sites of closed fractures, especially the ankle. They appear a few days to 3 weeks after the injury, are felt to be caused by vascular compromise, and may create complications such as infection. They generally heal spontaneously in 5 to 14 days but may result in delay of surgical reduction of the fracture.

Sclerosing Lymphangiitis

This lesion is a cordlike structure encircling the coronal sulcus of the penis, or running the length of the shaft, that has been attributed to trauma during vigorous sexual play (Fig. 3-35). It is produced by a sclerosing lymphangiitis.

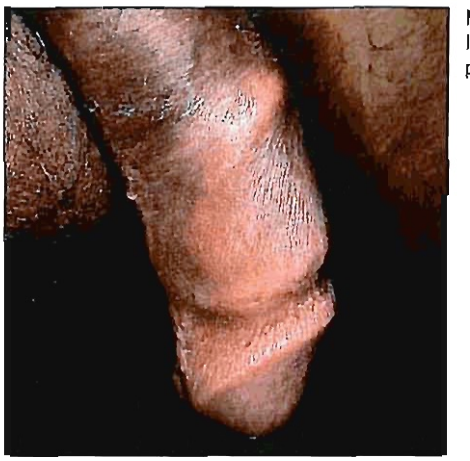

Fig. 3-35 Sclerosing lymphangitis of the penis.

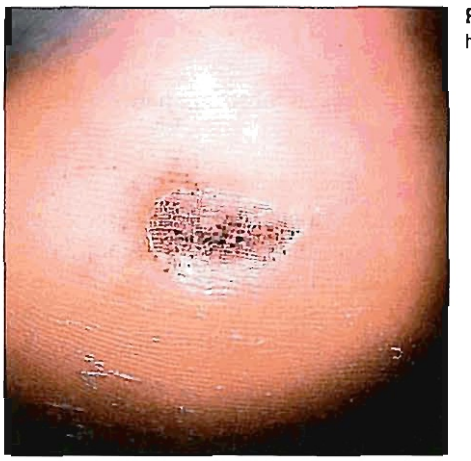

Fig. 3-36 Black heel.

Treatment is not necessary; it follows a benign, self-limiting course.

Black Heel

Synonyms for black heel include *talon noir, calcaneal petechiae*, and *chromidrose plantaire*. A sudden shower of minute, black, punctate macules occurs most often on the posterior edge of the plantar surface of one or both heels (Fig. 3-36), but sometimes distally on one or more toes. Black heel is often seen in basketball, volleyball, tennis, or lacrosse players. Seeming confluence may lead to mimicry of melanoma. The bleeding is caused by shearing stress of sports activities. Paring with a No 15 blade and performing a guaiac test will confirm the diagnosis. Treatment is unnecessary.

Subcutaneous Emphysema

Free air occurring in the subcutaneous tissues is detected by the presence of cutaneous crepitations. This raises the fear of infection with gas-producing organisms, especially clostridial gas gangrene, or leakage of free air from the lungs or gastrointestinal tract (Fig. 3-37). Samlaska et al reviewed the wide variety of causes of subcutaneous emphysema, including penetrating and nonpenetrating injuries, iatrogenic causes occurring during various procedures in hospitalized patients, spontaneous pneumomediastinum such as may occur with a violent cough, childbirth, asthma, Boerhaave syndrome (esophageal rupture after vomiting), or the Heimlich maneuver, intra-abdominal causes, such as inflammatory

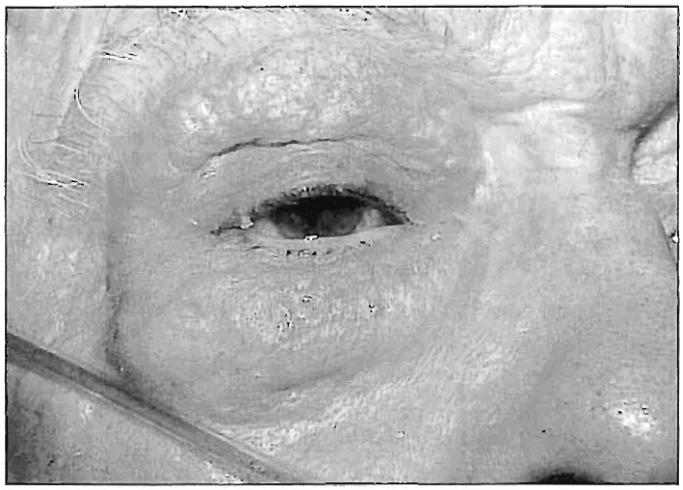

Fig. 3-37 Subcutaneous emphysema. (Courtesy of C. Samlaska MD)

bowel disease, cancer, perirectal abscess, pancreatitis, or cystitis, and factitial disease.

Traumatic Asphyxia

Cervicofacial cyanosis and edema, multiple petechiae of the face, neck, and upper chest, and bilateral subconjunctival hemorrhage may occur after prolonged crushing injuries of the thorax or upper abdomen. Such trauma reverses blood flow in the superior vena cava or its tributaries.

Painful Fat Herniation

Also called *painful piezogenic pedal papules*, this rare cause of painful feet represents fat herniations through thin fascial layers of the weight-bearing parts of the heel (Fig. 3-38). These dermatoceles become apparent when weight is placed on the heel and disappear as soon as the pressure is removed. These fat herniations are present in many people but the majority experience no symptoms. However, extrusion of the fat tissue together with its blood vessels and nerves may initiate pain on prolonged standing. Avoidance of prolonged standing will obviously relieve this pain. Other options include taping of the foot, use of compression stockings, or use of plastic heel cups or padded orthotics to restrict the herniations. Intralesional steroid injections can also be effective. Laing et al found 76% of 29 subjects had pedal papules, and interestingly, by placing pressure on the wrists, found 86% to have piezogenic wrist papules.

Narcotic Dermopathy

Heroin (diacetylmorphine) is a narcotic prepared for injection by dissolving the heroin powder in boiling water and then injecting it. The favored route of administration is intravenous. This results in thrombosed, cordlike, thickened veins at the sites of injection. Subcutaneous injection ("skin popping") can result in multiple, scattered ulcerations, which heal with discrete atrophic scars (Fig. 3-39). In addition, amphetamines, cocaine, and other drugs may be injected. Subcutaneous injection may result in infections, complications of bacterial abscess and cellulites, or sterile nodules, apparently acute foreign body reactions to the injected drug, or the adulterants mixed with it. These lesions may ulcerate. Chronic persistent, firm nodules, a combination of scar and foreign body reaction, may result. If cocaine is being injected

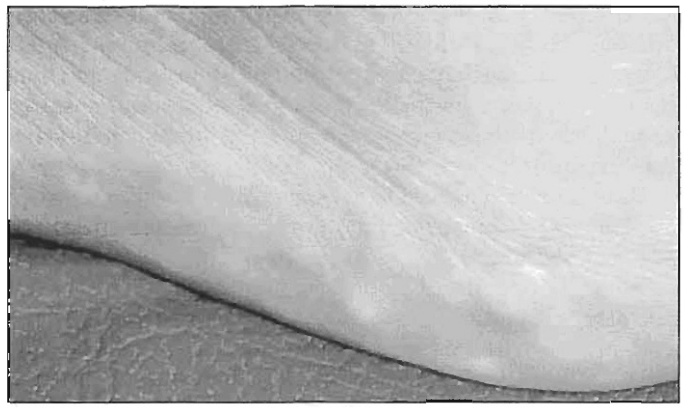

Fig. 3-38 Piezogenic papules.

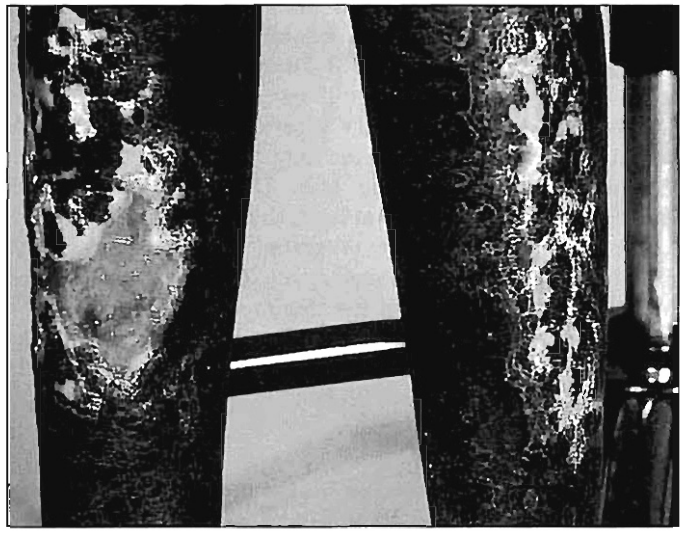

Fig. 3-39 Ulceration secondary to "skin popping."

it may cause ulcers because of its direct vasospastic effect. Addicts will continue to inject heroin and cocaine into the chronic ulcer bed.

The cutaneous manifestations of injection of heroin and other drugs also include camptodactylia, edema of the eyelids, persistent nonpitting edema of the hands, urticaria, abscesses, atrophic scars, and hyperpigmentation. Pentazocine abuse leads to a typical clinical picture of tense, woody fibrosis, irregular punched-out ulcerations, and a rim of hyperpigmentation at the sites of injections. Extensive calcification may occur within the thickened sites.

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FOREIGN BODY REACTIONS

Tattoo

Tattooing is the introduction of insoluble pigments into the skin. They may be traumatic, cosmetic, or medicinal in nature, and be applied by a professional or an amateur. Pigment is applied to the skin and then needles pierce the skin to force the material into the dermis. Accidental tattoo marks may be induced by narcotic addicts who sterilize the needles for injection by flaming the needle with a lighted match. The carbon formed on the needle is then tattooed into the skin as the needle is inserted. Inserted pigments may be carmine, indigo, vermilion, India ink, chrome green, manganese, Venetian red, aluminum, titanium or zinc oxide, lead carbonate, copper, iron, logwood, cobalt blue, cinnabar (mercuric sulfide), and cadmium sulfide. Cadmium, cobalt, mercury, and lead are not often used; however, occasional photosensitive reactions to cadmium, which was used for yellow color or to brighten the cinnabar red, are still seen.

Tattoo-associated dermopathies may be reactive (allergic, lichenoid, granulomatous, or photosensitive) (Fig. 3-40) or infective (inoculation of syphilis, infectious hepatitis, tuberculosis, HIV, and leprosy), or may induce a Koebner response in patients with active lichen planus or psoriasis. Discoid lupus erythematosus has been reported to occur in the red-pigmented portion of tattoos. Occasionally the tattoo marks may become keloidal.

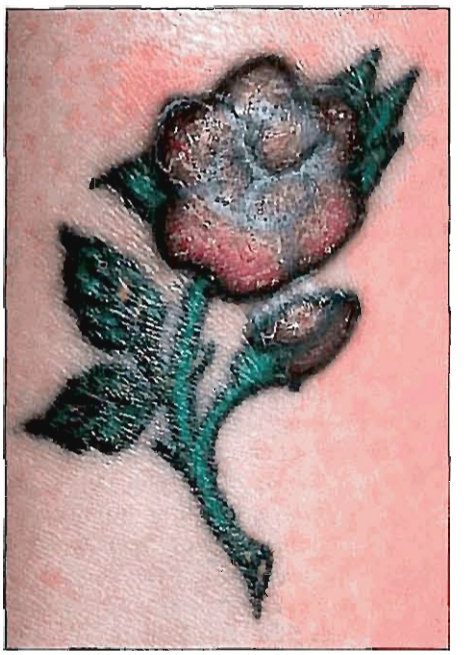


Fig. 3-40 Red tattoo reaction. (Courtesy of C Samlaska, MD)

Severe allergic reactions to temporary (skin painted tattoos) occur when the allergen *p*-phenylenediamine is added to henna. Red tattoos are the most common cause of delayed reactions, with the histologic findings typically showing a lichenoid process. These may be successfully treated with the Q-switched 532-nm neodymium-YAG laser, although immediate hypersensitivity reactions may occur. Dermatitis in areas of red (mercury), green (chromium), or blue (cobalt) have been described in patients who are patch-test positive to these metals. Sarcoidal nodules, pseudolymphoma, and granuloma annulare-like lesions may also occur. One example is aluminum-induced granulomas which may occur at vaccination sites.

Treatment by excision is satisfactory when the lesions are small enough and situated so that ellipsoid excisions are feasible. Older treatment modalities such as dermabrasion, salabrasion, cryosurgery, tangential planing, and certain lasers may result in scarring. Laser treatment of tattoos is described in Chapter 37.

Tattoo darkening and nonresponse to laser treatment is not uncommon. Caution must be used when treating flesh-colored and pink–red tattoos as they may darken after treatment. This is likely due to the reduction of ferric oxide to ferrous oxide. White ink, composed mostly of titanium dioxide, is commonly used to brighten green, blue, yellow, and purple tattoos. Laser irradiation reduces titanium to a blue colored pigment. Test areas are recommended when treating facial light-colored tattoos. CO_2 resurfacing lasers used conservatively are an alternative to the Q-switched lasers in such patients.

Paraffinoma (Sclerosing Lipogranuloma)

At one time the injection of oils into the skin for cosmetic purposes, such as the smoothing of wrinkles and the

augmentation of breasts, was popular. Paraffin, camphorated oil, cottonseed or sesame oil, and beeswax may produce plaquelike indurations with ulcerations after a time lapse of months to many years. Several reports document penile parrafinomas caused by self-injection. When vaseline gauze or a topical ointment is used to dress unsutured wounds, lipogranulomas or inflammatory mild erysipelas-like lesions with marked tenderness may occur. Present treatment methods for sclerosing lipogranuloma are unsatisfactory. Surgical removal must be wide and complete.

Granulomas

Silicone Granuloma Liquid silicones, composed of long chains of dimethyl siloxy groups, are biologically inert. They have been used for the correction of wrinkles, for the reduction of scars, and for building up of atrophic depressed areas of the skin. Many case reports detail granulomatous reactions to silicone, some with migration and reactive nodules at points distant from the injection site (Figs 3-41 and 3-42). As acupuncture needles are coated with silicone, granulomas may occur at the entry points of the needle. The incidence of the nodular swellings, which may be quite destructive and treatment resistant, remains unknown. It is clear that medical-grade silicone injected in small volumes should be the rule and that it should not be injected into the penis or the glandular tissue of the breast.

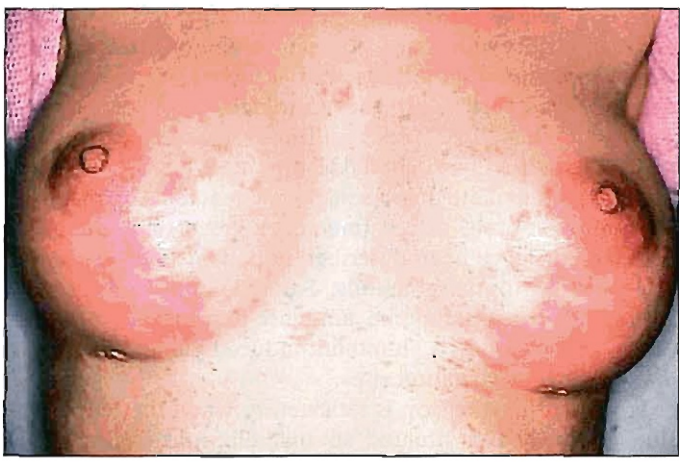


Fig. 3-41 Silicone reaction. (Courtesy of J Fitzpatrick, MD)

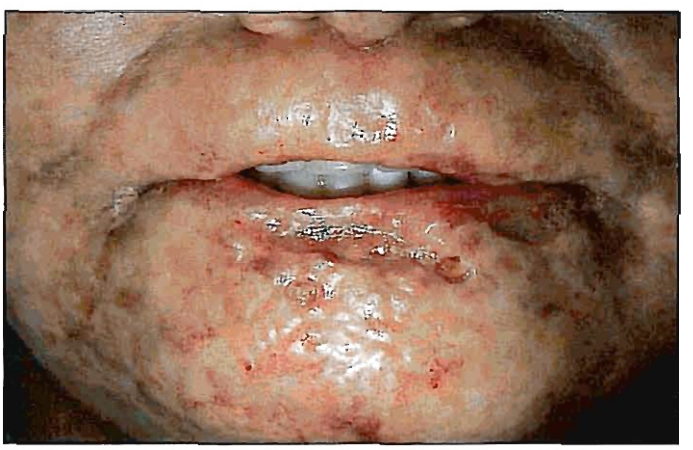


Fig. 3-42 Silicone granuloma.

For breast augmentation, silicone may be used as silastic implants. If trauma causes rupture of the bag, subcutaneous fibrotic nodules often develop. Human adjuvant disease and sclerodermatous reactions after such events have been reported; however, large reviews have failed to establish an etiologic link to silicone and connective tissue disease.

Treatment of silicone granulomas is often not successful. Surgical removal may lead to fistulas, abscesses, and marked deformity. Both minocycline 100 mg twice a day for several months and imiquimod cream have been anecdotally useful.

Bioplastique consists of polymerized silicone particles dispersed in a gel carrier. When used for lip augmentation, nodules may develop. Histologically, these are foreign body granulomas.

Mercury Granuloma Mercury may cause a foreign-body giant cell granuloma (Fig. 3-43) or membranous fat necrosis. Systemic toxicity may develop from cutaneous injury and may result in death.

Beryllium Granuloma This is seen as a chronic, persistent, granulomatous inflammation of the skin with ulceration that may follow accidental laceration, usually in an occupational setting. There is a known genetic susceptibility among those with a glutamic acid in position 69 of the human leukocyte antigen class II b chain.

Zirconium Granuloma This papular eruption involving the axillae is sometimes seen as an allergic reaction in those shaving their armpits and using a deodorant containing zirconium lactate. Although zirconium was eliminated from aerosol-type deodorants in 1978, aluminum–zirconium complex is present in antiperspirants and may lead to granulomatous papules in the axilla (Fig. 3-44). Additionally, various poison ivy lotions contain zirconium compounds. The lesions are brownish-red, dome-shaped, shiny papules suggestive of sarcoidosis. This is an acquired, delayed-type, allergic reaction resulting in a granuloma of the sarcoidal type. After many months the lesions involute spontaneously.

Silica Granuloma Automobile and other types of accidents may produce tattooing of dirt (silicon dioxide) into the skin, which induces silica granulomas (Fig. 3-45). These are usually black or blue papules or macules arranged in a linear fashion and are extremely unsightly, especially on the face. At times the granulomatous reaction to silica may be delayed

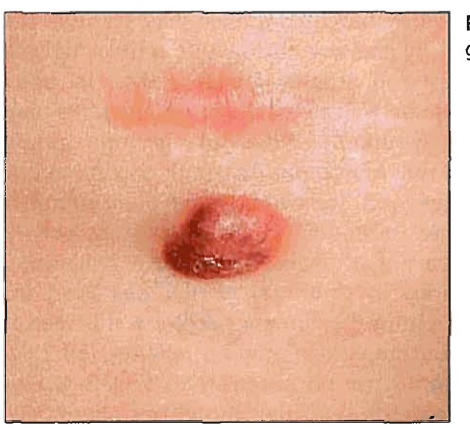


Fig. 3-43 Mercury granuloma.

for many years, until sensitization develops, and the ensuing dermatitis may be both chronic and disfiguring. They may be caused by amorphous or crystalline silicon dioxide (quartz), magnesium silicate (talcum), or complex polysilicates (asbestos). Talcum granulomas of the skin and peritoneum may develop after surgical operations from the talcum powder used on surgical gloves. Silica granulomas have a statistical association with systemic sarcoidosis, and silica may act as a stimulus for granuloma formation in patients with latent sarcoidosis.

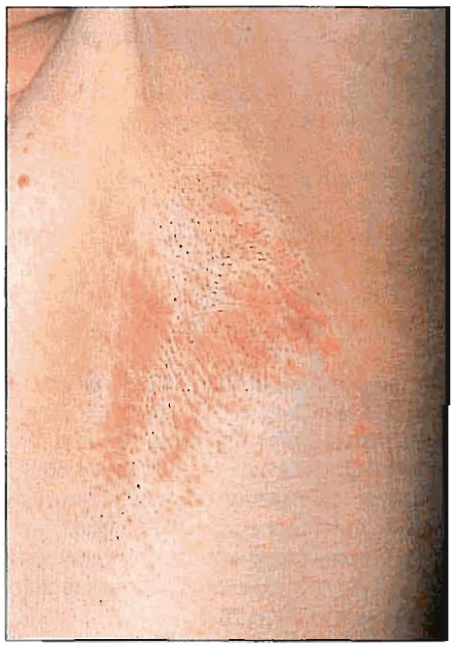


Fig. 3-44 Aluminum–zirconium granuloma secondary to antiperspirant use.

Removal of these granulomas is fraught with difficulties. The best method of care is immediate and complete removal to prevent these reactions. Excision and systemic steroids have been used but recurrences are common. Some reactions may subside spontaneously after 1 to 12 months. Dermabrasion is a satisfactory method for the removal of dirt accidentally embedded into the skin of the face or scalp.

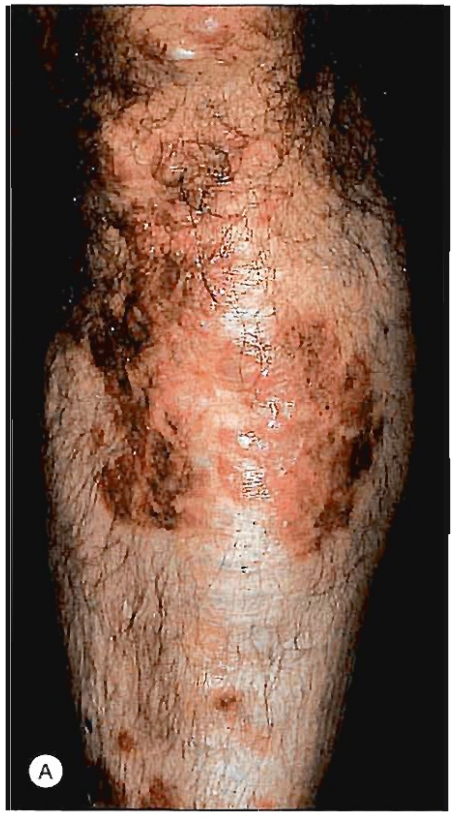
Carbon Stain

Discoloration of the skin from embedded carbon usually occurs in children from the careless use of firearms or firecrackers, or from a puncture wound by a pencil, which may leave a permanent black mark of embedded graphite, easily mistaken for a metastatic melanoma (Figs 3-46 and 3-47). The carbon is deposited at various depths, which produces a connective tissue reaction and even keloids.

Carbon particles may be removed immediately after their deposition using a toothbrush and forceps. This expeditious and meticulous early care results in the best possible cosmetic result. If the particles are left in place long enough, they are best removed using the Q-switched neodymium-YAG laser at 1064 nm. Suzuki reported success in 50 of 51 treated tattoos with an average of 1.7 treatments. However, microexplosions producing poxlike scars have occurred with each laser pulse. Alternatively, dermabrasion may be used.

Injected Filler Substances

Injectable enzyme-digested purified bovine collagen solution may be complicated by local, and uncommonly, disseminated granulomatous reactions (Fig. 3-48). The major histologic differential diagnosis is granuloma annulare. Additionally, abscess formation and local necrosis are risks that may occur on the order of 4 to 9 in 10,000 patients. Artecoll consists of



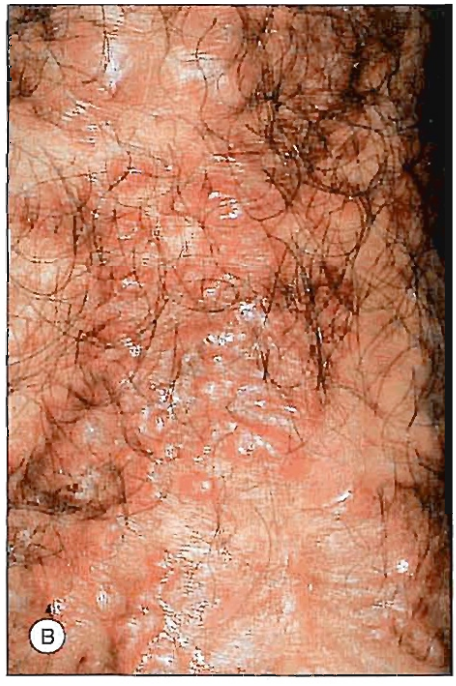


Fig. 3-45 *A* and *B*, Silica granuloma years after a motorcycle accident.

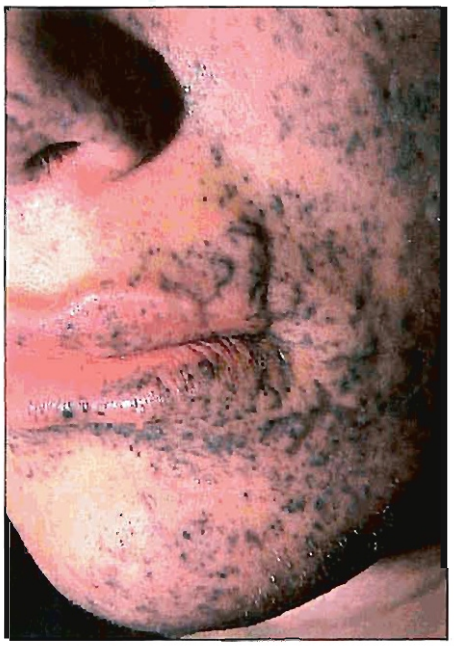


Fig. 3-46 Gunshot tattoo.

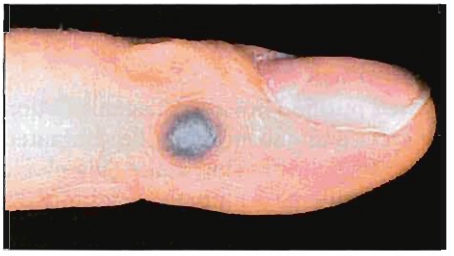


Fig. 3-47 Graphite granuloma. (Courtesy of J Fitzpatrick, MD)

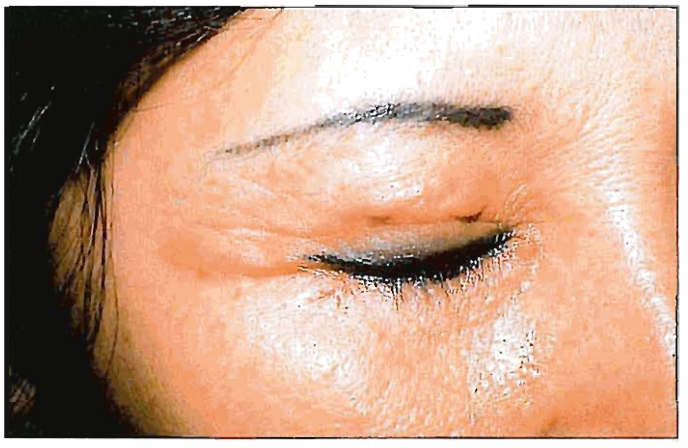


Fig. 3-48 Injected collagen reaction.

polymethyl–methacrylate microspheres suspended in bovine collagen. Palpable thickening and nodules may occur when it is used for lip augmentation. Similarly, both Bioplastique, consisting of polymerized silicone particles in a gel carrier, and injectable hyaluronic acid gel may also cause painful nodularity which is caused by a granulomatous reaction. Topical, intralesional or systemic steroids, at times augmented by tacrolimus, are helpful medical interventions.

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CHAPTER

4 Pruritus and Neurocutaneous Dermatoses

PRURITUS

Pruritus, commonly known as itching, is a sensation exclusive to the skin. It may be defined as the sensation that produces the desire to scratch. Approximately 10% of the afferent, fine, unmyelinated C neurons respond to pruritogenic and thermal stimuli and not to painful or mechanical stimuli. Itch sensations that arise in these nerve fiber endings in the subepidermal area are often due to inflammation, dryness or other skin damage. This type of itch is termed *pruritoceptive itch*. This sensation is then transmitted via the lateral spinothalamic tract to the thalamus and sensory cortex. *Neuropathic itch* arises because of disease located along the afferent pathway, such as post-zoster neuropathy. *Central*, or *neurogenic*, *itch* mechanisms may be as important as peripheral cutaneous mediators, as suggested by the increased effectiveness of sedating over nonsedating antihistamines in the treatment of atopic dermatitis, and the reported success of parenteral administration of naloxone in patients with severe cholestasis. The fourth type of itch, *psychogenic*, is the type observed in parasitophobia.

Itching may be elicited by many normally occurring stimuli, such as light touch, temperature change, and emotional stress. Chemical, mechanical, thermal, and electrical stimuli may also elicit itching. Pruritus is mediated by the release of chemical substances such as histamine, serotonin, and tryptase. Substance P is an 11 amino acid peptide that has been implicated in causing itching in some disorders. There are no specific antagonists of substance P; however, capsaicin depletes cutaneous nociceptor nerve endings of substance P after repeated topical application. Prostaglandin E lowers the threshold for histamine-induced pruritus, while enkephalins, pentapeptides that bind to opiate receptors in the brain, modulate pain and itching centrally. Certain opioids cause pruritus both peripherally and centrally, the latter likely through serotonin receptors. Interleukin-2 has also been implicated, particularly in atopic dermatitis.

Patterns of Itching

There are wide variations from person to person; indeed, in the same person there may be a variation in reactions to the same stimulus. Heat will usually aggravate preexisting pruritus. Stress, absence of distractions, anxiety, and fear may all enhance itching. It is apt to be most severe at the time of undressing for bed. Variations also occur by region of the skin. The ear canals, eyelids, nostrils, and perianal and genital areas are especially susceptible to pruritus.

Severe, persistent, or recurrent pruritus, with or without prior skin lesions, is often paroxysmal in character: sudden in onset, irresistibly severe, frequently awakening the patient, and stopping instantly and completely as soon as pain is induced by scratching. The pleasure of scratching is so intense that the patient—despite the realization that he/she is damaging the skin—is often unable to stop short of inflicting such damage (Fig. 4-1).

Itching of this distinctive type is characteristic of only a few dermatoses: lichen simplex chronicus, atopic dermatitis, nummular eczema, dermatitis herpetiformis, neurotic excoriations, eosinophilic folliculitis, uremic pruritus, subacute prurigo, and prurigo nodularis. In general, only these disorders produce such intense pruritus and scratching as to induce bleeding. In individual cases, other diseases may manifest such severe symptoms.

Treatment

General guidelines for therapy of the itchy patient include keeping cool, and avoidance of hot baths or showers and of wool clothing. The latter is a nonspecific irritant, as is xerosis. Many patients note itching increases after showers, where they wash with soap and then dry roughly. Using soap only in the axilla and inguinal area, patting dry, and applying a moisturizer will often help avoid such exacerbations. Patients often use an ice bag or hot water to calm pruritus; however, this irritates the skin, is effective only for short periods, and over time exacerbates the condition.

Relief of pruritus with topical remedies may be achieved with "caine" preparations. Many contain benzocaine, which may produce contact sensitization. Pramoxine in a variety of vehicles, lidocaine 5% ointment, EMLA ointment (a eutectic

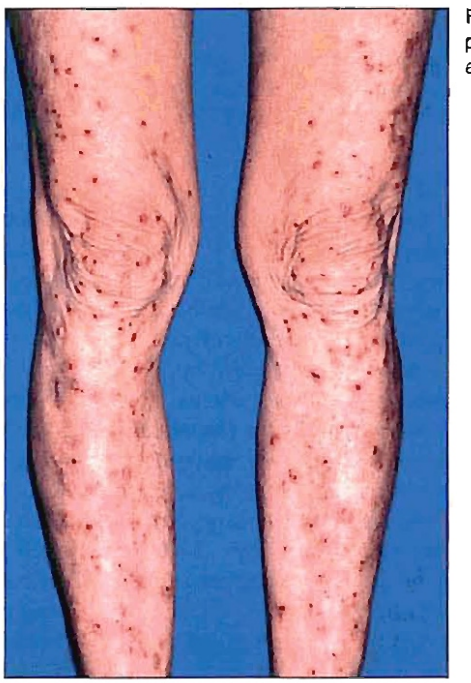

Fig. 4-1 Severe pruritus with excoriations.

mixture of lidocaine and prilocaine) or lidocaine gel are preferred anesthetics that may be quite useful in localized conditions. Topical antihistamines are generally not recommended, although doxepin cream may be effective for mild pruritus when used alone. Contact allergy, a burning sensation, and somnolence are risks when doxepin is used over large areas. Topical lotions that contain menthol or camphor can feel cool and improve pruritus. Capsaicin, by depleting substance P, can be effective, but the burning sensation present during initial use frequently causes patients to discontinue its use. Topical steroids appear to effect a decrease in itching via their anti-inflammatory action, and therefore are not effective in many pruritic disorders.

Phototherapy with ultraviolet (UV)B, UVA, and PUVA may be useful in a variety of dermatoses and pruritic disorders. Many oral agents are available to treat pruritus. The most frequently utilized by nondermatologists are the antihistamines. First-generation H_1 antihistamines, such as hydroxyzine and diphenhydramine, may be helpful in nocturnal itching, but their efficacy as antipruritics in many disorders, with the exception of urticaria, is disappointing. Doxepin is an exception in that it has the ability to reduce anxiety and depression and has utility in several pruritic disorders. Caution in prescribing such sedative types of antihistamines should be taken because of their impairment of cognitive ability. The nonsedating antihistamines and H_2 blockers are only effective in urticaria. Some successes have been reported with the opiate antagonists naloxone and naltrexone, and the serotonin antagonist ondansetron; however, the studies have mixed results and further investigations are needed.

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Greaves MW, et al: Pathophysiology of itching. Lancet 1996; 348:938.

Millikan LE: Pruritus: unapproved treatments or indications. Clin Dermatol 2000;18:149.

Schmelz M: Itch-mediators and mechanism. J Dermatol Sci 2002;28:91.

Yosipovitch G, et al: The diagnostic and therapeutic approach to idiopathic generalized pruritus. Int J Dermatol 1999;38:881.

Yosipovitch G, et al. Itch. Lancet 2003;361:690.

Internal Causes of Pruritus

Itching may be present as a symptom in a number of internal disorders. The intensity and duration of itching vary from one disease to another. Among the most important internal causes of itching are liver disease, especially obstructive and hepatitis C (with or without evidence of jaundice or liver failure), renal failure (uremic pruritus), hypo- and hyperthyroidism, hematopoietic diseases such as iron-deficiency anemia, polycythemia vera, lymphoma (especially Hodgkin's disease), leukemia, myeloma, internal malignancies, intestinal parasites, carcinoid, multiple sclerosis, acquired immunodeficiency syndrome (AIDS), and neuropsychiatric diseases, with anorexia nervosa prominent among the latter. Diabetes mellitus is frequently listed as an internal cause of pruritus but most individuals with diabetes do not itch. If a diabetic patient has pruritus with no primary skin lesions, other causes of pruritus should be investigated.

The pruritus of Hodgkin's disease is usually continuous and at times is accompanied by severe burning. The incidence of pruritus is between 10% and 25% and is the first symptom of this disease in 7% of patients. Its cause is unknown. The pruritus of leukemia, except for chronic lymphocytic leukemia, has a tendency to be less severe than in Hodgkin's disease.

Internal cancer may be found in patients with generalized pruritus that is unexplained by skin lesions. However, no significant overall increase of malignant neoplasms can be found in patients with idiopathic pruritus, and no general efforts at cancer screening are warranted. A suggested work-up for chronic, generalized pruritus includes taking a complete history and performing a thorough physical examination; tests include a complete blood count (CBC) and differential thyroid, liver, and renal panels, hepatitis C serology, an human immunodeficiency virus (HIV) antibody (if risk factors are present), urinalysis, stool for occult blood, serum protein electrophoresis, and chest x-ray evaluation. Presence of eosinophilia on the CBC is a good screen for parasitic diseases, but if the patient has been on systemic corticosteroids, blood eosinophilia may not be a reliable screen for parasitic diseases and stool samples for ova and parasites should be submitted.

Etter L, et al: Pruritus in systemic disease. Dermatol Clin 2002; 20:459.

Fisher DA, et al: Pruritus as a symptom of hepatitis C. J Am Acad Dermatol 1995;32:629.

Lidsone V, et al: Pruritus in cancer patients. Cancer Treat Rev 2001;27:305.

Lober CW: Pruritus and malignancy. Clin Dermatol 1993;11:125.

Paul R, et al: Itch and malignancy prognosis in generalized pruritus: a 6-year follow-up of 125 patients. J Am Acad Dermatol 1987;16:1179.

Chronic Renal Failure and Uremic Pruritus Chronic renal failure is the most common internal systemic cause of pruritus; 15% to 49% of patients with chronic renal failure have pruritic symptoms. Uremic pruritus is often generalized, intractable, and severe. Chronic distressing itch is less common as dialysis techniques have improved, with as few as 10% to 40% now affected, down from twice that years ago. Dialysis-associated pruritus may be episodic, mild, or localized to the dialysis catheter site, face, or legs.

The mechanism of pruritus associated with chronic renal failure and uremia may be multifactorial. Xerosis, secondary hyperparathyroidism, increased serum histamine levels, hypervitaminosis A, iron-deficiency anemia, and neuropathy have been implicated. Complications such as Kyrle's disease, lichen simplex chronicus, and prurigo nodularis may develop and contribute to the degree and severity of pruritus.

Uremic pruritus responds well to narrow band UVB phototherapy but often recurs after discontinuation. Many patients have concomitant xerosis and aggressive use of emollients may help them. Gabapentin given three times weekly at the end of hemodialysis sessions is safe and effective. Topical tacrolimus has reported efficacy in a small number of patients. In recalcitrant disease, the options include cholestyramine 5 g twice a day, or activated charcoal 6 g/day. Naltrexone and ondansetron were both reported useful in

initial trials, but subsequent studies indicate they are ineffective. Thalidomide, topical capsaicin, and intravenous lidocaine are less practical options. Renal transplantation will relieve uremic pruritus.

Ada S, et al: Treatment of uremic pruritus with narrow band UVB. J Am Acad Dermatol 2005;53:149.
Gunel AI, et al: Gabapentin therapy for pruritus in haemodialysis patients. Nephrol Dial Transplant 2004;19:3;37.
Mettang T, et al. Uraemic pruritus. Nephrol Dial Transplant 2002; 17:1558.
Murphy M, et al: A randomized placebo-controlled, double-blind trial of ondansetron in renal itch. Br J Dermatol 2003;148:314.
Robinson-Bostom L, et al: Cutaneous manifestations of end-stage renal disease. J Am Acad Dermatol 2002;43:975.
Szepietowski JC, et al: Uremic pruritus. J Dermatol 2002;29:621.

Biliary Pruritus Chronic liver disease with obstructive jaundice may cause severe generalized pruritus; 20% to 50% of patients with jaundice have pruritus. This itching is probably caused by central mechanisms. This is suggested by elevated central nervous system (CNS) opioid peptide levels, downregulation of opioid peptide CNS receptors, and the therapeutic effectiveness of naloxone, naltrexone, or nalmefene. The serum-conjugated bile acid levels do not correlate with the severity of pruritus.

Primary Biliary Cirrhosis

Primary biliary cirrhosis occurs almost exclusively in women older than 30 years of age. Itching may begin insidiously; with time, extreme pruritus develops. This almost intolerable itching is accompanied by jaundice and a striking melanotic hyperpigmentation of the entire skin; the patient may turn almost black, except for a hypopigmented "butterfly" area in the upper back. Xanthomatosis in the form of plane xanthomas of the palms (Fig. 4-2), xanthelasmas, and tuberous xanthomas over the joints may be seen.

Dark urine, steatorrhea, and osteoporosis occur frequently. Serum bilirubin, alkaline phosphatase, serum ceruloplasmin, serum hyaluronate, and cholesterol values are increased. The antimitochondrial antibody test is positive.

The disease is usually relentlessly progressive with the development of hepatic failure and esophageal varices. The latter may produce hemorrhage and even death. Several cases have been accompanied by scleroderma.

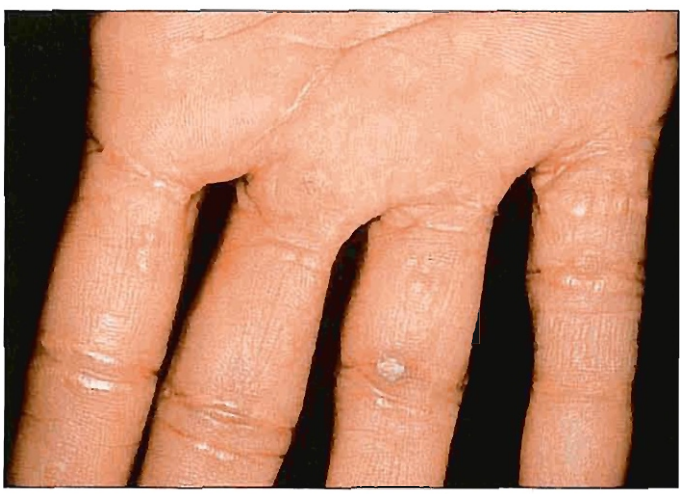

Fig. 4-2 Primary biliary cirrhosis with plane xanthomas. (Courtesy of James Fitzpatrick, MD)

To treat the pruritus, opioid antagonists, such as naltrexone 50 mg/day, have proven efficacy. Additionally, cholestyramine 4 g one to three times a day, UVB twice weekly, and rifampin 300 to 450 mg/day have been reported to be effective. The latter should be used with caution as it may cause hepatitis. Ondansetron was not effective in a controlled trial. When used to treat primary biliary cirrhosis, methotrexate and colchicine both improved pruritus, with the former having a better response. Liver transplantation is the definitive treatment for end-stage disease and provides dramatic relief from the severe pruritus.

Coyle S, et al: Hepatobiliary pruritus: what are effective treatments? J Am Acad Dermatol 1995;33:801.
Kaplan MM, et al: A prospective trial of colchicine and methotrexate in the treatment of primary biliary cirrhosis. Gastroenterology 1999;117:1173.
Jones EA, et al: The pathogenesis and treatment of pruritus and fatigue in patients with PBC. Eur J Gastroenterol Hepatol 1999;11:623.
O'Donohue JW, et al: A controlled trial of ondansetron in the pruritus of cholestasis. Aliment Pharmacol Ther 2005;21:1041.
Prince MI, et al: Hepatitis and liver dysfunction with rifampicin therapy for pruritus in primary biliary cirrhosis. Gut 2002; 50:436.
Wolfhagen FH, et al: Oral naltrexone treatment for cholestatic pruritus: a double-blind, placebo-controlled study. Gastroenterology 1997;113:1264.
Yerushalmi B, et al: Use of rifampin for severe pruritus in children with chronic cholestasis. J Pediatr Gastroenterol Nutr 1999; 29:442.
Zylicz Z, et al: Codeine for pruritus in primary biliary cirrhosis. Lancet 1999;33:813.

Polycythemia Vera More than one-third of patients with polycythemia vera report pruritus; it is usually induced by temperature changes or several minutes after bathing. The cause is unknown.

Aspirin has been shown to provide immediate relief from itching; however, there is a risk of hemorrhagic complications, and low doses are recommended. PUVA and broadband UVB have given good results; however, narrow-band UVB is safer and also effective. A marked improvement was noted after an average of six treatments, while a complete remission occurred within 2 to 10 weeks in 8 of 10 treated patients. Paroxetine, 20 mg/day, produced clearing or near-complete clearing in a series of nine patients. Interferon (IFN)-α2 has been shown to be effective for treating the underlying disease and associated pruritus. Myelosuppressive therapy is useful for long-term control of symptoms.

Baldo A, et al: Narrowband (TL-01) ultraviolet B phototherapy for pruritus in polycythaemia vera. Br J Dermatol 2002; 147:979.
Hernandez-Nunez A, et al: Water-induced pruritus in haematologically controlled polycythaemia vera. J Dermatol Treat 2001;12:107.
Muller EW, et al: Long-term treatment with interferon-alpha 2b for severe pruritus in patients with polycythaemia vera. Br J Haematol 1995;89:313.

Tefferi A, et al: Selective serotonin reuptake inhibitors are effective in the treatment of polycythemia vera-associated pruritus. Blood 2002;99:2627.

PRURITIC DERMATOSES

Winter Itch

Asteatotic eczema, eczema craquelé, pruritus hiemalis, and xerotic eczema are other names given to this pruritic condition. It is characterized by generalized body pruritus that usually first manifests and is most severe on the arms and legs (Fig. 4-3). The skin is dry with fine flakes (Fig. 4-4). It tends to spare the face, scalp, groin, and axilla. The pretibial regions are particularly susceptible and may develop eczema craquelé, exhibiting fine cracks in the eczematous area that resemble the cracks in old porcelain dishes.

Frequent and lengthy bathing with plenty of soap during the winter is the most frequent cause. This is especially prevalent in elderly persons, whose skin has a decreased rate of repair of the epidermal water barrier and whose sebaceous glands are less productive. Low humidity in overheated rooms during cold weather contributes to this condition. In a study of 584 elderly individuals, the prevalence of asteatosis (28.9%) was second only to seborrheic dermatitis as the most common finding.

Treatment consists of educating the patient regarding using soap only in the axilla and inguinal area, and lubrication of the skin with emollients immediately after showering. Lactic acid- or urea-containing preparations are helpful after-bath applications for some patients; however, they may cause irritation and worsening of itching in patients with erythema and eczema.

For those with more severe symptoms, long-standing disease, or a significant inflammatory component, a regimen referred to as "soaking and smearing," is dramatically effective. The patient soaks in a tub of plain water at a comfortable temperature for 20 min prior to bedtime. Immediately on exiting the tub, without drying, triamcinolone, 0.025% to 0.1%, ointment is applied to the wet skin. This will trap the moisture, lubricate the skin, and allow for excellent penetration of the steroid component. An old pair of pajamas is then donned and the patient will note relief even on the first night. The night-time soaks are repeated for several nights after which the ointment alone suffices, with the maintenance therapy of limited soap use and moisturization after showering. Plain petrolatum may be used as the lubricant after the soaking if simple dryness without inflammation is present.

Gutman A, et al: Soak and smear therapy. Arch Dermatol (In press).

Pruritus Ani

Pruritus is often centered in the anal or genital area (less commonly in both), with little or no pruritus elsewhere. Anal neurodermatitis is characterized by paroxysms of violent itching, at which time the patient may tear at the affected area until bleeding is induced. Manifestations are identical to those of lichen simplex chronicus elsewhere on the body. There should always be a thorough search for specific etiologic factors.

Allergic contact dermatitis occurs from various medicaments, fragrance in toilet tissue or preservatives in moist toilet tissue, with one study reporting 18 of 40 consecutive patients being patch-test positive. Also, irritant contact dermatitis from gastrointestinal contents, such as hot spices or cathartics, or failure to adequately cleanse the area after

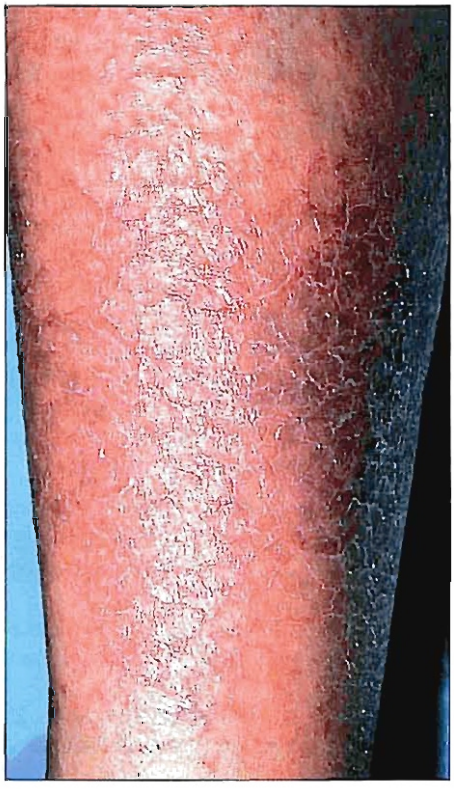

Fig. 4-3 Dry skin of the leg.

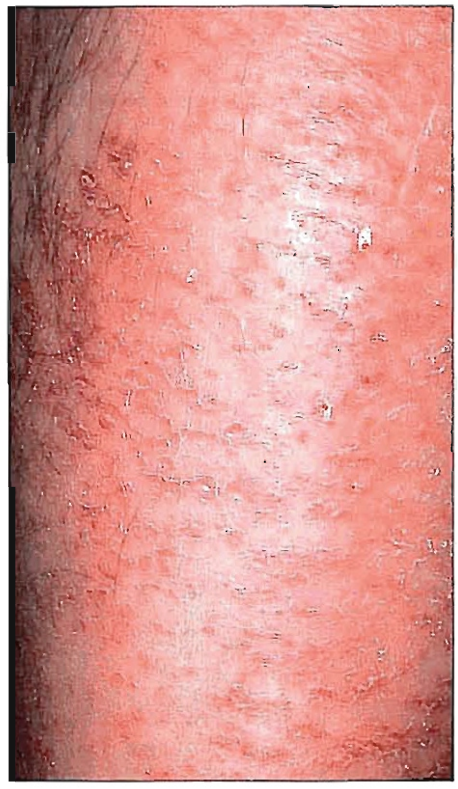

Fig. 4-4 Eczema craquelé.

bowel movements may be causes. Anatomic factors may lead to leakage of rectal mucus onto perianal skin and thus promote irritation. Physical changes such as hemorrhoids, anal tags, fissures, and fistulas may aggravate or produce pruritus. Anal warts and condyloma latum (syphilis) may be causative agents, although these rarely itch. Anal gonorrhea, especially in men, is frequently overlooked when pruritus is the only symptom.

Mycotic pruritus ani is characterized by fissures and a white, sodden epidermis. Scrapings from the anal area are examined directly with potassium hydroxide mounts for fungi. Cultures for fungi are also taken. *Candida albicans*, *Epidermophyton floccosum*, and *Trichophyton rubrum* are frequent causative fungi in this area. Other sites of fungal infection, such as the groin, toes, and nails, should also be investigated. Erythrasma in the groin and perianal regions may also occasionally produce pruritus. The diagnosis is established by coral red fluorescence under the Wood's light. Beta-hemolytic streptococcal infections have also been implicated. The use of tetracyclines may cause pruritus ani, most often in women, by inducing candidiasis. Diabetic patients are susceptible to perianal candidiasis.

Pinworm infestations may cause pruritus ani, especially in children, and sometimes in their parents. Nocturnal pruritus is most prevalent. Other intestinal parasites such as *Taenia solium*, *T. saginata*, amebiasis, and *Strongyloides stercoralis* may produce pruritus. Pediculosis pubis may cause anal itching; however, attention is focused by the patient on the pubic area, where itching is most severe. Scabies may be causative, but will usually also involve the finger webs, wrists, axillae, areolae, and genitals.

Seborrheic dermatitis of the anal area may cause pruritus ani. It also involves other areas, such as the inguinal regions, scalp, chest, and face. Similarly, lichen planus may involve the perianal region. Anal psoriasis may cause itching. The perianal lesions are usually sharply marginated, and psoriatic lesions may be present on other parts of the body. Other frequent sites for psoriasis should be examined, such as the fingernails.

A thorough examination for malignancies should be carried out; extramammary Paget's disease is easily overlooked.

Treatment

Meticulous toilet care should be followed no matter what the cause of the itching. After defecation, the anal area should be cleansed with soft cellulose tissue paper and, whenever possible, washed with mild soap and water. Cleansing with wet toilet tissue is advisable in all cases. Medicated cleansing pads such as Tucks should be used regularly. A variety of moist toilet tissue products are now available. Contact allergy to preservatives in these products is occasionally a problem. An emollient lotion, Balneol, is helpful for cleansing without producing irritation.

Except in psychogenic pruritus ani, once the etiologic agent has been identified, a rational and effective treatment regimen may be started. Topical corticosteroids are effective for most noninfectious types of pruritus ani; however, use of topical tacrolimus ointment will frequently suffice and is safer. Pramoxine hydrochloride, a nonsteroidal topical anesthetic, is also often effective, especially in a lotion form combined with hydrocortisone. Capsaicin 0.006% is also effective in some cases.

Dasan S, et al: Treatment of persistent pruritus ani in a combined colorectal and dermatological clinic. Br J Surg 1999;86:1337.
Giordano M, et al: Pruritus ani. Minerva Chir 1999;54:885.
Redondo P, et al: Pruritus ani in an elderly man. Extramammary Paget's disease. Arch Dermatol 1995;131:952.
Weismann K, et al: Pruritus ani caused by beta-haemolytic streptococci. Acta Derm Venereol (Norway) 1996;76:415.

Pruritus Scroti

The scrotum of an adult is relatively immune to dermatophyte infection, but it is a favorite site for circumscribed neurodermatitis (lichen simplex chronicus) (Fig. 4-5). Psychogenic pruritus is probably the most frequent type of itching seen. Why it preferentially affects this area, or in women the vulva, is unclear. Lichenification may result, be extreme, and persist for many years despite intensive therapy.

Infectious conditions may complicate or cause pruritus on the scrotum but are less common than idiopathic scrotal pruritus. Fungal infections, except candidiasis, usually spare the scrotum. When candidal infection affects the scrotum, burning rather than pruritus is frequently the primary symptom. The scrotum is eroded, weepy, or crusted. The scrotum may be secondarily, and to a lesser degree, affected in cases of pruritus ani, but this pruritus usually affects the midline, extending from the anus along the midline to the base of the scrotum, rather than the dependent surfaces of the scrotum, where pruritus scroti usually occurs. Scrotal pruritus may be associated with allergic contact dermatitis from topical medications, including topical steroidal agents.

Topical corticosteroids are the mainstay of treatment, but caution should be exercised. The "addicted scrotum syndrome," may be caused by the use of high-potency topical steroidal agents. Although this is usually seen after chronic use, even short-term high-potency steroid medications may produce this syndrome. As with facial skin, high-potency steroids used on the scrotum can result in addictive skin: every time the patient attempts to taper off the steroid, severe burning and redness occurs. Topical tacrolimus ointment is just as useful in overcoming the effects of overuse of potent topical steroids as when used in the steroid-induced

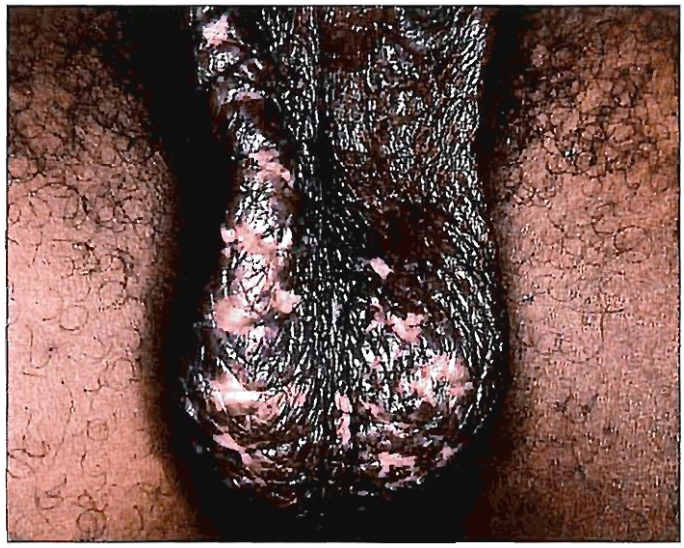

Fig. 4-5 Pruritus scroti.

red face. The scrotum is frequently in contact with inner thigh skin, producing areas of occlusion, which increases the penetration of topical steroidal agents. If topical steroids are utilized in this area, those of low potency are favored. Other useful nonsteroidal alternatives include topical pramoxine, doxepin, or simple petrolatum.

Pruritus Vulvae

The vulva is a common site for pruritus of different causes. Pruritus vulvae is the counterpart of pruritus scroti. In a prospective series of 141 women with chronic vulvar symptoms, the most common causes were unspecified dermatitis (54%), lichen sclerosus (13%), chronic vulvovaginal candidiasis (10%), dysesthetic vulvodynia (9%), and psoriasis (5%). In prepubertal children such itching is most frequently irritant in nature and they generally benefit from education about improved hygienic measures.

Vaginal candidiasis is a frequent cause of pruritus vulvae. This is true especially during pregnancy and when oral antibiotics are taken. The inguinal, perineal, and perianal areas may be affected. Microscopic examination for *Candida albicans* and cultures for fungus should be performed. *Trichomonas vaginitis* may cause vulvar pruritus. For the detection of *T. vaginalis*, examination of vaginal secretions is often diagnostic. The organism is recognized by its motility, size (somewhat larger than a leukocyte), and piriform shape.

Contact dermatitis from sanitary pads, contraceptives, douche solutions, fragrance, colophony, corticosteroids, and a partner's condoms are some of the causes of vulvar pruritus. Urinary incontinence should also be considered. Lichen sclerosus is another frequent cause of pruritus in the genital area in middle-aged and elderly women. Lichen planus may involve the vulva, resulting in pruritus and mucosal changes, including resorption of the labia minora and atrophy.

When burning rather than itching predominates, the patient should be evaluated for signs of sensory neuropathy.

Treatment

Candidiasis is treated with topical anticandidal agents. A single 150-mg dose of fluconazole is effective for acute candidiasis, but chronic disease with pruritus may require 150 mg/day for 5 days followed by 150 mg/week for several months. *Trichomonas* infection is best treated with oral metronidazole or by vaginal gel or inserts. Lichen sclerosus responds best to pulsed dosing of high-potency topical steroids or to topical tacrolimus. Topical steroidal agents and topical tacrolimus may be used to treat psychogenic pruritus or irritant or allergic reactions. High-potency topical steroids are effective in treating lichen planus, but other options are also available (see Chapter 12). Topical lidocaine, pramoxine, or an oral tricyclic antidepressant may be helpful in select cases. Any chronic skin disease that does not appear to be responding to therapy should prompt a biopsy. Referral to a physician specializing in vulvar diseases should be considered for patients whose condition is unresponsive to therapy. In chronic idiopathic forms hypnosis therapy may be useful.

Foster DC: Vulvar disease. Obstet Gynecol 2002;100:145.

Lewis FM, et al: Contact sensitivity in pruritus vulvae: a common and manageable problem. Contact Dermat (Denmark) 1994; 31:264.

Paek SC, et al: Pruritus vulvae in prepubertal children. J Am Acad Dermatol 2001;44:795.

Weichert GF: An approach to the treatment of anogenital itch. Dermatol Ther 2004;17:129.

Puncta Pruritica (Itchy Points)

"Itchy points" consists of one or two intensely itchy spots in clinically normal skin, sometimes followed by the appearance of seborrheic keratoses at exactly the same site. Others believe puncta pruritica is a variant of notalgia paresthetica. Curettage, cryosurgery, or punch biopsy of the itchy points may cure the condition.

Boyd AS, et al: Puncta pruritica. Int J Dermatol 1992;31:370.

Crissey JT: Puncta pruritica. Int J Dermatol 1992;31:166.

Aquagenic Pruritus and Aquadynia

Aquagenic pruritus is itching evoked by contact with water of any temperature. Degranulation of mast cells and increased concentration of histamine and acetylcholine in the skin after contact with water are found. In most cases there is severe, prickling discomfort within minutes of exposure to water or on cessation of exposure to water, and there is often a family history of similar symptoms.

Aquagenic pruritus must be distinguished from xerosis or asteatosis and an initial trial of "soaking and smearing" as described for winter itch above is recommended. The condition may be associated with polycythemia vera, hypereosinophilic syndrome, juvenile xanthogranuloma, and myelodysplastic syndrome. Treatment options include the use of antihistamines, systemic steroids, sodium bicarbonate dissolved in bath water, propranolol, and UVB or PUVA phototherapy. One patient found tight-fitting clothing settled the symptoms after only 5 min.

Shelley et al reported two patients with widespread burning pain that lasted 15 to 45 min after water exposure. They called this reaction *aquadynia* and consider the disorder a variant of aquagenic pruritus. Clonidine and propranolol seemed to provide some relief.

du Peloux Menage H, et al: Aquagenic pruritus. Semin Dermatol 1995;14:313.

Goodkin R, et al: Repeated PUVA treatment of aquagenic pruritus. Clin Exp Dermatol 2002;27:164.

Shelley WB, et al: Aquadynia. J Am Acad Dermatol 1998;38:357.

Wolf R, et al: Variations in aquagenic pruritus and treatment alternatives. J Am Acad Dermatol 1988;18:1081.

Scalp Pruritus

Pruritus of the scalp, especially in elderly persons, is rather common. When excoriations, scaling, or erythema is not found, seborrheic dermatitis, psoriasis, dermatomyositis or lichen simplex chronicus cannot be diagnosed. The cause of this is unknown in most cases, but some represent chronic folliculitis. Treatment is challenging. Topical tar shampoos, salicylic acid shampoos, corticosteroid topical gels, mousse, shampoos and liquids, and in severe cases with localized itch, an intralesional injection of corticosteroid suspension can sometimes provide relief. Minocycline or oral antihistamines may be helpful. In other patients, low doses of antidepressants, such as doxepin, are useful.

Hoss D, et al: Scalp dysethesia. Arch Dermatol 1998;134:327.

Drug-Induced Pruritus

Medications should be considered a possible cause of protracted pruritus with or without a skin eruption. For instance, of 109 patients treated for malaria 60% developed chloroquine-induced pruritus without associated cutaneous findings. The pruritic reaction was generalized, with a peak intensity 25 h after dosing. Antihistamines were ineffective. The pruritus at times can be severe enough to necessitate withdrawal of the medication. Others have reported chloroquine- and amodiaquine-induced pruritus in 8% to 15% of patients in the acute, febrile stages of malaria.

Hydroxyethyl starch (HES) is used as a volume expander, a substitute for human plasma. One-third of all patients treated will develop severe pruritus with long latency of onset (3–15 weeks) and persistence. Up to 30% of patients have localized symptoms. Antihistamines are ineffective. HES deposits are found in the skin of all patients tested, distributed in dermal macrophages, endothelial cells of blood and lymph vessels, perineural cells, endoneural macrophages of larger nerve fascicles, keratinocytes, and Langerhans cells. Substance P release from macrophages is not increased, and basophil degranulation test results are negative, suggesting that the actions of HES-induced pruritus result from the direct stimulation of cutaneous nerves.

Gall H, et al: Clinical and pathophysiological aspects of hydroxyethyl starch-induced pruritus evaluation of 96 cases. Dermatology (Switz) 1996;192:222.

Jurecka W, et al: Hydroxyethyl starch deposits in human skin: a model for pruritus? Arch Dermatol Res 1993;285:13.

Osifo NG: Chloroquine-induced pruritus among patients with malaria. Arch Dermatol 1984;120:80.

Chronic Pruritic Dermatoses of Unknown Cause

Prurigo simplex is the preferred term for the chronic itchy idiopathic dermatosis described below. Papular dermatitis, subacute prurigo, "itchy red bump" disease, and Rosen papular eruption in black men most likely represent variations of prurigo simplex. The term *prurigo* continues to lack nosologic precision.

Prurigo is characterized by the lesion known as the *prurigo papule*, which is dome-shaped and topped with a small vesicle. The vesicle is usually present only transiently because of its immediate removal by scratching, so that a crusted papule is more frequently seen. Prurigo papules are present in various stages of development and are seen mostly in middle-aged or elderly persons of both sexes. The trunk and extensor surfaces of the extremities are favorite sites, symmetrically distributed. Other areas include the face, neck, lower trunk, and buttocks. The lesions usually appear in crops, so that papulovesicles and the late stages of scarring may be seen at the same time.

The histopathology of prurigo simplex is nonspecific. Spongiosis accompanied by a perivascular mononuclear infiltrate with some eosinophils is often found.

Many conditions may cause pruritic erythematous papules. Scabies, atopic dermatitis, insect bite reactions, papular urticaria, dermatitis herpetiformis, contact dermatitis, pityriasis lichenoides et varioliformis acuta (PLEVA), transient acantholytic dermatosis (TAD), papuloerythroderma of Ofuji, dermatographism, and physical urticarias should be considered. Biopsy may be helpful in differentiating dermatitis herpetiformis, PLEVA, TAD, and, on occasion, scabies (a scabies preparation is less invasive).

Treatment

The medications for initial treatment of prurigo simplex and its variants should be topical corticosteroids and oral antihistamines. Early in the disease process, moderate-strength steroids should be used; if the condition is found to be unresponsive, a change to high-potency forms is indicated. Rebound may occur. Intralesional injection of triamcinolone will eradicate individual lesions. For more recalcitrant disease, UVB or PUVA therapy may be beneficial.

Clark AR, et al: Papular dermatitis (subacute prurigo, "itchy red bump" disease). J Am Acad Dermatol 1998;38:929.

Streit V, et al: Foil bath PUVA in the treatment of prurigo simplex subacuta. Acta Dermatol Venereol (Norway) 1996;76:319.

Prurigo Pigmentosa Prurigo pigmentosa is a rare dermatosis of unknown cause characterized by the sudden onset of erythematous papules that leave reticulated hyperpigmentation when they heal. The condition mainly affects Japanese women and occurs in the spring and summer. Only a few cases have been reported in white persons. Recurrence or exacerbations are common; the areas most frequently involved are the upper back, nape, clavicular region, and chest. Mucous membranes are spared. Histology of early lesions shows neutrophils in the dermal papillae and epidermis. Following this a lichenoid dermatitis with variable psoriasiform hyperplasia occurs. Direct immunofluorescence yields negative findings. The cause is unknown. Minocycline 100 to 200 mg/day is the treatment of choice and may prevent recurrences. Dapsone is also effective.

Boer A, et al: Prurigo pigmentosa. Am J Dermatopathol 2003; 25:117.

Gur-Toy G, et al: Prurigo pigmentosa. Int J Dermatol 2002; 41:288.

Roehr P, et al: A pruritic eruption with reticular pigmentation. Prurigo pigmentosa. Arch Dermatol 1993;129:370.

Yanguas I, et al: Prurigo pigmentosa in a white woman. J Am Acad Dermatol 1996;35:473.

Papuloerythroderma of Ofuji A rare disorder most commonly found in Japan, papuloerythroderma of Ofuji is characterized by pruritic papules that spare the skinfolds, producing bands of uninvolved cutis, the so-called deck-chair sign. Frequently there is associated blood eosinophilia. This condition is considered by some to be a form of erythroderma in the elderly and a paraneoplastic syndrome by others. Skin biopsies reveal a dense lymphohistiocytic infiltrate, eosinophils in the papillary dermis, and increased Langerhans cells (S-100 positive). Reported malignancies include T-cell lymphomas, B-cell lymphomas, Sézary syndrome, and visceral carcinomas. Not enough cases have been reported to determine a true association with malignancies.

The differential diagnosis is the same as for prurigo simplex. Systemic steroids are the treatment of choice, and may result in long-term remissions. Topical steroids, tar derivatives, emollients, systemic retinoids, cyclosporin, and PUVA may also be therapeutic.

DeVries JH, et al: Ofuji papuloerythroderma associated with Hodgkin's lymphoma. Br J Dermatol 2002;147:186.
Fujii K, et al: Etretinate therapy for papuloerythroderma. Eur J Dermatol 1999;9:610.
Nazzari G, et al: Papuloerythroderma (Ofuji). J Am Acad Dermatol 1992;26:499.

Lichen Simplex Chronicus As a result of long-continued rubbing and scratching, more vigorously than a normal pain threshold would permit, the skin becomes thickened and leathery (Fig. 4-6). The normal markings of the skin become exaggerated, so that the striae form a criss-cross pattern, and between them a mosaic is produced composed of flat topped, shiny, smooth, quadrilateral facets. This change, known as *lichenification*, may originate on seemingly normal skin or may develop on skin that is the site of another disease, such as atopic or allergic contact dermatitis or ringworm. Such underlying etiologies should be sought and if found, treated specifically. Paroxysmal pruritus is the main symptom. This is known as *lichen simplex chronicus*.

Circumscribed, lichenified, pruritic patches that may develop on any part of the body characterize lichen simplex chronicus, also known as *neurodermatitis circumscripta*. The disease has a predilection for the back and sides of the neck, and the extremities—especially the wrists and ankles. At times, the eruption is decidedly papular, resembling lichen planus; in other instances, the patches are excoriated, slightly scaly or moist, and, rarely, nodular.

Several distinctive types are recognized. Lichen simplex nuchae often occurs on the back of the neck. It is not unusual to find this area excoriated and bleeding. Nodular neurodermatitis of the scalp consists of multiple pruritic and excoriated papules and may be called prurigo of the scalp. The nodules or papules may ooze and form crusts and scales. The vulva, scrotum, and anal area can be sites of severe neurodermatitis. Genital and anal areas, however, are seldom involved at the same time. An upper eyelid, the orifice of one or both ears, or a palm or sole may also be involved; the ankle flexure is also a favorite site. Persistent rubbing of the shins or upper back may result in dermal deposits of amyloid and the subsequent development of lichen and macular amyloidosis, respectively.

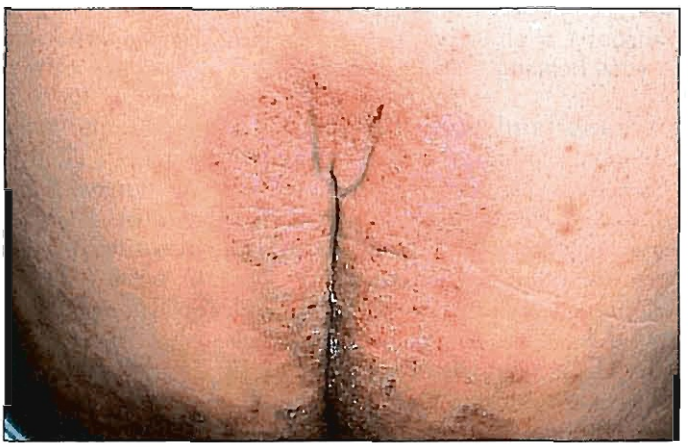

Fig. 4-6 Lichen simplex chronicus. (Courtesy of James Fitzpatrick, MD)

To what extent mechanical trauma plays a role in producing the original irritation is not known. The onset of this dermatosis is usually gradual and insidious. Chronic scratching of a localized area is a response to unknown factors; however, stress and anxiety have long been thought important.

Treatment

Essentially, cessation of pruritus is the goal. It is important to stress the need for the patient to avoid scratching the areas involved if the sensation of itch is ameliorated. Only in this way will the habitual itch–scratch cycle be broken. Recurrences are frequent, even after the most thorough treatment, and there are instances in which the clearance of one lesion will see the onset of another elsewhere.

High-potency agents such as clobetasol propionate, diflorasone diacetate, or betamethasone dipropionate cream or ointment should be used initially but not indefinitely because of the potential for steroid-induced atrophy. Occlusion of medium-potency steroids may be beneficial. Use of a steroid-containing tape to provide both occlusion and anti-inflammatory effects may have benefit. Treatment can be shifted to the use of medium-to-lower strength topical steroid creams as the lesions resolve. Topical doxepin cream, capsaicin cream or tacrolimus ointment provide significant antipruritic effects and are good adjunctive therapies. Botulinum toxin type A injection was curative in three patients within 2 to 4 weeks.

Intralesional injections of triamcinolone suspension, using a concentration of 5 or (with caution) 10 mg/mL may be required. Too superficial injection invites the twin risks of epidermal and dermal atrophy and depigmentation, which may last for many months. The suspension should not be injected into infected lesions for fear of causing abscesses. In the most severe cases, complete occlusion with an Unna boot may break the cycle.

Heckmann M, et al: Botulinum toxin type A injection in the treatment of lichen simplex. J Am Acad Dermatol 2002;46:617.
Jacob CI, et al: Strongyloides stercoralis infection presenting as generalized prurigo nodularis and lichen simplex chronicus. J Am Acad Dermatol 1999;41:357.
Jones RO: Lichen simplex chronicus. Clin Podiatr Med Surg 1996;13:47.

Prurigo Nodularis Prurigo nodularis is a disease with multiple itching nodules situated chiefly on the extremities, especially on the anterior surfaces of the thighs and legs (Fig. 4-7). A linear arrangement is common. The individual lesions are pea sized or larger, firm, and erythematous or brownish. When fully developed they become verrucous or fissured. The course of the disease is chronic and the lesions evolve slowly. Itching is severe but usually confined to the lesions themselves. Bouts of extreme pruritus often occur when these patients are under stress. Prurigo nodularis is one of the disorders in which the pruritus is characteristically

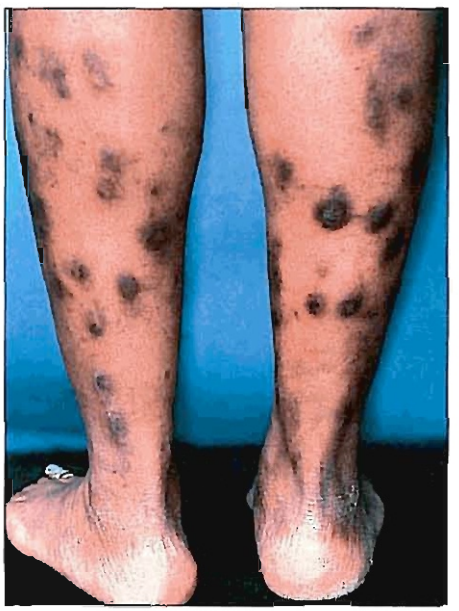

Fig. 4-7 Prurigo nodularis. (Courtesy of Lawrence Lieblich, MD)

paroxysmal: intermittent, unbearably severe, and relieved only by scratching to the point of damaging the skin, usually inducing bleeding and often scarring.

The cause of prurigo nodularis is unknown; multiple factors may contribute; including atopic dermatitis, anemia, hepatic diseases (including hepatitis C), HIV disease, pregnancy, renal failure, lymphoproliferative disease, photodermatitis, gluten enteropathy, stress, and insect bites. Pemphigoid nodularis may be confused with prurigo nodularis clinically.

The histologic findings are those of markedly lichenified chronic dermatitis with compact hyperkeratosis, irregular acanthosis, and a perivascular mononuclear cell infiltrate in the dermis. Dermal collagen may be increased, especially in the dermal papillae, and subepidermal fibrin may be seen, both evidence of excoriation. In cases associated with renal failure, transepidermal elimination of degenerated collagen may be found.

Treatment

Treatment is challenging. Local measures include antipruritic lotions and emollients. Administration of antihistamines, antidepressants or anxiolytics is of moderate benefit in allaying symptoms. The initial treatment of choice is intralesional or topical administration of steroids. Usually, superpotent topical products are required, but at times lower strength preparations used with occlusion may be beneficial. The use of steroids in tape (Cordran) and prolonged occlusion with semipermeable dressings, such as used for treating nonhealing wounds, can be useful in limited areas. Intralesional steroids will usually eradicate individual lesions, but unfortunately many patients have too extensive disease for these local measures. PUVA has also been shown to be effective in some cases. Vitamin D_3 ointment, calcipotriene ointment or tacrolimus ointment applied topically twice a day may be therapeutic and steroid sparing. Accutane, 1 mg/kg/day for 2 to 5 months, may benefit some patients.

Good results have been obtained with thalidomide and cyclosporin. With thalidomide the onset may be rapid or slow and sedation may occur. The initial dose is 100 mg/day, titered to the lowest dose required. Patients treated with thalidomide are at risk of developing a dose-dependent neuropathy at cumulative doses of 40 to 50 g. Combination therapy with sequential UVB and thalidomide may be better than either alone. Cyclosporin at doses of 3 to 4.5 mg/kg/day has also been shown to be effective in treating recalcitrant disease. Cryotherapy has been used adjunctively.

Alfadley A, et al: Treatment of prurigo nodularis with thalidomide. Int J Dermatol 2003;42:372.

Berth-Jones J, et al: Nodular prurigo responds to cyclosporin. Br J Dermatol 1995;132:795.

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Setoyama M, et al: Prurigo as a clinical prodrome to adult T-cell leukaemia/lymphoma. Br J Dermatol 1998;138:137.

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PSYCHODERMATOLOGY

There are purely cutaneous disorders that are psychiatric in nature, their cause being directly related to psychopathologic causes in the absence of primary dermatologic or other organic causes. Delusions of parasitosis, neurotic excoriations, factitial dermatitis, and trichotillomania compose the major categories of psychodermatology. The differential diagnosis for these four disorders is two-fold, requiring the exclusion of organic causes and the definition of a potential underlying psychologic disorder. Other delusional disorders include bromidrosiphobia and body dysmorphic disorder.

Psychosis is characterized by the presence of delusional ideation, which is defined as a fixed misbelief that is not shared by the patient's subculture. Monosymptomatic hypochondriacal disorder is a form of psychosis characterized by delusions regarding a particular hypochondriacal concern. In contrast to schizophrenia, there are no other mental deficits, such as auditory hallucination, loss of interpersonal skills, or presence of other inappropriate actions. Patients with monosymptomatic hypochondriacal psychosis often function appropriately in social settings, except for a single fixated belief that there is a serious problem with their skin or other parts of their body.

Skin Signs of Psychiatric Illness

The skin is a frequent target for the release of emotional tension. Self-injury by prolonged, compulsive repetitious acts may produce various mutilations, depending on the act and site of injury.

Self-biting may be manifested by biting the nails (onychophagia) (Fig. 4-8), skin (most frequently the forearms, hands, and fingers) and lip. Dermatophagia is a habit or compulsion, which may be conscious or subconscious. Bumping of the head produces lacerations and contusions, which may be

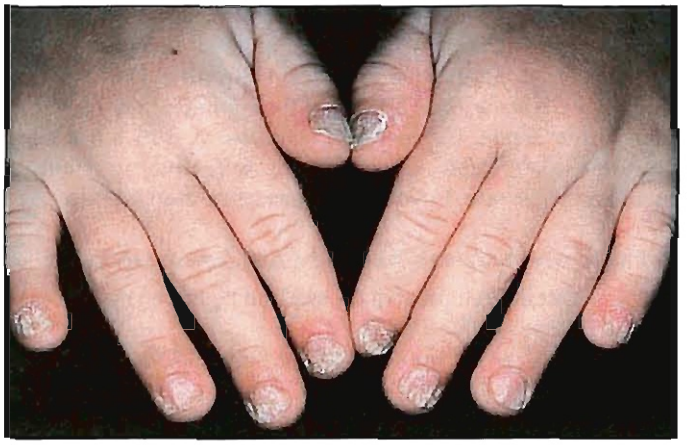

Fig. 4-8 Onychophagia. (Courtesy of C. Samlaska MD)

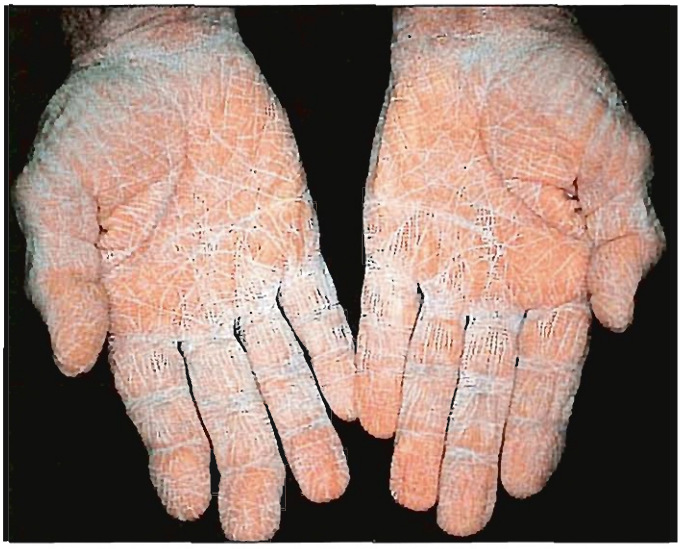

Fig. 4-9 Irritant dermatitis from chronic handwashing.

so severe as to produce cranial defects and life-threatening complications. Compulsive repetitive handwashing may produce an irritant dermatitis of the hands (Fig. 4-9).

Bulimia, with its self-induced vomiting, results in Russell's sign—crusted papules on the dorsa of the dominant hand from cuts by the teeth. Clenching of the hand produces swelling and ecchymosis of the fingertips and subungual hemorrhage. Self-inflicted lacerations may be of suicidal intent. They are sometimes seen in adolescents who are trying to demonstrate their bravery. Lip-licking produces increased salivation and thickening of the lips. Eventually the perioral area becomes red and produces a distinctive picture resembling the exaggerated mouth make-up of a clown (Fig. 4-10). Pressure produced by binding the waistline tightly with a cord will eventually lead to atrophy of the subcutaneous tissue.

Evidence is mounting in support of a neurobiologic basis for the causes of compulsive- obsessive disorders. Psychopharmacologic agents, such as clomipramine, fluoxetine, fluvoxamine, sertraline, paroxetine, and venlafaxine, and behavioral therapy alone or in combination with these agents are the treatments of choice.

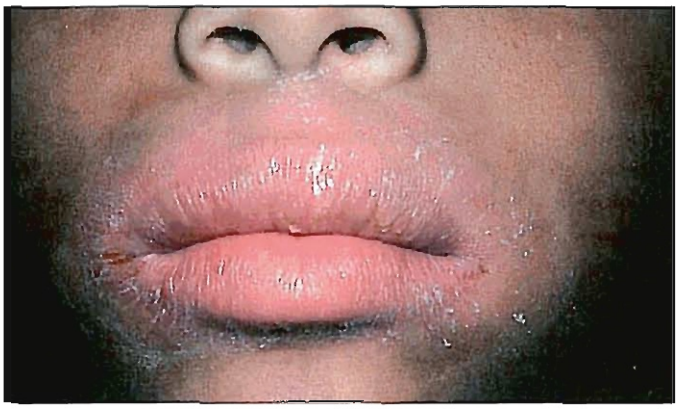

Fig. 4-10 Dermatitis caused by lip-licking.

Delusions of Parasitosis

Delusions of parasitosis (acarophobia, dermatophobia, parasitophobia, entomophobia) are firm fixations in a person's mind that he/she suffers from a parasitic infestation of the skin. At times close contacts may share the delusion. The belief is so fixed that the patient may pick small pieces of epithelial debris from the skin and bring them to be examined, always insisting that the offending parasite is contained in such material. Samples of alleged parasites enclosed in assorted containers, paper tissue, or sandwiched between adhesive tape are so characteristic that it is referred to as the "matchbox sign." Usually the only symptom is pruritus or a stinging, biting, or crawling sensation. Cutaneous findings may range from none to excoriations, prurigo nodularis, and frank ulcerations.

Frequently these patients have paranoid tendencies. Women are affected 2:1 over men, and are often affected during middle or old age. It has been reported to be associated with schizophrenia, bipolar disorders, depression, anxiety disorders, and obsessional states but is usually a monosymptomatic hypochondriacal disorder. A variety of organic causes have been suggested to include cocaine and amphetamine abuse, dementia, malignancies, cerebrovascular disease, multiple sclerosis, and vitamin B_{12} deficiency. Some of these may produce cutaneous symptoms, particularly pruritus, which may contribute to the delusion.

The differential diagnosis is influenced by the cutaneous findings and history. Initial steps should be directed at excluding a true infestation, such as scabies, or an organic cause. A thorough history, particularly in reference to therapeutic and recreational drug use (amphetamines and cocaine), review of systems, and physical examination, should be performed. A skin biopsy is frequently performed more to reassure the patient than to uncover occult skin disease. Screening laboratory tests to exclude systemic disorders should be obtained: a CBC, urinalysis (UA), liver function tests (LFTs), thyroid function tests (TFTs), iron studies, and serum B_{12}, folate, and electrolyte levels. Multiple sclerosis may present with dysesthesia, which may at times be mistaken for infestation. Once organic causes have been eliminated, the patient should be evaluated to determine the cause of the delusions. Schizophrenia, monosymptomatic hypochondriacal psychosis, psychotic depression, dementia, and depression with somatization are considerations in the differential diagnosis.

Management of this difficult problem varies. While referral to a psychiatrist may be considered best for the patient, most frequently the patient will reject suggestions to seek psychiatric help. The dermatologist is cautioned against confronting the patient with the psychogenic nature of the disease. It is preferable to develop trust, which will usually require several visits. If pharmacologic treatment is undertaken, the patient may accept it if the medication is presented as one which will alter the perception of this bothersome sensation. Pimozide is the long-standing treatment of choice. It is associated with a variety of side effects, including stiffness, restlessness, prolongation of the Q–T interval, and extrapyramidal signs. Patients often respond to relatively low dosages, in the 1- to 4-mg range, which limits these problems. Pimozide is an antipsychotic medication approved for the treatment of Tourette syndrome and patients should understand the labeling prior to obtaining the drug. Insufficient evidence exists to state that pimozide is superior to newer antipsychotic agents, such as risperidone and olanzapine, which have fewer side effects, but many believe it is superior in the treatment of delusions of parasitosis. With appropriate pharmacologic intervention it is likely 25% to 50% of patients will remit.

Neurotic Excoriations

Many persons have unconscious compulsive habits of picking at themselves, and at times the tendency is so persistent and pronounced that excoriations of the skin are produced. The lesions are caused by picking, digging, or scraping, and they usually occur on parts readily accessible to the hands. These patients admit their actions induce the lesions, but cannot control their behavior.

The excavations are superficial or deep and are often linear. The bases of the ulcers are clean or covered with a scab. Right-handed persons tend to produce lesions on their left side and left-handed persons on their right side. Many people will persistently pluck at an area until they can "pull a thread" from it. There is evidence of past healed lesions, usually with linear scars, or rounded hyper- or hypopigmented lesions, in the area of the active excoriations. The face, upper arms, and upper back (Fig. 4-11) are favorite sites for these excoriations. Sometimes the focus is on acne lesions, producing *acne excoriee*.

Most of these patients are otherwise healthy adults. They usually lead normal lives. The organic differential diagnosis is vast and includes any condition that may manifest with excoriations. The most common psychopathologies associated with neurotic excoriations are depression, obsessive–compulsive disorder, and anxiety.

The treatment of choice is doxepin because of its antidepressant and antipruritic effects, with doses slowly increased to 100 mg or higher, if tolerated. Many alternatives to doxepin may be indicated, especially in those affected by an obsessive–compulsive component. These include clomipramine, fluoxetine, and sertraline. Other drugs with utility include desipramine, buspirone, and quick-acting benzodiazepines. Treatment is difficult, often requiring a combined psychiatric and pharmacologic intervention. It is important to establish a constructive patient–therapist alliance. Training in diversion strategies during "scratching episodes" may be helpful. An attempt should be made to identify specific conflicts or stressors preceding onset. The therapist should concentrate on systematic training directed at the behavioral reaction pattern. There should be support and advice given with regard to the patient's social situation and social relations.

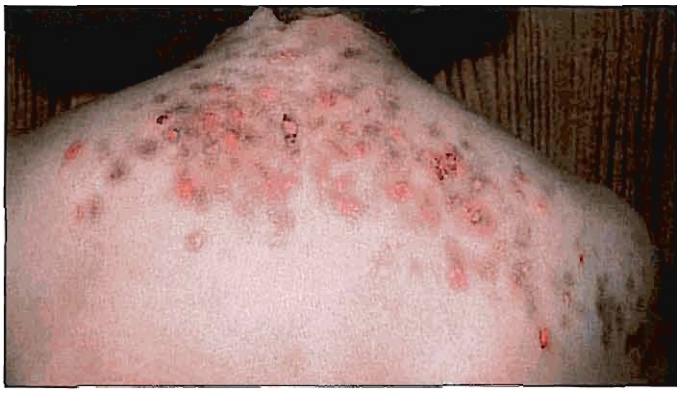

Fig. 4-11 Neurotic excoriations. (Courtesy of Lawrence Lieblich, MD)

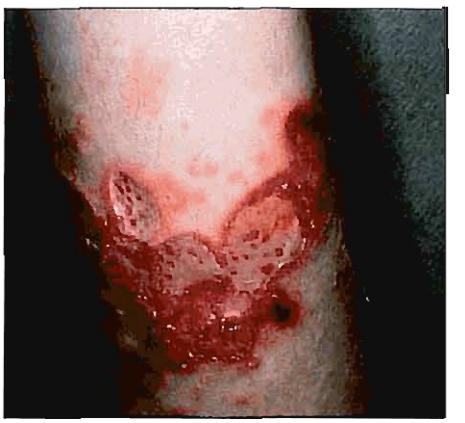

Fig. 4-12 Cigarette burns.

Factitious Dermatitis (Dermatitis Artefacta)

Factitious dermatitis is the term applied to self-inflicted skin lesions made consciously and often with the intent to elicit sympathy, escape responsibilities, or collect disability insurance (Fig. 4-12). These skin lesions are provoked by mechanical means or by the application of chemical irritants and caustics. The lesions may simulate other dermatoses but usually have a distinctive, geometric, bizarre appearance (Fig. 4-13), whose shape and arrangement frequently are not encountered in any other affection (Fig. 4-14). The lesions are generally distributed on parts easily reached by the hands and have a tendency to be linear and arranged regularly and symmetrically. They are rarely seen on the right hand, right wrist or right arm unless the patient is left-handed.

When chemicals are used, red streaks or guttate marks are often seen beneath the principal patch, where drops of the chemical have accidentally run or fallen on the skin. According to the manner of production, the lesions may be erythematous, vesicular, bullous, ulcerative, or gangrenous. The more common agents of destruction used are the fingernails, pointed instruments, hot metal; chemicals such as carbolic, nitric, or acetic acid; caustic potash or soda, turpentine, table salt, urine, and feces. The lesions are likely to appear in crops. At times only the indefinitely delayed healing of an operative wound, which is purposely kept open

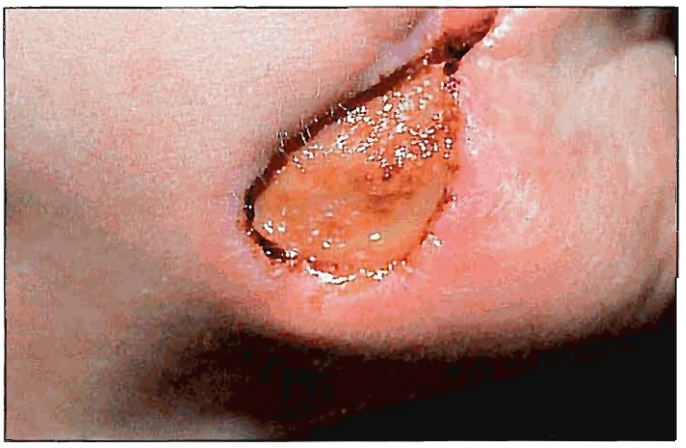

Fig. 4-13 Factitial ulcers.

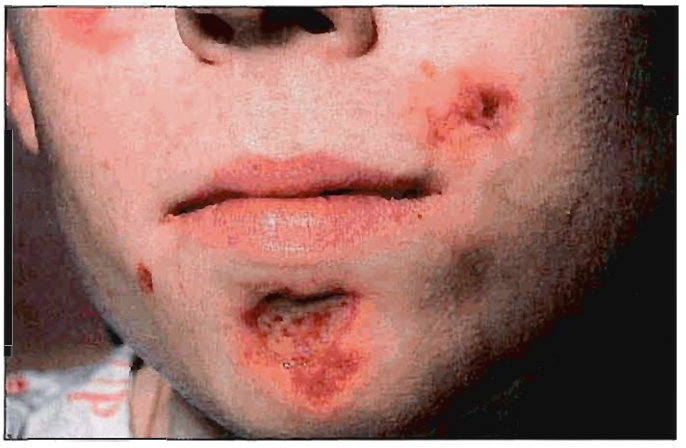

Fig. 4-14 Factitial ulcers.

by the patient, manifests the disorder. Tight cords or clothing tied around an arm or leg may produce factitious lymphedema, which may be mistaken for postphlebitic syndrome, nerve injury, as well as other forms of chronic lymphedema.

Subcutaneous emphysema, manifesting as cutaneous crepitations, may be factitial in origin. Recurrent migratory subcutaneous emphysema involving the extremities, neck, chest, or face can be induced through injections of air into tissue with a needle and syringe. Circular pockets and bilateral involvement without physical findings that suggest a contiguous spread from a single source suggest a factitial origin. Puncturing the buccal mucosa through to facial skin with a needle and puffing out the cheeks can produce alarming results. Neck and shoulder crepitation is also a complication in manic patients that results from hyperventilation and breath-holding.

The organic differential diagnosis depends on the cutaneous signs manifested (e.g. gas gangrene for patients with factitious subcutaneous emphysema, and the various forms of lymphedema for factitious lymphedema). Considerations for psychopathology include malingering, borderline personality disorders, and psychosis.

Proof of diagnosis is sometimes difficult. Occlusive dressings may be necessary to protect the lesions from ready access by the patient. It is usually best not to reveal any suspicion of the cause to the patient and to establish the diagnosis definitely without the patient's knowledge. If the patient is hospitalized, a resourceful, cooperative nurse may be useful in helping to establish the diagnosis. When injection of foreign material is suspected, examination of biopsy material by spectroscopy may reveal talc or other foreign material.

Treatment should ideally involve psychotherapy, but most frequently the patient promptly rejects the suggestion and goes to another physician to seek a new round of treatment. It is best for the dermatologist to maintain a close relationship with the patient and provide symptomatic therapy and nonjudgmental support. Pimozide or atypical antipsychotic agents in low dose have been used with some success. High doses of selective serotonin reuptake inhibitors may also be beneficial. Consultation with an experienced psychiatrist is prudent.

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Trichotillomania

Trichotillomania (trichotillosis) is a neurosis characterized by an abnormal urge to pull out the hair. The sites involved are generally the frontal region of the scalp, eyebrows, eyelashes, and the beard. There are irregular areas of hair loss, which may be linear or bizarrely shaped. Uncommonly, adults may pull out pubic hair. The classic presentation is the "Friar Tuck" form of vertex and crown alopecia. Hairs are broken and show differences in length (Fig. 4-15). The nails may show evidence of onychophagy (nail biting), but no pits are present. The disease is seven times more common in children than in adults, and girls are affected 2.5 times more often than boys.

This disease often develops in the setting of psychosocial stress in the family, which may revolve around school problems, sibling rivalry, moving to a new house, hospital-

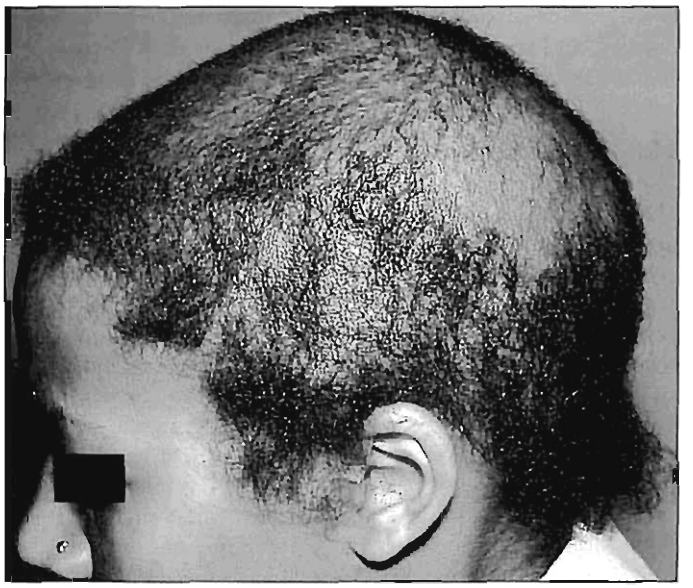

Fig. 4-15 Trichotillomania.

ization of the mother, or a disturbed mother–daughter relationship.

Differentiation from alopecia areata is possible because of the varying lengths of broken hairs present, the absence of nail pitting, and the microscopic appearance of the twisted or broken hairs as opposed to the tapered fractures of alopecia areata. Other organic disorders to consider are androgenic alopecia, tinea capitis, monilethrix, pili torti, pseudopelade of Brocq, traction alopecia, syphilis, nutritional deficiencies, and systemic disorders such as lupus and lymphoma. If necessary a biopsy can be performed and is usually quite helpful. It reveals traumatized hair follicles with perifollicular hemorrhage, fragmented hair in the dermis, empty follicles, and deformed hair shafts (trichomalacia). Multiple catagen hairs are typically seen. An alternative technique to biopsy, particularly for children, is to shave a part of the involved area and observe for regrowth of normal hairs. The differential diagnosis for underlying psychopathology is obsessive–compulsive disorder (most common), depression, and anxiety.

In children the diagnosis should be addressed openly, and referral to a child psychiatrist for behavioral therapy should be encouraged. In adults with the problem, psychiatric impairment may be severe. Pharmacotherapy with clomipramine, fluoxetine, venlafaxine, and olazapine have proven effective in some patients.

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Dermatothlasia

Dermatothlasia is a cutaneous neurosis characterized by a patient's uncontrollable desire to rub or pinch him/herself to form bruised areas on the skin, sometimes as a defense against pain elsewhere.

Bromidrosiphobia

Bromidrosiphobia is a neurosis in which a person is convinced that his/her sweat has a repugnant odor that keeps other people away. The patient is unable to accept any evidence to the contrary. Three-quarters of patients with bromidrosiphobia are male, with an average age of 25. Pimozide may be beneficial. It may be an early symptom of schizophrenia.

Body Dysmorphic Disorder (Dysmorphic Syndrome, Dysmorphophobia)

Body dysmorphic disorder is the delusion of having an ugly body part. It is most common in young adults of either sex. The concern is frequently centered about the nose, mouth, genitalia, breasts or hair. Objective evaluation will reveal a normal appearance or slight defect. Patients may manifest obsessional features, spending large amounts of time inspecting the area. Depression may present a risk of suicide. Therapy with selective serotonin reuptake inhibitors may help those who manifest this obsessive–compulsive disease. Those more severely affected have delusions that may lead to repeated surgeries of the site, and require antipsychotic medications.

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NEUROCUTANEOUS DERMATOSES

Burning Mouth Syndrome (Glossodynia, Burning Tongue)

Postmenopausal women are particularly prone to a feeling of burning of the tongue, mouth, and lips, with no objective findings. Symptoms vary in severity but are more or less constant. Patients with burning mouth syndrome often complain that multiple oral sites are involved. It has been blamed on deficiency of B_{12}, iron, or folate; on hypoestrogenism, diabetes, local trauma, and psychologic disturbance. It may be seen as a complication of Sjögren syndrome. In 130 patients reviewed by Gorsky et al, the most common site was the tongue, and 39% complained of dry mouth. The most effective management in this series was use of mood-altering drugs.

Burning lips syndrome may be a separate entity; it appears to affect both men and women equally and occurs in

individuals between the ages of 50 and 70 years. The labial mucosa may be smooth and pale, and the minor salivary glands of the lips are frequently dysfunctional. Treatment with α-lipoic acid showed improvement in 2 months in a double-blind controlled study.

Scalp Dysesthesia

Cutaneous dysesthesia syndromes are characterized by pain and burning sensations without objective findings. Many patients report coexisting pruritus or transient pruritus associated with the dysesthesia. Scalp dysesthesia occurs primarily in middle-aged to elderly women. A psychiatric cause or overlay is frequently associated and treatment with low-dose antidepressants is often helpful.

Vulvodynia

Vulvodynia is defined as burning and pain of the vulva without medical findings. It is chronic, defined as lasting 3 months or longer. Two subtypes are seen, vulvar vestibulitis and dysethetic vulvodynia. In the former, the discomfort is not usually constant or spontaneous, but instead occurs on vestibular touch or attempted vaginal entry. Tenderness to pressure is localized to the vulvar vestibule. Erythema of this site may be present. In dysethetic vulvodynia the vulvar symptoms are not limited to the vestibule and may occur without touch or pressure.

The typical patient is a nulligravid married woman in her late 30s. Up to 15% of women seen in some gynecologic practices may be affected. Dyspareunia may completely prevent sexual intercourse. This problem and the chronic pain may lead to compromise of interpersonal relations. They may be exacerbated by stress, depression, or anxiety, and may lead to such conditions over time. A male counterpart may be seen and has been called the burning genital skin syndrome or dysesthetic peno/scrotodynia.

The diagnosis of vulvodynia includes initially eliminating other causes of acute or chronic vulvitis, such as candidiasis, group B streptococcus, and trichomonal and human papillomavirus (HPV) infections. Careful examination for evidence of a physical finding that may prompt culture or biopsy is imperative. Contact dermatitis, while a treatable cause of vulvar discomfort, usually has a pruritic quality to the complaint and will have associated erythema and edema that often spreads away from the vulva onto the surrounding skin. Patch testing is rarely helpful in vulvodynia. Pudendal neuralgia has an area of pain and hypoesthesia that extends away from the vulva, and is often accompanied by constipation and stress urinary incontinence. Pinprick sensation is decreased. A pudendal nerve block is a useful diagnostic and therapeutic test which may predict successful outcome with pudendal nerve decompressive surgery.

Treatment should always include patient education and psychological support. Topical anesthetics and lubricants, such as petrolatum, applied before intercourse may be tried initially. Elimination of irritants, treatment of atopy with topical tacrolimus (allowing for the discontinuance of topical steroids which have usually been tried without success), and the use of antihistamines for dermatographism may be helpful. Vulvodynia is considered among the chronic pain syndromes that can have a psychological impact. Treatment then centers on the use of tricyclic antidepressants and neuroleptics, chiefly gabapentin. Other interventions such as IFN-α, biofeedback of the pelvic floor muscles, estrogen creams, and surgery may be considered in individual cases, but the evidence for any of the above therapies is limited.

Notalgia Paresthetica

Notalgia paresthetica is a unilateral sensory neuropathy characterized by infrascapular pruritus, burning pain, hyperalgesia, and tenderness, often in the distribution of the second to sixth thoracic spinal nerves. A pigmented patch localized to the area of pruritus is often found. This is due to postinflammatory change; when amyloid is found on biopsy the diagnosis of macular amyloid is rendered instead. In the majority of cases degenerative changes in the corresponding vertebrae leading to spinal nerve impingement are seen.

Topical capsaicin has been shown effective; however, relapse occurs in most patients within 4 weeks of discontinuing its use. The topical lidocaine patch may provide relief. Paravertebral blocks, ultrasound, and physiotherapy are useful interventions when a structural change in the vertebrae is found to be the cause.

Brachioradial Pruritus

This condition is characterized by itching localized to the brachioradial area of the arm. To relieve the burning, stinging or even painful quality of the itch patients will frequently use ice packs. Cervical spine pathology is frequently found on radiographic evaluation. Searching for causes of the abnormality should include discussion of spinal injury, such as trauma, arthritis, or chronic repetitive microtrauma, e.g. as in sports, whiplash injury or assessment for a tumor in the cervical spinal column. Interventions of value include gabapentin, carbamazine, topical capsaicin, cervical spine manipulation, neck traction, anti-inflammatory medications, physical therapy, or surgical resection of a cervical rib. Patients often present in the spring and report that UV light precipitates the pruritus. Cervical spine disease may then be a predisposing factor with sunlight the eliciting factor.

Meralgia Paresthetica (Roth-Bernhardt Disease)

This affection is a variety of paresthesia, with persistent numbness and periodic transient episodes of burning or lancinating pain on the anterolateral surface of the thigh. The lateral femoral cutaneous nerve innervates this area and is subject to entrapment and compression along its course. Sensory mononeuropathies besides nostalgia and meralgia paraethetica include mental and intercostal neuropathy and cheiralgia, gonyalgia, and digitalgia paresthetica.

Meralgia paresthetica occurs most frequently in middle-aged, obese men. Alopecia localized to the area innervated by the lateral femoral nerve may be a skin sign of this disease. Arthritis of the lumbar vertebrae, a herniated disk, pregnancy, iliac crest bone graft harvesting, seat-belt injury associated with a automobile accident, diabetes, neuroma, and rarely, a retroperitoneal tumor have been reported causes in individual cases. The diagnostic test of choice is somatosensory evoked potentials of the lateral femoral cutaneous nerve. Local anesthetics, such as use of a lidocaine patch, nonsteroidal anti-inflammatories, rest, and avoidance of aggravating factors may lead to improvement. Surgical decompression of the lateral femoral cutaneous nerve

produces good to excellent outcomes. Gabapentin is useful in various neuropathic pain disorders.

Complex Regional Pain Syndrome

Encompassing the descriptors reflex sympathetic dystrophy, causalgia, neuropathic pain, algoneurodystrophy, clenched first syndrome, Sudek syndrome, and maintained pain, complex regional pain syndrome (CRPS) is characterized by burning pain, hyperesthesia, and trophic disturbances resulting from injury to a peripheral nerve. It usually occurs in one of the upper extremities. The most common symptom is burning pain aggravated by movement or friction. The skin of the involved extremity becomes shiny, cold, profusely perspiring, and frequently cracked, and there is usually hyperesthesia and radiographic evidence of osteoporosis. Additional cutaneous manifestations include atrophy, folliculitis, cellulitis, petechiae, erosions, edema, telangiectasias, hyperpigmentation, bullae, and ulcerations (Fig. 4-16).

The intensity of the pain varies from trivial burning to a state of torture accompanied by extreme hyperesthesia and, frequently, hyperhidrosis. The part is not only subject to an intense burning sensation, but also a touch or a tap of the finger causes exquisite pain. Exposure to the air is avoided with a care that seems absurd, and the patient walks carefully, carrying the limb tenderly with the sound hand. Patients are tremulous and apprehensive and keep the hand constantly wet, finding relief in the moisture rather than in the temperature of the application. A condition resembling permanent chilblains or even trophic ulcers may be present.

CRPS usually begins with severe, localized, burning pain, focal edema, muscle spasm, rapid growth of hair and nails, stiffness or restricted mobility, hyperesthesia, and vasospasm affecting skin color and temperature. This is at times followed by a crescendo and diffusion of the pain and edema, diminished hair growth, brittle nails, osteoporosis, joint thickening, and onset of muscle atrophy. Finally, irreversible trophic changes, intractable pain involving the entire limb, flexor contractures, marked atrophy of the muscles, severe limitation in joint and limb mobility, and severe osteoporosis result.

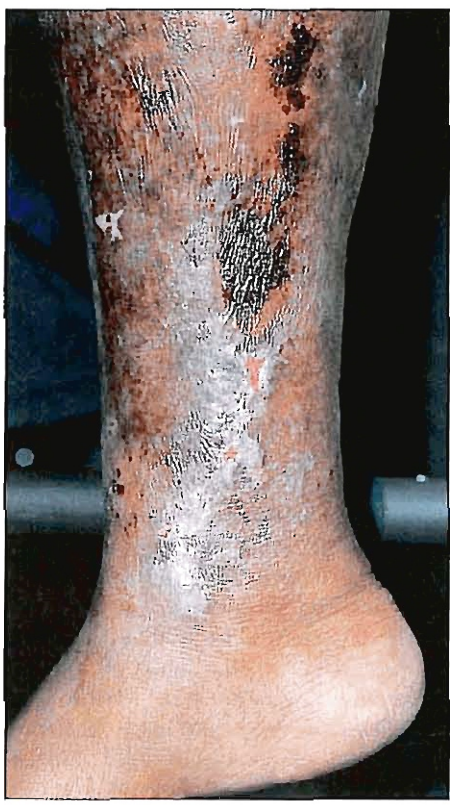

Fig. 4-16 Complex regional pain syndrome.

The term *type II CRPS* is used synonymously with reflex sympathetic dystrophy or causalgia and is the most severe form of the illness. There may be a precipitating event, such as a nail biopsy, crush injury, laceration, fracture, sprain, burn, or surgery that produces some degree of soft-tissue or nerve complex injury. The most frequent causes include peripheral revascularization of the extremities (5% of cases), hypothermic insult, such as trench foot (5%), myocardial infarction (5%), peripheral nerve injury (2–5%), and fractures (1–2%). Associations with Munchausen syndrome and factitial ulcerations have also been reported.

Not all patients will have all of the features of CRPS, and an early diagnosis is essential if the patient is to have any chance of a cure. The five major components are pain, edema, dysregulation of autonomic function, alterations in motor function, and dystrophic changes. A three-phase technetium bone scan is helpful in confirming the diagnosis of CRPS in patients who fail to meet all five of these criteria.

Treatment should be started before CNS changes occur and narcotic addiction develops. Consultation with a neurologist or an anesthesiologist specializing in pain is advisable. Osteoporosis is a frequent complication, and studies using pamidronate, a powerful inhibitor of bone absorption, have been shown to significantly improve symptoms of pain, tenderness, and swelling. Tricyclic antidepressants and antipsychotic agents are often helpful. Transcutaneous electrical nerve stimulation (TENS) is also useful in the treatment of early disease. Paravertebral block or sympathectomy is most effective, but not without potential complications. In upper extremity disease, axillary blocks with lidocaine and hyaluronidase, rather than stellate ganglionic block, should be considered to eliminate the risk of pneumothorax.

Trigeminal Trophic Lesions

Interruption of the peripheral or central sensory pathways of the trigeminal nerve may result in a slowly enlarging, uninflamed ulcer on the cheek beside the ala nasi (Fig. 4-17). It may infrequently occur elsewhere on the face. Onset of ulceration varies from weeks to several years after trigeminal nerve injury. Self-inflicted trauma to the anesthetic skin is believed to be the cause and the appropriate treatment is to prevent this by persuasion or coercion. It is usually successful, but scarring may be severe.

In addition, the following complications may occur after operation for trigeminal neuralgia: herpes simplex, neuropathic keratitis, corneal ulcer, iritis, conjunctivitis, paresthesias, facial paralysis, and dryness of the nasal mucous membrane.

Postencephalitic Trophic Ulcer Ulceration of the nose similar to the trigeminal trophic ulcer has been reported following epidemic encephalitis and herpes zoster of the trigeminal nerve.

Malum Perforans Pedis

Also known as *perforating ulcer of the foot* and *neurotrophic ulcer*, malum perforans is a chronic, trophic, ulcerative disease seen on the sole in denervating diseases, particularly

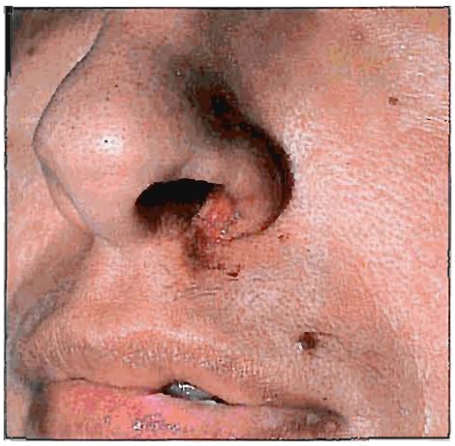

Fig 4-17 Trigeminal trophic syndrome.

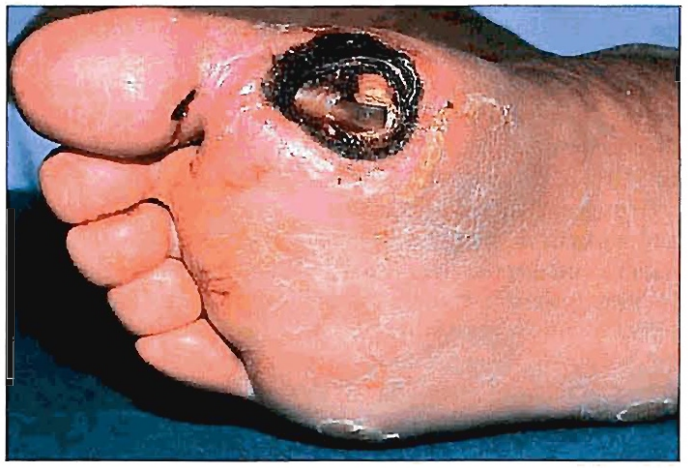

Fig 4-18 Diabetic foot ulcer.

tabes dorsalis, leprosy, arteriosclerosis, or diabetes, resulting from loss of pain sensation at a site of constant trauma (Fig. 4-18). The primary cause lies either in the posterolateral tracts of the cord (in tabes and arteriosclerosis), lateral tracts (in syringomyelia), or peripheral nerves (in diabetes or leprosy).

In most cases, malum perforans begins as a circumscribed hyperkeratosis, usually on the ball of the foot. This lesion becomes soft, moist, and malodorous, and later exudes a thin, purulent discharge. A slough slowly develops and an indolent, necrotic ulcer is left that lasts indefinitely. Whereas the neuropathy renders the ulceration painless and walking continues, plantar ulcers in this situation have a surrounding thick callous (Fig. 4-19). Deeper perforation and secondary infection often lead to osteomyelitis of the metatarsal or tarsal bones.

Treatment should consist of relief of pressure on the ulcer through use of a total-contact cast and debridement of the surrounding callosity. Removable cast walkers and half-shoes were significantly less effective means of off-loading in a randomized clinical trial. Administration of local and systemic antibiotics is sometimes helpful.

Sciatic Nerve Injury

Serious sciatic nerve injury can result from improperly performed injections into the buttocks. Older patients are more susceptible to injection-induced sciatic nerve injury

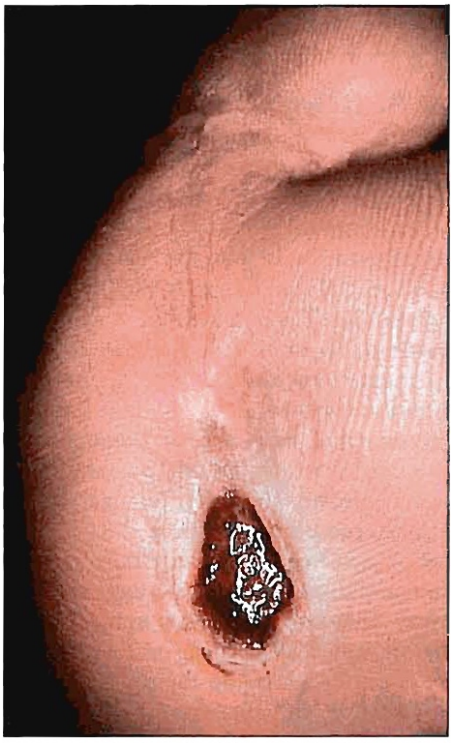

Fig 4-19 Mal perforans ulcer.

because of their decreased muscle mass and/or debilitating diseases. The most common scenario for nerve damage is improper needle placement. Other common causes of sciatic neuropathy are hip surgery complications, hip fracture and dislocation, and compression by benign and malignant tumors. A paralytic foot drop is the most common finding. There is sensory loss and absence of sweating over the distribution of the sciatic nerve branches. The skin of the affected extremity becomes thin, shiny, and often edematous.

Surgical exploration, guided by nerve action potentials, with repair of the sciatic nerve is worthwhile in selected cases.

Familial Dysautonomia (Riley-Day Syndrome)

Familial dysautonomia, first recognized by Riley in 1949, has features of defective lacrimation, excessive sweating, drooling, and transient erythema, predominantly on the trunk. In addition, there may be acrocyanosis, especially of the hands. Other major features include decreased pain sensation, impaired temperature and blood pressure regulation, and absent tendon reflexes. There are two interesting features: one is the absence of fungiform and circumvallate papillae of the tongue, and the other is the sensation of tickling of the scalp experienced when the head is stroked lightly. There are measurable deficiencies in taste from water, sweet, bitter, and salty stimuli. Dental features may be prominent and include hypersalivation and orododental trauma progressing to self-mutilation.

The disease is inherited as an autosomal-recessive trait, most often in Jewish families. The Schirmer test for lacrimal dysfunction is positive. The intradermal histamine test shows a diminished flare, and immersion of the hands in water at 40° C (104° F) causes erythematous mottling of the skin. The major mutation in Riley-Day syndrome leads to tissue-specific reduction in splicing efficiency of I-κB kinase-associated protein. Treatment is supportive.

Syringomyelia

Also known as *Morvan's disease*, syringomyelia results from progressive expansion of the central canal of the spinal cord, compressing the lateral tracts especially and producing sensory and trophic changes on the upper extremities, particularly in the fingers. The disease begins insidiously and gradually causes muscular weakness, hyperhidrosis, and sensory disturbances, especially in the thumb and index and middle fingers. The skin changes are characterized by dissociated anesthesia with loss of pain and temperature sense but with retention of tactile sense. Burns are the most frequent lesions noted. Bullae, warts, and trophic ulcerations occur on the fingers and hands, and ultimately there are contractures and gangrene. Other unusual features may be hypertrophy of the limbs, hands, or feet, and asymmetric scalp hair growth with a sharp midline demarcation. The disease must be differentiated chiefly from leprosy. Unlike leprosy, syringomyelia does not interfere with sweating or block the flare around a histamine wheal.

Congenital Insensitivity to Pain with Anhidrosis

Also described as hereditary sensory and autonomic neuropathy type IV (HSAN-IV), this is an autosomal-recessive disorder characterized by anhidrosis, recurrent hyperpyrexia, absence of the pain sensation, self-mutilating behavior, and mental retardation. Repeated injuries produce ulcers, most commonly of the acral and oral tissues. Secondary infection of the digits with osteromyelitis are not infrequent complications.

The disease has been found to be caused by mutations and polymorphisms in the TRKA (NTRK1) gene which is present on chromosome 1 and encodes for the receptor tyrosine kinase for nerve growth factor. Treatment of this disorder is symptomatic. Care should be taken to avoid burning, scratching, and the various other traumatic events that can happen in ordinary living.

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CHAPTER

5 Atopic Dermatitis, Eczema, and Noninfectious Immunodeficiency Disorders

ATOPIC DERMATITIS

In 1925, Coca introduced the concept of *atopy*, meaning "out of place" or "strange," to signify the hereditary tendency to develop allergies to food and inhalant substances. Affected families may manifest eczema, asthma, and hay fever in any combination. In 1933, Wise and Sulzberger introduced the concept of atopic dermatitis, emphasizing the cutaneous manifestations of the atopic diathesis. Atopic dermatitis is also known as *atopic eczema*, *infantile eczema*, *flexural eczema*, *disseminated neurodermatitis*, and *prurigo diathsique (Besnier)*. Dermatitis generally begins in childhood, but varying manifestations often persist into adulthood.

Although the tendency to develop atopic dermatitis is inherited, inheritance patterns do not follow strict Mendelein patterns, and the overall prevalence of atopic disease is increasing. A child is at increased risk of developing atopy if either parent is affected. More than one-quarter of offspring of atopic mothers develop atopic dermatitis in the first 3 months of life. If one parent is atopic, more than half his/her children will develop allergic symptoms by age 2. This rate rises to 79% if both parents are atopic.

Atopic dermatitis can be divided into three stages: infantile atopic dermatitis, occurring from 2 months to 2 years of age; childhood atopic dermatitis, from 2 to 10 years; and adult atopic dermatitis. In all stages, pruritus is the hallmark of atopic dermatitis. Itching often precedes the appearance of lesions, hence the concept that atopic dermatitis is "the itch that rashes." Useful diagnostic criteria include those of Hanifin and Rajka, the UK Working Party, and the American Academy of Dermatology's Consensus Conference on Pediatric Atopic Dermatitis (Boxes 5-1 and 5-2).

Infantile Atopic Dermatitis

Sixty percent of cases of atopic dermatitis present in the first year of life, but usually not until after 2 months of age. Eczema in infancy usually begins as erythema and scaling of the cheeks (Fig. 5-1). The eruption may extend to the scalp, neck, forehead, wrists, and extensor extremities. Lesions may be papular or exudative. The areas involved correlate with the capacity of the child to scratch or rub the site, and the activities of the infant, such as crawling. There may be a significant amount of exudate, and there are many secondary effects from scratching, rubbing, and infection: crusts, pustules, and infiltrated areas. The infiltrated plaques eventually take on a characteristic lichenified appearance. The infantile pattern of atopic dermatitis usually disappears by the end of the second year of life.

Worsening of atopic dermatitis is often observed after immunizations and viral infections. Partial remission may occur during the summer with relapse in winter. This may relate to the therapeutic effects of ultraviolet (UV)B and humidity in many atopic patients, and the aggravation by wool and dry air in the winter. The role of food allergy in infantile and childhood atopic dermatitis remains controversial. Open food challenges yield many false-positive results. Blinded food challenges, assays for food-specific IgE, or prick testing are required before recommending restricted

Box 5-1 Criteria for atopic dermatitis

Major criteria
Must have three of the following:

1. Pruritus
2. Typical morphology and distribution
   - Flexural lichenification in adults
   - Facial and extensor involvement in infancy
3. Chronic or chronically relapsing dermatitis
4. Personal or family history of atopic disease (asthma, allergic rhinitis, atopic dermatitis)

Minor criteria
Must also have three of the following:

1. Xerosis
2. Ichthyosis/hyperlinear palms/keratosis pilaris
3. IgE reactivity (immediate skin test reactivity, RAST test positive)
4. Elevated serum IgE
5. Early age of onset
6. Tendency for cutaneous infections (especially *S. aureus* and herpes simplex virus)
7. Tendency to nonspecific hand/foot dermatitis
8. Nipple eczema
9. Cheilitis
10. Recurrent conjunctivitis
11. Dennie-Morgan infraorbital fold
12. Keratoconus
13. Anterior subcapsular cataracts
14. Orbital darkening
15. Facial pallor/facial erythema
16. Pityriasis alba
17. Itch when sweating
18. Intolerance to wool and lipid solvents
19. Perifollicular accentuation
20. Food hypersensitivity
21. Course influenced by environmental and/or emotional factors
22. White dermographism or delayed blanch to cholinergic agents

Box 2-2 Modified criteria for children with atopic dermatitis

Essential features

1. Pruritus
2. Eczema
   - Typical morphology and age-specific pattern
   - Chronic or relapsing history

Important features

1. Early age at onset
2. Atopy
3. Personal and/or family history
4. IgE reactivity
5. Xerosis

Associated features

1. Atypical vascular responses (e.g. facial pallor, white dermatographism)
2. Keratosis pilaris/ichthyosis/hyperlinear palms
3. Orbital/periorbital changes
4. Other regional findings (e.g. perioral changes/periauricular lesions)
5. Perifollicular accentuation/lichenification/prurigo lesions

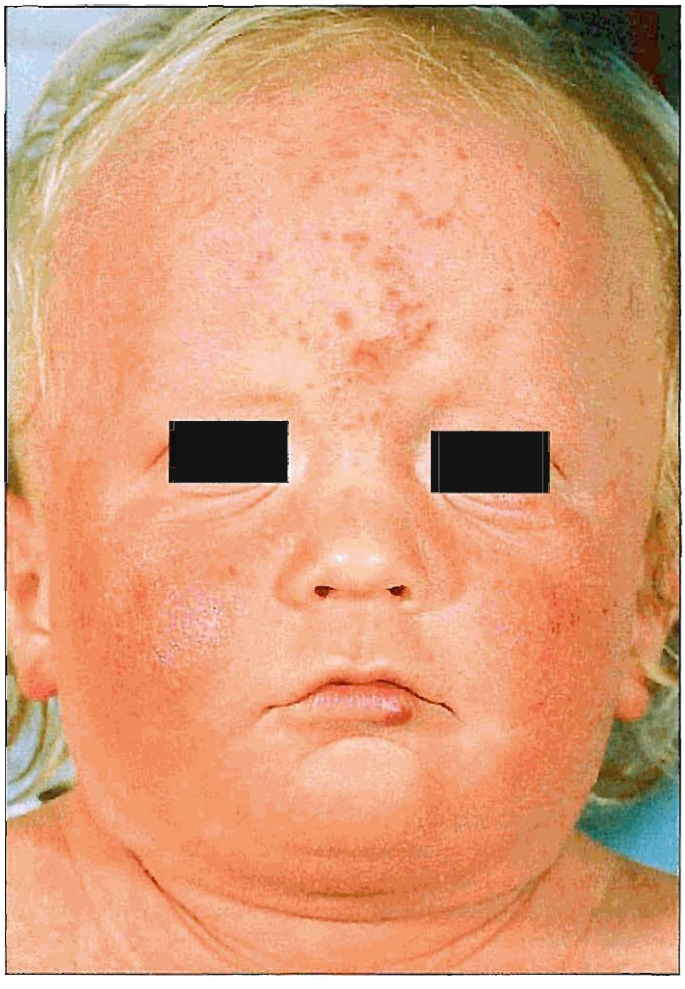

Fig. 5-1 Involvement of the cheeks in infantile atopic dermatitis.

diets. Most positive tests are to milk, eggs, peanuts, tree nuts, grains, fish, and soy; however, testing must include the range of foods to which the child is exposed. A negative skin-prick test together with negative blinded food-challenge tests is a reliable indicator of absence of food sensitivity. Atopy patch testing is controversial and lacks standardization. Food allergy may play a significant role in a selected population of young atopic patients. Withholding cow's milk foods from infants has been studied with conflicting results. Some studies have shown dramatic decreases in atopy, while others showed no difference in the cumulative prevalence over time. Some studies have suggested that maternal avoidance of allergens may reduce the incidence of atopic dermatitis in their offspring, but such diets are difficult to maintain, and data are mixed. Some large, randomized trials have failed to show that withholding cow's milk and eggs from mothers reduces the prevalence of atopy in their infants. Restrictive diets may be considered in unique situations where infantile atopic dermatitis is severe and unresponsive to therapy. Particular attention must be paid to nutritional status if the diet is restricted. In the US, an increased risk of atopic dermatitis during the first 6 months of life is noted in infants with African and Asian race/ethnicity, male gender, greater gestational age at birth, and a family history of atopy, particularly a maternal history of eczema.

Childhood Atopic Dermatitis

During childhood, lesions are apt to be less exudative. The classic locations are the antecubital and popliteal fossae (Fig. 5-2), flexor wrists, eyelids, face, and around the neck. Lesions are often lichenified, indurated plaques. These are intermingled with isolated, excoriated 2- to 4-mm papules that are scattered more widely over the uncovered parts.

Pruritus is a constant feature and most of the cutaneous changes are secondary to it. Scratching induces lichenification and may lead to secondary infection. A vicious cycle may be established (the itch–scratch cycle), as pruritus leads to scratching, and scratching causes secondary changes that in themselves cause itching. The scratching impulse is usually

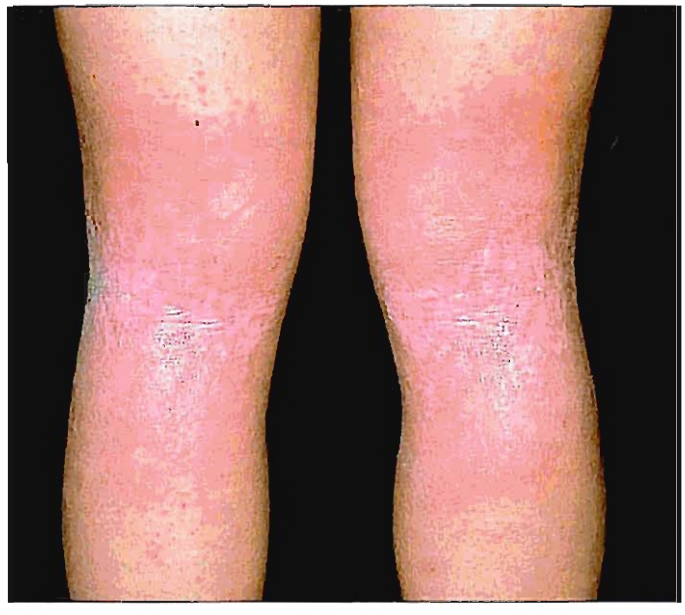

Fig. 5-2 Flexural involvement in childhood atopic dermatitis.

beyond the control of the patient. The itching is of the same compelling, paroxysmal type, with inability to feel pain during the paroxysms, that occurs in circumscribed neurodermatitis (lichen simplex chronicus). Indeed, Brocq called atopic dermatitis *neurodermite disseminé*.

Severe atopic dermatitis involving more than 50% of the body surface area is associated with growth retardation. Restriction diets and steroid usage may exacerbate growth retardation. Aggressive management of such children with topical calcineurin inhibitors (macrolactams) or phototherapy may allow for rebound growth. Children with severe atopic dermatitis may also have substantial psychological disturbances. Parents should be questioned in regard to school performance and socialization.

Atopic Dermatitis in Adolescents and Adults

In older patients, atopic dermatitis may occur as localized erythematous, scaly, papular, exudative, or lichenified (Fig. 5-3) plaques. In adolescents, the eruption often involves the classic antecubital and popliteal fossae, front and sides of the neck, forehead, and area around the eyes. In older adults the distribution is generally less characteristic, and chronic hand eczema may predominate. At times the eruption may generalize, with accentuation in the flexures. The skin, in general, is usually dry and somewhat erythematous. Lichenification and prurigo-like papules are common (Fig. 5-4). Papular lesions tend to be dry, slightly elevated, and flat-topped. They are nearly always excoriated and often coalesce to form plaques. Staphylococcal colonization is nearly universal. In darker skinned patients, the lesions are often dramatically hyperpigmented, often with focal hypopigmented areas related to healed excoriations.

Itching usually occurs in crises or paroxysms, often in response to heat or stress, and during the evening when trying to relax, or during the night. Adults frequently complain that flares of atopic dermatitis are triggered by acute emotional upsets. Stress, anxiety, and depression reduce the threshold at which itch is perceived and may contribute significantly to the disorder. Atopic persons often have difficulty delivering sweat to the surface, resulting in severe pruritus related to heat or exercise. Physical conditioning and liberal use of emollients improve this component, and atopic patients can participate in competitive sports.

Even in patients with atopic dermatitis in adolescence or early adulthood, improvement usually occurs over time, and dermatitis is uncommon after middle life. In general, these patients retain mild stigmata of the disease, such as dry skin, easy skin irritation, and itching in response to heat and perspiration. They remain susceptible to a flare of their disease when exposed to the specific allergen or environmental situation. Some will flare in response to aeroallergens, and a few patients will develop flexural dermatitis in response to niacin-induced flushing. Human immunodeficiency virus (HIV) infection can also serve as a trigger, and new-onset atopic dermatitis in an at-risk adult should lead to counseling and testing for HIV if warranted.

The hands, including the wrists, are frequently involved in adults, and hand dermatitis is the most common problem for adults with a history of atopic dermatitis. Atopic individuals account for the largest share of adults with chronic hand dermatitis. It is extremely common for atopic hand dermatitis to appear in young women after the birth of their first child, when increased exposure to soaps and water triggers their disease. Wet work is a major factor in hand eczema in general, including those patients with atopic dermatitis. Atopic hand dermatitis can affect both the dorsal and palmar surfaces. Hyperlinearity of the palms is a manifestation of ichthyosis vulgaris, which often accompanies atopic dermatitis. Fifty percent of patients with ichthyosis vulgaris have a personal or family history of atopic dermatitis. Keratosis punctata of the creases, a disorder seen almost exclusively in black persons, is also more common in atopics. Patients with atopic dermatitis have frequent exposure to preservatives and other potential allergens in the creams and lotions that are continually applied to their skin. Contact allergy may manifest as chronic hand eczema. Although a history of atopy and palmar involvement are more commonly associated with irritant dermatitis, and nailfold involvement suggests a contact allergen, there is significant overlap. Patch

Fig. 5-3 Flexural lichenification in adult atopic dermatitis.

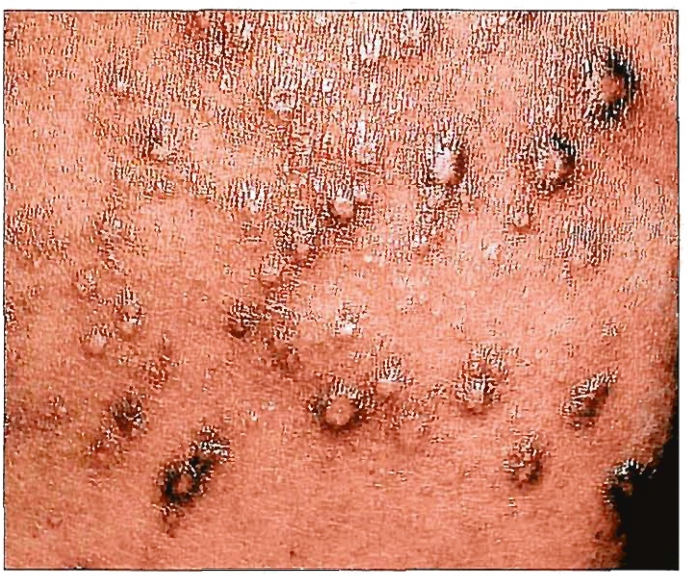

Fig. 5-4 Prurigo-like papules in adult atopic dermatitis.

testing with clinical correlation is the only certain way to exclude contact allergy in an atopic patient with chronic hand dermatitis.

Eyelids are commonly involved. In general, the involvement is bilateral and the condition flares with cold weather. As in hand dermatitis, irritants and allergic contact allergens must be excluded by a careful history and patch testing.

Associated Features and Complications

Cutaneous Stigmata A linear transverse fold just below the edge of the lower eyelids, known as the *Dennie–Morgan fold* (Fig. 5-5), is widely believed to be indicative of the atopic diathesis, but may be seen with any chronic dermatitis of the lower lids. In atopic patients with eyelid dermatitis, increased folds and darkening under the eyes is common. When taken together with other clinical findings, they remain helpful clinical signs. A prominent nasal crease may also be noted (Fig. 5-6).

The less-involved skin of atopic patients is frequently dry, slightly erythematous, and may be scaly. Transepidermal water loss is increased. As the stratum corneum is compromised, the irritancy threshold is decreased. Histologically, the apparently normal skin of atopics is frequently inflamed subclinically. The dry, scaling skin of atopic dermatitis represents low-grade dermatitis.

Pityriasis alba is a form of subclinical dermatitis, frequently atopic in origin. It presents as poorly marginated, hypopigmented, slightly scaly patches on the cheeks (Fig. 5-7), upper arms, and trunk, typically in young children. It usually responds to emollients and mild topical steroids, preferably in an ointment base.

Keratosis pilaris, horny follicular lesions of the outer aspects of the upper arms, legs, cheeks, and buttocks, is commonly associated with atopic dermatitis. It is often refractory to treatment. Moisturizers alone are only partially beneficial. Some patients will respond to topical lactic acid, urea or retinoids. Retinoids can easily irritate the skin of atopics, and treatment should begin with applications only once or twice a week. Keratosis pilaris must be distinguished from follicular eczema. Atopic dermatitis and other eczemas are commonly folliculocentric, especially in black patients.

Thinning of the lateral eyebrows, Hertoghe's sign, is sometimes present. Hyperkeratosis and hyperpigmentation producing a "dirty neck" appearance is also frequent in atopic individuals.

Vascular Stigmata Atopic individuals often exhibit perioral (Fig. 5-8), perinasal, and periorbital pallor ("headlight sign"). White dermographism is blanching of the skin at the site of stroking with a blunt instrument. This reaction differs from the triple response of Lewis in that it typically lacks a

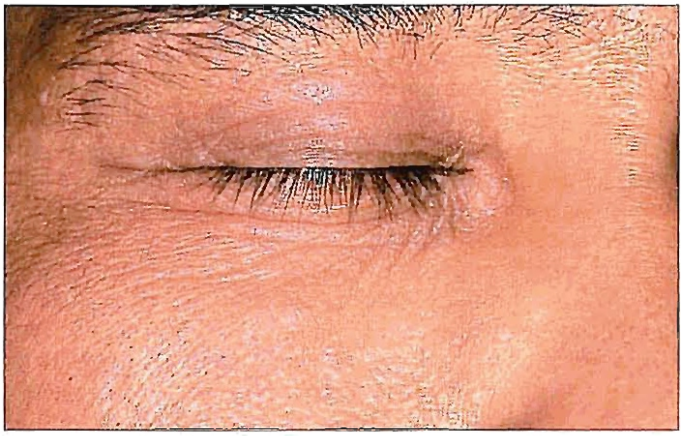

Fig. 5-5 Dennie–Morgan folds.

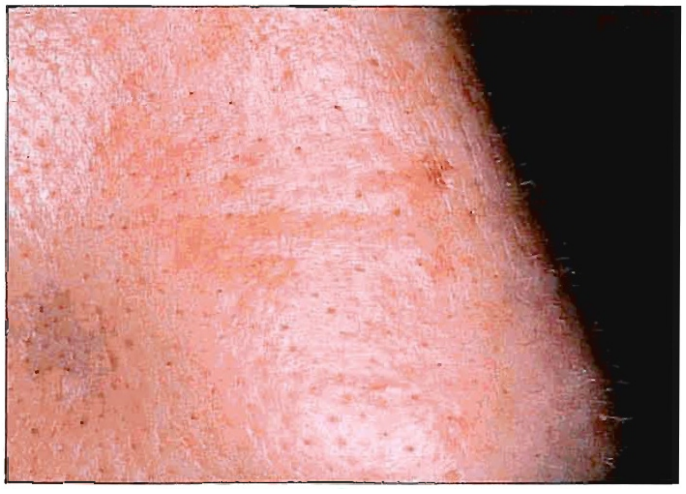

Fig. 5-6 Nasal crease.

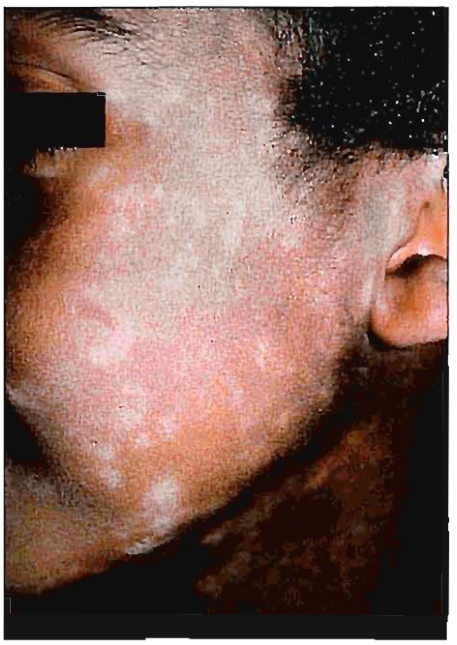

Fig. 5-7 Pityriasis alba.

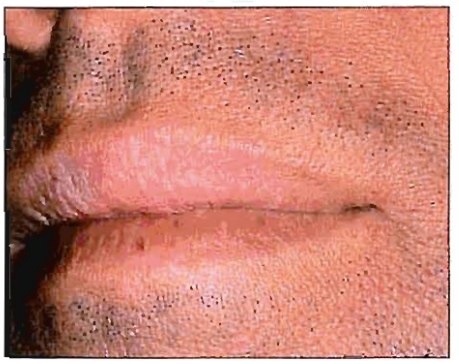

Fig. 5-8 Perioral pallor.

wheal, and the third response (flaring) is replaced by blanching to produce a white line. When 0.1 mL of a 1:100,000 solution of histamine is injected intradermally, the flare phase of the triple response is absent or diminished.

Atopics are at increased risk of developing various forms of urticaria, including contact urticaria. Episodes of contact urticaria may be followed by typical eczematous lesions at the affected site.

Ophthalmologic Abnormalities Up to 10% of patients with atopic dermatitis develop cataracts, either anterior or posterior subcapsular ones. Posterior subcapsular cataracts in atopic individuals are indistinguishable from corticosteroid-induced cataracts. Development of cataracts is more common in patients with severe dermatitis. Keratoconus is an uncommon finding, occurring in approximately 1% of atopic patients. Contact lenses, keratoplasty, and intraocular lenses may be required to treat this condition.

Susceptibility to Infection More than 90% of chronic eczematous lesions contain *Staphylococcus aureus*, often in large numbers. In addition, the apparently normal nonlesional skin of atopic patients is also commonly colonized by *S. aureus*. A finding of increasing numbers of pathogenic staphylococci is frequently associated with weeping and crusting of skin lesions, folliculitis, and adenopathy. In any flaring atopic the possibility of secondary infection must be considered. Antibiotics are commonly of benefit in treating flares of atopic dermatitis. Treatment of lesions of atopic dermatitis with topical steroids is associated with reduced numbers of pathogenic bacteria on the surface, even if antibiotics are not used. IgE antibodies directed against staphylococcus and its toxins have been documented in some atopic individuals. Staphylococcal production of superantigens is another possible mechanism for staphylococcal flares of disease. In a subset of patients with atopic dermatitis and frequent infections, chronic suppressive oral antibiotic therapy may stabilize the disease. Options include cephalosporins, trimethoprim–sulfamethoxazole, clindamycin, and (in older patients) doxycycline. Identifying and treating *S. aureus* carriers in the family may also be of benefit. An unusual complication of *S. aureus* infection in patients with atopic dermatitis is subungual infection with osteomyelitis of the distal phalanx. In atopic patients with fever who appear very toxic, the possibility of streptococcal infection must be considered. These children may require hospital admission and intravenous antibiotics.

Atopic patients have increased susceptibility to generalized herpes simplex infection (*eczema herpeticum*), as well as widespread vaccinia infection (*eczema vaccinatum*) and complicated varicella. Eczema herpeticum is seen most frequently in young children and is usually associated with herpes simplex virus (HSV)-1 transmitted from a parent or sibling. Once infected, the atopic may have recurrences of HSV and repeated episodes of eczema herpeticum. Eczema herpeticum presents as the sudden appearance of vesicular, pustular, crusted or eroded lesions concentrated in the areas of dermatitis. The lesions may continue to spread and most of the skin surface may become involved. Secondary staphylococcal infection is frequent and local edema and regional adenopathy commonly occur. If lesions of eczema herpeticum occur on or around the eyelids, ophthalmologic evaluation is recommended. The severity of eczema herpeticum is quite variable, but most cases require systemic antiviral therapy and an antistaphylococcal antibiotic.

Vaccination against smallpox is contraindicated in persons with atopic dermatitis, even when the dermatitis is in remission. Widespread and even fatal vaccinia can occur in patients with an atopic diathesis.

Atopic individuals may also develop extensive flat warts or molluscum contagiosum. Because the skin is very easily irritated, chemical treatments such as salicylic acid and cantharidin are poorly tolerated. Destruction with curettage (for molluscum), cryosurgery, or electrosurgery may be required to clear the lesions.

Pathogenesis

Atopic dermatitis is a multifactoral disease that is increasing in prevalence. There is a strong genetic component, but the environment also appears to play a role, and the disease is more common in higher socioeconomic groups. Lesions appear to be produced by an overzealous immunologic reaction to various antigens. While this immunologic component appears to be the major abnormality, defects in barrier function, blood vessel reactivity, and nerves are also considered to be important in the production of the signs and symptoms of atopic dermatitis.

Immunologic events noted in atopic individuals include activation of the T-helper 2 (Th2) immune response, with synthesis of cytokines IL-4, IL-5, IL-10, and IL-13, and inhibition of the T-helper 1 (Th1) response. IL-4 and IL-5 produce elevated IgE levels and eosinophilia in tissue and peripheral blood. IL-10 inhibits delayed-type hypersensitivity. IL-4 downregulates interferon (IFN)-γ production. Early lesions of atopic dermatitis are often urticarial in character, a manifestation of Th2 hyperreactivity. These immunologic alterations impair the capacity of the host to develop antiviral cytotoxic cells, and may predispose atopics to widespread viral infections, e.g. eczema herpeticum. Epicutaneous exposure to staphylococcal superantigens further skews the immune response toward Th2 cytokine production; hence, the known association of staphylococcal infection with exacerbations of atopic dermatitis. Reduced Th1 activity (IFN-γ production) may explain the decreased sensitivity to topically applied antigens. For example, toxicodendron sensitivity occurs in only 15% of individuals with atopic dermatitis compared with 61% of nonatopic controls. Although harder to sensitize, atopics not infrequently develop allergic contact dermatitis to components of their medicaments, probably because of long-term exposure to these agents.

While atopic dermatitis begins as a Th2-mediated disorder, in its chronic phase, cutaneous inflammation is characterized by Th1 cytokines. This explains why chronic atopic dermatitis histologically resembles other chronic dermatoses.

Langerhans cells in the skin of patients with atopic dermatitis also demonstrate abnormalities. They directly stimulate helper T-cells without the presence of antigen, selectively activating helper T-cells into a Th2 phenotype. The trimeric high-affinity IgE receptor (FcepsilonRI) on Langerhans cells mediates IgE-dependent antigen uptake. Its expression is upregulated on Langerhans cells in the skin of patients with atopic dermatitis.

Monocytes in the peripheral blood of patients with atopic dermatitis produce elevated levels of prostaglandin E2

(PGE2). PGE2 reduces IFN-γ production but not IL-4 from helper T-cells, enhancing the Th2 dominance. PGE2 also directly enhances IgE production from B-cells. Monocytes also demonstrate elevated phosphodiesterase activity. The propensity to develop atopic dermatitis is already evident in newborns. Neonatal cord blood mononuclear cells stimulated with phytohemagglutinin show significantly higher IL-13 levels in children who subsequently develop atopic dermatitis.

Abnormalities of cutaneous nerves and the products they secrete (neuropeptides) have been identified in atopic patients. These may explain the abnormal vascular responses, reduced itch threshold, and perhaps some of the immunologic imbalances seen in atopic skin. Decreased activation of peripheral pruriceptors has been demonstrated in patients with atopy, suggesting that itch in lesional skin might be based on altered spinal impulses rather than in primary afferent neurons. The acetylcholine content of atopic skin is markedly elevated and acetylcholine may play a role in atopic signs and symptoms. In subjects with atopic dermatitis, acetylcholine injected intradermally will produce marked pruritus, while it produces pain in control patients.

In atopic patients, the epidermal barrier is abnormal, even in apparently normal skin. An increase in transepidermal water loss (TEWL) correlates with the severity of the disease. Atopic dermatitis usually worsens in the winter due to decreased ambient humidity. Stress also increases TEWL. This correlates with the flares of atopic dermatitis seen with rapid steroid reduction and stress. Correcting barrier dysfunction is critical to improving atopic dermatitis, hence the value of skin hydration, ointments, and occlusion.

An inherited mutation in the high-affinity IgE receptor has been reported in unrelated cohorts with atopic disease. Atopy mapped to this region of chromosome 11q in 60% of atopic families, and 17% of atopic families had the same specific point mutation in the β-subunit of the high-affinity IgE receptor gene. The high-affinity IgE receptor exists on mast cells, monocytes, and Langerhans cells. Stimulation of this receptor on mast cells results in the production of Th2 cytokines, including IL-4, and such stimulated mast cells may directly regulate local B-cell IgE synthesis.

Environmental factors clearly play a role in the expression of the atopic diathesis. Atopic disease has increased dramatically with overall improvements in the standard of living and hygiene. Atopic dermatitis is more prevalent in developed regions. A disproportionate percentage of Th2 cells in atopic dermatitis skin may be specific to allergens such as house dust mites or grass pollen. Patients with atopic dermatitis frequently have high levels of IgE antibodies to house dust mites and this IgE is bound to Langerhans cells in atopic skin. There is, however, poor correlation between improvement and house dust mite eradication and prick tests to house dust mite antigen. Patch testing for dust mite allergy remains controversial. Rates of reactivity are exceedingly high and often correlate poorly with atopic symptoms. House dust mites are ubiquitous and it is difficult to eliminate them from the environment. Hypoallergenic pillow and mattress covers, designed to reduce dust mite exposure, are expensive and data regarding their efficacy have been mixed. The high prevalence of food and aeroallergen sensitivity in atopic patients is undeniable, but may represent a general propensity for allergic disease. A cause-and-effect relationship between these allergens and cutaneous disease must be proved in each patient with assays for IgE and blinded challenges. Dietary restriction should only be undertaken if there is a strong historical or laboratory suggestion that foods are an important trigger. In infants, milk restriction must be carefully undertaken to insure that adequate nutrition is maintained.

Some epidemiologic studies suggest transmissibility of the atopic diathesis or the involvement of transmissible environmental factors. The incidence of atopic dermatitis increases in populations that move from countries with a low incidence to ones with a high incidence. African and New Guinea villagers demonstrate a higher incidence of atopic disease when they move to cities. When they return to their villages, the incidence of asthma in all villagers increases. These findings suggest a complex interplay of inherited and environmental factors.

Differential Diagnosis

Typical atopic dermatitis is not difficult to diagnose because of its predilection for symmetric involvement of the face, neck, and antecubital and popliteal fossae. Dermatoses that may resemble atopic dermatitis include seborrheic dermatitis (especially in infants), irritant or allergic contact dermatitis, nummular dermatitis, scabies, and psoriasis (especially palmoplantar). Certain immunodeficiency syndromes (see below) may exhibit a dermatitis remarkably similar or identical to atopic dermatitis.

Histopathology

The histology of atopic dermatitis varies with the stage of the lesion, with many of the changes induced by scratching. Hyperkeratosis, acanthosis, and excoriation are common. Staphylococcal colonization may be noted histologically. Although eosinophils may not be seen in the dermal infiltrate, staining for eosinophil major basic protein (MBP) reveals deposition in many cases. Heavy MBP deposition is often seen in specimens from patients with atopic dermatitis and a personal or family history of respiratory atopy. This is less likely to be seen in specimens from patients with neither a personal nor a family history of respiratory atopy.

General Management

Infants and Children Stress, heat, sweating, and external irritants may precipitate an attack of itching and dermatitis. Hot baths, alkaline soaps, vigorous rubbing and scrubbing are to be avoided. Water should be kept tepid and a mild cleanser should be used only on soiled skin. Immediately after bathing, an evaporation barrier should be applied to the skin. This technique of "soaking and greasing" is remarkably effective in the majority of patients. Because preservatives in creams and lotions represent possible contact allergens, ointment bases are preferred if tolerated. A vanishingly thin coat of white petrolatum can be applied by rubbing a very small amount between the palms before applying it to the skin. Allergy to white petrolatum is extremely rare, although one of the authors (DME) has seen a patient with symptoms of contact hypersensitivity and a documented patch test response to pharmaceutical-grade white petrolatum. Aquaphor and vegetable shortening can also be used after bathing. Hydrated Aquaphor (Eucerin) is commonly used and is highly effective, but because of the aqueous content, the product requires a preservative. Because soap may aggravate the disease, olive oil, Cetaphil,

Aquanil, or similar products may be used for cleansing without water. Particular attention should be given to the genitals and buttocks, and diapers should be changed whenever they are wet or soiled. These waterless regimens are seldom necessary, and most children do well with once-a-day, short, tepid baths. Antibacterial cleansers should be avoided because of the risk of contact sensitivity.

As most clinical manifestations are the result of scratching, protection of the affected parts from scratching and rubbing is critical, but difficult to achieve. During an intense bout of itching, rubbing an ice cube on the affected skin can sometimes stop the itch and prevent further damage through scratching. Antihistaminic drugs are somewhat beneficial, especially if given at night, when the accompanying sedative effects may be helpful in preventing scratching. The dosage must be adequate and regular. The nonsedating antihistamines provide little or no benefit in reducing pruritus in atopic patients.

In cases where specific food allergies are implicated, dietary restrictions may be helpful. Eliminating the foods on a trial basis for several weeks is an alternative to blinded food challenge and food-specific IgE testing, but is not nearly as accurate. As mentioned before, open challenges are commonly misleading, and because food challenges may induce anaphylaxis they should always be done under controlled conditions. Different substitution products have been proposed for children with documented milk allergy. Unfortunately, allergic reactions to soy products, hydrolysates of lactoserum proteins, powdered casein hydrolysates, and hydrolysates of soy have been described. For infants or children with documented milk allergy, it is best to work together with a knowledgeable pediatrician or allergist. For adolescents, an elimination diet of rice, apple sauce, pears, carrots, squash, and lamb has been advocated, but each of these foods is still a potential allergen. To confirm food allergy, serum food-specific IgE testing, prick testing or blinded challenges are ultimately required.

Adults Atopics should avoid extremes of cold and heat. The dry skin of atopics tends to be worse in the winter and should be hydrated daily with moisturizers. Overbathing must be avoided and soap used only on the axillae, anogenital region, and scalp. Less irritating soaps include Alpha-Keri, Dove, Basis, Neutrogena, Aveeno, and Emulave. Showers should be tepid, not hot. Tub soaking is acceptable if followed by adequate lubrication. Humidifiers are helpful and modern forced air systems can be modified with a central humidifier and humidostat. The patient should not wear wool, because its fibers are irritating. The patient should be aware that emotional stress can be an important factor in causing exacerbations. In adults with atopic disease, relaxation techniques and biofeedback may be useful. In atopics, but not in normal subjects, 30 min of intense kissing in the presence of soft music led to a significantly reduced wheal responses induced by house dust mites and cedar pollen, but not by histamine, and decreased plasma levels of neurotrophins and brain-derived neurotrophic factor.

Specific Treatment Modalities

Topical Therapy Corticosteroid therapy is the dominant method of treatment of atopic dermatitis. In infants, low-potency steroid ointments such as hydrocortisone 1% or 2.5% are preferred. Emphasis must be placed on regular application of emollients. Once corticosteroid receptors are saturated, additional applications of a steroid preparation contribute nothing more than an emollient effect. In most body sites, once-a-day application of a corticosteroid is almost as effective as more frequent applications, at lower cost and with less systemic absorption. In some areas, twice-a-day applications may be beneficial, but more frequent applications are almost never of benefit. Application of steroid under wet wraps can increase penetration and saturation of steroid receptors. For refractory areas, a slightly stronger corticosteroid such as desonide or Aclovate ointment may be used. A more potent molecule is more appropriate than escalating concentrations of a weaker molecule, as the effect of the latter plateaus rapidly as receptors become saturated. In older children and adults, medium-potency steroids such as triamcinolone are commonly used, except on the face, where milder steroids or calcineurin inhibitors are preferred. For thick plaques and lichen simplex chronicus-like lesions very potent steroids may be necessary. These are generally applied on weekends, with a milder steroid used during the week. Ointments provide a superior vapor barrier and generally require no preservatives. They therefore have a lower potential to induce contact allergy than creams or lotions. Contact allergy to the corticosteroid itself is not uncommon. Corticosteroid allergy seldom manifests as worsening of the eczema. Instead, it manifests as flare of eczema whenever the corticosteroid is discontinued, even for a day. This may be difficult to differentiate from stubborn dermatitis (see Chapter 6).

Although the potential for local and even systemic toxicity from corticosteroids is real, the steroid must be strong enough to control the pruritus and remove the inflammation. Even in small children, strong topical steroids may be necessary in weekly pulses to control severe flares. Weekend pulses are always preferable to daily application of a potent steroid. Monitoring of growth parameters should be done in infants and young children. Acute flares frequently respond to a course of antistaphylococcal therapy, and such therapy can be steroid-sparing. If an atopic patient worsens or fails to improve after the use of topical steroids and moisturizers, the possibility of allergic contact dermatitis to a preservative or the corticosteroids must be considered.

Topical calcineurin inhibitors, such as tacrolimus or pimecrolimus, offer an alternative to topical steroids. Systemic absoption is generally not significant with either of these agents. Although a 0.03% tacrolimus ointment is marketed for use in children, it is unclear if it really offers any safety advantage over the 0.1% formulation. Tolerability is improved if the ointment is applied to bone-dry skin. Patients experience less burning if eczematous patches are treated initially with a corticosteroid with transition to a calcineurin inhibitors after partial clearing. Improvement tends to be steady, with progressively smaller areas requiring treatment. These agents are particularly useful on the eyelids and face, in cases of refractory dermatitis, in areas prone to steroid atrophy, when steroid allergy is a problem, or when systemic steroid absorption is a concern.

For the hydration of xerotic skin of atopic dermatitis, petrolatum, 10% urea in a hydrophilic cream, Eucerin cream, or 1% hydrocortisone in 10% urea cream is effective.

Lactic acid-containing moisturizers in concentrations higher than 5% are generally poorly tolerated by atopic patients with active dermatitis.

Crude coal tar 1% to 5% in white petrolatum or hydrophilic ointment USP, or liquor carbonis detergens (LCD) 5% to 10% in hydrophilic ointment USP, are sometimes helpful for an area of refractory eczema. Tar preparations are especially beneficial when used for intensive treatment for adults in an inpatient or daycare setting.

Systemic Therapy Antihistamines may be used for their sedative effects. Hydroxyzine (Atarax or Vistaril), diphenhydramine (Benadryl) or chlorpheniramine (Chlor-Trimeton) are commonly used in children. In adults, hydroxizine or doxepin (Sinequan) in doses of 10 to 75 mg as a single evening dose can be helpful. Patients must be warned that they should not drive if they are still drowsy in the morning. Nonsedating antihistamines are of no benefit in reducing pruritus.

S. aureus has long been known to be a frequent resident of both normal and involved skin in atopic dermatitis. Many patients benefit from short courses of antistaphylococcal antibiotics during flares of dermatitis, even when clinical evidence of infection is lacking. Cephalosporins and semisynthetic penicillins are generally used, although trimethoprim–sulfamethoxazole and tetracyclines are options, especially when faced with methacillin-resistant staphylococci. Nasal carriage can be treated with topical mupirocin or a cephalosporin or semisynthetic penicillin together with oral rifampin 600 mg/day (for an adult) for 10 days.

In general, systemic steroids should be used only to control acute exacerbations. In patients requiring systemic steroid therapy, short courses (3 weeks or less) are preferred. In rare cases, when longer treatment is needed, the minimum dose given on alternate days if possible is advised. If doses in excess of 15 to 20 mg on alternate days are required, or if side effects result, consideration should be given to alternative therapies for their steroid-sparing effect. Osteoporosis in women requires special consideration and should be addressed with a bisphosphonate early in the course of therapy when bone loss is greatest. Preventive strategies such as calcium supplements, vitamin D supplementation, regular exercise, and stopping smoking should be strongly encouraged. DEXA scans are recommended.

Cyclosporin is effective in the treatment of severe atopic dermatitis, but the response is rarely sustained after the drug is discontinued. Its potential side effects and high cost preclude its use in all but the most severe patients.

Immunosuppressive and antiproliferative drugs, such as azathiprine (Immuran), mycophenolate mofetil (Cellcept), and methotrexate (Rheumatrex), can be effective in various forms of refractory eczema, but are reserved for debilitating disease unresponsive to other therapy. Effective dosing of azathioprine is based on the serum thiopurine methyltransferase level. Immune modulators, such as intravenous immunoglobulin (IVIG), IFN, and thymopentin, have demonstrated some efficacy in atopic dermatitis, but are rarely used. Traditional Chinese herb mixtures have shown efficacy in children, but the active ingredients and their mechanism of action remain unknown. Chinese herbs are usually delivered as a brewed tea to be drunk daily, but are unpalatable to most Western patients. Hepatitis and cardiomyopathy have occurred during herbal treatments, and some formulations have been found to be adulterated with corticosteroids.

Phototherapy Photochemotherapy (PUVA), UVA1, or broad- or narrow-band UVB, may be helpful in severe atopic dermatitis. Broad-band UVB tends to be the least effective. Goeckerman therapy with tar may improve the efficacy of broad-band UVB. The combination of UVA and UVB is superior to broad-band UVB alone.

Management of an Acute Flare

Initially, the precipitating cause of the flare should be sought. Recent stressful events may be associated with flares. Secondary infection with *S. aureus* should be assumed in most cases. Less commonly, herpes simplex or coxsackie virus may be involved. Pityriasis rosea may also flare atopic dermatitis. The development of contact sensitivity to an applied medication must be considered.

In the setting of an acute flare, treating triggers (see above) may lead to improvement. A short course of systemic steroids may be of benefit, but patients should be counseled that prolonged systemic corticosteroid therapy must be avoided. "Home hospitalization" may be useful: the patient goes home to bed, isolated from work and other stressors; large doses of an antihistamine are given at bedtime; the patient soaks in the tub daily, then applies a topical steroid ointment under wet pajamas and a sauna suit. Often, 3 to 4 days of such intensive home therapy will break a severe flare.

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ECZEMA

The word *eczema* seems to have originated in AD 543 and is derived from the Greek work *ekzein*, meaning to "to boil forth" or to "effervesce." In its modern sense, the term refers to a broad range of conditions that begin as spongiotic dermatitis and may progress to a lichenified stage. The term encompasses such disorders as dyshidrotic eczema and nummular eczema. The acute stage generally presents as a red edematous plaque which may have grossly visible small grouped vesicles. Subacute lesions present as erythematous plaques with scale or crusting. Later, lesions may be covered by a dryer scale or become lichenified.

Histologically, the hallmark of all eczematous eruptions is a serous exudate between cells of the epidermis (spongiosis), with an underlying dermal perivascular lymphoid infiltrate and exocytosis (lymphocytes noted within spongiotic foci in the dermis). Spongiosis is generally out of proportion to the lymphoid cells in the epidermis. This is in contrast to mycosis fungoides which demonstrates minimal spongiosis confined to the area immediately surrounding the lymphocytes.

In most eczematous processes, spongiosis is very prominent in the acute stage, where it is accompanied by little acanthosis or hyperkeratosis. Subacute spongiotic dermatitis demonstrates epidermal spongiosis with acanthosis and hyperkeratosis. Chronic lesions may have little accompanying spongiosis, but it is not uncommon for acute and chronic stages to overlap, as episodes of eczematous dermatitis follow one another. Scale corresponds to foci of parakeratosis produced by the inflamed epidermis. A crust is composed of serous exudate, acute inflammatory cells, and keratin. Eczema, regardless of cause, will manifest similar histologic changes if allowed to persist chronically. These features are related to chronic rubbing or scratching and correspond clinically to lichen simplex chronicus or prurigo nodularis. Histologic features at this stage include compact hyperkeratosis, irregular acanthosis, and thickening of the collagen bundles in the papillary portion of the dermis. The papillary dermis may have an appearance of vertical streaking, or may present as a widened papillary dermis with angiofibroplasia.

The dermal infiltrate at all stages is predominantly lymphoid, but an admixture of eosinophils may be noted. Neutrophils generally appear in secondarily infected lesions. Spongiosis with many intraepidermal eosinophils may be seen in the early spongiotic phase of pemphigoid and pemphigus, incontinentia pigmenti, as well as some cases of allergic contact dermatitis.

In most eczematous reactions, severe pruritus is a prominent symptom. The degree of irritation at which itching begins (the itch threshold) is lowered by stress. Itching is often prominent at bedtime and commonly results in insomnia. Heat and physical exertion may also provoke episodes of itching.

Regional Eczemas

Ear Eczema Eczema of the ears or otitis externa may involve the helix, postauricular fold, and external auditory canal. By far the most frequently affected site is the external canal, where it is often a manifestation of seborrheic dermatitis or allergic contact dermatitis. Secretions of the ear canal derive from the apocrine and sebaceous glands, which form cerumen. Traumatization of the ear canal by rubbing, wiping, scratching, and picking induces edema and inflammation. Secondary bacterial colonization or infection are common. Infection is usually caused by staphylococci, streptococci or pseudomonas. Contact dermatitis from neomycin, benzocaine, and preservatives may result from topical remedies used to treat these conditions. *Pseudomonas aeruginosa* can result in malignant external otitis with ulceration and sepsis. Earlobe dermatitis is virtually pathognomonic of nickel allergy and occurs most frequently in women who have pierced ears.

Treatment should be directed at removal of causative agents, such as topically applied allergens. Scales and

cerumen should be removed by gentle lavage with an ear syringe. Antibiotic–corticoid preparations, such as Cortisporin otic suspension, have frequently been prescribed, and ingredients such as neomycin are therefore frequently found as relevant contact allergens. Corticosteroids alone can be effective for noninfected dermatitis. For very weepy lesions, Domeboro otic solution may be drying and beneficial.

Eyelid Dermatitis Eyelid dermatitis is commonly related to atopic dermatitis or allergic contact dermatitis (see Chapter 6). Volatile substances, tosylamide, epoxy hardeners, insect sprays, and lemon peel oil may be implicated. Many cases of eyelid contact dermatitis are caused by substances transferred by the hands to the eyelids. Any sensitizer or irritant on the palms or fingers may cause dermatitis of the eyelids long before it affects any other parts of the face. When eye drops contain an allergen, the allergen passes through the nasolacrimal duct, and dermatitis is often noted below the nares in addition to the eyelids.

Allergic contact dermatitis usually affects the upper eyelids. Atopic dermatitis frequently causes eyelid dermatitis involving both the upper and lower eyelids. In both conditions, edema, erythema, scale, and crusting may occur.

Breast Eczema (Nipple Eczema) Eczema of the breasts may affect the nipples, areolae, or the surrounding skin. Usually, eczema of the nipples is of the moist type with oozing and crusting. Painful fissuring is frequently seen, especially in nursing mothers.

Circumscribed neurodermatitis, seborrheic dermatitis, atopic dermatitis, and contact dermatitis must be considered in the differential diagnosis. Nipple eczema if often an isolated manifestation of atopic dermatitis. In patients in whom eczema of the nipple or areola has persisted for more than 3 months, especially if it is unilateral, a biopsy is mandatory to rule out the possibility of Paget's disease of the breast. Topical or intralesional corticosteroids are effective in the treatment of non-Paget eczema of the breast. Nevoid hyperkeratosis of the nipples is a chronic condition that may mimic nipple eczema, but is not steroid responsive.

Hand Eczema The hands are commonly involved in atopic dermatitis, allergic contact dermatitis, and psoriasis. On the palms and soles, it may sometimes be difficult or impossible to differentiate these conditions clinically (Fig. 5-9). Even a biopsy may not result in a definitive diagnosis, as all three conditions may demonstrate spongiosis and crusting on the hands. A complete history, careful examination of the rest of the body surface, and patch testing may be helpful in establishing a diagnosis. Frequently, patients with hand eczema have multiple causes for their dermatitis, such as an atopic diathesis plus irritant or allergic contact dermatitis. The importance of patch testing cannot be overemphasized. Allergens in consumer goods, in the workplace, and in topical medications may be important in a given patient. Patch testing must include broad screens of common allergens or most cases of allergic contact dermatitis will be missed.

Hand eczema represents a major occupational problem and accounts for more than 80% of all occupational dermatitis. Patients with hand eczema frequently miss work and may need to change occupations. Occupations that involve wet work have an extraordinarily high incidence of hand dermatitis. Hair dressers, food service workers, and healthcare workers are particularly affected. In healthcare workers, the impaired barrier poses a risk for infection by blood-borne pathogens.

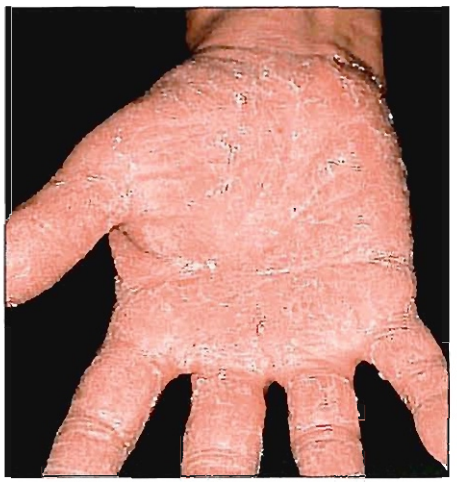

Fig. 5-9 Hand eczema.

Almost a third of baker's apprentices develop hand dermatitis within 12 months of entering the profession. Among hairdressers, the incidence approaches 50% after several years. Both irritant dermatitis and allergic contact dermatitis are important factors, with glyceryl monothioglycolate and ammonium persulfate being the most common allergens among hairdressers. Among those with preservative allergy, the hands are preferentially involved in patients allergic to isothiazolinones and formaldehyde, while the hands and face are equally involved with paraben allergy. Cement workers have a high rate of hand dermatitis related to contact allergy, alkalinity, and hygroscopic effects of cement. Dorsal hand dermatitis in a cement worker suggests contact allergy to chromate or cobalt. The addition of ferrous sulfate to cement has no effect on irritant dermatitis, but reduces the incidence of allergic chromate dermatitis by two-thirds.

Both wet work and low humidity are risk factors for hand dermatitis. Low air humidity impairs the cutaneous barrier, increasing allergen and irritant penetration. Low humidity also results in an increase in epidermal Langerhans cells. Hard water also increases the incidence of hand dermatitis.

Among patients with occupational hand dermatitis, atopic patients are disproportionately represented. Hand dermatitis is frequently the initial or only adult manifestation of an atopic diathesis. The likelihood of developing hand eczema is greatest in patients with atopic dermatitis, more common if the atopic dermatitis was severe, but still increased in incidence in patients with only respiratory atopy. Atopic patients should receive career counseling in adolescence to avoid occupations such as hairdressing, food service, automotive repair, metal, or custodial work, that are likely to induce hand dermatitis.

Contact urticaria syndrome may present as immediate burning, itching or swelling of the hands, but a chronic eczematous phase may also occur. Latex is an important cause of the syndrome, but raw meat, lettuce, garlic, onion, carrot, tomato, spinach, grapefruit, orange, radish, fig, parsnip,

cheese, or any number of other foods may be implicated. Delayed-type sensitivity may develop to *Compositae* plants, metals such as nickel, dyes such as *p*-phenylenediamine, formaldehyde in cleaning products, and numerous other allergenic contactants. A careful occupational and hobby history is essential to identify possible contactants.

Acute Vesiculobullous Hand Eczema (Pompholyx, Dyshidrosis)

Idiopathic acute vesicular hand dermatitis is not related to blockage of sweat ducts, although palmoplantar hyperhidrosis is common in these patients, and control of hyperhidrosis improves the eczema. Acute pompholyx, also known as cheiropompholyx if it affects the hands, presents with severe, sudden outbreaks of intensely pruritic vesicles. Primary lesions are macroscopic, deep-seated multilocular vesicles resembling tapioca on the sides of the fingers (Fig. 5-10), palms, and soles. The eruption is symmetrical and pruritic, with pruritus often preceding the eruption. Coalescence of smaller lesions may lead to bulla formation severe enough to prevent ambulation. Individual outbreaks resolve spontaneously over several weeks. Bullous tinea or an id reaction from a dermatophyte should be excluded, and patch testing should be considered to rule out allergic contact dermatitis.

Chronic Vesiculobullous Hand Eczema

In chronic cases the lesions may be hyperkeratotic, scaling, and fissured, and the "dyshidrosiform" pattern may be recognized only during exacerbations. Females outnumber males by 3:1. There is a tendency for the pruritic 1- to 2-mm vesicles to be most pronounced at the sides of the fingers. In long-standing cases the nails may become dystrophic. The distribution of the lesions is, as a rule, bilateral and roughly symmetrical.

Hyperkeratotic Hand Dermatitis

Males outnumber females by 2:1, and the patients are usually older adults. The eruption presents as hyperkeratotic, fissure-prone, erythematous areas of the middle or proximal palm. The volar surfaces of the fingers may also be involved. Plantar lesions occur in about 10% of patients. Histologically, the lesions show chronic spongiotic dermatitis. The most important differential diagnosis is psoriasis, and a significant number of patients with chronic hyperkeratotic hand dermatitis will ultimately prove to be psoriatic. The presence of sharply demarcated plaques, nail pitting or occasional crops of pustules are important clues to psoriatic hand involvement.

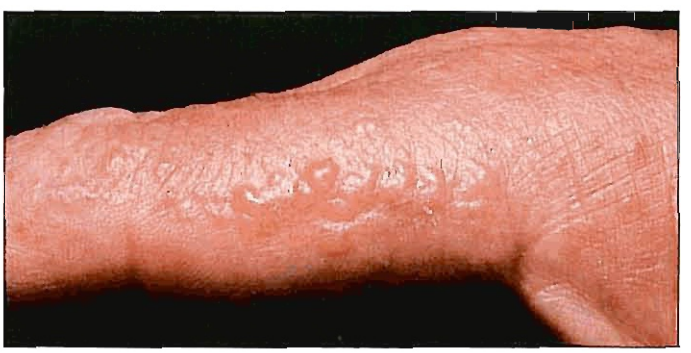

Fig. 5-10 Acute vesiculobullous hand eczema.

Treatment

The hands are essential for work both in and out of the home. Treatment regimens must be practical and allow patients to function as normally as possible. Vinyl gloves may be worn during wet work, especially when detergents are used. Although vinyl gloves are protective from chemicals, they do not prevent exposure to heat through the glove or the macerating effect of sweat, which accumulates under the gloves. They are also far less durable than rubber gloves. Rubber gloves may be used at home if patients do not exhibit allergy to rubber chemicals or latex. Wearing white cotton gloves under the vinyl gloves is beneficial. For rough work, such as gardening, wearing protective cloth or leather gloves is essential. Cotton can adsorb allergens in the environment, and cotton gloves worn throughout the day offer little protection from many allergens.

Moisturizing is a critical component of the management of hand dermatitis. Application of a moisturizing protective cream or ointment after each hand washing or water exposure is recommended. Creams require a preservative and have a higher risk of contact sensitivity. Ointments tend to have few ingredients and do not generally require a preservative. At night, even during periods of remission, a heavy moisturizing ointment should be applied to the hands after soaking in water. If palmar dryness is present, occlusion of the moisturizer with a plastic bag or vinyl gloves is recommended.

White petrolatum remains within the stratum corneum and can restore barrier function. White petrolatum is cheap and nonsensitizing, and remains a valuable agent in the treatment of hand dermatitis.

Superpotent and potent topical steroid agents are first-line pharmacologic therapy. Their efficacy is enhanced by occlusion. A single application with occlusion at night is often more effective than multiple daytime applications. As in the treatment of atopic dermatitis, once steroid receptors are saturated, additional applications of a corticosteroid contribute only an emollient effect. Triamcinolone 0.1% ointment is available in a nonsensitizing white petrolatum base. It is fairly potent, inexpensive, does not irritate, and has a low incidence of sensitization. In refractory cases, superpotent steroids may be used for a period of 2 to 3 weeks, then on weekends, with a milder corticosteroid applied during the week. Chronic use of potent fluorinated corticosteroids may be associated with skin atrophy.

The use of systemic corticosteroids usually results in dramatic improvement. Unfortunately, relapse frequently occurs almost as rapidly, so systemic steroids are recommended in only the most severe cases or to control acute exacerbations. Patients with persistent severe hand dermatitis often require alternative, steroid-sparing therapy.

Topical calcinuerin inhibitors may be of benefit in some patients. Soaks with a tar bath oil or applications of 5% liquor carbonis detergens may be of benefit in some cases. Phototherapy in the form of UVA1 alone, UVB, narrow-band UVB or soak PUVA can be effective. PUVA is more effective in reducing Langerhans cell numbers and in clearing the dermatitis than UVB, but the risk of phototoxicity is higher. Phototoxicity depends on the concentration of the soak solution and dose of light. Relatively few phototoxic reactions

are seen with regimens that use a 15- to 20-min soak in a 3 mg/L solution of 8-methoxypsoralen and starting with 0.25 to 0.5 J/cm^2 and increasing by 0.25 to 0.5 J/cm^2 three times a week. Superficial Grenz ray radiotherapy remains a viable modality, but well-maintained machines are few in number. The depth of penetration is limited, so it is best used after acute crusting and vesiculation have been cleared with other treatment. Doses of 200 cG are delivered at weekly intervals for a total of 800 to 1000 cG. Therapy may be repeated after 6 months. The total lifetime dose should not exceed 5000 cG.

As many patients with apparent hand dermatitis actually have psoriasis, a trial of calcipotriene ointment or tazarotene gel may be reasonable. Both of these agents may irritate eczematous skin, so they are best used after an initial course of topical steroid therapy. Oral methotrexate, in psoriatic doses, can be helpful in some cases of refractory hand eczema, as may azathioprine. Mycophenolate mofetil is sometimes useful in doses of 1 to 1.5 g twice a day (for an adult). The blood count must be monitored and some patients will experience gastrointestinal intolerance. Cyclosporin is rarely used in chronic hand eczema, but may be useful for short-term remittive therapy.

The incidence of hand dermatitis in the workplace can be reduced by identifying major irritants and allergens, preventing exposure through engineering controls, substituting less irritating chemicals when possible, enforcing personal protection and glove use, and instituting organized worker education. Hand eczema classes have been documented to reduce the burden of occupational dermatitis. It is important to note that prevention of exposure to a weak but frequent irritant can have more profound effects than removal of a strong but infrequently contacted irritant. Proper gloves are essential in industrial settings. Nitrile gloves are generally less permeable than latex gloves. Gloves of ethylene vinyl alcohol copolymer sandwiched with polyethylene are effective against epoxy resin, methyl methacrylate, and many other organic compounds. Latex and vinyl gloves offer little protection against acrylates. The 4H (4 h) glove and nitrile are best in this setting. As hospitals transition to nonlatex gloves, it is important to note than even low protein, powder-free latex gloves reduce self-reported skin problems among health workers.

Barrier products can improve hand dermatitis if used in the appropriate setting. Foams containing dimethicone and glycerin can reduce hand dermatitis related to wet work.

Although most patients with hand dermatitis should limit water exposure and avoid hot water, some data suggest that heat shock therapy can be useful in selected patients to reduce Langerhans cell numbers. Heat shock therapy can be accomplished with controlled temperature wax or hot water (48–50° C) two or three times a day. Care must be taken to avoid burns, and to monitor for flares of dermatitis. In acute vesicular disease, soaking the hands and feet in Burow's solution may be of benefit. Chronic fissured dermatitis with heavy bacterial colonization may improve with soaks in a silver nitrate solution (1:1000) or a potassium permanganate solution (1:5000). Both will discolor the skin. Individual fissures can be mended with a topical acrylate. These are now available commercially as liquid bandages.

Diaper (Napkin) Dermatitis Dermatitis of the diaper area in infants is a common cutaneous disorder. The highest prevalence occurs between 6 and 12 months of age. Diaper dermatitis is also seen in adults with urinary or fecal incontinence.

Irritant diaper dermatitis is an erythematous dermatitis limited to exposed surfaces. The folds remain unaffected, in contrast to intertrigo, inverse psoriasis, and candidiasis where the folds are frequently involved. In severe cases of irritant dermatitis there may be superficial erosion or even ulceration. The tip of the penis may become irritated and crusted, with the result that the baby urinates frequently and spots of blood appear on the diaper.

Complications of diaper dermatitis include punched-out ulcers or erosions with elevated borders (Jacquet erosive diaper dermatitis); pseudoverrucous papules and nodules; and violaceous plaques and nodules (granuloma gluteale infantum).

The importance of ammonia in common diaper dermatitis has been overstated, but constant maceration of the skin is critical. The absence of diaper dermatitis in societies in which children do not wear diapers clearly implicates the diaper environment as the cause of the eruption. Moist skin is more easily abraded by friction of the diaper as the child moves. Wet skin is more permeable to irritants. Skin wetness also allows the growth of bacteria and yeast. Bacteria increase the local pH, increasing the activity of fecal lipases and proteases. *Candida albicans* is frequently a secondary invader and when present produces typical satellite erythematous lesions or pustules at the periphery as the dermatitis spreads.

Napkin psoriasis (Fig. 5-11), seborrheic dermatitis, atopic dermatitis, Langerhans cell histiocytosis, tinea cruris, allergic contact dermatitis, acrodermatitis enteropathica, aminoacidurias, biotin deficiency, and congenital syphilis should be included in the differential diagnosis.

Prevention is the best treatment. Diapers that contain superabsorbent gel have been proved effective in preventing diaper dermatitis in both neonates and infants. They work by absorbing the wetness away from the skin and by buffering the pH. Cloth diapers and regular disposable diapers are equal to each other in their propensity to cause diaper dermatitis and are inferior to the superabsorbent gel diapers. The frequent changing of diapers is also critical.

Protecting the skin of the diaper area is of great benefit in all forms of diaper dermatitis. Zinc oxide paste is excellent.

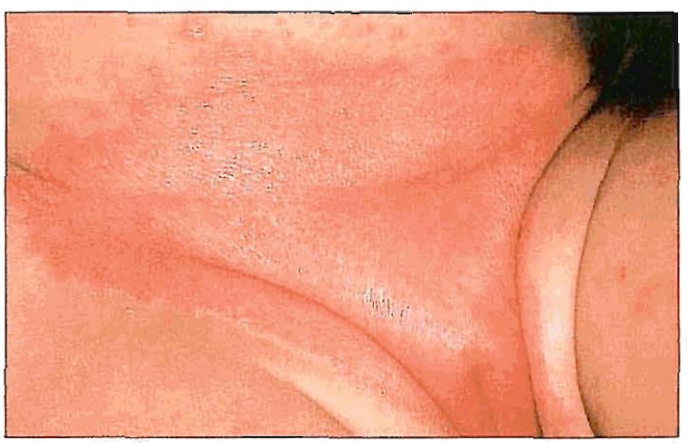

Fig. 5-11 Napkin psoriasis.

The application of a mixture of equal parts Nystatin ointment and 1% hydrocortisone ointment at each diaper change offers both anticandidal activity and an occlusive protective barrier from urine and stool.

Circumostomy Eczema Eczematization or autosensitization of the surrounding skin frequently occurs after an ileostomy or colostomy. It is estimated that some 75% of ileostomy patients have some postoperative sensitivity as a result of the leakage of intestinal fluid onto unprotected skin. As the consistency of the intestinal secretion becomes viscous, the sensitization subsides. Proprietary medications containing karaya powder have been found to be helpful. Twenty percent cholestyramine (an ion-exchange resin) in Aquaphor or topical sucralfate as a powder or emollient at 4 g% concentration are both effective treatments. Psoriasis may also appear at ostomy sites. Topical treatment may be difficult as the appliance adheres poorly after the topical agents are applied. The ostomy adhesive pad may have wedges cut from the periphery to allow wedges of skin to be treated in a rotating fashion.

Autosensitization Dermatitis *Autoeczematization* refers to the development of widespread dermatitis or dermatitis distant from a local inflammatory focus. The agent causing the local inflammatory focus is not the direct cause of the dermatitis at the distant sites. Autoeczematization most commonly presents as generalized acute vesicular eruptions associated with chronic eczema of the legs with or without ulceration. The "angry back" or "excited skin" syndromes observed with strongly positive patch tests and the local dermatitis seen around infectious foci (infectious eczematoid dermatitis) may represent a limited form of this reaction.

Id Reactions Patients with a variety of infectious disorders may present with eczematous dermatitis. Classic examples are vesicular id reactions of the hands in response to an inflammatory tinea of the feet. Nummular eczematous lesions or pityriasis rosea-like lesions may occur in patients with louse infestation. Id reactions are frequently unresponsive to corticosteroid therapy, but clear when the focus of infection or infestation is treated.

Molluscum Dermatitis Molluscum dermatitis represents a unique form of id reaction. Patients may present with localized or widespread eczema surrounding scattered lesions of molluscum contagiosum. The dermatitis is typically refractory to topical steroid therapy, but clears when the molluscum lesions are destroyed. Erythema multiforme-like lesions have been reported.

Juvenile Plantar Dermatosis Juvenile plantar dermatosis is an eczematous disorder of children, first described by Enta and Moller in 1972, and named by Mackie in 1976. It probably is the same disease as symmetrical lividity of the soles described by Pernet in 1925. It usually begins as a patchy, symmetrical, smooth, red, glazed macule on the base or medial surface of the great toes, sometimes with fissuring and desquamation, in children aged 3 to puberty. Lesions evolve into red scaling patches involving the weight-bearing and frictional areas of the feet, usually symmetrically (Fig. 5-12). The forefoot is usually much more involved than the heel. Toe webs and arches are spared. The eruption is disproportionately more common in atopic children. In some patients, a similar eruption occurs on the fingers.

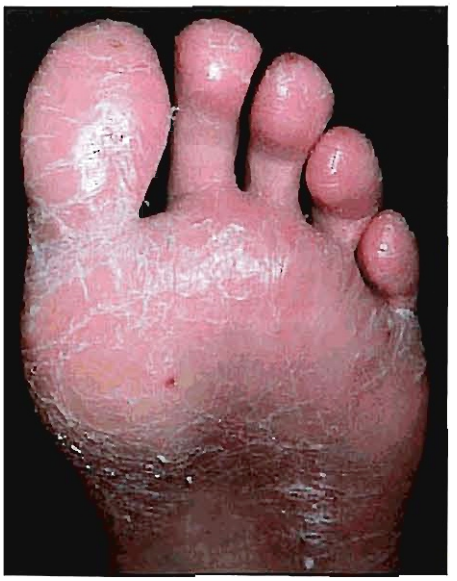

Fig. 5-12 Glazed appearance of the weight-bearing surfaces in juvenile plantar dermatosis.

The disease is caused by the repeated maceration of the feet by occlusive shoes, especially athletic shoes, or by the abrasive effects of pool surfaces or diving boards. The affected soles remain wet in the rubber bottoms of the shoes or are macerated by pool water. Thin, nonabsorbent, synthetic socks contribute to the problem.

Histologically there is psoriasiform acanthosis and a sparse, largely lymphocytic infiltrate in the upper dermis, most dense around sweat ducts at their point of entry into the epidermis. Spongiosis is commonly present and the stratum corneum is thin but compact.

The diagnosis is apparent on inspection, especially if there is a family or personal history of atopy and the toe webs are spared. Allergic contact dermatitis to shoes and dermatophytosis should be considered in the differential diagnosis. Allergic shoe dermatitis usually involves the dorsal foot, but some patients with mercaptobenzothiozole sensitivity have predominant involvement of the soles. Other allergens in rubber insoles may produce a similar dermatitis.

Treatment involves avoidance of maceration. Eliminating the offending shoes or socks is generally easier. Foot powders, thick absorbent socks, absorbent insoles, and having alternate pairs of shoes to wear to allow the shoes to dry out are all beneficial. Topical steroid medications are of limited value and often are no more effective than occlusive barrier protection. Petrolatum or urea preparations can sometimes be of benefit. Most cases clear within 4 years of diagnosis.

Xerotic Eczema

Xerotic eczema is also known as winter itch, eczema craquelé, and asteatotic eczema. These vividly descriptive terms are all applied to dehydrated skin showing redness, dry scaling, and fine crackling that may resemble crackled porcelain or the fissures in the bed of a dried lake or pond. The primary lesion is an erythematous patch covered with an adherent scale. As the lesion enlarges, fine cracks in the epidermis occur (Fig. 5-13). Nummular lesions may occur. Xerotic "nummular" eczema is less weepy than classic

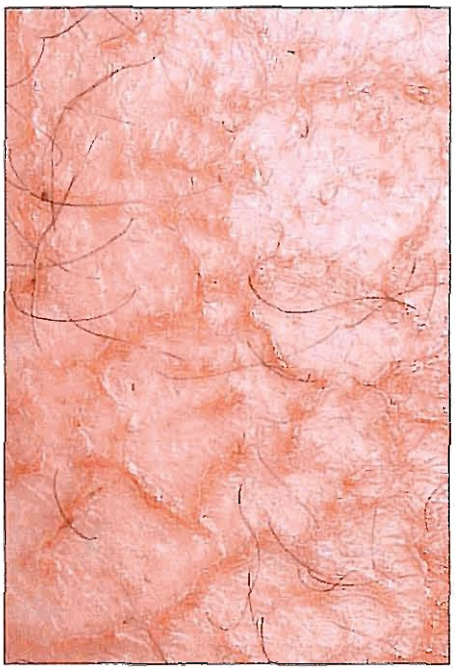

Fig. 5-13 Fine network of epidermal fissures in eczema craquelé.

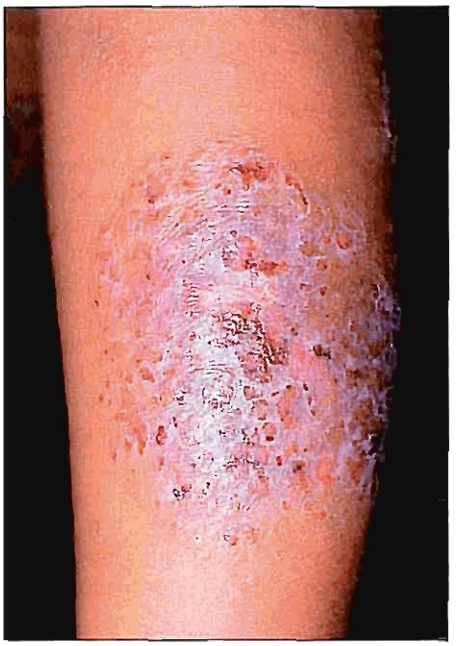

Fig. 5-14 Nummular eczema.

nummular dermatitis. Favored sites are the anterior shins, extensor arms, and flank. Elderly persons are particularly predisposed, and xerosis appears to be the most common cause of pruritus in older individuals. Xerotic eczema is seen most frequently during the winter, when there is low relative humidity. Bathing with hot water and harsh soaps contribute. The epidermal water barrier is impaired and transepidermal water loss is increased.

Short tepid baths, limitation of the use of soap to soiled and apocrine-bearing areas, and prompt application of an emollient are usually effective. White petrolatum and emollients containing 10% urea or 5% lactic acid are effective. Topical steroids in ointment vehicles are useful for inflamed areas.

Nummular Eczema (Nummular Neurodermatitis)

Nummular eczema usually begins on the lower legs, dorsa of the hands, or extensor surfaces of the arms. The primary lesions are discrete, coin-shaped, erythematous, edematous, vesicular, and crusted patches (Fig. 5-14). Most lesions are 20 to 40 mm in diameter. Lesions may form after trauma (Koebner's phenomenon). As new lesions appear, the old lesions expand by tiny papulovesicular satellite lesions appearing at the periphery and fusing with the main plaque. In severe cases the condition may spread into palm-sized or larger patches. Pruritus is usually severe and of the same paroxysmal, compulsive quality, and nocturnal timing seen in circumscribed neurodermatitis. Mast cells are noted in close approximation to nerves in lesional skin, and the neuropeptides substance P and calcitonin gene-related peptide are increased in lesional skin.

Atopic dermatitis frequently has nummular morphology in adolescents, but in atopy the lesions tend to be more chronic and lichenified. Histologically, nummular eczema is characterized by acute or subacute spongiotic dermatitis.

Initial treatment consists of simple soaking and greasing with an occlusive ointment, and once to twice a day application of a potent or superpotent topical steroid cream or ointment. Ointments are more effective, and occlusion may be necessary. If secondary staphylococcal infection is present, an antibiotic with appropriate coverage is recommended. Sedating antihistamines at bedtime are useful to help with sleep and reduce night-time scratching. Topical calcineurin inhibitors are also effective. In some cases refractory to topical agents, intralesional or systemic corticosteroid therapy may be required.

Nutritional Deficiency Eczema

A pattern of eczema with localized, thickened, scaling patches that have some characteristics of nummular eczema, seborrheic dermatitis, and neurodermatitis may be seen in alcoholics. This probably does not represent a discrete entity, but exacerbation of these various dermatoses by poor hygiene and secondary infection. Head dermatitis may complicate head louse infestation; body itching and dermatitis may occur because of body lice, and genital involvement may resemble candidal diaper dermatitis associated with urinating and defecating in the clothing.

HORMONE-INDUCED DERMATOSES

Autoimmune progesterone dermatitis may appear as urticarial papules, deep gyrate lesions, papulovesicular lesions, an eczematous eruption, or as targetoid lesions. Pruritus is common. When urticaria is the predominant skin lesion, there is a generalized distribution, and it may be accompanied by laryngospasm. Anaphylactoid reactions may occur. Oral erosions may be present. The eruption typically appears during the luteal phase of the menstrual period, and spontaneously clears following menstruation, only to return in the next menstrual period. Many of the reported patients had received artificial progestational agents before the onset of the eruption. In some it appeared after a normal pregnancy. The eruption may worsen or clear during pregnancy. The pathogenesis appears to be autoimmunity directed toward the patient's own progesterone, mediated by

T(H)1-type cytokines. Patients have a positive skin test to progesterone and treatment responses to anovulatory agents and/or oophorectomy.

In most cases, diagnosis has been confirmed by intradermal testing with 0.01 mL of aqueous progesterone suspension (50 mg/mL). A positive test may be immediate (30 min) or delayed (24–96 h). Flares may be induced by intramuscular or oral progesterone. The most commonly used treatment is an oral contraceptive to suppress ovulation, thereby reducing progesterone levels. Conjugated estrogen, leuprolide acetate, danazol, and tamoxifen may be effective in some cases.

Autoimmune *estrogen* dermatitis also presents as a cyclic skin disorder that may appear eczematous, papular, bullous, or urticarial. Pruritus is typically present. Skin eruptions may be chronic but are exacerbated premenstrually or occur only immediately before the menses. Characteristically, the dermatosis clears during pregnancy and at menopause. Intracutaneous skin testing with estrone produces a papule lasting longer than 24 h or an immediate urticarial wheal (in cases with urticaria). Injections of progesterone yield negative results, ruling out autoimmune progesterone dermatitis. Tamoxifen is effective in some cases.

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IMMUNODEFICIENCY SYNDROMES

Many of the congenital immunodeficiency syndromes have cutaneous manifestations. The most common of these skin diseases are bacterial or fungal infections (especially mucocutaneous candidiasis), lupus erythematosus-like syndromes, and atopic-like dermatitis. The primary immunodeficiencies may be classified as those with impaired antibody production (B-cell immunodeficiencies), impaired cell-mediated immunity (T-cell immunodeficiencies), and combined B- and T-cell deficiencies.

Some of the many immunodeficiencies with cutaneous involvement are presented in this section. Others, such as the acquired immunodeficiency syndrome and chronic mucocutaneous candidiasis, are discussed in later chapters according to the specific infectious agent involved.

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X-Linked Agammaglobulinemia

Also known as *Bruton syndrome* and *sex-linked agammaglobulinemia*, this rare hereditary immunologic disorder usually becomes apparent after the first 3 to 6 months of life, with increased susceptibility to Gram-positive pyogenic infections such as pneumococcal and streptococcal infections. Resistance to viral infections is intact, except for an unusual susceptibility to infections with enteroviruses that may result in vaccine-related paralytic poliomyelitis or a dermatomyositis–meningoencephalitis syndrome. Affected boys are more likely to develop atopic dermatitis, vasculitis, and urticaria. Growth failure, chronic diarrhea, and an absence of palpable lymph nodes are characteristic.

IgA, IgM, IgD, and IgE are virtually absent from the serum, although IgG may be present in small amounts. The spleen and lymph nodes lack germinal centers, and plasma cells are absent from the lymph nodes, spleen, bone marrow, and connective tissues. Cell-mediated immunity is intact. T-lymphocytes are normal in number and function, but B-cells are usually completely lacking. Evidence indicates that the defect lies in a maturation block in pre–B-cell to B-cell differentiation. The defect involves protein tyrosine kinase (PTK). The gene is a member of the *src* family of protooncogenes. Bruton tyrosine kinase (Btk) is essential for the development of B-lymphocytes. Deletions and point mutations have been detected in many unrelated patients, and these result in detrimental effects on the catalytic function of the kinase.

Treatment with gamma globulin is helpful, but it does not completely control the disease. Progressive fatal encephalitis resulting from an enterovirus may develop. Respiratory disease with pulmonary fibrosis is also frequently seen, because there is no means of restoring secretory IgA to mucous membrane surfaces. Lymphoreticular malignancy, especially leukemia, may develop.

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Isolated IgA Deficiency

An absence or marked reduction of serum IgA occurs in approximately 1 in 600 people in the white population. Most of these individuals are entirely well. Of those with symptoms, half have repeated infections, and one-quarter have autoimmune or collagen vascular disease. Allergies such as anaphylactic reactions to transfusion or IVIG, asthma, and atopic dermatitis are common in the symptomatic group. There is an increased association of celiac disease, ulcerative colitis, and regional enteritis. Systemic lupus erythematosus, dermatomyositis, scleroderma, thyroiditis, rheumatoid arthritis, and Sjögren syndrome have all been reported to occur in these patients. Malignancy is increased in adults with IgA deficiency. Symptomatic IgA deficiency represents 10% to 15% of clinically serious inherited immunodeficiency patients.

It is believed that these patients have a maturation defect of the B-lymphocyte as it develops into an IgA-producing plasma cell. The defect can be transmitted as an autosomal-dominant or -recessive trait. It may also be an acquired deficiency, induced by certain drugs such as phenytoin or cancer chemotherapy.

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Sikora AG, et al: Otolaryngologic manifestations of immunodeficiency. Otolaryngol Clin North Am 2003;36:647.

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Common Variable Immunodeficiency

Common variable immunodeficiency, also known as *acquired hypogammaglobulinemia*, is a heterogeneous disorder and is the most common immunodeficiency syndrome after IgA deficiency. Children or young adults with higher than expected expression of the HLA markers B8 and DR3 are affected, and 11% of family members may have a demonstrable immunoglobulin deficiency. These patients have low levels of most immunoglobulin classes, do not form antibodies to bacterial antigens, and have recurrent sinopulmonary infections. They have a predisposition to autoimmune disorders, such as vitiligo and alopecia areata, gastrointestinal abnormalities, and lymphoreticular malignancies. Cutaneous as well as visceral granulomas have been reported in several patients. B-cells are present in most patients but do not differentiate normally. Half of these patients will also have evidence of T-cell dysfunction. There is evidence of polarization towards a Th1 immune response and upregulation of IL-12-mediated pathways.

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Isolated Primary IgM Deficiency

Eczematous dermatitis is present in about one-fifth of cases with this abnormality. The other immunoglobulin classes are usually present in normal amounts. Isohemagglutinins are absent. Affected persons are predisposed to severe infections, especially those caused by meningococci, pneumococci, and *Haemophilus influenzae*. Verruca vulgaris may occur in great numbers. Thyroiditis, splenomegaly, and hemolytic anemia may occur. Patients with mycosis fungoides, and gluten-sensitive enteropathy may have a secondary IgM deficiency. This disease is probably caused by a defect in the maturation of IgM-producing plasma cells.

Immunodeficiency with Hyper-IgM

This rare disorder is characterized by recurrent infections, low or absent IgG, IgE, and IgA levels, and normal or elevated levels of IgM and IgD. The disorder may be inherited as an autosomal-dominant or -recessive, or X-linked trait. Respiratory infections, diarrhea, otitis, large painful oral ulcers, widespread therapy-resistant warts, autoimmunity, and recurrent neutropenia are common. Treatment is with IVIG. Allogeneic bone marrow transplantation has been successful.

The X-linked form has been found to be caused by point mutations or deletions in the Xq26.3–27.1 region, which encodes for a ligand of CD40, gp39. Abnormalities of this protein on T-cells interfere with the T-cell–B-cell interaction (gp39–CD40 interaction) that signals for immunoglobulin isotype switching.

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Thymic Hypoplasia

Congenital thymic hypoplasia, also known as *DiGeorge anomaly*, the velocardiofacial syndrome, and III and IV pharyngeal pouch syndrome, may be inherited as an autosomal-dominant or -recessive trait, or may be a sporadic disorder. It is characterized by a distinctive facies: notched, low-set ears, micrognathia, shortened philtrum, and hypertelorism.

The syndrome includes congenital absence of the parathyroids and thymus, and an abnormal aorta. Neonatal tetany from hypocalcemia is usually the first sign of the disease. Aortic and cardiac defects are the most common cause of death. T-cell defects are present and cell-mediated immunity is absent or depressed. Fungal and viral infections commonly occur despite usually normal immunoglobulin levels. DiGeorge anomaly is one of several syndromes associated with deletions within the proximal long arm of chromosome 22, specifically 22q11.2, which encodes for a zinc finger DNA-binding motif (ZNF74).

Patel JY, et al: Thymus transplantation advances in DiGeorge syndrome. Curr Allergy Asthma Rep 2005;5:348.

Perez EE, et al: Safety of live viral vaccines in patients with chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). Pediatrics 2003;112:e325.

Thymic Dysplasia with Normal Immunoglobulins (Nezelof Syndrome)

In Nezelof syndrome there is faulty development of the thymus gland. Onset is in early infancy, with severe, recurrent candidiasis, severe varicella, recurrent bacterial infections of the skin and lungs, or diarrhea.

It is an autosomal-recessive disorder. Serum immunoglobulins are normal or increased, but cell-mediated immunity is lacking. The syndrome differs from DiGeorge syndrome in that the thymus is present but underdeveloped, and there are no cardiac abnormalities. Bone marrow transplantation may be successful.

Purine Nucleoside Phosphorylase Deficiency

This autosomal-recessive enzyme defect leads to greatly reduced T-cell counts and depressed cell-mediated immunity, but B-cells and antibody formation are intact. Mutations on chromosome 14q13 are responsible. Patients usually present at between 3 and 18 months of age with nonbacterial infections involving the lungs, upper airways, skin, and urinary tract. They usually die from overwhelming viral infections. Spastic diplegia may be present.

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Miscellaneous T-cell Deficiencies

The bare lymphocyte syndrome is characterized by profound defects in HLA class II expression. Some patients also lack class I expression. The molecular basis for the class II defect is a lack of RF-X, the specific DNA-binding protein that normally binds to the HLA class II promoters.

A deficiency of the T-cell receptor CD3 complex may result from mutations affecting either the γ or ε chains. Many of these patients have relatively benign clinical courses.

Activation of T-cells may be deficient. Surface molecules may be deficient, as in the bare lymphocyte syndrome or CD3 deficiency, but also intracytoplasmic signaling molecules are needed to transmit information inside the cell to the nucleus. Zap 70 deficiency is now recognized as a defect in a nuclear factor necessary for activation of T-cells.

Cartilage-hair hypoplasia syndrome is an autosomal-recessive disorder in which patients with short-limbed dwarfism and fine, sparse, hypopigmented hair have defective cell-mediated immunity.

Omenn syndrome is an autosomal-recessive disorder that closely mimics graft-versus-host disease. Clinical features are exfoliative erythroderma beginning at a few weeks of life, eosinophilia, diarrhea, hepatosplenomegaly, lymphadenopathy, hypogammaglobulinemia with elevated IgE, recurrent infections, and early death (usually by 6 months of age). Both antibody production and cell-mediated immune function are impaired. T-cell receptor rearrangements are severely restricted in patients with Omenn syndrome, and inefficient and/or abnormal generation of T-cell receptors is a consistent feature of this disease.

Severe Combined Immunodeficiency Disease

This heterogeneous group of genetic disorders is characterized by severely impaired humoral and cellular immunity. Patients may manifest various cutaneous manifestations, including a simple morbilliform eruption and seborrheic dermatitis. In addition, severe recurrent infections may occur, caused by *Pseudomonas, Staphylococcus, Enterobacteriaceae*, or *Candida*. Moniliasis of the oropharynx and skin, intractable diarrhea, and pneumonia are the triad of findings that commonly lead to the diagnosis of severe combined immunodeficiency disease (SCID). Overwhelming viral infections are the usual cause of death. Engraftment of maternally transmitted or transfusion-derived lymphocytes can lead to graft-versus-host disease.

SCID is characterized by deficiency or total absence of circulating lymphocytes. Mature T-cells are almost invariably absent, but B-cell numbers may be greatly reduced or increased. Immunoglobulin levels are consistently very low. The thymus is very small; its malformed architecture at autopsy is pathognomonic.

The inheritance may be autosomal recessive or X-linked; the most common type of SCID is X-linked. A deficiency of a common γ chain that is an essential component of the IL-2 receptor is responsible for the profound lymphoid dysfunction in X-linked SCID. This abnormality also has effects on both the IL-4 and -7 receptors. The mutation has been mapped to Xq13.1. About half the autosomal-recessive cases have a deficiency of adenosine deaminase, the gene for which is located on chromosome 20q13.

Lymphogenic agammaglobulinemia, also known as *Swiss-type* or *hereditary thymic dysplasia*, is inherited as an autosomal-recessive trait. The presumed level of the basic cellular defect is in the lymphopoietic stem cell, which fails

to differentiate into lymphoid cells. Lymphoid tissue in the body is usually absent.

Prenatal diagnosis and carrier detection are possible for X-linked SCID, and adenosine deaminase deficiency. Short-term replacement therapy is available. The definitive treatment is bone marrow transplantation. In utero hematopoietic stem cell transplantation has been successful in X-linked SCID. Affected patients rarely live longer than age 2 without transplantation. Patients with these diseases are prime candidates for gene therapy.

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Peranteau WH, et al: In utero hematopoietic cell transplantation: What are the important questions? Fetal Diagn Ther 2004; 19:9.

Rahiminejad MS, et al: Posttransfusion graft-versus-host disease in an infant with severe combined immunodeficiency. Transplant Proc 2003;35:2825.

Thymoma with Immunodeficiency

Thymoma with immunodeficiency, also known as *Good syndrome*, occurs in adults in whom hypogammaglobulinemia, deficient cell-mediated immunity, and benign thymoma may develop almost simultaneously. Recurrent abscesses and pyoderma develop. There is a striking deficiency of B- and pre-B-cells. Lymphopenia, eosinopenia, thrombocytopenia, anemia, or pancytopenia may occur. Thymectomy does not affect the immunodeficiency.

Wiskott-Aldrich Syndrome

Wiskott-Aldrich syndrome, an X-linked syndrome seen in boys, consists of a triad of chronic eczematous dermatitis resembling atopic dermatitis (Fig. 5-15); increased susceptibility to recurrent infections, such as pyoderma or suppurative otitis media; and thrombocytopenic purpura, with hepatosplenomegaly. Death occurs usually by age 6 from infection, or, less often, bleeding. Only a few patients survive to adulthood. They are highly prone to developing lymphoreticular malignancies.

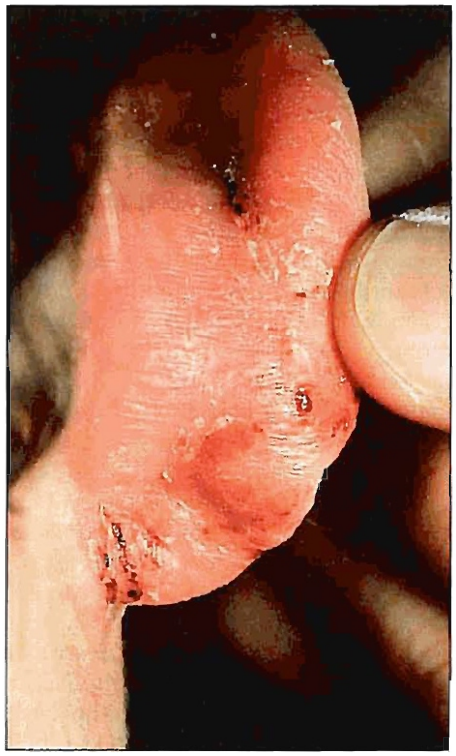

Fig. 5-15
Eczematous eruption with purpura in Wiscott-Aldrich syndrome.

Synthesis of IgA, IgM, and IgE is accelerated; however, accelerated catabolism usually results in low levels of IgM and low or normal levels of IgG. Elevated levels of IgA and IgE are present. There seems to be an intrinsic platelet abnormality. T-cells progressively decline in number and activity.

Treatment is with platelet transfusions, antibiotics, immunoglobulin, and splenectomy. Bone marrow transplantation from an HLA-identical sibling as early as possible in the disease course provides complete reversal of the platelet and immune dysfunction, as well as improvement or clearing of the eczematous dermatitis.

The gene locus for Wiskott-Aldrich syndrome has been mapped to the proximal portion of the short arm of the X chromosome (Xp11). The gene codes for a protein called WASP, thought to be involved in the reorganization of the actin cytoskeleton in hematopoetic cells in response to external stimuli. The hematopoetic cells of affected patients cannot polarize or migrate in response to physiologic stimuli, accounting for the protean clinical features of the syndrome. WASP also appears important in the regulation of the high-affinity IgE receptor on mast cells.

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Patel JY, et al: Gene therapy in Wiskott-Aldrich syndrome: the next step? Curr Allergy Asthma Rep 2005;5:347.

X-Linked Lymphoproliferative Syndrome

This disorder, also known as *Duncan's disease*, is characterized by an inability of affected individuals to effectively control an Epstein-Barr virus infection. Patients are normal until they develop severe, acute infectious mononucleosis. Necrotic hepatitis and an exanthema are common. Aplastic anemia, chronic infectious mononucleosis, a spectrum of B-cell lymphoproliferative diseases, and acquired hypogammaglobulinemia develop. The locus has been mapped to the Xq26 region.

Chronic Granulomatous Disease

Clinically, chronic granulomatous disease (CGD) is characterized by recurring purulent and granulomatous infections involving the long bones, lymphatic tissue, liver, skin, and lungs. It occurs most frequently in boys (because X-linked inheritance is the most frequent type) who have eczema of the scalp, backs of the ears, and face. Ulcerative stomatitis, furunculosis, subcutaneous abscesses, and suppurative lymphadenopathy may occur.

There is decreased ability to destroy catalase-positive bacteria. This is caused by a deficiency in one of the components of the NADPH-oxidase complex, which catalyzes the conversion of molecular oxygen to superoxide. These organisms destroy any hydrogen peroxide they generate, thus leaving the phagocytes, which have a defective ability to generate hydrogen peroxide, without full antimicrobial killing ability. *S. aureus* infection is the most frequent patho-

gen in these patients. Other important pathogens include *Aspergillus fumigatus* and *Burkholderia cepacia*. Infections by streptococci and pneumococci are less common.

The predominant X-linked form results from defects in the CYBB gene, leading to absence of the high molecular weight subunit of cytochrome b 558 (gp 91-phox) and a total absence of NADPH oxidase activity. Patients with some residual NADPH oxidase activity have been described, but they still suffer from severe infections despite this residual enzyme activity. In autosomal-recessive forms, mutations in the genes encoding for the remaining three oxidase components have been described: p22-phox (chromosome 16), p47-phox (chromosome 7), and p67-phox (chromosome 1). Patients may have deletions, insertions, and point mutations leading to premature stop codons, amino acid substitutions, and splice site defects. In addition to defective bacterial killing, IgG, IgM, and IgA hyperglobulinemia and neutrophil leukocytosis may be noted.

Low reduction of nitro-blue tetrazolium (NBT) to blue formazan is the basis of the NBT test for the disorder. Female carriers of the X-linked form have a mixed population of normal and abnormal cells and therefore show intermediate NBT reduction. Carriers may demonstrate an increase in infections, arcute dermal and discoid lupus-like skin lesions, and aphthous stomatitis. Several patients with autosomal-recessive disease have also developed discoid lupus lesions.

Treatment of infections should be early, aggressive, and prolonged; trimethoprim–sulfamethoxazole prophylaxis significantly prolongs disease-free intervals. Injections of IFN-γ also decrease the frequency of serious infections. Itraconazole prophylaxis reduces the frequency of fungal infections in patients with chronic granulomatous disease. Bone marrow or stem cell transplantation has been successful in restoring enzyme function, and encouraging experiments with gene therapy have been reported.

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Guugor T, et al: Successful low toxicity hematopoietic stem cell transplantation of high-risk adult chronic granulomatous disease patients. Transplantation 2005;79:1596.

Stasia MJ, et al: Severe clinical forms of cytochrome b-negative chronic granulomatous disease (X91-) in 3 brothers with a point mutation in the promoter region of CYBB. J Infect Dis 2003;188:1593.

Myeloperoxidase Deficiency

This condition is a relatively common autosomal-recessive disorder characterized by an absent or enzymatically inactive myeloperoxidase protein. Myeloperoxidase is normally abundant in neutrophils and monocytes. Cells with this deficiency are unable to terminate their respiratory burst. Although many affected patients are asymptomatic and lifespan is usually unaffected, patients may be susceptible to candidiasis and bacterial infections. Noma-like cheilitis has been described in a patient with cyclic neutropenia and hereditary myeloperoxidase deficiency. However, Sweet syndrome and acne may occur despite the deficiency.

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Ichimori K, et al: Myeloperoxidase has directly-opposed effects on nitration reaction—study on myeloperoxidase-deficient patient and myeloperoxidase-knockout mice. Free Radical Res 2003;37:481.

Leukocyte Adhesion Molecule Deficiency

This rare autosomal-recessive disorder is characterized by recurrent bacterial and fungal infections and impaired neutrophil migration. Periodontitis or gingivitis and poor wound healing may also occur. The severity of the clinical presentation is variable. There is faulty complexing of the CD11 and CD18 integrins as a result of a defect in the CD18 gene. This leads to absent or severely reduced cell-surface expression of the β2-leukocyte integrins, resulting in abnormal chemotaxis and opsonization. Death usually occurs in the first 4 years of life unless bone marrow transplantation is undertaken; however, less severe defects may be present, in which case the patient survives into adulthood.

Chédiak-Higashi Syndrome

Chédiak-Higashi syndrome is a progressively degenerative, fatal, familial disease of young children, characterized by partial oculocutaneous albinism, cutaneous and intestinal infections early in childhood, and leukocytes with very large azurophilic granules. The hair of these patients is blond and sparse. The ocular albinism is accompanied by nystagmus and photophobia. In darker skinned races, speckled hyper- and hypo-pigmentation may be seen.

The inheritance is autosomal recessive. Prenatal diagnosis is possible by examining the hair shaft and neutrophils microscopically for large granules. The Chédiak-Higashi gene product has been identified and mapped on chromosome 1q 42–1843. The defect is in the gene LYST, resulting in defective vesicular transport to and from the lysosome and late endosome and dysregulated homotypic fusion. This causes the giant perinuclear vesicles that characterize this disorder. Patients have increased susceptibility to infections, especially those of enteric bacterial origin. There is neutropenia and the abnormal neutrophils do not phagocytose normally. Chemotaxis is usually decreased. Immunoglobulins are present in normal amounts. Early death usually occurs, most frequently as a result of malignant lymphoma or other forms of cancer. Bone marrow transplantation may be curative.

Griscelli Syndrome

Another form of partial albinism and recurrent infections with immunodeficiency is Griscelli syndrome of silver–gray hair, neurologic abnormalities, skin and systemic pyogenic infection, neutropenia, thrombocytopenia, hypogammaglobulinemia, impaired natural killer cell activity, and defective cell-mediated immunity. Microscopic analysis of the hair reveals large, unevenly distributed melanin aggregates in the medulla. Skin biopsies show numerous mature melanosomes in melanocytes and few melanosomes in keratinocytes without giant melanosomes. The latter two findings may help in the prenatal diagnosis of Griscelli syndrome. The genetic locus colocalizes on chromosome 15q21 with the myosin-Va gene, which may play a role in membrane transport and

organelle trafficking. The age at onset varies from 6 weeks to 4 years, but most patients die by age 5 without bone marrow transplantation. Elejalde syndrome shows similar hair findings and frequent fatal central nervous system alterations, but immunodeficiency is not a feature.

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Lazarchick J, et al: Chediak-Higashi syndrome. Blood 2005; 10:4162.

Stein SM, et al: Molecular basis and therapy of disorders associated with chronic neutropenia. Curr Allergy Asthma Rep 2003;3:385.

Hyperimmunoglobulinemia E Syndrome

This immunodeficiency syndrome (including Job syndrome) consists of atopic-like eczematous dermatitis, recurrent pyogenic infection, high levels of serum IgE and IgD, IgE *antistaphylococcal antibodies, and eosinophilia.* Cold abscesses and sinopulmonary infections are common. The eczematous eruption, seen in more than 80% of patients, is typically found at the sites of predilection for atopic dermatitis. The face is consistently involved. It is chronic and *begins early in life (2 months to 2 years of age).* Many of the lesions resemble papular prurigo, and there may be keratoderma of the palms and soles. Ichthyosis, urticaria, asthma, and chronic mucocutaneous candidiasis may also occur. The hands and feet may have lesions suggestive of *contact dermatitis.* Furuncles, carbuncles, and abscesses of variable severity, as well as chronic nasal discharge and recurrent otitis media, are common.

The serum shows an extremely high concentration of IgE (> 10,000 IU/mL), and eosinophilia is present, with *diminished local resistance to staphylococcal infections.* Chemotaxis of neutrophils and monocytes is impaired. Circulating activated T-cells demonstrate reduced expression of transforming growth factor-β and IFN-γ genes.

Job syndrome is a subset of hypergammaglobulinemia E *syndrome that occurs mainly in girls with red hair, freckles,* blue eyes, and hyperextensible joints. Cold abscesses occur.

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Complement Deficiency

The complement system is an effector pathway of proteins that results in membrane damage and chemotactic activity. *Four major functions result from complement activation:* cell lysis, opsonization/phagocytosis, inflammation, and immune complex removal. In the "classic" complement pathway, complement is activated by an antigen–antibody reaction involving IgG or IgM. Some complement components are directly activated by binding to the surface of infectious organisms; this is called the "alternate" pathway. The central component common to both pathways is C3. In the classic pathway, antigen–antibody complexes sequentially bind and activate three complement proteins, C1, C4, and C2, leading to the formation of C3 convertase, an activator of C3. The alternate pathway starts with direct activation of C3. From activated C3, C5 to C9 are sequentially activated. Cytolysis is induced mainly via the "membrane attack complex," which is made up of the terminal components of complement. Opsonization is mainly mediated by a subunit of C3b, and inflammation by subunits of C3, C4, and C5.

Inherited deficiencies of complement are usually autosomal-recessive traits. Deficiencies of all 11 components of the classic pathway, as well as inhibitors of this pathway, have been described. Genetic deficiency of the C1 inhibitor results in hereditary angioedema (see Chapter 7). In general, deficiencies of the early components of the classic pathway result in connective tissue disease states, while deficiencies of the late components of complement lead to recurrent neisserial sepsis or meningitis. Overlap exists, and patients with late-component deficiencies may exhibit connective tissue disease while patients with deficiencies of early components, such as C1q, may manifest infections. Deficiency of C3 results in recurrent infections with encapsulated bacteria such as *Pneumococcus, H. influenzae,* and *Streptococcus pyogenes.* C3 inactivator deficiency, like C3 deficiency, results in recurrent pyogenic infections. Properdin (a component of the alternate pathway) dysfunction is inherited as an X-linked trait and predisposes to fulminant meningococcemia. Lupus is not associated with C9 deficiency. Deficiency of C9 is the most common complement deficiency in Japan but is uncommon in other countries. Most patients appear healthy.

C2 deficiency is the most frequent complement deficiency in the US and Europe. Most patients are healthy, but systemic lupus erythematosus (SLE), SLE-like syndromes, disseminated cutaneous lupus erythematosus, frequent infections, anaphylactoid purpura, dermatomyositis, vasculitis, and cold urticaria may be seen. C2- and C4-deficient patients with lupus erythematosus commonly have subacute annular morphology, Sjögren syndrome, and Ro antibodies. They less commonly have anti-dsDNA antibodies and anticardiolipin antibodies. Patients with C4 deficiency may have lupus and involvement of the palms and soles.

Most of the inherited complement deficiencies are well characterized on a genetic level. Deficiency may result from specific mutations, deletions, or insertions in the gene loci controlling the synthesis of the deficient complement component. Many different alterations may give rise to phenotypically identical disease. Additionally, most of these deficiencies may be acquired as an autoimmune phenomenon or a paraneoplastic finding. Examples include acquired angioedema, as when C1 inhibitor is the target, or lipodystrophy and nephritis, when C3 convertase is the target.

When complement deficiency is suspected, a useful screening test is a CH50 (total hemolytic complement) determination, because deficiency of complement components will usually result in CH50 levels that are markedly reduced.

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Graft-Versus-Host Disease

Graft-versus-host disease (GVHD) usually occurs when immunocompetent cells are introduced as a graft or blood transfusion into an antigenically foreign host who is unable to reject these grafted cells. In some instances, however, stem cells or marrow from the patient (autologous) or from a monozygotic twin (syngeneic) may lead to a limited form of GVHD. Autologous GVHD may be induced by administration of low-dose cyclosporin or IFN-γ during engraftment. GVHD may also occur after transfusion of whole blood to immunocompromised patients or patients who receive blood from a donor homozygous for one of the patient's extended HLA haplotypes. This scenario is most common with blood donation by family members, or in populations with little genetic variability. GVHD may also be seen in immunocompromised neonates after in utero transfusions, and following solid organ transplantation.

Acute GVHD presents with cutaneous, hepatic, and gastrointestinal manifestations. Chronic GVHD may be lichenoid or sclerodermoid. Maternal–fetal transfer of blood cells occurs during pregnancy, miscarriage, and delivery, and some women with scleroderma have been shown to have male (fluorescent body positive) lymphocytes in lesional skin. This finding suggests that some conditions regarded as autoimmune, may actually be alloimmune with a pathogenesis similar to GVHD. This may account for the striking clinical overlap between chronic GVHD and "autoimmune" diseases.

In acute GVHD the cutaneous eruption begins between the fifth and 47th day, most often between the fourth and fifth weeks after transplantation. With changes in transplantation techniques, long delays in the onset of GVHD may occur, and the diagnosis should rest on the constellation of signs and symptoms, rather than the timing of the eruption. Acute GVHD is characterized by an erythematous morbilliform eruption of the face and trunk, which may become confluent and result in exfoliative erythroderma. It often begins with punctuate lesions corresponding to hair follicles and eccrine ducts (Fig. 5-16). Even when morbilliform, darker punctuate areas are a helpful clinical sign. In children, the diaper area is often involved (Fig. 5-17). The eruption may appear papular and eczematous, involving web spaces, periumbilical skin, and ears. The appearance bears some resemblance to scabies. Grade IV GVHD is characterized by full-thickness slough and may resemble toxic epidermal necrolysis (Fig. 5-18). In patients with liver transplants who develop GVHD, the clinical manifestations differ from those observed after bone marrow transplantation in that liver involvement does not occur (the liver has donor antigens) and there is early and severe pancytopenia which is the major cause of mortality. Syngeneic/autologous GVHD usually involves only the skin and is self-limited. It may result from alteration of the normal "recognition of self" during engraftment.

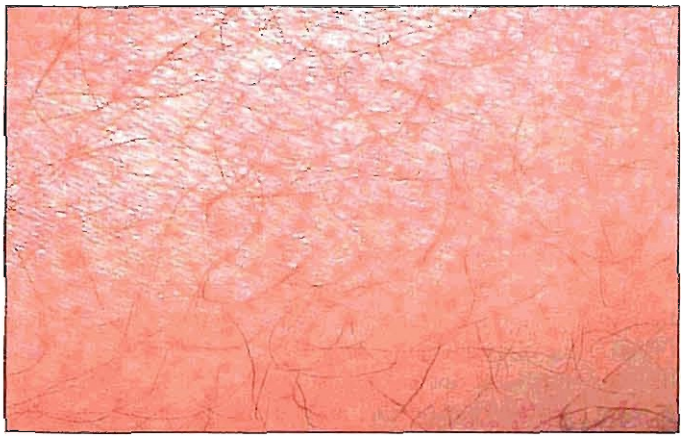

Fig. 5-16 Early punctate eruption of graft-versus-host disease.

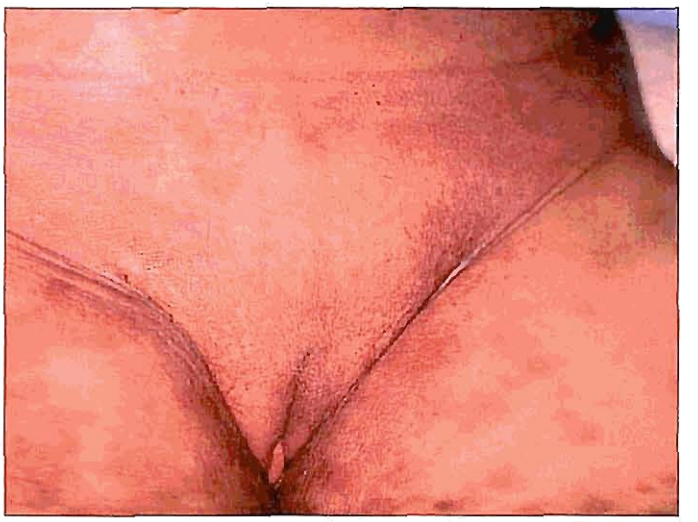

Fig. 5-17 Involvement of the diaper area in graft-versus-host disease.

Fig. 5-18 Grade IV graft-versus-host disease with full-thickness slough of skin resembling toxic epidermal necrolysis.

In 80% of patients who develop chronic GVHD a lichen planus-like eruption occurs 3 to 5 months after grafting, usually beginning on the hands and feet, but becoming generalized. Sclerosis develops less frequently. It may remain localized, but generalized sclerosis with dyspigmentation, alopecia, atrophy, chronic ulcers, and joint contractures may

also be seen. The sclerodermoid variant often presents with a corrugated appearance or feel to affected skin. Parrot-beak deformity of the nose, sicca syndrome, polymyositis, acquired ichthyosis, erythroderma, and total leukoderma may also be manifestations of chronic GVHD.

Histologically, acute GVHD demonstrates vacuolar interface dermatitis with vacuoles outnumbering lymphocytes. Individual keratinocyte necrosis with adjacent lymphocytes (satellite necrosis) is typically present, suggesting cell-mediated cytotoxicity. The extent of necrosis, bulla formation, and slough are used in grading schemes. In early acute GVHD, the findings may be focal and restricted to hair follicles and sweat ducts. The histologic findings in very early disease may be nonspecific, and many treatment protocols do not depend on histologic features to initiate therapy. For these reasons, biopsies are performed less frequently in the setting of early GVHD. A background of epidermal disorder and atypia resembling bowenoid actinic keratosis is almost universally present in later lesions of acute GVHD, and is a helpful diagnostic feature. Similar epidermal changes may be seen with cancer chemotherapy, especially in acral erythema or after busulfan. Chronic GVHD demonstrates lichenoid dermatitis or dermal sclerosis with hyalinization of collagen bundles and narrowing of the space between the collagen bundles.

Prevention of post-transfusion GVHD is most safely achieved by irradiating the blood before transfusion in high-risk individuals. Some countries with limited HLA haplotype variability have studied the feasibility of irradiating all blood products. Glucocorticoids, cyclosporin, tacrolimus, photophoresis, and phototherapy are used to treat both acute and chronic GVHD. GVHD often exerts a beneficial graft-versus-tumor effect, and current research centers on ways to attenuate the harmful effects of GVHD while maintaining the graft-versus-tumor effect.

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CHAPTER

6 Contact Dermatitis and Drug Eruptions

CONTACT DERMATITIS

There are two types of dermatitis caused by substances coming in contact with the skin: irritant dermatitis and allergic contact dermatitis. Irritant dermatitis is an inflammatory reaction in the skin resulting from exposure to a substance that causes an eruption in most people who come in contact with it. Allergic contact dermatitis is an acquired sensitivity to various substances that produce inflammatory reactions in those, and only those, who have been previously sensitized to the allergen.

Irritant Contact Dermatitis

Many substances act as irritants that produce a nonspecific inflammatory reaction of the skin. This type of dermatitis may be induced in any person if a sufficiently high concentration is used. No previous exposure is necessary and the effect is evident within minutes, or a few hours at most. The only variation in the severity of the dermatitis from person to person, or from time to time in the same person, is related to the condition of the skin at the time of exposure to a given concentration of the irritant. The skin may be more vulnerable by reason of maceration from excessive humidity, or exposure to water, heat, cold, pressure, or friction. Dry skin is less likely to react to contactants. Thick skin is less reactive than thin. Repeated exposure to some of the milder irritants may, in time, produce a hardening effect. This process makes the skin more resistant to the irritant effects of a given substance. Symptomatically, pain and burning are more common in irritant dermatitis, contrasting with the usual itch of allergic reactions.

Alkalis Irritant dermatitis is often produced by alkalis such as soaps, detergents, bleaches, ammonia preparations, lye, and drain pipe cleaners, and toilet bowl and oven cleansers. Alkalis penetrate and destroy deeply because they dissolve keratin. Strong solutions are corrosive and immediate application of a weak acid such as vinegar, lemon juice, or 0.5% hydrochloric acid solution will lessen their effects.

The principal compounds are sodium, potassium, ammonium, and calcium hydroxides. Occupational exposure is frequent among workers in soap manufacturing. Alkalis in the form of soaps, bleaching agents, detergents, and most household cleansing agents figure prominently in the causes of hand eczema. Sodium silicate (water glass) is a caustic used in soap manufacture and paper sizing, and for the preservation of eggs. Alkaline sulfides are used as depilatories (Fig. 6-1). Calcium oxide (quicklime) forms slaked lime when water is added. Severe burns may be caused in plasterers.

Acids (Fig. 6-2) The powerful acids are corrosive, whereas the weaker ones are astringent. Hydrochloric acid produces burns that are less deep and more liable to form blisters than injuries from sulfuric and nitric acids. Hydrochloric acid burns are encountered in those who handle or transport the product, and in plumbers and those who work in galvanizing or tin-plate factories. Hydrofluoric acid is used widely in rust remover, in the semiconductor industry, and in germicides, dyes, plastics, and glass etching. Nitric acid is a powerful oxidizing substance that causes deep burns; the tissue is stained yellow. Such injuries are observed in those who manufacture or handle the acid or use it in the making of explosives in laboratories. Sulfuric acid produces a brownish charring of the skin, beneath which is an ulceration that heals slowly. Sulfuric acid is used more widely than any other acid in industry; it is handled principally by brass and iron workers and by those who work with copper or bronze. It is the weapon of so-called vitriol throwers.

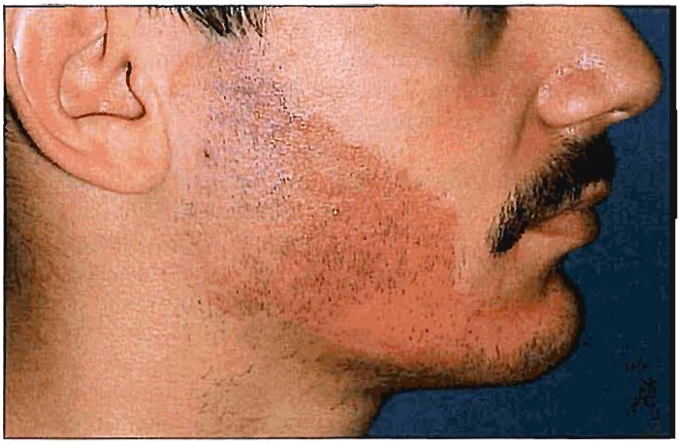

Fig. 6-1 Alkali burn from depilatory.

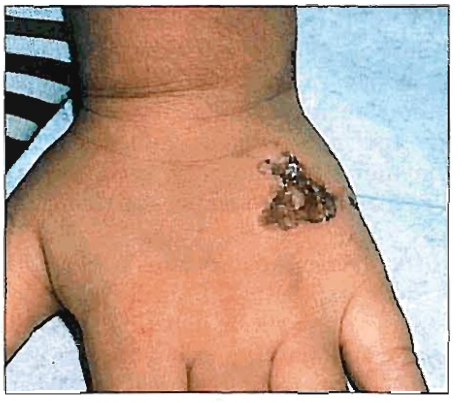

Fig. 6-2 Acid burn.

Oxalic acid may produce paresthesia of the fingertips, with cyanosis and gangrene. The nails become discolored yellow. Oxalic acid is best neutralized with limewater or milk of magnesia to produce precipitation. Hydrofluoric acid may act insidiously at first, starting with erythema and ending with vesiculation, ulceration, and, finally, necrosis of the tissue. It is one of the strongest inorganic acids, capable of dissolving glass.

Phenol (carbolic acid) is a protoplasmic poison that produces a white eschar on the surface of the skin. It can penetrate deep into the tissue. If a large surface of the skin is treated with phenol for cosmetic peeling effects, the absorbed phenol may produce glomerulonephritis and arrhythmias. Locally, temporary anesthesia may also occur. Phenol is readily neutralized with 65% ethyl or isopropyl alcohol.

Other strong acids that are irritants include acetic, trichloracetic, arsenious, chlorosulfonic, chromic, fluoroboric, hydriodic, hydrobromic, iodic, perchloric, phosphoric, salicylic, silicofluoric, sulfonic, sulfurous, tannic, and tungstic acid.

Treatment of acid burns consists of immediate rinsing with copious amounts of water and alkalization with sodium bicarbonate, calcium hydroxide (limewater), or soap solutions. Some chemicals require unusual treatment measures. Fluorine is best neutralized with magnesium oxide. Periungual burns should be treated intralesionally with 10% calcium gluconate solution, which deactivates the fluoride ion and averts more tissue damage. Hypocalcemia, hypomagnesemia, hyperkalemia, and cardiac dysrhythmias may complicate hydrofluoric acid burns. Phosphorus burns should be rinsed off with water followed by application of copper sulfate to produce a precipitate.

Titanium hydrochloride is used in the manufacture of pigments. Application of water to the exposed part will produce severe burns. Therefore, treatment consists only of wiping away the noxious substance.

Airbag Dermatitis Airbags are deployed as a safety feature on cars when rapid deceleration occurs. Activation of a sodium azide and supric oxide propellant cartridge releases nitrogen gas, which expands the bag at speeds exceeding 160 km/h. Talcum powder, sodium hydroxide, and sodium carbonate are released into the bag. Abrasions; thermal, friction, and chemical burns; and an irritant contact dermatitis may result. Superficial erythema may respond well to topical steroids, but full-thickness burns may occur and require debridement and grafting.

Other Irritants Some metal salts that act as irritants are the cyanides of calcium, copper, mercury, nickel, silver, and zinc, and the chlorides of calcium and zinc. Bromine, chlorine, fluorine, and iodine are also irritants. Occupational exposure to methyl bromide may produce erythema and vesicles in the axillary and inguinal areas. Insecticides, including 2,2-dichlorovinyl dimethyl phosphate used in roach powder and fly repellents and killers, can act as irritants.

Fiberglass Dermatitis Fiberglass dermatitis is seen after occupational or inadvertent exposure. The small spicules of glass penetrate the skin and cause severe irritation with tiny erythematous papules, scratch marks, and intense pruritus. Usually there is no delayed hypersensitivity reaction. Wearing clothes that have been washed together with fiberglass curtains, handling air conditioner filters, or working in the manufacture of fiberglass material may produce severe folliculitis, pruritus, and eruptions that may simulate scabies or insect or mite bites. Fiberglass is also used in thermal and acoustic installations, padding, vibration isolation, curtains, draperies, insulation for automobile bodies, furniture, gasoline tanks, and spacecraft. A thorough washing of the skin after handling fiberglass is helpful. Talcum powder thoroughly dusted on the flexure surfaces of the arms makes the fibers slide off the skin. Patch testing to epoxy resins should be done when evaluating workers in fiberglass/reinforced plastics operations.

Dusts Some dusts and gases may irritate the skin in the presence of heat and moisture, such as perspiration. The dusts of lime, zinc, and arsenic may produce folliculitis. Dusts from various woods, such as teak, may incite itching and dermatitis. Dusts from cinchona bark, quinine, and pyrethrum produce widespread dermatitis. Tobacco dust in cigar factories, powdered orris root, lycopodium, and dusts of various nutshells may cause swelling of the eyelids and dermatitis of the face, neck, and upper extremities. Dusts formed during the manufacture of high explosives may cause erythematous, vesicular, and eczematous dermatitis that may lead to generalized exfoliative dermatitis.

Capsaisin Hand irritation produced by capsaicin in hot peppers used in Korean and North Chinese cuisine (Hunan hand) may be severe and prolonged. Pepper spray, used by police in high concentrations, and by civilians in less concentrated formulas, contains capsaisin and may produce severe burns. Cold water is not much help: capsaicin is insoluble in water. Acetic acid 5% (white vinegar) or antacids (Maalox) may completely relieve the burning even if applied an hour or more after the contact. Application should be continued until the area can be dried without return of the discomfort.

Tear Gas Dermatitis Lacrimators such as chloroacetophenone in concentrated form may cause dermatitis, with a delayed appearance some 24 to 72 h after exposure. Irritation or sensitization, with erythema and severe vesiculation, may result. Treatment consists of lavage of the affected skin with sodium bicarbonate solution and instillation of boric acid solution into the eyes. Contaminated clothing should be removed.

Sulfur mustard gas, also known as *yperite*, has been used in chemical warfare such as in the Iraq–Iran war. Erythema, vesicles, and bullae, followed by healing with hyperpigmentation over a 1-week period, result from mild-to-moderate exposure (Fig. 6-3). Toxic epidermal necrolysis-like appearance may follow more concentrated contact. The earliest and most frequently affected sites are areas covered by clothing and humidified by sweat, such as the groin, axilla, and genitalia.

Mace is a mixture of tear gas (chloroacetophenone) in trichloroethane and various hydrocarbons resembling kerosene. It is available in a variety of self-defense sprays. It is a potent irritant and may cause allergic sensitization. Treatment consists of changing clothes, washing with oil or milk, followed by washing with copious amounts of water.

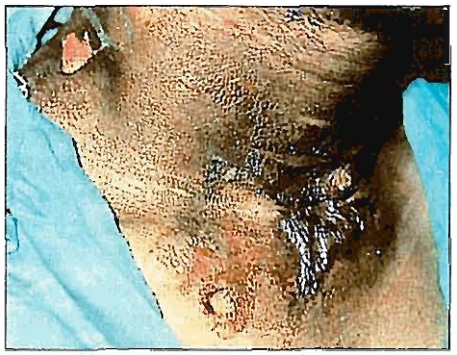

Fig. 6-3 Mustard gas burn. (Courtesy of James WD [ed]: Textbook of Military Medicine. Office of the Surgeon General, United States Army, 1994.)

Chloracne

Workers in the manufacture of chlorinated compounds may develop chloracne, with small straw-colored follicular plugs and papules, chiefly on the malar crescent, retroauricular areas, earlobes, neck, shoulders, and scrotum. The synthetic waxes chloronaphthalene and chlorodiphenyl, used in the manufacture of electric insulators and in paints, varnishes, and lacquers, similarly predispose workers engaged in the manufacture of these synthetic waxes to chloracne. Exposure to 2,6-dichlorobenzonitrile during the manufacture of a herbicide, and to 3,4,3′,4′-tetrachloroazooxybenzene, which is as an unwanted intermediate byproduct in the manufacture of a pesticide, may also produce chloracne.

A contaminant in the synthesis of herbicides and hexachlorophene, 2,3,7,8-tetracholorodibenzo-*p*-dioxin, produces a chemical burn in the acute stage, but chloracne, hyperpigmentation, hirsutism, and skin fragility (with or without criteria for porphyria cutanea tarda) are manifestations of chronic toxicity. Gastrointestinal tract cancer and malignancies of the lymphatic and hematopoetic system are suspected to result but the studies are still inconclusive. While contact is the usual method of exposure, inhalation, ingestion, or contact with contaminated clothing also may result in chloracne. Chloracne may persist for long periods because it is stored in the liver and released slowly into the circulation. Treatment is with medications used in acne vulgaris, including isotretinoin.

Hydrocarbons

Many hydrocarbons produce skin eruptions. Crude petroleum causes generalized itching, folliculitis, or acneiform eruptions. The irritant properties of petroleum derivatives are directly proportional to their fat–solvent properties and inversely proportional to their viscosity. Oils of the naphthalene series are more irritating than those of the paraffin series. Refined fractions from petroleum are less irritating than the unrefined products, although benzene, naphtha, and carbon disulfide may cause a mild dermatitis.

Lubricating and cutting oils are causes of similar cutaneous lesions. They represent a frequent cause of occupational dermatoses in machine tool operators, machinists, layout men, instrument makers, and set-up men. Insoluble (neat) cutting oils are responsible for a follicular acneiform eruption on the dorsa of the hands, the forearms, face, thighs, and back of the neck. Hyperpigmentation, keratoses, and scrotal cancer have been found in those exposed to insoluble cutting oils. Soluble oils and synthetic fluids used in metalworking do not result in acne, but rather an eczematous dermatitis, usually of the dorsal forearms and hands. Approximately 50% of the time it is irritant and in the remainder it is allergic. Allergic contact dermatitis arises from various additives, such as biocides, coloring agents, and deodorizers.

Coal briquette makers develop dermatitis as a result of a tarry residue from petroleum used in their trade. Workers in paraffin show an irritation of the skin that leads to pustules, keratoses, and ulcerations. Shale oil workers develop an erythematous, follicular eruption that eventually leads to keratoses, which may become the sites of carcinoma. It is estimated that 50% of shale oil workers have skin problems.

Impure and low-grade paraffins and mineral oils cause similar skin eruptions. Initially the skin changes are similar to those in chloracne. In due time, a diffuse erythema with dappled pigmentation develops. Gradually, keratoses appear, and after many years some of these are the sites of carcinoma. Melanoderma may occur from exposure to mineral oils and lower-grade petroleum, from creosote, asphalt, and other tar products. Photosensitization may play a role. Creosote is a contact irritant, sensitizer, and photosensitizer. Allergy is demonstrated by patch testing with 10% creosote in oil.

Petrolatum dermatitis may appear as a verrucous thickening of the skin caused by prolonged contact with impure petroleum jelly or, occasionally, lubricating oil. A follicular type occurs in which erythematous horny nodules are present, usually on the anterior and inner aspects of the thighs. There are no comedones and the lesions are separated by apparently normal skin.

Acne corne consists of follicular keratosis and pigmentation resulting from crude petroleum, tar oils, and paraffin. The dorsal aspects of the fingers and hands, the arms, legs, face, and thorax are the areas usually involved. The lesions are follicular, horny papules, often black, and are associated at first with a follicular erythema and later with a dirty brownish or purplish spotty pigmentation, which in severe cases becomes widespread and is especially marked around the genitals. This syndrome may simulate pityriasis rubra pilaris or lichen spinulosus.

Coal tar and pitch and many of their derivatives produce photosensitization and an acneiform folliculitis of the forearms, legs, face, and scrotum. Follicular keratoses (pitch warts) may develop and later turn into carcinoma. Soot, lamp black, and the ash from peat fires produce dermatitis of a dry, scaly character, which in the course of time forms warty outgrowths and cancer. Chimney sweep's cancer occurs under a soot wart and is usually located on the scrotum, where soot, sebum, and dirt collect in the folds of the skin. This form of cancer has virtually disappeared.

Acquired perforating disease may occur in oil field workers who use drilling fluid containing calcium cholide. Patients develop tender, umbilicated papules of the forearms that microscopically show transepidermal elimination of calcium.

Solvents

These cause approximately 10% of occupational dermatitis. When applied to the hands to cleanse them the surface oil is dissolved and a chronic fissured dermatitis results. Additionally, peripheral neuropathy and chemical lymphangitis may occur after being absorbed through the fissured skin. Solvent sniffers may develop an eczematous eruption about the mouth and nose. There is erythema and edema. It is a direct irritant dermatitis caused by the inhalation of the solvent placed on a handkerchief.

Trichloroethylene is a chlorinated hydrocarbon solvent and degreasing agent, and is used also in the dry-cleaning and refrigerant industry. Inhalation may produce exfoliative erythroderma, mucous membrane erosions, eosinophilia, and hepatitis.

Allergic contact dermatitis caused by alcohol is rarely encountered with lower aliphatic alcohols. A severe case of bullous and hemorrhagic dermatitis on the fingertips and deltoid region was caused by isopropyl alcohol. Though rare, ethyl alcohol dermatitis may also be encountered. Cetyl and stearyl alcohols may provoke contact urticaria.

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Allergic Contact Dermatitis

Allergic contact dermatitis results when an allergen comes into contact with previously sensitized skin. It results from a specific acquired hypersensitivity of the delayed type, also known as *cell-mediated hypersensitivity* or *immunity*. Occasionally, dermatitis may be induced when the allergen is taken internally by a patient first sensitized by topical application; this occurs, for example, with substances such as cinnamon oil or various medications. The anamnestic response is termed *systemic contact dermatitis*. It may appear first at the site of the prior sensitization or past positive patch test, but may spread to a generalized morbilliform or eczematous eruption. Additional morphologic patterns include vesicular hand eczema, urticaria, erythema multiforme, vasculitis, or the baboon syndrome. The latter is a deep red–violet eruption on the buttocks, genital area, inner thighs, and sometimes axilla.

The most common causes of contact dermatitis in the US are: toxicodendrons (poison ivy, oak, or sumac), nickel, Balsum of Peru (Myroxylon pereirae), neomycin, fragrance, thimerosal, gold, formaldehyde and the formaldehyde-releasing preservatives, bacitracin, and rubber compounds. Frequent positive reactions to thimerosal do not often correlate with clinical exposure histories. These reactions are probably related to its use as a preservative in commonly administered vaccines and skin-testing material. It also serves as a marker for piroxicam photosensitivity. These sensitizers do not cause demonstrable skin changes on first contact. Persons may be exposed to allergens for years before finally developing hypersensitivity. Once sensitized, however, subsequent outbreaks may result from extremely slight exposure.

When allergens are applied to the skin, Langerhans cells in the epidermis process them and display them in a complex with HLA-DR on their surface. This is presented to a CD4+ T-cell, interaction with the T-cell receptor–CD3 complex occurs, the allergen is recognized, and inflammatory mediators are released. The latter leads to proliferation and recruitment of and release of vasoactive substances and direct inflammatory mediators. Genetic variability in these processes and other factors, such as concentration of the allergen applied, its vehicle, timing and site of the exposure, presence of occlusion, age, sex, and race of the patient, and presence of other skin or systemic disorders likely determine whether any given exposure will result in sensitization.

Eczematous delayed-type hypersensitivity reaction, as exemplified by allergic contact dermatitis and the patch test, must be distinguished from the urticarial immediate type of contact urticaria. The latter presents within minutes of exposure with urticaria and is proven with a scratch test. It should be kept in mind, however, that persons who develop contact urticaria to a substance may concomitantly have a type IV delayed-type sensitization and eczema from the same allergen.

In some instances, impetigo, pustular folliculitis, and irritations or allergic reactions from applied medications are superimposed on the original dermatitis. A particularly vexing situation is when allergy to topical steroids complicates an eczema, in which case the preexisting dermatitis usually does not flare, but simply does not heal as expected. The cutaneous reaction also may provoke a hypersusceptibility to various other previously innocuous substances, which continues the inflammation indefinitely as eczema.

These eruptions resolve when the cause is identified and avoided. For acute generalized allergic contact dermatitis treatment with systemic steroidal agents is effective, beginning with 40 to 60 mg/day prednisone in a single oral dose, and tapering slowly to topical steroids. When the eruption is limited in extent and severity, local application of topical corticosteroid creams, lotions, or aerosol sprays is preferred.

Testing for Sensitivity

Patch Test

The patch test is used to detect hypersensitivity to a substance that is in contact with the skin so that the allergen may be determined and corrective measures taken. So many allergens can cause allergic contact dermatitis that it is impossible to test a person for all of them. In addition, a good history and observation of the pattern of the dermatitis, its localization on the body, and its state of activity are all helpful in determining the cause. The patch test is confirmatory and diagnostic but only within the framework of the history and physical findings; it is rarely helpful if it must stand alone. Interpretation of the relevance of positive tests and the subsequent education of patients is challenging in some cases. The Contact Allergen Avoidance Database (CARD) provides names of alternative products that may be used by patients when an allergen is identified. This is available through the American Contact Dermatitis Society.

The patch test consists of application to intact uninflamed skin, in nonirritating concentration, of substances suspected to be causes of the contact dermatitis. Patch testing may be administered by the thin-layer rapid-use epicutaneous (TRUE) test or by individually prepared aluminum (Finn) chambers mounted on Scanpor tape. The TRUE test has resulted in more screening for allergic contact dermatitis than in the past; however, if this test does not reveal the allergen for a highly suspect dermatitis, testing with an expanded series by the Finn chamber technique may yield relevant allergens in more than half of these patients.

Test substances are applied usually to the upper back, although if only one or two are applied, the upper outer arm may be used. Each patch should be numbered to avoid confusion. The patches are removed after 48 h (or sooner if severe itching or burning occur at the site) and read. The patch sites need to be evaluated again at day 4 or 5, because positive reactions may not appear earlier. Some allergens may take up to day 7 to show a reaction and the patient should be made aware to return if such a delayed reaction occurs. Erythematous papules and vesicles with edema are indicative of allergy (Fig. 6-4). Occasionally, patch tests for potassium iodide, nickel, or mercury will produce pustules at the site of the test application. Usually no erythema is produced; therefore, the reaction has no clinical significance.

Strong patch-test reactions may induce a state of hyperirritability ("excited skin syndrome") in which negative tests appear as weakly positive. Weakly positive tests in the presence of strong ones do not prove sensitivity. There is wide variation in the ability of the skin and mucous membranes to react to antigens. The oral mucosa is more resistant to primary irritants and is less liable to be involved in allergic reactions. This may be because the keratin layer of the skin more readily combines with haptens to form allergens. Also, the oral mucosa is bathed in saliva, which cleanses and buffers the area and dilutes irritants. However, patch testing for various types of oral signs and symptoms, such as swelling, tingling and burning, perioral dermatitis, and the appearance of oral lichen planus, is useful in determining a cause in many cases.

The ability of the skin to react to allergens also depends on the presence of functional antigen-presenting cells, the Langerhans cells. Potent topical steroids, ultraviolet (UV) light, and acquired immunodeficiency syndrome (AIDS) all have been reported to interfere with the number and function of these key cells. Vitiliginous skin is less reactive than normally pigmented adjacent skin.

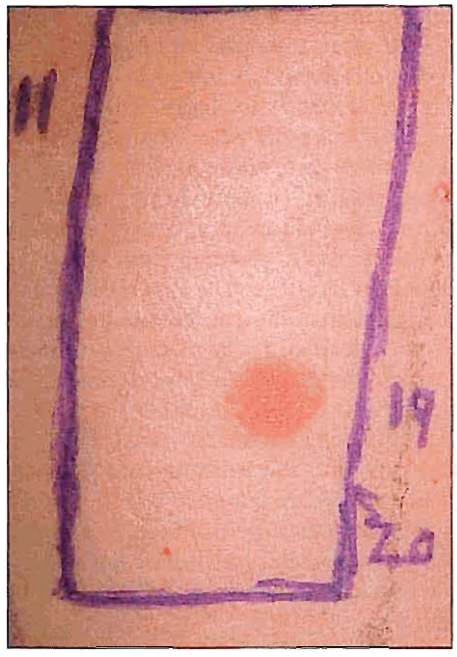

Fig. 6-4 Positive patch-test reaction.

Provocative Use Test

The provocative use test will confirm a positive closed patch-test reaction to ingredients of a substance, such as a cosmetic; it is used to test products that are made to stay on the skin once applied. The material is rubbed onto normal skin of the inner aspect of the forearm several times a day for 5 days.

Photopatch Test

The photopatch test is used to evaluate for contact photoallergy to such substances as sulfonamides, phenothiazines, *p*-aminobenzoic acid, oxybenzone, 6-methyl coumarin, musk ambrette, or tetrachlorsalicylanilide. A standard patch test is applied for 24 h; this is then exposed to 5 to 15 J/m^2 of UVA and read after another 48 h. To test for 6-methyl coumarin sensitivity, the patch is applied in the same manner but for only 30 min before light exposure, rather than for 24 h. A duplicate set of nonirradiated patches is used in testing for the presence of routine delayed hypersensitivity reactions. Also, a site of normal skin is given an identical dose of UVA to test for increased sensitivity to light without prior exposure to chemicals. There is a steady increase in incidence of sunscreening agent sensitivity and falling incidence of fragrance photoallergy.

Regional Predilection Familiarity with certain contactants and the typical dermatitis they elicit on specific parts of the body will assist in diagnosis of the etiologic agent.

Head and Neck

The scalp is relatively resistant to the development of contact allergies; however, involvement may be caused by hair dye, hair spray, shampoo, or permanent wave solutions. The

surrounding glabrous skin, including the ear rims and backs of the ears, may be much more inflamed and suggestive of the cause. Persistent otitis of the ear canal may be caused by sensitivity to the neomycin that is an ingredient of most aural medications. The eyelids are the most frequent site for nail polish dermatitis. Volatile gases, false-eyelash adhesive, fragrances, preservatives, mascara, rubber in sponges used to apply cosmetics, and eyeshadow are also frequently implicated (Fig. 6-5). Perioral dermatitis and cheilitis may be caused by flavoring agents in dentifrices and gum, as well as fragrances, shellac, medicaments, and sunscreens in lipstick and lip balms. Perfume dermatitis may cause redness just under the ears or on the neck. Earlobe dermatitis is indicative of nickel sensitivity. Photocontact dermatitis may involve the entire face and may be sharply cut off at the collar line or extend down onto the sternum in a V shape. There is a typical clear area under the chin where there is little or no exposure to sunlight. In men, in whom shaving lotion fragrances are often responsible, the left cheek and left side of the neck (from sun exposure while driving) may be the first areas involved.

Trunk

The trunk is an infrequent site; however, the dye or finish of clothing may cause dermatitis. The axilla may be the site of deodorant and clothing-dye dermatitis. Involvement of the axillary vault suggests the former; of the axillary folds, the latter. In women, brassieres cause dermatitis either from the material itself, elastic, or metal snaps or underwires.

Arms

The wrists may be involved because of jewelry or the backs of watches and clasps, all of which may contain nickel. Wristbands made of leather are a source of chrome dermatitis.

Hands

Innumerable substances may cause contact dermatitis of the hands, which typically occurs on the backs of the hands and spares the palms. Florists will often develop fingertip or palmar lesions. A hand dermatitis that changes from web spaces to fingertips or from palms to dorsal hands should trigger patch testing. Poison ivy and other plant dermatitides frequently occur on the hands and arms. Rubber glove sensitivity must be kept constantly in mind. Usually irritancy is superimposed on allergic contact dermatitis of the hands, altering both the morphologic and histologic clues to the diagnosis.

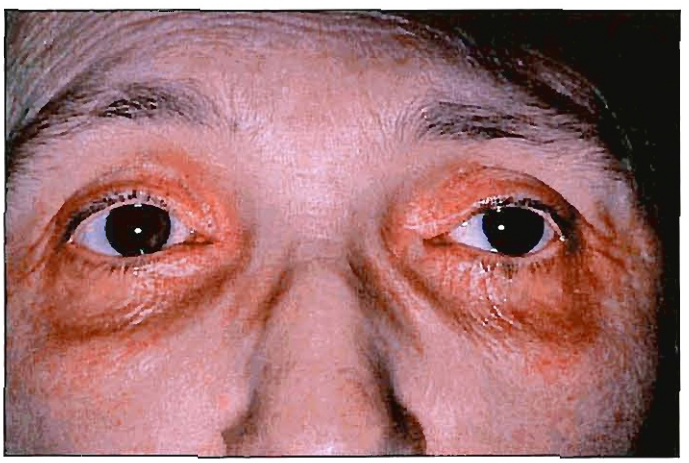

Fig. 6-5 Eyelid dermatitis.

Abdomen

The abdomen, especially the waistline, may be the site of rubber dermatitis from the elastic in pants and undergarments. The metallic rivets in blue jeans may lead to periumbilical dermatitis in nickel-sensitive patients, as may piercings of the umbilicus.

Groin

The groin is usually spared, but the buttocks and upper thighs may be sites of dermatitis caused by dyes. The penis is frequently involved in poison ivy dermatitis. Condom dermatitis may also occur. The perianal region may be involved from the "caine" medications in suppositories, as well as preservatives and fragrances in cleansing materials. Nearly half of women with pruritus vulvae have one or more relevant allergens; often these are medicaments, fragrances or preservatives.

Lower Extremities

The shins may be the site of rubber dermatitis from elastic stockings. Feet are sites for shoe dermatitis, most often attributable to rubber sensitivity, chrome-tanned leather, dyes, or adhesives. Application of topical antibiotics to stasis ulcers commonly leads to sensitivity and allergic contact dermatitis.

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Dermatitis Resulting from Plants

A large number of plants, including trees, grasses, flowers, vegetables, fruits, and weeds, are potential causes of dermatitis. Eruptions from them vary considerably in appearance but are usually vesicular and accompanied by marked edema. After previous exposure and sensitization to the active substance in the plant, the typical dermatitis results from re-exposure. The onset is usually a few hours or days after contact. The characteristic linearly grouped lesions are probably produced by brushing the skin with a leaf edge or a broken twig, or by carriage of the allergen under the nails. Contrary to general belief, the contents of vesicles are not capable of producing new lesions.

Toxicodendron (Poison Ivy)

Toxicodendron dermatitis includes dermatitis from members of the *Anacrdiaceae* family of plants: poison ivy (Fig. 6-6), poison oak, poison sumac, Japanese lacquer tree, cashew nut tree (the allergen is in the nutshell), mango (the allergen is in the rind, leaves, or sap), Rengas tree, and Indian marking nut tree. The ginkgo (the allergen is in the fruit pulp), spider flower or silver oak, *Gluta* species of trees and shrubs in Southeast Asia, Brazilian pepper tree, also known as Florida holly, and poisonwood tree contain nearly identical antigens.

Toxicodendron dermatitis appears within 48 h after exposure of a previously sensitized person to the plant. It usually begins on the backs of the fingers, interdigital spaces, wrists, and eyelids, although it may begin on the ankles or other parts that have been exposed. Marked pruritus is the first symptom; then inflammation, vesicles, and bullae may appear. The vesicles are usually grouped and often linear (Fig. 6-7). Large bullae may be present, especially on the forearms and hands. The eyelids are puffy; they will be worst in the morning and improve as the day progresses (Fig. 6-8). Pruritus ani and involvement of the genital areas occur frequently. A black lacquer deposit may occur in which the sap of the plant has been oxidized after being bound to the stratum corneum (Fig. 6-9). Untreated toxicodendron dermatitis usually last 2 to 3 weeks

The fingers transfer the allergen to other parts, especially the forearms and the male prepuce, which become greatly

Fig. 6-6 *Toxicodendron radicans* subsp *radicans*. Poison ivy species found commonly in the eastern US. (Courtesy of James WD [ed]: Textbook of Military Medicine. Office of the Surgeon General, United States Army, 1994.)

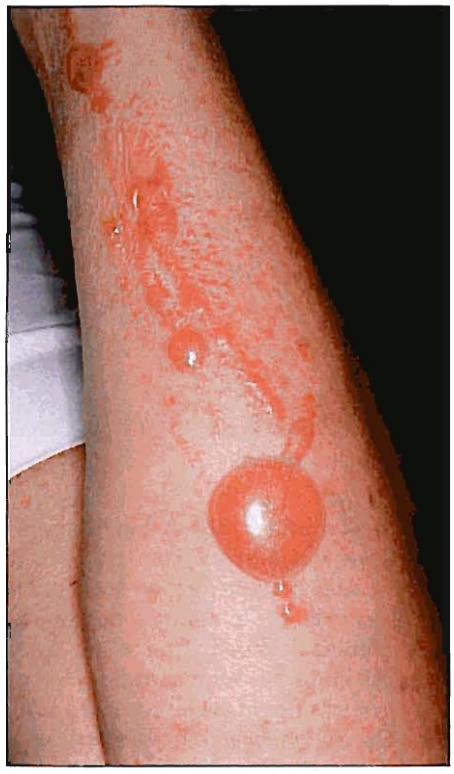

Fig. 6-7 Acute poison ivy reaction.

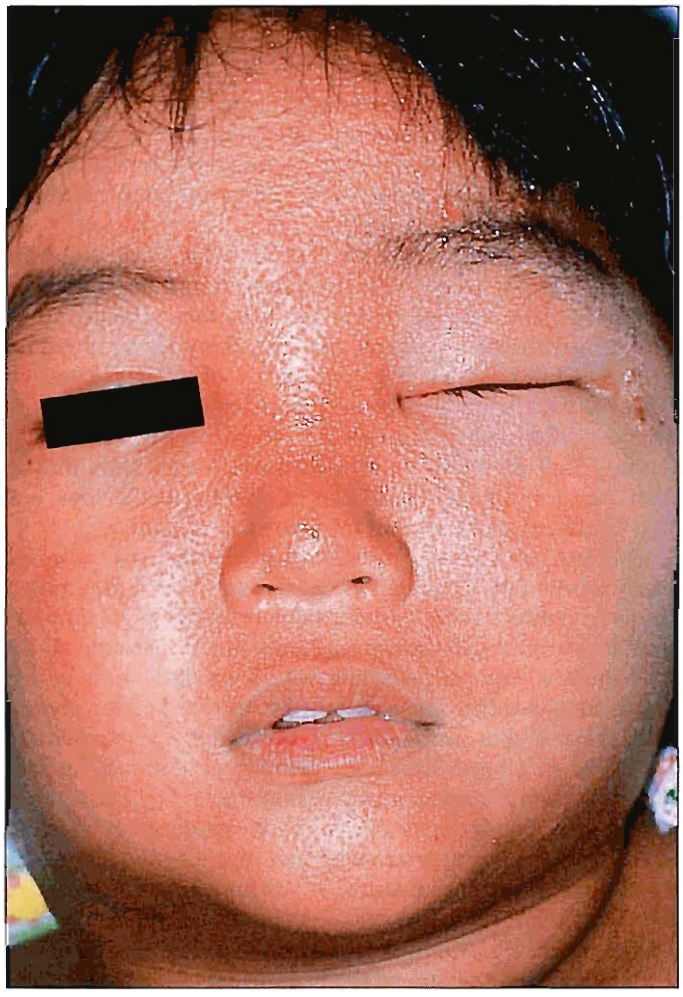

Fig. 6-8 Acute poison ivy reaction.

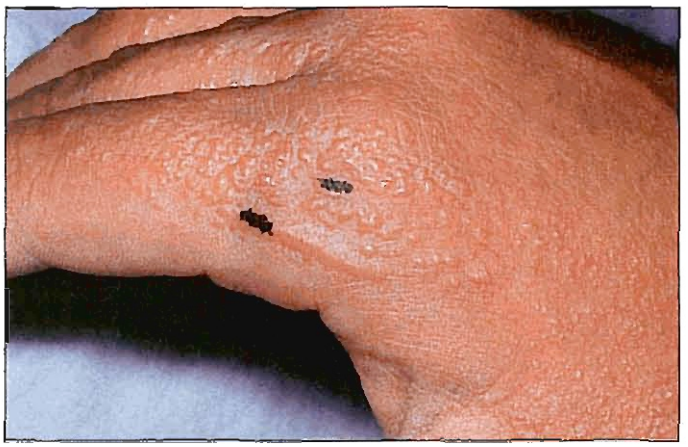

Fig. 6-9 Black dot sign in poison ivy reaction.

swollen. However, once the causative oil has been washed off, there is no spreading of the allergen and no further spread of the dermatitis. Some persons are so susceptible that direct contact is not necessary, the allergen apparently being carried by the fur of their pets or by the wind. It can also be acquired from golf clubs or fishing rods, or even from furniture that a dog or cat might have occupied after exposure to the catechol. Occasionally, eating the allergen, as occurred in a patient who ingested raw cashew nuts in an imported pesto sauce, may result in the baboon syndrome (a deep red–violet eruption on the buttocks, genital area, inner thighs, and sometimes axilla), or a systematized allergic contact dermatitis with the morphology of a generalized erythematous papular eruption.

The cause is an oleoresin known as *urushiol*, of which the active agent is a mixture of catechols. This and related resorcinol allergens are present in many plants and also in philodendron species, wood from *Persoonia elliptica*, wheat bran, and marine brown algae.

The most striking diagnostic feature is the linearity of the lesions. It is rare to see vesicles arranged in a linear fashion except in plant-induced dermatitis. A history of exposure in the country or park to plants that have shiny leaves in groups of three, followed by the appearance of vesicular lesions within 2 days, usually establishes the diagnosis. Persons with known susceptibility not only should avoid touching plants having the grouped "leaves-of-three," but should also exercise care in handling articles of clothing, tools, toys, and pets that have come in contact with such plants.

Eradication of plants growing in frequented places is one easy preventive measure, as is recognition of the plants to avoid contact with. An excellent resource is a pamphlet available from the American Academy of Dermatology. If the individual is exposed, washing with soap and water within 5 min may prevent an eruption. Protective barrier creams are available that are somewhat beneficial. Quaternium-18 bentonite has been shown to prevent or diminish experimentally produced poison ivy dermatitis.

Innumerable attempts have been made to immunize against poison ivy dermatitis by ingestion of the leaves, oral administration of the tincture, or subcutaneous injections of oily extracts. To date, no accepted method of immunization has evolved. Repeated attacks do not confer immunity, although a single severe attack may achieve this by what has been called *massive-dose desensitization.*

When the diagnosis is clear and the eruption severe or extensive, systemic steroidal agents are effective, beginning with 40 to 60 mg of prednisone in a single oral dose daily, tapered off over a 3-week period. When the eruption is limited in extent and severity, local application of topical corticosteroid creams, lotions, or aerosol sprays is preferred. Time-honored calamine lotion without phenol is helpful and does no harm. Antihistaminic ointments should be avoided because of their sensitization potential. This also applies to the local application of the "caine" topical anesthetics.

Other Toxicodendron-Related Dermatitis

Lacquer dermatitis is caused by a furniture lacquer made from the Japanese lacquer tree, used on furniture, jewelry, or bric-a-brac. Antique lacquer is harmless, but lacquer less than 1 or 2 years old is highly antigenic. Cashew nutshell oil is extracted from the nutshells of the cashew tree (*Anacardium occidentale*). This vesicant oil contains cardol, a phenol similar to urushiol in poison ivy. The liquid has many commercial applications, such as the manufacture of brake linings, varnish, synthetic glue, paint, and sealer for concrete.

Mango dermatitis is uncommon in natives of mango-growing countries (the Philippines, Guam, Hawaii, Cuba) who have never been exposed to contact with toxicodendron species. Many persons who have been so exposed, however, whether they had dermatitis from it or not, are sensitized by one or a few episodes of contact with the peel of the mango fruit. The palms of the hands are contaminated from the first, so the eyelids and the male prepuce are often early sites of involvement. Sponging all contaminated or itchy areas meticulously and systematically with equal parts of ether and acetone at the outset will often remove the oleoresin and ameliorate any worsening of the dermatitis, which can be treated with topical or oral steroids as needed.

Ginkgo tree dermatitis simulates toxicodendron dermatitis with its severe vesiculation, erythematous papules, and edema. The causative substances are ginkgolic acids from the fruit pulp of the ginkgo tree. Ingestion of the ginkgo fruit may result in perianal dermatitis. Ginkgo biloba given orally for cerebral disturbances is made from a leaf extract so it does not elicit a systemic contact allergy when ingested.

Flowers and Houseplants

Among the more common houseplants, the velvety-leafed philodendron, *Philodendron crystallinum* (and its several variants), known in India as the money plant, is a frequent cause of contact dermatitis. The eruption is often seen on the face, especially the eyelids, carried there by hands that have watered or cared for the plant. English ivy follows philodendron in frequency of cases of occult contact dermatitis. Primrose dermatitis affects the fingers, eyelids, and neck with a punctate or diffuse erythema and edema. It was formerly most frequently encountered in Europe; however, it is now a common houseplant in the US. Primin, a quinone, is the causative oleoresin abounding in the glandular hairs of the plant *Primula obconica*.

The popular cut flower, the Peruvian lily, is the most common cause of allergic contact dermatitis in florists. When handling flowers of the genus *Alstroemeria* the florist utilizes the thumb, and second and third digits of the dominant hand. Since it is chronic, fissured hyperkeratotic dermatitis

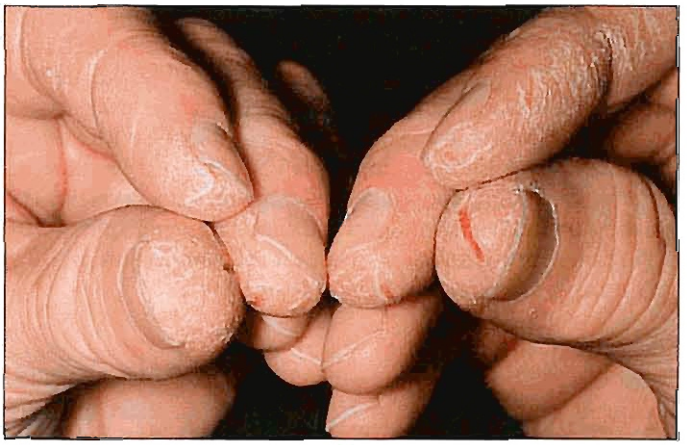

Fig. 6-10 Chronic fissured fingertip dermatitis in a florist.

results and is identical to the so-called tulip fingers seen among sensitized tulip workers (Fig. 6-10). Testing is done with the allergen tuliposide A. It does not penetrate nitrile gloves.

Chrysanthemums frequently cause dermatitis. The eyelids are frequently involved. Florists are most commonly affected. The α-methylene portion of the sesquiterpene lactone molecule is the antigenic site, as it is in the other genera of the *Compositae* family.

A severe inflammatory reaction with bulla formation may be caused by the prairie crocus (*Anemone patens L*), the floral emblem of the province of Manitoba. Several species of ornamental "bottle brush" from Queensland, *Grevillea banksii, G. Robyn Gordon*, and *G. robusta*, may cause allergic contact dermatitis. It is exported to the US and other Western countries. The allergen is a long-chain alkyl resorcinol. A cross-sensitivity to toxicodendron has been demonstrated.

Contact dermatitis may be caused by handling many other flowers, such as the geranium, scorpion flower (*Phacelia crenulata* or *campanularia*), hydrangea, creosote bush (*Larvia tridentata*), Heracula, daffodil, foxglove, lilac, lady slipper, magnolia, and tulip and narcissus bulbs. The poinsettia and oleander almost never cause dermatitis, despite their reputation for it, although they are toxic if ingested. Treatment of all these plant dermatitides is the same as that recommended for toxicodendron dermatitis.

Parthenium hysterophorus, a photosensitizing weed, was accidentally introduced into India in 1956 and has spread over most of the country; it is also spreading in Australia, China, and Argentina. The well-deserved reputation for harmfulness of dieffenbachia, a common, glossy-leafed house plant, rests on the high content of calcium oxalate crystals in its sap, which burn the mouth and throat severely if any part of the plant is chewed or swallowed. Severe edema of the oral tissues may result in complete loss of voice; hence its common nickname, "dumb cane." It does not appear to sensitize. The castor bean, the seed of *Ricinus communis*, contains ricin, a poisonous substance (phytotoxin). Its sap contains an antigen that may cause anaphylactic hypersensitivity and also dermatitis.

Vegetables

Many vegetables may cause contact dermatitis, including asparagus, carrot, celery, cow-parsnip, cucumber, garlic, Indian bean, mushroom, onion, parsley, tomato, and turnip. Onion and celery, among other vegetables, have been incriminated in the production of contact urticaria and even anaphylaxis. Several plants, including celery, fig, lime, and parsley, can cause a phototoxic dermatitis because of the presence of psoralens.

Trees

Trees whose timber and sawdust may produce contact dermatitis include ash, birch, cedar, cocobolo, elm, Kentucky coffee tree, koa, mahogany, mango, maple, mesquite, milo, myrtle, pine, and teak. The latex of fig and rubber trees may also cause dermatitis, usually of phototoxic type. Melaleuca oil (tea tree oil), which may be applied to the skin to treat a variety of maladies, can cause allergic contact dermatitis, primarily through the allergen D-limonene. The exotic woods, especially cocobolo and rosewood, and tea tree oil are prominent among allergens that may produce *erythema multiforme* after cutaneous exposure. Toxicodendron, various medicaments, and a variety of other allergens may induce this reaction.

Tree-Associated Plants

Foresters and lumber workers can be exposed to allergenic plants other than trees. Lichens are a group of plants composed of symbiotic algae and fungi. Foresters and wood choppers exposed to these lichens growing on trees may develop severe allergic contact dermatitis. Exposure to the lichens may also occur from firewood, funeral wreaths, and also masculine fragrances added to aftershave lotions (oak moss and tree moss). Hypersensitization is produced by the D-usnic acid and other lichen acids contained in lichens. The leafy liverwort (*Frulliana nisquallansis*), a forest epiphyte growing on tree trunks, has produced allergic dermatitis in forest workers. The eruption is commonly called *cedar poisoning*. It resembles toxicodendron dermatitis; its attacks are more severe during wet weather. The allergen is sesquiterpene lactone.

Pollens and Seeds

The pollens in ragweed are composed of two antigens. The protein fraction causes the respiratory symptoms of asthma and hay fever and the oil-soluble portion causes contact dermatitis. Ragweed oil dermatitis is a seasonal disturbance seen mainly during the ragweed growing season from spring to fall. Contact with the plant or with wind-blown fragments of dried plant produces the typical dermatitis. The oil causes swelling and redness of the lids and entire face and a red blotchy eruption on the forearms that, after several attacks, may become generalized, with lichenification; it closely resembles chronic atopic dermatitis, with lichenification of the face, neck, and major flexures, and severe pruritus. The distribution mimics that of photodermatitis, the differentiating point being that in ragweed dermatitis there is involvement of the upper eyelids and the retroauricular and submental areas. Chronic cases may continue into the winter; however, signs and symptoms are most severe at the height of the season. Sesquiterpene lactones are the cause. Coexistent sensitization to pyrethrum may account for prolongation of ragweed dermatitis. Men outnumber women in hypersensitivity reactions; farmers outnumber patients of all other occupations.

Marine Plants

Numerous aquatic plants are toxic or produce contact dermatitis. Algae seem to be the worse offenders. Fresh-water plants are rarely of concern. Seaweed dermatitis is a type of swimmer's eruption produced by contact with a marine blue–green alga, which has been identified as *Lyngbya majuscula Gomont*. The onset is within a few minutes after leaving the ocean, with severe itching and burning, followed by dermatitis, blisters, and deep and painful desquamation that affects the areas covered by the bathing suit (in men, especially the scrotum, perineum, and perianal areas; occasionally, in women, the breasts). Patch tests with the alga are neither necessary nor helpful, since it is a potent irritant. Bathing in fresh water within 10 or 15 min after leaving the ocean may prevent the dermatitis. The Bermuda fire sponge may produce contact erythema multiforme. Trawler fishermen in the Dogger Bank area of the North Sea develop allergic dermatitis after contact with *Alcyonidium hirsutism*. This is a seaweed-like animal colony that becomes caught in the fishermen's net and produces erythema, edema, and lichenification on the hands and wrists.

Plant-Associated Dermatitis

Phototoxic contact dermatitis from plants is discussed in Chapter 3 (Fig. 6-11).

The residua of various insecticides on plants may also produce dermatitis. This is especially true of arsenic- and malathion-containing sprays. Randox (2-chloro-*N*, *N*-diallyl-acetamide) has been reported as the cause of hemorrhagic bullae on the feet of farmers. Lawn-care companies spray herbicides and fungicides throughout the spring, summer, and fall. Dryene, thiuram, carbamates, and chlorothalonil are potential sensitizers in these workers, whose clothing frequently becomes wetted while spraying.

Barbs, bristles, spines, thorns, spicules, and cactus needles are some of the mechanical accessories of plants that may produce dermatitis. Sabra dermatitis is an occupational dermatitis resembling scabies. It is seen among pickers of the prickly pear cactus plant. It also occurs in persons handling Indian figs in Israel, where the condition is seen from July to November. The penetration of minute, invisible thorns into the skin is the cause. *Agave Americana* is a low-growing plant grown for ornamental purposes in many Southwestern communities. Trimming during landscaping can induce an irritant dermatitis caused by calcium oxalate crystals. The stinging nettle is a common weed that bears tiny spines with biologically active substances such as histamine that produce itching and urticaria within minutes of contact.

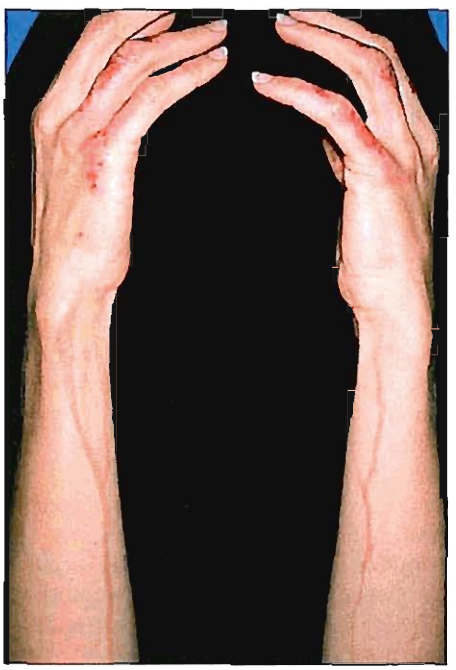

Fig. 6-11
Photosensitivity caused by dripping fruit juice.

Plant Derivatives

Sensitizing substances derived from plants are found in the oleoresin fractions that contain camphors, essential oils, phenols, resins, and terpenes. The chief sensitizers are the essential oils. They may be localized in certain parts of the plant, such as in the peel of citrus fruits, leaves of the eucalyptus tree, and bark of the cinnamon tree. Aromatherapy, an increasingly popular treatment for relief of stress, involves either inhaling or massaging with essential oils; this may cause allergic contact dermatitis in therapists or clients. Exposure to botanical extracts is through many cosmetics and homeopathic remedies and there is an ever increasing number of reports of allergic contact sensitivity to individual ingredients, especially tea-tree oil.

Cinnamon oil (cassia oil) is a common flavoring agent, especially in pastries. Hand dermatitis in pastry bakers is often caused by cinnamon. It is also used as a flavor for lipstick, bitters, alcoholic and nonalcoholic beverages, toothpaste, and chewing gum. Perioral dermatitis may be caused by cinnamon in chewing gum. A 5% cinnamon solution in olive oil is used for patch testing. Eugenol, clove oil, and eucalyptus oil are used by dentists, who may acquire contact dermatitis from them. Anise, peppermint, and spearmint oils may cause sensitization.

Nutmeg, paprika, and cloves are causes of spice allergy. Fragrance-mix is a useful indicator allergen. Lemon oil from lemon peel or lemon wood may cause sensitization in the various handlers of these substances. Citric acid may cause dermatitis in bakers. Lime oil in lime-scented shaving cream or lotion may cause photoallergy. Balsam of Peru contains numerous substances, among which are essential oils similar to the oil of the lemon peel. Balsam of Peru is known to cross-react with vanilla and cinnamon, among many others. Vanillin is derived from the vanilla plant and frequently produces contact dermatitis, vanillism, in those connected with its production and use.

Turpentine frequently acts as an irritant and as an allergic sensitizer (carene). It is contained in paints, paint thinners, varnishes, and waxes.

Testing for Plant Allergens

The method of testing for plant hypersensitivity is the application of the crushed plant leaf, stem, and petal, and then covering with micropore tape. The plant should be washed thoroughly as infection with fungi from the soil may complicate testing. A test should also be performed on several controls to make sure that the leaf is not an irritant. It must be remembered that some of the plants are photosensitizers. Test sites for these must be done in duplicate, with one set kept covered and the other exposed to artificial light or sunlight for the detection of photosensitivity.

Anderson BE, et al: Stinging nettle dermatitis. Am J Contact Dermat 2003;14:44.
Bedi MK, et al: Herbal therapy in dermatology. Arch Dermatol 2002;138:232.
Crawford GH, et al: Tea tree oil. Am J Contact Dermat 2004; 15:59.
Crawford GH, et al: Use of aromatherapy products and increased risk of hand dermatitis in massage therapists. Arch Dermatol 2004;140:991.
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Hamilton TK, et al: Systemic contact dermatitis to raw cashew nuts in a pesto sauce. Am J Contact Dermat 1998;9:51.
High WA: Agave contact dermatitis. Am J Contact Dermat 2003;14:213.
Kiken DA, et al: Contact dermatitis to botanical extracts. Am J Contact Dermat 2002;13:148.
Kurlan JG, et al: Black spot poison ivy. J Am Acad Dermatol 2001;45:246.
LeSuer BW, et al: Necrotizing cellulites caused by *Apophysomyces elegans* at a patch test site. Am J Contact Dermat 2002;13:140.
Marks JG Jr, et al: Prevention of poison ivy and poison ask allergic contact dermatitis by quaternium-18 bentonite. J Am Acad Dermatol 1995;33:212.
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McGovern TW, et al: Is it, or isn't it? Poison ivy look-a-likes. Am J Contact Dermat 2000;11:104.
Paulsen E. Contact sensitisation from Compositae-containing herbal remedies and cosmetics. Contact Dermatitis 2002; 47:189.
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Stibich AS, et al: Cost-effective post-exposure prevention of poison ivy dermatitis. Int J Dermatol 2000;39:515.
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Weiss RR, et al: Allergic contact dermatitis from aromatherapy. Am J Contact Dermat 1997;8:250.

Dermatitis from Clothing A predisposition to contact dermatitis from clothing occurs in persons who perspire freely or who are obese and wear clothing that tends to be tight. Depending on the offending substance, various regions of the body will be affected. Regional location is helpful in identifying the sensitizing substance. The axillary folds are commonly involved; the vaults of the axillae are usually spared. Sites of increased perspiration and sites where evaporation is impeded, such as the intertriginous areas, will tend to leach dyes from fabrics to produce dermatitis. Areas where the material is tight against the skin, such as the waistband or neck, are frequently involved (Fig. 6-12). The thighs are commonly affected when pants contain the offending allergen. Sparing of the hands, face and undergarment sites is usual. Secondary changes of lichenification and infection occur frequently because of the chronicity of exposure.

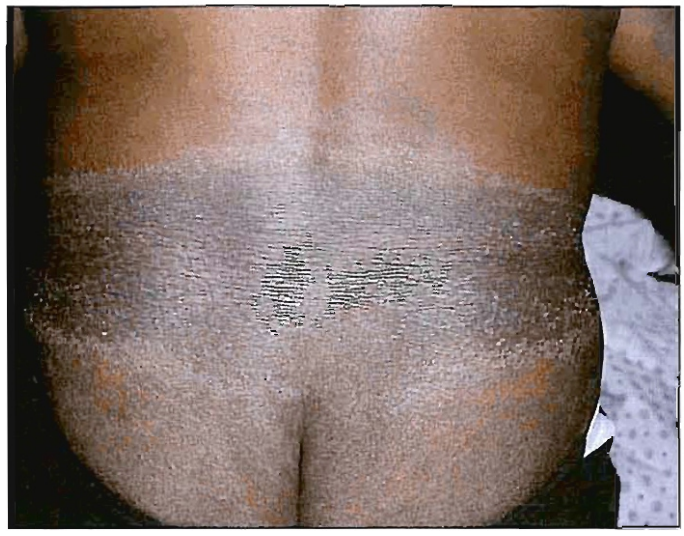

Fig. 6-12 Waistband clothing dermatitis.

Cotton, wool, linen, and silk fabrics were used exclusively before the advent of synthetic fabrics. Most materials are now blended in definite proportions with synthetics to produce superior lasting and esthetic properties. Dermatitis from cotton is virtually nonexistent. In most instances there is no true sensitization to wool. Wool acts as an irritant because of the barbs on its fibers. These barbs may produce severe pruritus at points of contact with the skin, especially in the intertriginous areas. In sensitive-skinned persons, such as those with atopic dermatitis, the wearing of wool is not advisable because of its mechanical irritative properties. Silk is a sensitizer, but rarely; the nature of the allergen is not known. Many patients believe their detergent is the source of a dermatitis, but this is rarely the case.

Numerous synthetic fibers are available for clothing and accessory manufacture, all of which again are remarkably free of sensitizing properties. Polyvinyl resins are the plastics used in such apparel as raincoats, rainhoods, wristbands, suspenders, plastic mittens, and gloves. These again are only infrequently found to be causes of contact dermatitis.

The most common causes of clothing dermatitis are the fabric finishers, dyes, and rubber additives. Fabric finishes are used to improve the durability, appearance, and feel of a material. Antiwrinkling and crease-holding chemicals are mostly resins, which are incorporated into the fibers as they are being manufactured or applied to the completed (finished) fabric. Fabrics are treated to make them less vulnerable to the effects of perspiration and ironing. Clothing may be treated with these substances to make it dry rapidly after washing. They are used to make clothing fabrics shrink-resistant, and water- and stain-repellent. When all these uses are taken into consideration, the low incidence of dermatitis from these formaldehyde resin materials is remarkable.

Ethylene urea melamine formaldehyde resin and dimethylol dihydroxyethehylene urea formaldehyde resin are the best screening agents. Many also react to formaldehyde and the formaldehyde-releasing preservatives such as quaternium-15. Avoidance of exposure of the skin to formaldehyde resin is most difficult. New clothes should be thoroughly washed twice before wearing, the first time.

Jeans, Spandex, silk, 100% linen, 100% nylon, and 100% cotton that is not wrinkle resistant or colorfast are best tolerated. T-shirts, sweat shirts, sweat pants, white underclothes suitable for bleaching, and any type of mixed synthetic fibers with cotton fibers that are added to make them drip-dry are most likely to cause problems in these patients.

An increasing number of patients allergic to clothing dye are being reported. Synthetic fabrics such as polyester and acetate liners in women's clothing are prime causes, and affected patients are more commonly women than men. In many cases patients do not react to paraphenylene diamine, but only to the disperse dye allergens. The best screening agents are disperse blue 106 and 124. Suspected fabrics may be soaked in water for 15 min and applied under a patch for 72 to 96 h.

Spandex is a nonrubber (but elastic) polyurethane fiber. It is widely used for garments such as girdles, brassieres, and socks. Dermatitis from Spandex has been reported with brassieres. It was found that Spandex containing mercaptobenzothiazole produced the contact dermatitis. Spandex manufactured in the US does not contain this and therefore does not produce allergic contact dermatitis Rubber allergens are discussed in more detail below.

Arisu K, et al: Tinuvin P in a spandex tape as a cause of clothing dermatitis. Contact Dermatitis 1992;26:311.
Carlson RM, et al: Diagnosis and treatment of dermatitis due to formaldehyde resin in clothing. Dermatitis 2004;15:169.
Cohen D, et al: Clothes make the woman: Diagnosis and management of clothing dermatitis. Am J Contact Dermat 2001;12:229.
Fowler JF Jr, et al: Allergic contact dermatitis from formaldehyde resins in permanent press clothing. J Am Acad Dermatol 1992;27:962.
Hatch K, et al: Textile dye dermatitis. J Am Acad Dermatol 1995;32:631.
Hatch KL, et al: Disperse dyes in fabrics of patients patch-test-positive to disperse dyes. Am J Contact Dermat 2003;14:205.
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Scheman AJ, et al: Formaldehyde-related textile allergy. Contact Dermatitis 1998;38: 332.
Seidenari S, et al: Sensitization to disperse dyes in a patch test population over a five-year period. Am J Contact Dermat 2002;13:101.

Shoe Dermatitis Footwear dermatitis may begin on the dorsal surfaces of the toes and may remain localized to that area indefinitely (Fig. 6-13). There is erythema and lichenification and, in severe cases, weeping and crusting. Secondary infection is frequent. In severe cases an id reaction may be produced on the hands similar to the reaction from fungus infection of the feet. A diagnostic point is the normal appearance of the skin between the toes, which has no contact with the offending substance. In fungus infections the toe webs are usually involved. Another pattern seen is involvement of the sole with sparing of the instep and flexural creases of the toes. Hyperhidrosis and atopy predispose to the development of shoe allergy.

Shoe dermatitis is most frequently caused by the rubber accelerators mercaptobenzothiazole and tetramethylthiuram disulfide. Dithiodimorpholine, a rubber accelerator not generally available for testing, was found by Shakleford and Belsito to be the most common allergen in their series of patients. Potassium dichromate in leather and the adhesives used in synthetic materials (especially *p*-tert-butylphenol formaldehyde resin) are also common shoe allergens. Diisocyanates are used in making foam rubber padding for athletic shoes and should be considered when testing for shoe allergy. Other causative agents are felt, cork liners, formaldehyde, dyes, asphalt, and tar. Patch testing with pieces of various shoe parts may be done by soaking them for 15 min in water and applying them to the back for 72 to 96 h. Once the allergen has been identified, selection of shoes without the offending substance will lead to resolution. This is, unfortunately, a difficult process as most shoes are made in areas without mandatory labeling requirements, and plastic, wooden or fabric shoes which contain fewer allergens are often impractical.

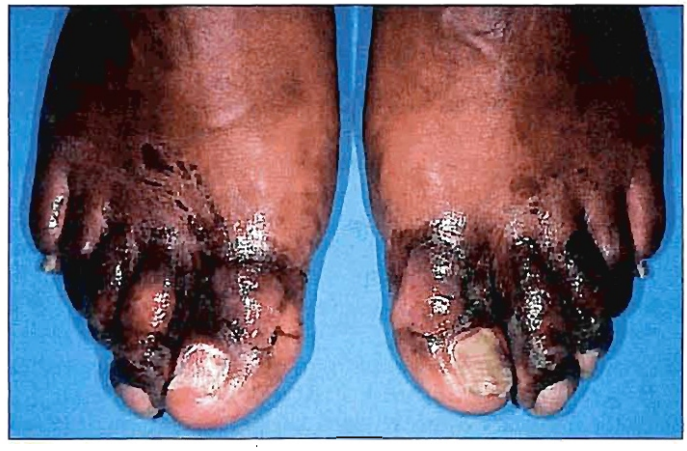

Fig. 6-13 Shoe dermatitis.

Belsito DV: Common shoe allergens undetected by commercial patch-testing kits. Am J Contact Dermat 2003;14:95.
Freeman S: Shoe dermatitis. Contact Dermatitis 1997;36:247.
Shakelford KE, et al: The etiology of allergic-appearing foot dermatitis. J Am Acad Dermatol 2002;47:715.
Trevisan G, et al: Allergic contact dermatitis due to shoes in children. Contact Dermatitis 1992;26:45.
Van Coevorden AM, et al: Contact allergens in shoe leather among patients with foot eczema. Contact Dermatitis 2002;46:145.

Dermatitis from Metals and Metal Salts Metal dermatitis is most frequently caused by nickel, chromates, and mercury. Usually, with the exception of nickel, the pure metals generally do not cause hypersensitivity; it is only when they are incorporated into salts that they cause reactions. Most objects containing metal or metal salts are combinations of several metals, some of which may have been used to plate the surface, thereby enhancing its attractiveness, durability, or tensile strength. For this reason suspicion of a metal-caused dermatitis should be investigated by doing patch tests to several of the metal salts.

Patients have been reported who developed a variety of dermatoses, most often eczematous in type, after placement of an orthopedic implant. It is rare that removal of the

implanted substance results in cure. A positive diagnosis requires at a minimum the appearance of a chronic dermatitis after placement of the implant, no other cause, corrosion of the implant, and a positive patch test for the metal in the implant, and healing after removal.

Black Dermatographism

Black or greenish staining under rings, metal wristbands, bracelets, and clasps is caused by the abrasive effect of cosmetics or other powders containing zinc or titanium oxide on gold jewelry. This skin discoloration is always black because of the deposit of metal particles on skin that has been powdered and that has metal, such as gold, silver, or platinum, rubbing on it. Abrasion of the metal results from the fact that some powders are hard (zinc oxide) and are capable of abrading the metal.

Nickel

Because we are all constantly exposed to nickel, nickel dermatitis is a frequent occurrence. While still more frequent among women, sensitization among men is increasing. A direct relationship between prevalence of nickel allergy and number of pierced sites has been documented. Nickel produces more cases of allergic contact dermatitis than all other metals combined. Erythematous and eczematous eruptions, sometimes with lichenification, appear beneath earrings (Fig. 6-14), bracelets, rings, wrist watches, clasps, and blue-jeans buttons (Figs 6-15 and 6-16). The euro coins have enough nickel in them to elicit allergic responses in nickel-sensitive individuals; however, coins are rarely a cause of hand dermatitis. Nickel ranks highly on lists of occupationally-induced allergic contact dermatitis.

Nickel dermatitis is seen most frequently on the earlobes. Piercing the earlobes with nickel-plated instruments or wearing nickel-plated jewelry readily induces nickel sensitivity. Earlobes should be pierced only with stainless steel instruments, and only stainless steel earrings should be worn until the ears have healed. Exposure to the metal may not be readily apparent most of the time. Even in gold jewelry the clasps and solder may contain nickel. Nickel objects may be plated with chrome and yet cause nickel dermatitis through the leaching of some of the nickel through the small pores of the chromium plating.

Nickel oxides in green paints may also produce nickel dermatitis. Sweat containing sodium chloride may combine with nickel to form nickel chloride. This affects the degree of nickel dermatitis, it being more severe in persons who perspire profusely. Prevention of sweating may help to prevent the areas exposed to nickel from developing dermatitis or may at least attenuate the condition.

The diagnosis is established by a positive patch-test reaction to nickel sulfate. Nickel may be detected by applying a freshly prepared 1% alcohol solution of dimethylglyoxime and a 10% aqueous solution of ammonia separately in equal amounts to the test object. In the presence of nickel, the cotton swab used to apply the solution will turn orange-pink. A positive test always means that nickel is present, but a negative test does not rule out its presence. Sweat, blood, or saline may leach nickel from stainless steel.

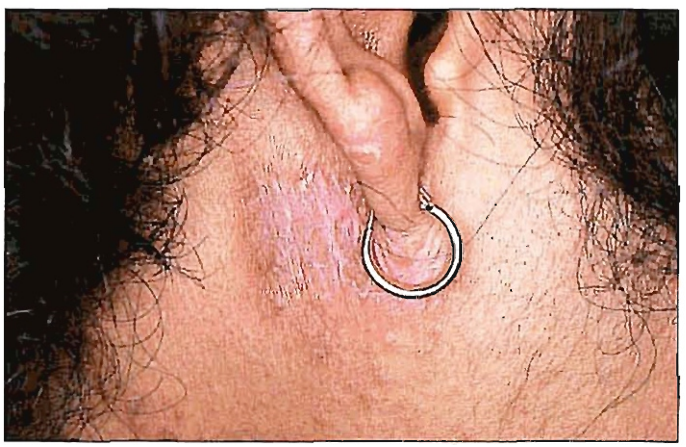

Fig. 6-14 Nickel dermatitis from earring.

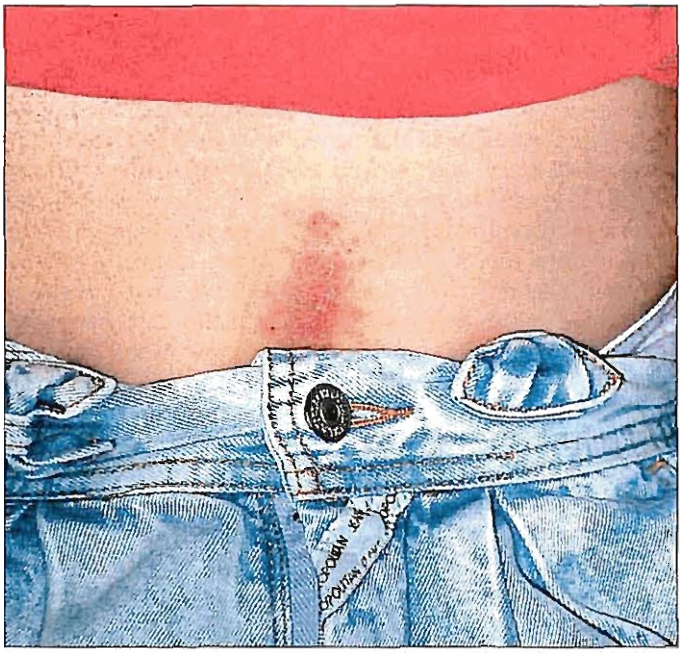

Fig. 6-15 Jeans button nickel dermatitis.

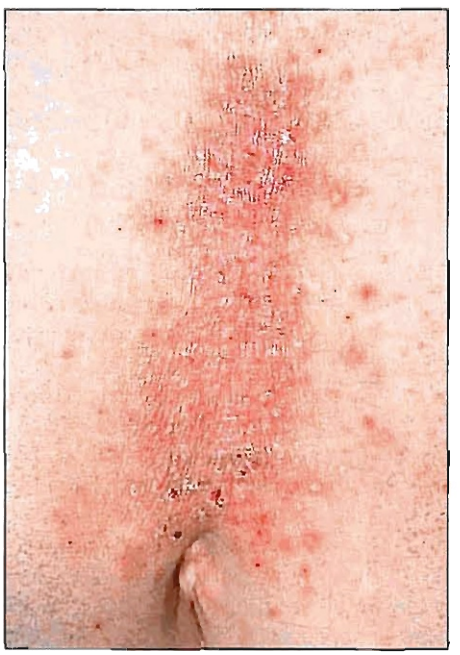

Fig. 6-16 Close-up of Fig. 6-15.

Prophylactic measures should include the reduction of perspiration in those sensitive to nickel. Topical corticosteroids applied before exposure to nickel, such as before putting on a wrist band, may be successful. Clasps and other objects are available in plastic material so that some of the exposure to nickel may be decreased. Polyurethane varathane 91 (Flecto) applied in three coats will give protection for several months. Treatment of nickel dermatitis consists of the application of topical corticosteroid creams, sprays, or lotions.

Hand eczema in nickel-sensitive patients has been aggravated by orally ingested nickel in the diet. In severe, treatment-resistant dermatitis a specific low-nickel diet may be tried.

Chromium

The chromates are strongly corrosive and irritating to the skin: they may act as primary irritants or as sensitizers to produce allergic contact dermatitis. Aside from occurrence among employees in chromate works, chrome dermatitis is encountered among tanners, painters, dyers, photographers, polishers, welders, aircraft workers, diesel engine workers, and those involved with the bleaching of crude oils, tallows, and fats. Traces of dichromates in shoe leather and gloves may cause eczema of the feet and hands. Many zippers are chromium-plated, and the nickel underneath the plate may be the causative agent. Chromium metal and stainless steel do not produce contact dermatitis; however, several patients with dermatitis in one ear or preauricular area were likely allergic to their cellphone, as they had a positive reaction when tested for potassium dichromate sensitivity.

Zinc chromate paint is a source of dermatitis. Matches, hide glues, chrome alloys, cigarette lighters, and leather hatbands, sandals or camera cases may cause chrome dermatitis. Anticorrosion solutions used for refrigeration and other recirculation systems often contain chromates that produce dermatitis. Most individuals in the cement industry suffering from cement eczema show positive patch tests to dichromates. Cement eczema is often a primary irritant dermatitis complicated by allergic contact dermatitis to the hexavalent chromates. The incidence of cement has decreased significantly over the years, which is believed to be because of the addition of ferrous sulfate, delivery of premixed cement to the job site, and improved education.

The skin changes are multiform, ranging from a mild follicular dermatitis to widespread nodular and crusted eruptions, all being worse on exposed parts. Often they are slow to clear up, lasting from a few weeks to 6 months after contact has ceased. Heavy exposure of industrial workers to chromates may produce chrome ulcers on the backs of the hands and forearms, usually beginning around a hair follicle, or in the creases of the knuckles or finger webs. The hole begins as a small abrasion that deepens and widens as its edges grow thick, eventually forming a conical indolent ulceration. Chrome ulcers may also arise on—and perforate—the nasal septum.

Diagnosis of chrome sensitivity is made by a positive patch test to potassium dichromate in petrolatum. The hexavalent chrome compounds are the most frequent cause of chrome dermatitis since they penetrate the skin more easily than the trivalent form. Both forms are sensitizers. The chromate-sensitive person should avoid zinc chromate paints, chrome-tanned leather, glue, cement, and other chromate-containing objects. Even with avoidance, chromate-induced dermatitis often is persistent.

Mercury

The mercurials may not only act as irritants but also as sensitizers. Mercuric chloride, even in weak solutions (1:1000), is irritating, causing dermatitis chiefly among surgeons, nurses, taxidermists, and those using insecticides; 1:2000 is not irritating. Phenylmercuric salts are used as weed killers and as agricultural fungicides and insecticides. Phenylmercuric salts have wide usage in industrial materials (gelatin waving solutions, glue, sizing, starch pastes, bentonite gels, mildew-proofing). Sensitization dermatitis may appear at the site of exposure to the phenylmercuric salts, on the legs after exposure to weed killers, and also on the hands.

Nitrate of mercury produces irritation. The eruptions are encountered among felt-hat workers and those who do etching, embossing, or art metalwork. The manufacturing of old-style thermometers and barometers, handling of furs, use of amalgams by dentists, fire gilding, and solder used for dry batteries are all common sources of contamination with mercury, causing various eczematous eruptions. Skin previously sensitized to mercury, as may occur with exposure to certain homeopathic cough remedies, may react severely when the sensitized person receives a mercurial compound systemically.

Thimerosal is an allergen that is rarely relevant. Allergy to this compound likely has been caused by exposure during childhood vaccinations and merbromin antiseptic. In general, these patients tolerate repeated vaccinations well. Most individuals are sensitized to the ethymercuric component; however, those who react to the thiosalicylic acid portion develop photodermatitis to piroxicam. Mercury in amalgam dental fillings has been shown in multiple large studies to cause oral lichoid eruptions. The relationship is especially strong when the oral lesion, often with a painful erosion present, is apposed to a gold or amalgam filling. In many cases where sensitivity is proven by patch testing and fillings are replaced, involution of the oral findings occurs.

Cobalt

Cobalt is frequently combined with nickel as a contaminant and patients allergic to cobalt are commonly also allergic to nickel. The metals have similar properties but do not produce cross-reactions. Cobalt dermatitis may occur in those involved in the manufacture of polyester resins and paints, in the manufacture of hard metal used for cutting and drilling tools, and in the manufacture and use of cement. Cobalt dermatitis may also occur in producers of pottery, ceramics, metal alloys, glass, carbides, and pigments. Individuals may be exposed to cobalt in hair dye, flypaper, and vitamin B_{12}. Blue tattoo pigment contains cobalt oxide. Rarely, cobalt chloride may cause nonimmunologic local release of vasoreactive materials, with a local urticarial response.

Arsenic

Arsenic is one of the most common chemical causes of dermatitis in those who mine copper and arsenical ores, and in those coming into contact with the artificial dyes used in wallpaper, eyeshadow, flowers, and chalk. Arsenical compounds are used in dyeing fabrics and domestic articles,

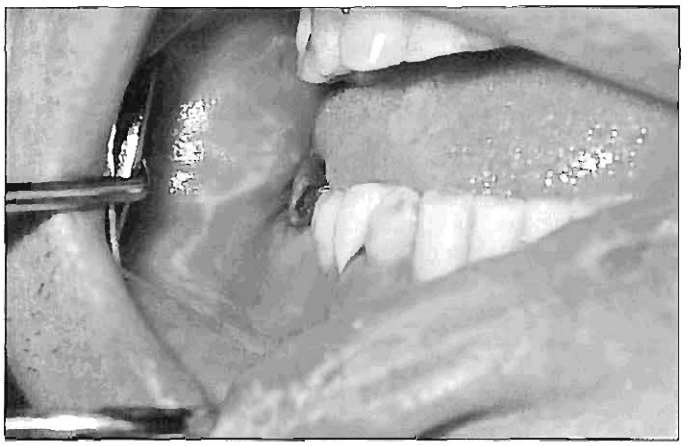

Fig. 6-17 Oral lichen planus caused by gold allergy.

for the preservation of animal skins and hides, and for embalming. Arsenic is an ingredient of some disinfectants and weed killers. It is encountered in the manufacture of insecticides, in chemical factories for the manufacture of sulfuric and other acids, in printing establishments where gilt or bronze powder is used, and in farming and gardening. Among those who may incur this disease in the course of their occupation are glucose and candy factory workers, those who use sizing and dextrin, bookbinders, fruit handlers, furriers who handle raw furs, machinists, and metal workers who handle brass, copper, and zinc.

The dermatitis caused by the arsenicals is frequently a folliculitis with secondary pyoderma. Furunculosis is also common. Ulcerations on the extremities and nasal perforation similar to chrome ulcers may occur.

Gold

Gold dermatitis may rarely occur from the wearing of gold jewelry. A predisposing factor in such patients is the presence of dental gold. Oral lichoid eruptions have also been reported with gold, similar to the situation with mercury-containing amalgams (Fig. 6-17). It is not infrequent to see positive reactions to gold when patch testing patients with facial, eyelid, or widespread dermatitis of unknown cause. Although it is difficult to make a direct clinical correlation with any one piece of jewelry, some patients will clear if they stop wearing all gold jewelry.

A number of cases of dermatitis resulting from gold jewelry, especially gold rings, contaminated with radon and its decay products, have been reported. This may eventuate in radiation dermatitis and squamous cell carcinoma of the finger. Evidently, the source of contaminated gold for the rings had been reclaimed decayed radon gold seeds.

Other Metals

Most other commonly used metals are not important in causing contact dermatitis. Platinum dermatitis may occur from exposure to platinum salts and sprays in industry. Platinum rings, earrings, white gold spectacles, clasps, and other jewelry cause eruptions resembling those caused by nickel. Zinc, aluminum, copper sulfate, titanium, and antimony dermatitis rarely occur; these metals may, however, act as irritants.

Ahlgren C, et al: Contact allergy to gold is correlated to dental gold. Acta Dermatol Berereol 2002;82:41.
Ahnfide I, et al: Exposure to metallic gold in patients with contact allergy to gold sodium thiosulfate. Contact Dermatitis 2000; 43:344.
Audicana MT, et al: Allergic contact dermatitis from mercury antiseptics and derivatives. Am J Contact Dermatitis 2002; 13:3.
Belsito DV: Thimerosal: contact (non)allergen of the year. Am J Contact Dermat 2002;13:1.
Filan FL, et al: Sensitization to palladium chloride. Am J Contact Dermat 2003;14:78.
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Fowler J Jr, et al: Gold allergy in North America. Am J Contact Dermat 2001;12:3.
Freiman A, et al: Patch testing with thirmerosal in a Canadian center. Am J Contact Dermat 2003;14:138.
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Scalf LA, et al: Dental metal allergy in patients with oral, cutaneous, and genital licheoid lesions. Am J Contact Dermat 2001;12:146.
Seishma M, et al: Cellular phone dermatitis with chromate allergy. Dermatology 2003;207:48.
Shah M, et al: Nickel as an occupational allergen. Arch Dermatol 1998;134:1231.
Veien NK, et al: Low nickel diet. J Am Acad Dermatol 1993; 29:1002.
Williams SP: Nickel dermatitis from coins. Contact Dermatitis 1999;40:60.
Wong L, et al: Oral lichenoid lesions and mercury in amalgam fillings. Contact Dermatitis 2003;48:74.

Contact Stomatitis Contact stomatitis may be seen in cases of sensitivity to metals used in dental fillings, to acrylic monomers, epoxy resins, and hardeners used in prosthedontics, dental impression materials, and to topical therapeutic drugs. Some of the metals known to produce stomatitis include mercury, bismuth, chromium, nickel, gold, copper, and zinc. Chewing gums and dentifrices may also produce contact stomatitis. Ingredients responsible for this are hexylresorcinol, thymol, dichlorophen, oil of cinnamon, and mint.

The role of contact allergy in oral symptomatology is significant. Approximately 30% of patients with oral symptoms will have relevant allergens; these are most commonly metals, food additives (flavorings and antioxidants), and dental products.

Clinical signs may be bright erythema of the tongue and buccal mucosa with scattered erosions. Angular cheilitis may also develop. Oral lichenoid lesions may be caused by sensitization to mercury in amalgam fillings. Usually these lesions are adjacent to the dental restoration and patients are patch-test positive to mercury.

Dawn G, et al: Dental veneers fitting: a cause for reactions to epoxy resin and BIS-GMA. Clin Exp Dermatol 2003;28:447.
Kanerva L, et al: A multicenter study of patch test reactions with dental screening series. Am J Contact Dermat 2001;12:83.
Koch P, et al: Oral lesions and symptoms related to metals used in dental restorations. J Am Acad Dermatol 1999;41:422.
Lim SW, et al: Epidemiology of eczematous cheilitis at a tertiary dermatological referral centre in Singapore. Contact Dermatitis 2000;43:322.

Shah M, et al: Contact allergy in patients with oral symptoms. Am J Contact Dermat 1996;7:146.
Tosti A, et al: Contact and irritant stomatitis. Semin Cutan Med Surg 1997;16:314.

Rubber Dermatitis Rubber dermatitis generally occurs on the hands from wearing rubber gloves (surgeons, nurses, homemakers) (Fig. 6-18). The eruption is usually sharply limited to the gloved area but may spread up the forearms. Rubber dermatitis also develops from exposure to condoms, diaphragms, swim goggles, caps and scuba masks, respirators, gas masks, rubber sheets, and cosmetic sponges. Shoe dermatitis may be caused by rubber allergy to insoles or sneakers (see above).

Natural and synthetic rubbers are used separately or in combination to make the final rubber product. It is the chemicals added in the rubber manufacturing process, most importantly the accelerators and antioxidants, which are the common causes of allergic contact dermatitis. A similar list of additives is present in neoprene, a synthetic rubber. Elastic in underwear is chemically transformed by laundry bleach, such as Clorox, into a potent sensitizing substance. The allergen is permanent and cannot be removed by washing. The offending garments must be thrown out and the use of bleaches interdicted.

Accelerators

During the manufacturing process, chemicals are used to hasten the vulcanization of rubber. Among the numerous chemicals available, tetramethylthiuram disulfide, mercaptobenzothiazole, and diphenylguanidine are frequently used. Tetramethylthiuram disulfide and its analogs, known as disulfiram and thiuram, may produce contact dermatitis when moist skin is exposed to the finished rubber product. In one 10-year study of 636 cases of allergy to rubber additives, thiuram mix was by far the most common sensitizer. Mercaptobenzathiazole is most often the cause in shoe allergy and thiuram in glove allergy.

Antioxidants Antioxidants are used to preserve rubber. Among antioxidants the amine type such as phenyl-α-naphthylamine is most effective. Hydroquinone antioxidants may cause depigmentation of the skin as well as allergic contact dermatitis. A frequent antioxidant sensitizer, propyl *p*-phenylenediamine, is used in tires, heavy-duty rubber goods, boots, and elastic underwear.

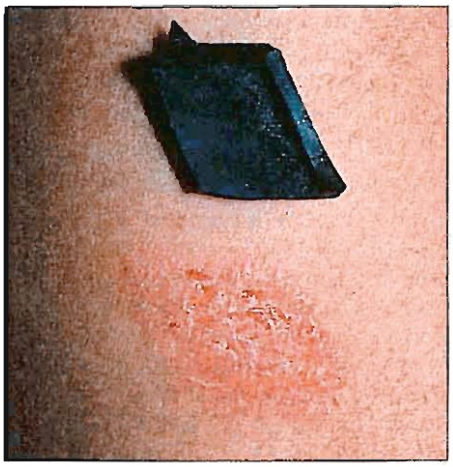

Fig. 6-18 Positive reaction to piece of rubber glove.

Conde-Salazar L, et al: Type IV allergy to rubber additives. J Am Acad Dermatol 1993;29:176.
Gibbon KL, et al: Changing frequency of thiuram allergy in healthcare workers with hand dermatitis. Br J Dermatol 2001; 144:347.
Rich P, et al: Allergic contact hypersensitivity to two antioxidants in latex gloves. J Am Acad Dermatol 1991;24:37.
Woo DK, et al: Neoprene Dermatitis 2004;15:206.

Adhesive Dermatitis Cements, glues, and gums may cause adhesive dermatitis. Formaldehyde resin adhesives contain free formaldehyde, naphtha, glue, and disinfectants. Synthetic resin adhesives contain plasticizers; hide glues may contain chromates from the tanned leather while other glues incorporate preservatives such as formaldehyde. Dental bonding adhesives may contain acrylic monomers and epoxy resins and hardeners. Pressure-sensitive adhesives contain rubber and acrylates, and anaerobic adhesives primarily acrylates.

Vegetable gums, such as gum tragacanth, gum arabic, and karaya, may be used in denture adhesives, hair wave lotions, topical medications, toothpastes, and depilatories, and many cause contact dermatitis. Resins are used in adhesive tapes and in various adhesives such as tincture of benzoin. Compound tincture of benzoin may be a potent sensitizer when applied under occlusion. Turpentine is frequently found in rosin; abietic acid in the rosin is the causative sensitizer.

Adhesive tape reactions are frequently irritant in nature. Allergic reactions to adhesive tape itself are caused by the rubber components, accelerators, antioxidants, and various resins or turpentine (Fig. 6-19). Some adhesive tapes contain acrylate polymers rather than rubber adhesives. These acrylates may cause allergic contact dermatitis. Pressure-sensitive adhesives are in widespread use in the tape and label industries. Allergens present in these adhesives include rosin, rubber accelerators, antioxidants, acrylates, hydroquinones, lanolin, thiourea compounds, and *N*-dodecylmaleamic compounds.

Avenel-Audran M, et al: Contact dermatitis from electrocardiograph-monitoring electrodes: role of *p*-tert-butylphenol-formaldehyde resin. Contact Dermatitis 2003;48:108.

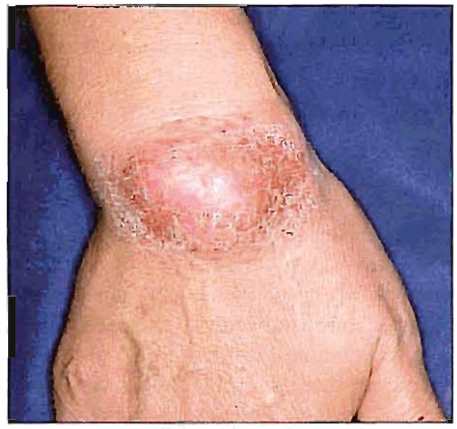

Fig. 6-19 Adhesive dermatitis caused by bandaid used to cover a ganglion cyst.

Brooke RC, et al: A new source of allergic contact dermatitis from UV-cured (meth)acrylate adhesive. Contact Dermatitis 2002;47:179.
Fitzgerald DA, et al: Contact sensitivity to cyanoacrylate nail-adhesive with dermatitis at remote sites. Contact Dermatitis 1995;32:175.
Kanerva L, et al: Patch-test reactions to plastic and glue allergens. Acta Dermatol Venereol 1999;79:296.
Moffitt DL, et al: Occupational allergic contact dermatitis from tetrahydrofurfuryl acrylate in a medical-device adhesive. Contact Dermatitis 2001;45:54.

Synthetic Resin Dermatitis The many varieties of synthetic resins preclude adequate discussion of each. The reactions incurred during the manufacture of these substances are more frequent than those encountered in their finished state.

Epoxy Resins

The epoxy resins in their liquid (noncured, monomene) form may produce severe dermatitis, especially during the manufacturing process. The fully polymerized or cured product is nonsensitizing. Nonindustrial exposure is usually to epoxy resin glues, nail lacquers, and artificial nails. Epoxy resins are used in the home as glues and paints (bathtub and refrigerator). Artists and sculptors frequently use epoxy resins.

Epoxy resins consist of two or more components, the resin and the curing agent. Approximately 90% of allergic reactions are to the resin and 10% to the hardener. There are numerous curing agents such as the amines, phenolic compounds, peroxides, and polyamides. These may be irritants and/or allergens. The resin, based on an acetone and phenol compound known as bisphenol A, in its raw state may cause allergic contact dermatitis. BIS-GMA, a combination of bisphenol A and glycidyl methacrylate, is the main allergen in dental bonding agents. Epoxy resins are used also as stabilizers and plasticizers. Their use in the manufacture of polyvinyl chloride (plastic) film has caused dermatitis from plastic handbags, beads, gloves, and panties.

Polyester Resins

Ordinarily, completely cured or polymerized resins are not sensitizers. The unsaturated polyester resins are dissolved and later copolymerized with vinyl monomers. Such polyester resins are used for polyester plasticizers, polyester fibers (Dacron), and polyester film (Mylar). The unsaturated polyester resins, on the other hand, will produce primary irritation in their fabrication. The dermatitis occurs typically as an eczematous eruption on the back of the hands, wrists, and forearms. Polyester resins are commonly incorporated into other plastic material as laminates to give them strength; applications include boat hulls, automobile body putty, safety helmets, fuel tanks, lampshades, and skylights.

Acrylic Monomers

Multifunctional acrylic monomers may produce allergic or irritant contact dermatitis. Pentaerythritol triacrylate, trimethylolpropane triacrylate, and hexanediol diacrylate are widely used acrylic monomers.

Printers handling multifunctional acrylic monomers in printing inks and acrylic printing plates may present with an erythematous, pruritic eruption, mainly of the hands and arms, swelling of the face, and involvement of the eyelids.

Orthopedic surgeons experience contact dermatitis from the use of acrylic bone cement (methyl methacrylate monomer) used in mending hip joints. Dentists and dental technicians are exposed when applying this to teeth. The sensitizer passes through rubber and polyvinyl gloves and may additionally cause paresthesias. In patients who are allergic to their acrylate dental prosthesis, coating this with UV light-cured acrylate lacquer may allow it to be worn without adverse effects.

Benzoyl peroxide is a popular acne remedy. It is also used for bleaching flour and edible oils, and for curing plastics, such as acrylic dentures. Infrequently, an allergic contact dermatitis may be caused.

el-Azhary RA, et al: Allergic contact dermatitis to epoxy resin in immersion oil for light microscopy. J Am Acad Dermatol 2002; 47:954.
Forschner K, et al: Benzoyl peroxide as a cause of airborne contact dermatitis in an orthopaedic technician. Contact Dermat 2002;46:177.
Kanerva L, et al: Patch-test reactions to plastic and glue allergens. Acta Dermatol Venereol 1999;79:296.
Rademaker M: Occupational epoxy resin allergic contact dermatitis. Australas J Dermatol 2000;41:222.
Scardamaglia L, et al: Compound tincture of benzoin. Austalas J Dermatol 2003;44:180.

Cosmetic Dermatitis Cutaneous reactions to cosmetics may be divided into irritant, allergic hypersensitivity, and photosensitivity reactions. More than half of the reactions occur on the face and are due primarily to skin care products, nail cosmetics, shaving preparations, and deodorants. The leading cause of allergic contact dermatitis associated with cosmetics is from fragrance. A close second is preservatives, such as Bronopol (2-bromo-2-nitropropane-1-3-diol), Kathon CG, quarternium-15, Euxyl K 400, and imidazolidinyl urea. Third is *p*-phenylenediamine in hair dye.

Fragrances

Almost all cosmetic preparations, skin-care products, and many medications contain fragrance; even those labeled nonscented often contain a "masking" fragrance that may be a sensitizer. Even "fragrance-free" products have been documented to contain the raw fragrance ingredients, e.g. rose oil in "all-natural" products. Fragrances are the most common cosmetic ingredient causing allergic contact dermatitis (Fig. 6-20). Photodermatitis, irritation, contact urticaria, and dyspigmentation are other types of reaction they may produce.

The most common individual allergens identified are cinnamic alcohol, oak moss, cinnamic aldehyde, hydroxy citronellal, musk ambrette, isoeugenol, geraniol, coumarin, and eugenol. Frequently, unspecified allergens are the cause as they are not listed on labels and fragrances are combinations of many different ingredients. Balsam of Peru will identify approximately half of those often unsuspected cases of allergic dermatitis, and fragrance mix will identify nearly 86%. Additionally, a natural fragrance mixture of Jasmine absolute, Ylang-ylang oil, narcissus absolute, spearmint oil, and sandalwood oil is recommended. New products should be tested for tolerance in those with a history of fragrance sensitivity.

Fig. 6-20 Fragrance allergy.

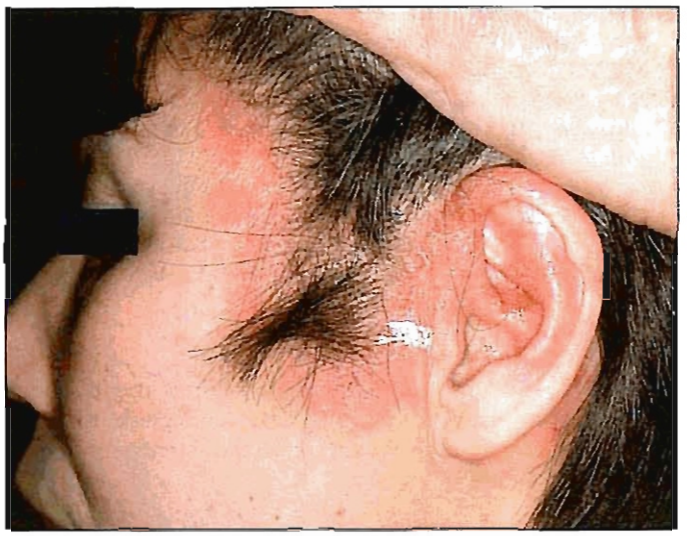

Fig. 6-21 Allergy to *p*-phenylemediamine (PPDA) in hair dye.

One percent of the population is fragrance sensitivity. Women still outnumber men, but as the frequency of fragrance contact reactions has increased over the years, men have shown a steeper increase in sensitivity. Ingestion of balsam-related foods, such as tomatoes, citrus fruits, and spices may flare some sensitive patients. In particular difficult-to-treat patients, balsam-restricted diets may be beneficial but difficult to follow.

Hair Dyes

Permanent hair dyes incorporate *p*-phenylemediamine (PPDA), a popular but potent sensitizer that may cross-react with many chemicals. In rinses and tints the azo dyes, acid violet 6B, water-soluble nigrosine, and ammonium carbonate may sensitize and cross-react with PPDA. Those engaged in the manufacture of PPDA, furriers, hairdressers, and those in the photographic and rubber vulcanization industries develop eruptions at first on the backs of the hands, wrists, forearms, eyelids, and nose, consisting of an eczematous, erythematous, oozing dermatitis. In those whose hair has been dyed, sensitivity is manifested by itching, redness, and puffiness of the upper eyelids, tops of the ears, temples, and back of the neck (Fig. 6-21). Beard dermatitis may be due to coloring of the facial hair. Lichenification and scaling are seen in the chronic type.

For those sensitive to this type of hair dye, use of semipermanent or temporary dyes might be the solution. In the case of sensitivity to the latter, vegetable dyes such as henna may be tried. Metallic dyes are usually not favored by women but are frequently used by men as "hair color restorers." The metallic hair dyes may contain nickel, cobalt, chromium, or lead. A new generation of hair dyes, FD&C and D&C dyes often do not cross-react with PPDA.

Hair Bleaches

Hair bleach products incorporate peroxides, persulfates, and ammonia, which may act as primary irritants. Hair bleaches that contain ammonium persulfate, a primary irritant, may produce a local urticarial and a generalized histamine reaction.

Permanent Wave Preparations

The alkaline permanent wave preparations, which use ammonium thioglycolate, are rarely, if ever, sensitizers, and usually cause only hair breakage and irritant reactions. The hot type, or acid perm, is a common sensitizer, the allergen being glyceryl monothioglycolate. Cosmetologists are at risk for development of hand dermatitis. The glyceryl monothioglycolate persists in the hair for at least 3 months after application and may cause a long-lasting dermatitis. It readily penetrates rubber and vinyl gloves. A more neutral pH newer permanent wave solution is less allergenic than the acid perms; however, allergy to cysteamine hydrochloride found in neutral permanent-wave products may occur. This allergen does not penetrate household-weight latex gloves and hair waved with it does not produce allergic reactions in sensitized individuals. Also, it is an amine salt and not a thioglycolate, so cross-reactivity is unlikely.

Hair Straighteners

The greases and gums are not sensitizers; however, the perfume incorporated in these preparations can be. Thioglycolates are also used, and hair breakage may occur with these products.

Hair Sprays

Shellac, gum arabic, sunscreens, and synthetic resins are sensitizers, and allergic reactions occur infrequently. Lanolin is frequently incorporated into aerosol sprays.

Depilatories

Calcium thioglycolate and the sulfides and sulfhydrates may cause primary irritant dermatitis. Mechanical hair removers are the mercaptans, waxes, and resins. The latter may produce allergic dermatitis.

Hair Tonics and Lotions

Tincture of cinchona produces allergic sensitization; tincture of cantharidin and salicylic acid, primary irritation. Resorcin, quinine sulfate, and perfumes such as bay rum are also sensitizers.

Nail Lacquers

These may contain tosylamide/formaldehyde resin and are a frequent cause of eyelid and neck dermatitis. Polishes free of this resin are available.

Nail Polish Remover
These are solvents such as acetone, which can cause nail brittleness.

Artificial Nails
The acrylic monomers, as well as the ethyl cyanoacrylate glue required to attach the prosthetic nail, may produce allergic sensitivity. Photoinitiating agents, such as benzophenone, used in photobonded acrylic sculptured nails are other potential allergens.

Lipsticks
Various R and C dyes, sunscreens, shellac, flavoring agents, preservative, and lipstick perfumes may cause sensitization reactions. Lipsticks are tested as is.

Eye Makeup
In mascara, eye shadow, and eyeliners, the preservative, shellac, metals, base wax, and perfumes are the components that may produce sensitization, but this occurs rarely. False-positive reactions to some mascaras occur when a closed patch test is used. This is caused by the irritative qualities of the solvents. An open or nonocclusive patch test is recommended. A provocative use test in the antecubital fossae may ultimately be necessary. The rubber sponges used to apply eye makeup also cause eyelid dermatitis.

Sunscreens
p-Aminobenzoic acid (PABA) and its derivatives, such as padimate O, padimate A, and glycerol PABA, and dibenzoylmethanes, salicylates, cinnamates, and benzophenones are photosensitizers as well as sensitizers. If allergy to PABA exists (Fig. 6-22), its derivatives should be avoided and there should be an awareness that thiazides, sulfonylurea antidiabetic medication, azo dyes, *p*-aminosalicylic acid, benzocaine, and *p*-phenylenediamine all may cause dermatitis from cross-reactions. Oxybenzone is the most common sunscreen allergen.

Bleaching Creams
Hydroquinones are occasional sensitizers. Ammoniated mercury is a sensitizing agent formerly used in bleaching creams.

Lanolin
The fatty alcohol lanolin is rarely a sensitizer on normal skin and most cosmetic and skin-care products do not cause dermatitis. It causes allergic reactions more frequently in therapeutic agents used by atopic patients.

Dentifrices and Mouthwashes
Dentifrices and mouthwashes contain sensitizers, such as the essential oils used as flavoring agents, preservatives, formalin, antibiotics, and antiseptics. Beacham et al reported 20 women who developed circumoral dermatitis and cheilitis from tartar-control types of dentifrices.

Axillary Antiperspirants
Aluminum salts, such as aluminum chloride and chlorhydroxide, and zinc salts, such as zinc chloride, act as primary irritants (Fig. 6-23), and may rarely produce a folliculitis. Aluminum chlorhydrate is considered to be the least irritating antiperspirant. Zirconium salt preparations, now removed from all antiperspirants, produced a granulomatous reaction. Zirconium–aluminum complexes have been considered to be nonsensitizing, so they are commonly used as the active ingredient in topical antiperspirants. A patient with cutaneous granulomas from this complex was however reported by Montemarano et al. Quaternary ammonium compounds in some roll-on deodorants may produce allergic contact dermatitis.

Axillary Deodorants and Feminine Hygiene Sprays
Fragrances, bacteriostats, and propellants cause the majority of the reactions seen with these products. Deodorants that contain cinnamic aldehyde can induce irritation on axillary skin even when tolerated on healthy skin in other sites.

Cosmetic Intolerance Syndrome
Occasionally, a patient will complain of intense burning or stinging after applying any cosmetic. Usually there are only subjective symptoms, but objective inflammation may also be present. The underlying cause may be difficult to document, even though thorough patch testing, photopatch testing, and contact urticaria testing are completed. Endogenous disease such as seborrheic dermatitis, rosacea, or atopic dermatitis may complicate the assessment. Avoidance

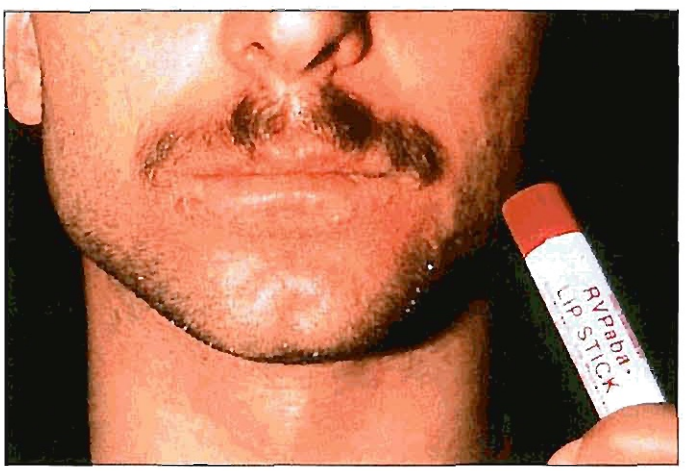

Fig. 6-22 *p*-Aminobenzoic acid (PABA) allergy in lip protectant.

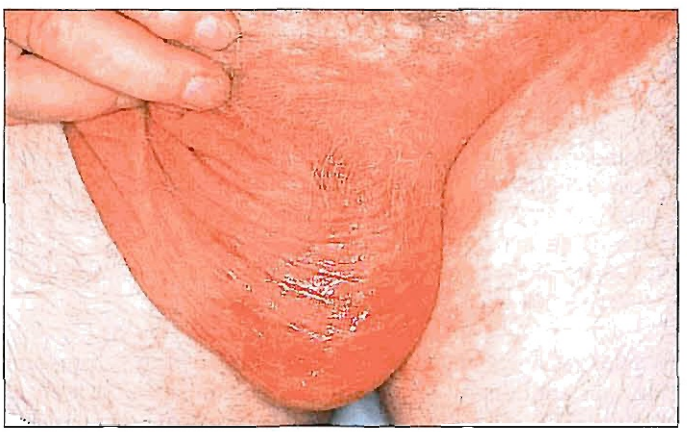
Fig. 6-23 Irritant dermatitis from antiperspirant.

of all cosmetics, with only glycerin being allowed, for 6 to 12 months is often necessary to calm the reactive state. Adding back cosmetics one at a time, no more frequently than one a week, may then be tolerated.

Baran R: Nail cosmetics: allergies and irritations. Am J Clin Dermatol 2002;3:547.
Beacham BE, et al: Circumoral dermatitis and cheilitis caused by tartar control dentifrices. J Am Acad Dermatol 1990;22:1029.
Bruze M, et al: Deodorants. J Am Acad Dermatol 2003;48:194.
Buckley DA, et al: The frequency of fragrance allergy in a patch test population over a 17-year period. Br J Dermatol 2000; 142:279.
Chan YC, et al: Positive patch-test reactions to PPDA, their clinical relevance and the concept of clinical tolerance. Contact Dermatitis 2001;45:217.
Francalanci S, et al: Multicentre study of allergic contact cheilitis from toothpastes. Contact Dermatitis 2000;43:216.
Frosch PJ, et al: Further important sensitizers in patients sensitive to fragrances. Contact Dermatitis 2002;47:78.
Hausen BM: Contact allergy to balsma of Peru. Am J Contact Dermat 2001;12:93.
Hsu TS, et al: Beard dermatitis due to PPDA use in Arabic men. J Am Acad Dermatol 2001;44:867.
Katsarou A, et al: Contact reactions to fragrances. Ann Allergy Asthma Immunol 1999;82:449.
Kohl L, et al: Allergic contact dermatitis from cosmetics. Dermatology 2002;204:334.
Landers MC, et al: Permanent wave dermatitis. Am J Contact Dermat 2003;14:157.
Larsen WG, et al: Fragrance testing in the 21st century. Contact Dermatitis 2002;47:60.
LeCoz CJ, et al: Allergic contact dermatitis to shellac in mascara. Contact Dermatitis 2002;46:149.
Lunder T, et al: Increase in contact allergy to fragrances. Contact Dermatitis 2000;43:107.
Montemarano AD, et al: Cutaneous granulomas caused by an aluminum–zirconium complex. J Am Acad Dermatol 1997; 37:496.
Sainio EL, et al: Metals and arsenic in eye shadows. Contact Dermatitis 2000;42:5.
Salam TN, et al: Balsam-related systemic contact dermatitis. J Am Acad Dermatol 2002;45:377.
Schauder S, et al: Contact and photocontact sensitivity to sunscreens. Contact Dermatitis 1997;37:221.
Scheinman PL: Allergic contact dermatitis to fragrance. Am J Contact Dermat 1996;7:65.
Scheinman PL: Is it really fragrance-free? Am J Contact Dermat 1997;8:239.
Thomson KF, et al: Allergic contact dermatitis to plant extracts in patients with cosmetic dermatitis. Br J Dermatol 2000; 142:84.
Trummer M, et al: Clinical relevance of positive patch test reactions to lanolin alcohol. Contact Dermatitis 2002;46:118.
Valks R, et al: Contact dermatitis in hairdressers, ten years later. Dermatitis 2005;16:28.
Wolf R, et al: Contact dermatitis to cosmetics. Dermatol Clin 2001;19:501.

Preservatives Preservatives are added to any preparation that contains water to kill microorganisms and prevent spoilage. The most important class is formaldehyde and the formaldehyde-releasing compounds, including quaternium-15 (the leading preservative sensitizer in the US; Fig. 6-24), imidazolidinyl urea, diazolidinyl urea, DMDM hydantoin, and 2-bromo-2 nitropropane-1,3-diol. Kathon CG or methylchloroisothia-zolinone/methyl isothiazolinone (MCI/MI) and Euxyl K 400 (methyldibromoglutaronitrile and phenoxyethanol in a 1:4 ratio) are other important preservative allergens. In the latter it is the methyldibromoglutaronitrile component that produces the allergic response. Thimerosal, discussed above, and parabens are other preservatives that may cause allergy.

Formaldehyde and Formaldehyde-Releasing Agents

Formaldehyde is used rarely, primarily in shampoos. Because it is quickly diluted and washed away, sensitization through this exposure is rare. Formaldehyde releasers are polymers of formaldehyde that may release small amounts of formaldehyde under certain conditions. Allergy may be to the formaldehyde-releasing preservatives (which act as antibacterial and antifungal agents in their own right) and/or to the released formaldehyde.

Parabens

Allergic contact dermatitis may develop from parabens, which are used in cosmetics, foods, drugs, dentifrices, and suppositories. The paraben esters (methyl, ethyl, propyl, and butyl *p*-hydroxybenzoates) are used in low concentrations in cosmetics and rarely cause dermatitis. They are found in higher concentration in topical medicaments and may be the

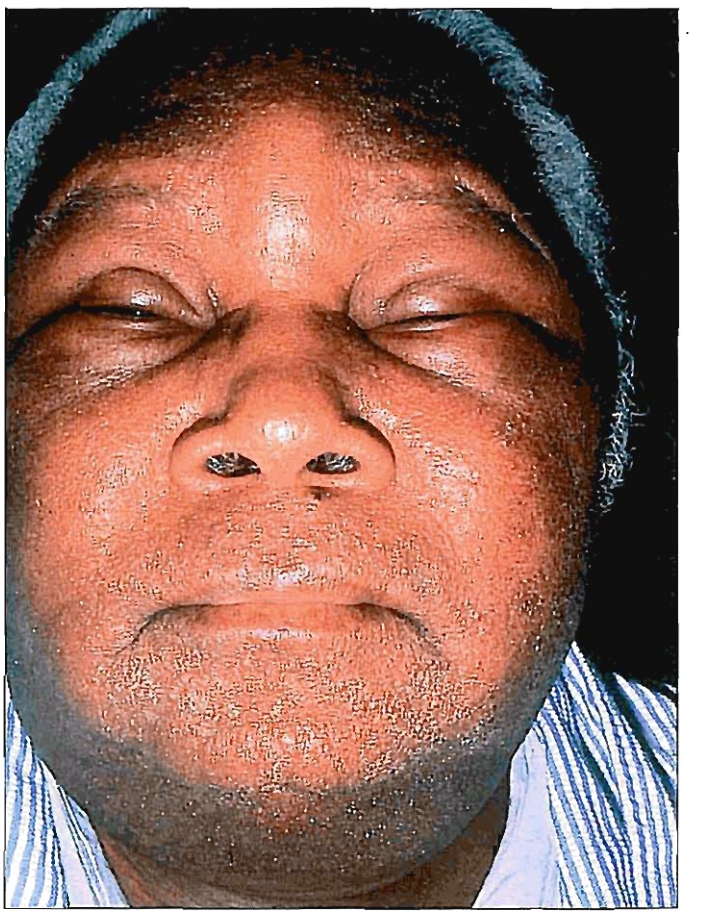

Fig. 6-24 Allergy to quaternium-15 in moisturizer.

cause of allergic reactions. Perpetuation of a dermatitis, despite effective topical medication, suggests the possibility of paraben or corticosteroid sensitivity, or that another sensitizer may be present. Parabens, which are frequently used as bacteriostatic agents, are capable of producing immunologically-mediated immediate systemic hypersensitivity reactions.

p-Chloro-Meta-Xylenol (PCMX)

This chlorinated phenol antiseptic is used in many over-the-counter products with the disinfectant properties of *p*-chloro-metacresol. Sensitization occurs primarily through exposure to betamethasone-containing cream. There is cross-reactivity to *p*-chloro-metacresol.

Sorbic Acid

While a rare sensitizer, it is a cause of facial flushing and stinging through its action as an inducer of nonimmunologic contact urticaria.

Cashman AL, et al: Parabens. Dermatitis 2005;16:57.

Guin JD, et al: Baby-wipe dermatitis. Am J Contact Dermat 2001;12:189.

Gruvberger B: Methylisothiazolinones. Acta Dermatol Venereol 1997;200(Suppl):1.

Jackson JM, et al: Methyldibromoglutaronitrile. J Am Acad Dermatol 1998;38:934.

Mowad CM: Methylchloroisothiazolinone revisited. Am J Contact Dermat 2000;11:115.

Patrizi A, et al: Allergic contact dermatitis caused by sorbic acid. Am J Contact Dermat 1999;10:52.

Skinner SL, et al: Allergic contact dermatitis to preservatives in topical medicaments. Am J Contact Dermat 1998;9:199.

Zachariae C, et al: Methyldibromoglutaronitrile. Contact Dermatitis 2003;48:150.

Vehicles Formulation of topically applied products is complex and additives are blended to make a pleasing base for carriage of the active ingredient to the skin. Various emulsifiers, humectants, stabilizers, surfactants, and surface active agents are used to make esthetically pleasing preparations. These may cause irritation, erythema, and allergy. The surfactant cocamidopropyl betaine produces dermatitis of the head and neck, often due to its presence in shampoos.

Propylene Glycol

Propylene glycol is widely used as a vehicle for topical medications, cosmetics, and various emollient lotions. It is used in the manufacture of automobile brake fluid and alky resins, as a lubricant for food machinery, and as an additive for food colors and flavoring agents. It is commonly used in antiperspirants. Propylene glycol must be considered as a sensitizer able to produce contact dermatitis, and it can cause a flare of the contact dermatitis when ingested. It is tested as a 4% aqueous solution, but irritant reactions or false negatives are common. A use test of the implicated propylene glycol-containing products may be required.

Ethylenediamine

Ethylenediamine is used as a stabilizer in medicated creams. It may cause contact dermatitis and cross-react with internally taken aminophylline, which consists of theophylline and ethylenediamine. Ash et al reported a patient with a generalized itchy, red eruption that recurred each time hydroxyzine was taken orally. Hydroxyzine is a piperazine derivative that is structurally based on a dimer of ethylenediamine, to which patients sensitive to the stabilizer may develop a generalized itchy, red eruption that recurs each time hydroxyzine is taken orally.

Ash S, et al: Systemic contact dermatitis to hydroxyzine. Am J Contact Dermat 1997;8:2.

Fowler JF Jr: Cocamidopropyl betaine. Dermatitis 2004;15:3.

Lamb SR, et al: Contact allergy to propylene glycol in brassiere padding inserts. Contact Dermatitis 2003;48:225.

Pereira F, et al: Contact dermatitis due to emulsifiers. Contact Dermatitis1997;36:114.

Topical Drug Contact Dermatitis Drugs, in addition to their pharmacologic and possible toxic action, also possess sensitizing properties. Sensitization may not only occur from topical application but also from ingestion. Some, such as the antihistamines, including topical doxepin, sensitize much more frequently when applied topically than when taken orally. With the advent of transdermal patches for delivery of medications such as nitroglycerin, hormones, nicotine, clonidine, fentanyl, and scopolamine reports of sensitization are increasing (Fig. 6-25). Clonidine induces the highest rate of allergic reactions. At times erythema multiforme-like reactions may occur with transdermally applied drugs.

Some drugs may produce sensitization of the skin when applied topically; if the medication is later taken internally an acute flare at the site of the contact dermatitis may result. This so-called anamnestic (recalled) eruption or systemic contact dermatitis can occur with antihistamines, sulfonamides, and penicillin. The same is true of the local anesthetic ointments containing "caine" medications. Usually, if sensitization occurs when using transdermal patches, the drugs do not cause systemic contact dermatitis when taken orally.

Although it is impossible to mention all topical medications that cause irritation or allergic contact dermatitis, some are important enough to be dealt with individually.

Local Anesthetics

Physicians and dentists may develop allergic contact dermatitis from local anesthetics. In addition, the continued use of these local anesthetics as antipruritic ointments and

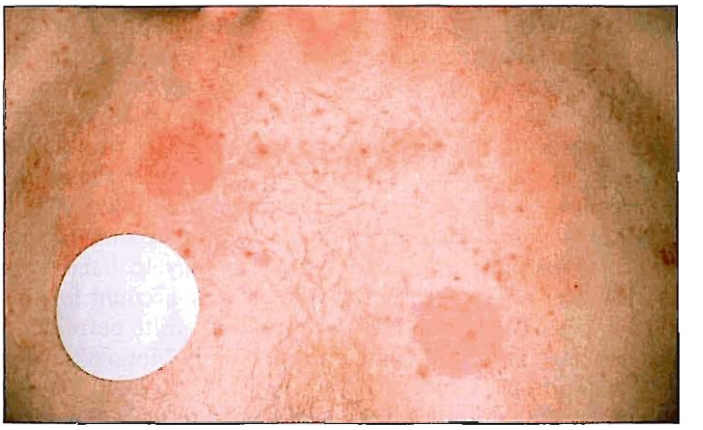

Fig. 6-25 Nitroglycerin patch allergy.

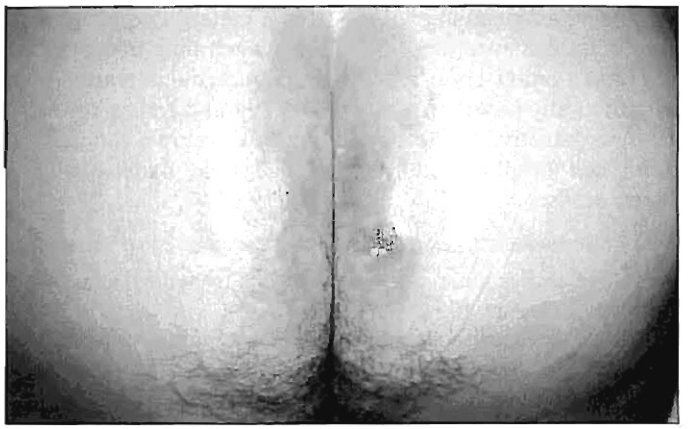

Fig. 6-26 Benzocaine allergy.

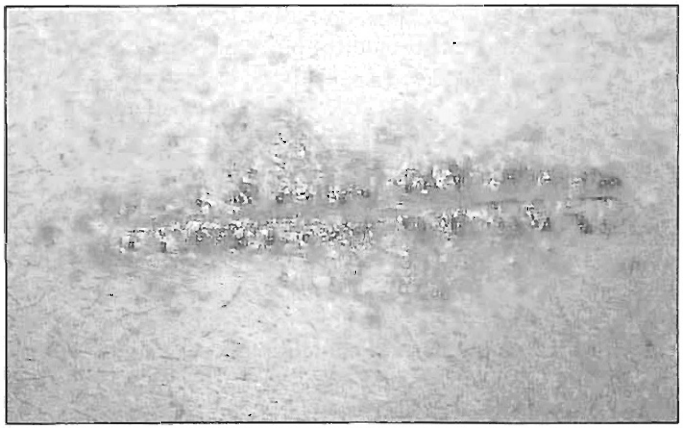

Fig. 6-27 Bacitracin allergy in surgical scar.

lotions causes sensitization of the skin. Benzocaine is a frequently used topical antipruritic and is the most common topical sensitizer of this group. Itchy dermatitis of the anogenital area may be due to a topically applied anesthetic (Fig. 6-26).

Local anesthetics may be divided into two groups: the first includes the *p*-aminobenzoic acid esters, such as benzocaine, butethemine, chloroprocaine, procaine (Novacaine), and tetracaine (Pantocaine); the second, which sensitizes much less frequently, includes the amides, such as dibucaine (Nupercainal), lidocaine (Lido-Mantle, EMLA, Lidoderm patch, LMX, Xylocaine), mepivacaine (Carbocaine), and prilocaine (Citanest). In addition, the preservative methylparaben, frequently found in these prepared solutions, may cause hypersensitivity reactions that can easily be misattributed to the local anesthetics. It should be kept in mind that numerous cross-reactions are seen in benzocaine-sensitive individuals. These are discussed in the section on sunscreens.

Antimicrobials

Physicians, dentists, nurses, and other medical personnel, as well as patients, may develop contact dermatitis from various antibiotics. Neomycin is a common sensitizer. As a topical antibiotic, neomycin sulfate has been incorporated into innumerable ointments, creams, and lotions. It is present in such preparations as underarm deodorants, otic and ophthalmologic preparations, and antibiotic creams and ointments available without prescription. The signs of neomycin sensitivity may be those of a typical contact dermatitis but are often those of a recalcitrant skin eruption that has become lichenified and even hyperkeratotic. This may be because many of the topical agents contain several types of antibiotics but also often have corticosteroids present. This picture may be seen in persistent external otitis, lichen simplex chronicus of the nuchal area, or dermatophytosis between the toes. A late-appearing reaction on patch testing is not uncommon, so an assessment at day 7 is recommended.

There has been a dramatic rise in allergy to bacitracin. Its use after minor surgical procedures may account for this (Fig. 6-27). After clean surgical procedures white petrolatum is as effective in aiding wound healing as antibiotic ointment and of course does not carry the allergenic potential. There is a high rate of coreaction (not cross-reaction) with neomycin because of simultaneous exposures. Contact urticaria and anaphylaxis are reported more often with bacitracin than with other antibiotics.

Allergic dermatitis of the fingertips caused by streptomycin may be encountered in nurses who prepare this infrequently used drug for injection. The dermatitis may become chronic, with eczematization and fissuring. Cross-reactivity to neomycin, gentamicin, and kanamycin may occur.

Antifungal Agents

Allergic contact dermatitis to imidazole and other antifungal agents may occur. There is a high cross-reactivity rate between miconazole, isoconazole, clotrimazole, and oxiconazole because of their common chemical structure.

Phenothiazine Drugs

Handling injectable solutions and tablets may produce dermatitis in those sensitized to chlorpromazine and other phenothiazine derivatives. The reactions may be photoallergic or nonphotoallergic.

Corticosteroids

Numerous reports of large series of patients who have developed allergy to these commonly used preparations emphasize the need for a high index of suspicion when treating patients with chronic dermatitis who fail to improve, or who worsen, when topical steroidal agents are used. Once sensitized to one type of corticosteroid cross-sensitization may occur. The corticosteroids have been separated into four structural classes: class A is the hydrocortisone, tixicortol pivalate group; class B is the triamcinolone acetonide, budesonide group; class C is the betamethasone group; and class D is the hydrocortisone-17-butyrate group. There are frequent cross-reactions between classes B and D. Tixicortol pivalate and budesonide have been found to be the best screen for such reactions, finding 93% of steroid allergies. In the absence of having these agents, patch testing to the implicated product with a reading at day 4 may be useful. An empiric trial of desoximetasone (Topicort) or mometasone (Elocon) in the absence of patch testing will give the best chance of selecting a topical steroid with an extremely low chance of sensitization.

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Occupational Contact Dermatitis

Workers in various occupations are prone to contact dermatitis from primary irritants and allergic contactants. In certain occupations it is a common occurrence. Irritant contact dermatitis is more frequent in the workplace, but it tends to be less severe and less chronic than allergic contact dermatitis. Occupational skin disease has declined over the past 30 years but still constitutes approximately 10% of all occupational disease cases. Agriculture, forestry, and fishing have the highest incidence of occupational skin disease, with the manufacturing and healthcare sectors contributing many cases as well.

Irritant contact dermatitis is commonly present in wet-work jobs, and allergy occurs in hairdressers, machinists, and many others with unique exposures to multiple sensitizing chemicals. The hands are the parts most affected, being involved in 60% of allergic reactions and 80% of irritant dermatitis. Epoxy resin is an allergen overrepresented when evaluating occupational patients, while the allergens most frequently encountered in occupational cases are carba mix, thiuram mix, epoxy resin, formaldehyde, and nickel.

Management

Occupational contact dermatitis is managed by eliminating contact of the skin with irritating and sensitizing substances. The work environment should be carefully controlled, with use of all available protective devices to prevent accidental and even planned exposures. Personal protective measures, such as frequent clothing changes, cleansing showers, protective clothing, and protective barrier creams should be used as appropriate. Hand cleansing procedures should be thoroughly surveyed, with particular attention paid to the soaps available and also what solvents may be used.

Treatment of the dermatitis follows closely that recommended for toxicodendron dermatitis. Topical corticosteroid preparations are especially helpful in the acute phase. For dry, fissured hands, soaking them in water for 20 min at night followed immediately upon removing (without drying them) with triamcinolone 0.1% ointment will help to hydrate and heal them. Topical tacrolimus ointment and pimecrolimus cream may assist in maintenance therapy. When rubber and polyvinyl gloves cannot be used against irritant and allergenic substances, skin protective creams may offer a solution, although they are often impractical. A wide variety is available, but two main types are used: one is for "wet work"—to protect against acids, alkalis, water-base paints, coolants, and cutting oils with water; and the other type is for "dry work"—to protect against oils, greases, cutting oils, adhesive, resins, glues, and wood preservatives.

Unfortunately, despite the best efforts at treatment and prevention the prognosis for occupational skin disease is guarded. One-third to one-quarter heal, another one-third to one-half improve, with the remainder the same or worse. A change or discontinuance of the job does not guarantee relief, as many individuals continue to have persistent post-occupational dermatitis. The importance of thorough patient education cannot be overemphasized. Atopics, males with chromate allergy, females with nickel allergy, those with a delay in diagnosis before institution of treatment, and construction industry workers fare the worst, while irritation from metalworking fluids, reactions to urushiols in foresters, and allergic contact dermatitis to acrylic monomers or amine-curing agents is usually short-lived.

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Contact Urticaria

Contact urticaria may be defined as a wheal and flare reaction occurring when a substance is applied to the intact skin. Urticaria is only one of a broad spectrum of immediate reactions, including pruritus, dermatitis, local or general urticaria, bronchial asthma, orolaryngeal edema, rhinoconjunctivitis, gastrointestinal distress, headache, or an anaphylactic reaction. Any combination of these is subsumed under the expression "syndrome of immediate reactions."

It may be nonimmunologic (no prior sensitization), immunologic, or of unknown mechanism. The nonimmunologic type is the most common, and may be caused by direct release of vasoactive substances from mast cells. The allergic type tends to be the most severe, as anaphylaxis is possible. The third type has features of both.

Nonimmunologic Mechanism

This type of reaction occurs most frequently and may produce contact urticaria in almost all exposed individuals. Examples of this type of reaction are seen with nettle rash (plants), dimethyl sulfoxide (DMSO), sorbic acid, benzoic acid, cinnamic aldehyde, cobalt chloride, and Trafuril.

Immunologic Mechanism

This reaction is of the immediate (IgE-mediated)-hypersensitivity type. Latex, potatoes, phenylmercuric propionate, and many other allergens have been reported to cause this.

Uncertain Mechanism

This type of reaction occurs with those agents that produce contact urticaria and a generalized histamine type of reaction but lack a direct or immunologic basis for the reaction.

Substances Causing Contact Urticaria

Many different substances can elicit such a reaction. It is seen in homemakers and food handlers who handle raw vegetables, raw meats and fish, shellfish, and other foods. Raw potatoes have been shown to cause not only contact urticaria but also asthma at the same time. It has been seen in hairdressers who handle bleaches and hair dyes containing ammonium persulfate, in whom the contact urticaria is accompanied by swelling and erythema of the face, followed by unconsciousness. Caterpillars, moths, and hedgehogs may cause contact urticaria just by touching the skin.

Additional substances inducing this reaction are oatmeal, flour, meat, turkey skin, calf liver, banana, lemon, monoamylamine, benzophenone, nail polish, tetanus antitoxin, streptomycin, cetyl alcohol, stearyl alcohol, estrogenic cream, cinnamic aldehyde, sorbic acid, benzoic acid, castor bean, lindane, carrots, spices, wool, silk, dog and cat saliva, dog hairs, horse serum, ammonia, sulfur dioxide, formaldehyde, acrylic monomers, exotic woods, wheat, cod liver oil, and aspirin.

Bacitracin ointment may cause anaphylactic reactions when applied topically, especially to chronic leg ulcer and dermatitis; however; it may rarely occur after acute wounds (Fig. 6-28).

Universal precautions led to a marked increase not only in delayed-type hypersensitivity reaction to rubber additives, but also to a large number of reports of contact urticaria and anaphylaxis to latex. Most of these reactions occur in health professionals. Reaction is characterized by itching and swelling of the hands within a few minutes after donning the gloves (Fig. 6-29), and will usually resolve within an hour after removing them. In patients with continued exposures the eruption may eventually appear as chronic eczema. Glove powder may aerosolize the allergen and produce more generalized reactions. While these reactions may occur on the job, many cases present as death or near-death events when sensitized individuals undergo operations or other procedures, especially when there is mucosal exposure (dental care, rectal examination, childbirth).

In addition to healthcare workers, who have a reported incidence of between 3% and 10%, atopics and spina bifida patients are other risk groups for the development of type I allergy to latex protein. The sensitized individual should also be aware that up to 50% of them will have a concomitant fruit allergy to foods such as banana, avocado, kiwi, chestnut, and passion fruit.

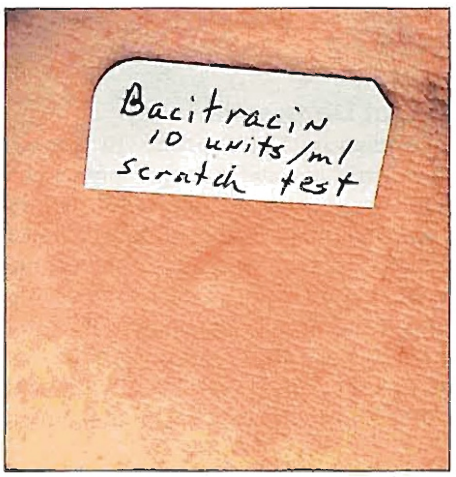

Fig. 6-28 Positive scratch test to dilute bacitracin.

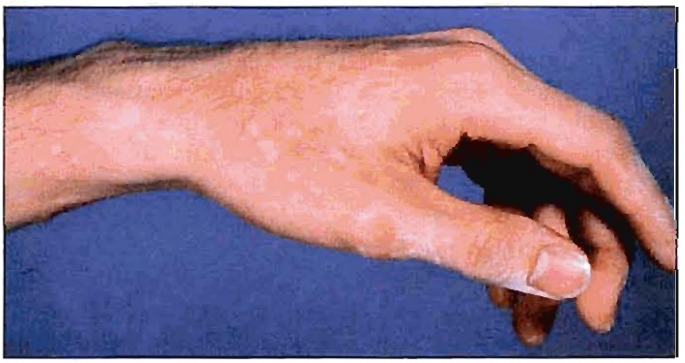

Fig. 6-29 Contact urticaria to rubber in gloves. (Courtesy of Arto Lahti MD, Dept of Dermatology Oulu University Hospital, Finland)

Testing

The usual closed patch tests do not show sensitivity reactions. Instead, open patch tests are performed for eliciting immediate-type hypersensitivity. The substance is applied to a 1-cm^2 area on the forearm and observed for 20 to 30 min for erythema that can evolve into a wheal and flare response. When foods are tested, a small piece of the actual food is placed on the skin. Rubber glove testing can be done by applying one finger of a latex glove to a moistened hand for 15 min. If no reaction is observed, the entire glove is worn for another 15 to 20 min. Radioallergosorbent testing (RAST) detects 75% of latex-allergic individuals. There is no standard allergen available for prick testing.

Prick, scratch or intradermal testing is resorted to only when there are problems of interpretation of the open patch tests. These tests have produced anaphylactic reactions and should only be attempted when support for this complication is available.

Management

Avoidance of the offending substance is best, but if this is not possible, antihistamines such as hydroxyzine hydrochloride, are of benefit. If generalized urticaria or asthmatic reactions occur then systemic glucocorticoids are best. For anaphylaxis, epinephrine and supportive measures are needed.

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DRUG REACTIONS

Epidemiology

Adverse drug reactions are a common cause of dermatologic consultation. In a large French study, about 1 in 200 inpatients on medical services developed a drug eruption, as compared to 1 in 10,000 on surgical services. In the US, similar studies have shown a reaction rate of 2 to 3 in 100 for medical inpatients. In only about 55% of patients who were carefully evaluated was it possible to definitely attribute a specific medication as the cause of the eruption. Simple exanthems (75–95%) and urticaria (5–6%) account for the vast majority of drug eruptions. Females are 1.3 to 1.5 times more likely to develop drug eruptions, except in children under the age of 3 where boys are more likely affected. Not all drugs cause reactions at the same rate. Aminopenicillins cause drug eruptions in between 1.2% and 8% of exposures, and the combination of trimethoprim–sulfamethoxazole at a rate of 2.8% to 3.7%. Nonsteroidal anti-inflammatory drugs (NSAIDs) have a reaction rate of about 1 in 200. In contrast, reaction rates for digoxin, lidocaine, prednisone, codeine, and acetaminophen are less than 1 in 1000. For some reaction patterns, the dose of the medication may also be a cofactor in the risk of developing a drug eruption.

The risk for development of a drug eruption is determined only in part by the above factors: age, gender, dose, and the nature of the medication itself. In addition, the immune status and genetic make-up of the patient strongly determine the risk of developing certain drug eruptions. For example, patients with human immunodeficiency virus (HIV) infection and Epstein-Barr virus (EBV) infection have dramatically increased rates of exanthematous reactions to certain antibiotics. Hypersensitivity syndromes from multiple drug classes have been associated with reactivation of latent viral infections, primarily human herpes virus (HHV)-6, but also EBV and cytomegalovirus. In addition, the status of the immune system, as measured by helper T-cell count in the case of HIV, defines a window of immune dysfunction in which this enhanced risk for adverse drug reactions occurs. Certain hypersensitivity syndromes are closely associated with genetic differences in the ability of the patient to metabolize a specific medication or a toxic metabolite of the medication. Therefore, drug eruptions are not simply drug "allergy," but result from variations in drug metabolism, immune status, coexistent viral disease, and the inherent chemical structure (allergenicity) and dosage of the medication itself (see below).

Evaluation

Three basic rules should always be applied in evaluating the patient with a suspected drug reaction. First, the patient is probably on unnecessary medications, and all of these should be stopped. Pare down the medication list to the bare essentials. Secondly, the patient must be asked about non-prescription medications and pharmaceuticals delivered by other means (eye drops, suppositories, implants, injections, and patches). Thirdly, no matter how atypical the patient's cutaneous reaction, always consider the patient's medication as a possible cause. In patients with unusual reactions, searching the medical literature and calling the manufacturer for prior reports may be very useful.

The first step in evaluating a patient with a potential drug reaction is to diagnose the cutaneous eruption by clinical pattern (e.g. urticaria, exanthem, vasculitis, erythema multiforme, etc.). In determining whether the patient's current eruption could be related to a specific medication, two basic questions should be asked. Which of this patient's medications cause this pattern of reaction? How commonly does this medication cause this reaction pattern? Bigby reviewed how to use this information to make clinical decisions about stopping possible reaction-inducing medications. A regularly

updated manual (such as Litt) or similar databases on the worldwide web are strongly recommended as ready reference sources for this information. An algorithm by which the likelihood can be evaluated of a certain medication causing a particular reaction has been developed. This algorithm, summarized below, can be used as a framework for the evaluation of a given patient:

1. Previous general experience with the drug: Has the suspected medication been reported to cause the reaction the patient is experiencing? If so, how commonly? Also ask the patient if he/she has had a previous reaction to any medications, as the current eruption may represent a cross-reaction from a prior exposure.
2. Alternative etiologic candidates: What are other possible causes of the patient's eruption? An exanthem, for instance, could be related to an associated viral illness, not the medication.
3. Timing of events: When did the eruption appear relative to the administration of the suspected medication? A detailed history from the patient and a careful review of the patient record, including the nursing notes, are useful to establish the chronologic sequence of all drug therapy.
4. Drug levels and evidence of overdose: Certain reactions are known to be related to rate of administration (vancomycin red man syndrome) or cumulative dose (lichenoid reactions to gold).
5. Response to discontinuation (dechallenge): Does the eruption clear when the suspected medication is stopped? Because certain eruptions may clear in the face of continuation, this is a useful, but not irrefutable criterion to ascribe a specific reaction to a medication.
6. Rechallenge: If the offending medication reproduces the reaction on readministration, this is strong evidence that the medication did indeed cause the reaction. Reactions associated with an increase in dosage may also be considered in this category. In certain reaction patterns (e.g. exanthems) even a fraction of the original dose may reproduce the reaction. It may be impossible to rechallenge if the reaction was severe.

In addition to the clinical evaluations noted above, complete evaluation may include special testing for confirmation. Skin testing is most useful in evaluating type I (immediate) hypersensitivity. It is most frequently used in evaluating adverse reactions to penicillin, local anesthetics, insulin, and vaccines. RAST tests have a 20% false-negative rate in penicillin type I allergy, so they must be followed by skin testing. In their current form, RAST tests cannot replace skin testing. Intradermal, prick skin, and patch testing are also reported to be beneficial in some cases of morbilliform reactions or fixed drug reaction. The patient's metabolism of certain drugs in lymphocytotoxicity assays may be associated with an adverse reaction. Such testing is commercially available, but is expensive, time consuming, and its value limited to certain situations such as anticonvulsant or sulfonamide hypersensitivity reactions.

The patient should be given concrete advice about his/her reaction. What was the probability the patient's reaction was caused by the medication? Can the patient take the medication again, and if so, what may occur? What cross-reactions are known? What other medications must the patient avoid? Unusual reactions should be reported to regulatory agencies and the manufacturer.

Pathogenesis

In most patterns of drug reactions, the pathogenesis is unknown. Classic immune mechanisms do not appear responsible for most adverse drug reactions. However, the rapid reappearance of many reactions on re-exposure strongly suggests immunologic memory. In some cases drug eruptions may result from normal pharmacologic effects of the medication (e.g. urticaria worsening with aspirin or beta-blockers). Reactions may be truly immunologic, based on an immune response by the patient to the medication or a metabolite. IgE antibodies to penicillin causing urticaria is an example. The patient's genetically determined metabolism of the medication may determine the likelihood of a reaction occurring. Slow acetylators of certain drugs appear to be at increased risk to develop adverse drug reactions. In the case of anticonvulsant and sulfonamide hypersensitivity syndromes, reactive and potentially toxic metabolites of the medication may bind to proteins and stimulate an immunologic reaction. Affected individuals appear to be more susceptible to these toxic metabolites by in vitro testing. In sulfonamide hypersensitivity reactions, the immunologic target may be normal or drug-altered proteins in the endoplasmic reticulum to which active sulfonamide metabolites bind, rather than the medication itself. If this is confirmed, it might explain the long duration of hypersensitivity syndromes once the medication is stopped. Family members of individuals suffering a hypersensitivity syndrome demonstrate similar sensitivities to toxic drug metabolites, and this susceptibility is linked to HLA subtypes. In addition, the patient's immune status and clinical condition may influence the rate of adverse reactions, e.g. the increased rate of drug reactions in AIDS patients.

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Clinical Morphology

Cutaneous drug reactions will initially be discussed by their morphologic pattern. In addition to the cutaneous eruption, some reactions may be associated with other systemic symptoms or findings. The modifier "simple" is used to describe reactions without systemic symptoms or internal organ involvement. "Complex" reactions are those with systemic findings. Complex reactions are also called "hypersensitivity syndromes," since the ancillary features of complex reactions are often a characteristic syndrome of findings (e.g. an infectious mononucleosis-like picture with anticonvulsant hypersensitivity reactions). Complex reaction is synonymous with "drug eruption with eosinophilia and systemic symptoms (DRESS)."

Drug reactions may cause cutaneous lesions and findings identical to a known disease or disorder. These may be of similar or disparate pathogenesis. For example, true serum sickness caused by the injection of foreign proteins, such as antithymocyte globulin, is associated with circulating immune complexes. Medications, notably cefaclor, induce a serum sickness-like illness, clinically extremely similar to, but not associated with, circulating immune complexes. The suffix "-like" is used to describe these syndromes with different or unknown pathogenesis but similar clinical features.

Exanthems (Morbilliform or Scarlatiniform Reactions)

Exanthems are the most common form of adverse cutaneous drug eruption. They are characterized by erythema, often with small papules throughout. They tend to occur within the first 2 weeks of treatment but may appear later, or even within 10 days after the medication has been stopped. Lesions tend to appear first proximally, especially in the groin and axilla, generalizing within 1 or 2 days. Pruritus is usually prominent, helping to distinguish a drug eruption from a viral exanthem. Antibiotics, especially semisynthetic penicillins and trimethoprim–sulfamethoxazole, are the most common causes of this reaction pattern (Fig. 6-30). Ampicillin–amoxicillin given during EBV and cytomegalovirus infections and trimethoprim–sulfamethoxazole given to AIDS patients cause exanthems in a large proportion of patients.

Morbilliform reactions to ampicillin–amoxicillin (including those occurring during EBV infection) may be mediated by helper T-cells in a manner similar to allergic contact dermatitis and tuberculin reactions. Delayed readings (longer than 24 h) of patch tests, prick tests, and intradermal tests may yield positive results, whereas immediate skin test readings and RAST tests are negative. Patients with EBV infection and a drug eruption to ampicillin–amoxicillin will only develop the rash about 10% of the time when rechallenged after the acute EBV infection has resolved.

Morbilliform eruptions may rarely be restricted to a previously sunburned site, the so-called "UV recall-like" phenomenon. It occurs during antibiotic therapy from various antibiotics. The sunburn may have occurred 1 to 7 months before the drug eruption. This pattern of eruption must be distinguished from a true UV recall caused by antimetabolites and true radiation recall (see adverse reactions to chemotherapy below).

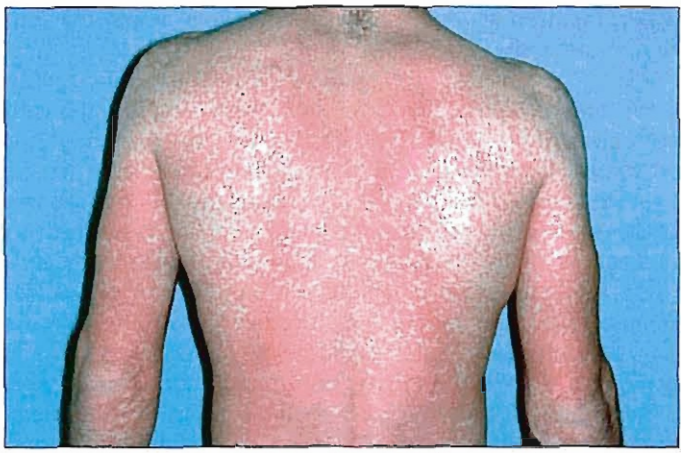

Fig. 6-30 Morbilliform (exanthematous) drug eruption due to an antibiotic.

In the case of simple exanthems, treatment is supportive. The eruption will clear within 2 weeks of stopping the offending medication, and may clear even if it is continued. Topical steroids and antihistamines may benefit and allow the course of therapy to be completed. Rechallenge usually results in the reappearance of the eruption, except in the setting of HIV. In many HIV-infected patients with simple reactions to trimethoprim–sulfamethoxazole, re-exposure by slow introduction or full dose re-exposure may be tolerated. Uncommonly in HIV infection, however, and rarely in persons with normal immune function, rechallenge may result in a more severe blistering reaction (erythema multiforme).

Cutaneous findings identical to simple exanthems may occur as part of complex drug eruptions/hypersensitivity syndromes. These are seen most commonly with anticonvulsants and long-acting sulfonamides; less commonly with allopurinol and dapsone. They present with fever, rash, and variably, with eosinophilia, lymphadenopathy, hepatitis, nephritis, and rarely, involvement of the heart, lungs, or brain. As opposed to simple exanthems, in complex exanthems the inciting agent must be stopped immediately and rechallenge should rarely be undertaken. The management of hypersensitivity syndromes is discussed below.

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Hypersensitivity Syndromes

Hypersensitivity syndromes are discussed by the class of medication that causes them. Each class of medication appears to cause a constellation of features characteristic of that medication class. This may be related to sensitivity of certain organs to the toxic or reactive metabolites produced in susceptible individuals. Anticonvulsants, sulfonamides, nevirapine, and dapsone are commonly reported causes of hypersensitivity syndromes. Amitriptyline, gabapentin, and

other medications may also produce this syndrome, but much less commonly.

Many hypersensitivity syndromes are associated with fever and eosinophilia; drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. Systemic symptoms of fever and malaise may precede the appearance of the skin eruption. In general, hypersensitivity syndromes occur later in the treatment course than simple exanthems (except in some cases of sulfonamide hypersensitivity), often more than 2 weeks and sometimes many weeks to months after the medication has been instituted. Within any drug class, multiple morphologies of eruption may be seen with a hypersensitivity syndrome. Patients may have a morbilliform eruption or a bullous eruption (erythema multiforme major, Stevens–Johnson syndrome [SJS], toxic epidermal necrolysis [TEN]). Drug-induced hypersensitivity syndromes often occur during the patient's initial exposure to the medication.

Anticonvulsant Hypersensitivity Syndrome Anticonvulsant hypersensitivity syndrome can be seen with diphenylhydantoin, phenobarbital, carbamazepine, lamotrigine, and other anticonvulsants, so the general term "anticonvulsant hypersensitivity syndrome" is preferred to the original descriptive term "dilantin hypersensitivity syndrome." The incidence of this condition has been estimated at between 1 in 1000 and 1 in 10,000 patients treated with these medications. The frequent use of anticonvulsants such as carbamazepine to treat depression has greatly expanded the at-risk pool for these reactions. Medication dosage does not determine risk for this syndrome.

The skin eruption is typically initially morbilliform, but may have variable morphologies in different patients or at various times in the same patient. There may be an exanthem, erythroderma, purpura, atypical targets, extensive skin sloughing, and mucous membrane involvement resembling SJS or TEN. The histologic picture of each type of eruption is compatible with the clinical morphology, and all are possible in this syndrome. The syndrome begins with fever between 2 and 6 weeks (average 3 weeks) after the offending medication is started. The eruption then appears, often with prominent facial swelling and sometimes with an acral accentuation. Associated with the eruption are findings similar to acute infectious mononucleosis. On physical examination, the patient usually appears quite ill with pharyngitis, lymphadenopathy (70% of cases), and sometimes hepatomegaly (57%). Laboratory evaluation reveals various combinations of eosinophilia (30% of cases), atypical lymphocytosis, elevated liver function tests (51%), and nephritis (11%). More sophisticated testing may demonstrate various immune abnormalities, such as hyper/hypoglobulinemia, elevated suppressor T-cells, defective cell-mediated immune function on skin testing, and various autoantibodies. Lymph node biopsies usually demonstrate reactive hyperplasia, but pseudolymphoma may also occur.

As the eruption evolves, it is typical for widespread pinpoint pustules to appear on the trunk and extremities, especially in dark skinned patients. The syndrome may continue to progress, even after the inciting medication has been stopped. The associated hepatitis can be life-threatening.

The pathogenesis of this syndrome is in part related to concurrent or reactivated viral infection and the affected individual's production of toxic and reactive arene oxide metabolites of these medications. These metabolites then apparently bind to proteins and elicit in susceptible individuals an immune response, or are directly toxic to certain organs (liver), leading to the multiple features of the syndrome. Because many of the anticonvulsants are metabolized through the same pathway, cross-reactions are frequent, making selection of an alternative agent quite difficult. The rate of cross-reactivity between phenytoin, phenobarbital, and carbamazepine is 70%. In vitro tests are commercially available and may aid in selecting an agent to which the patient will not cross-react.

Lamotrigine is associated with a high rate of adverse skin reactions (10% or more). Erythema multiforme major (SJS, TEN) occurs in approximately 1 in 1000 adults and 3 in 1000 children. Valproic acid inhibits the metabolism of lamotrigine, increasing the risk of developing a severe cutaneous reaction.

The management of anticonvulsant hypersensitivity syndrome begins with considering it in the appropriate setting and ruling out other possible explanations for the patient's findings. The offending medication must be immediately discontinued. Because cross-reactivity among these drugs is high, the therapeutic benefit of a medication from this class must be carefully reconsidered. If the treatment is for depression, prophylaxis after closed head injury, or atypical pain syndromes, medication from another class can often be substituted. Treatment is initially supportive until the extent and severity of the syndrome are assessed. Some patients clear with simply discontinuing the medication. If there is liver or renal involvement, or if the patient appears ill or requires hospitalization, and there is no contraindication, systemic steroids are given. This syndrome, independent of the skin eruption with which it presents, improves with systemic administration of steroids. Patients with TEN on systemic steroids are at increased risk for sepsis. Steroid therapy is continued at doses required for control and gradually tapered. It may require months of steroid therapy. If steroids are tapered too rapidly, the syndrome may recur. Intravenous immunoglobulin (IVIG) has been successfully used in a steroid-refractory case. Transient hypothyroidism may occur for 1 to 3 months following anticonvulsant hypersensitivity syndromes.

Sulfonamide Hypersensitivity Syndrome Sulfonamide hypersensitivity clinical syndrome is similar to that seen with the anticonvulsants, but the onset is often sooner in the treatment course (generally after 7–14 days of therapy). However, the syndrome may appear after months of therapy. Less than 0.1% of treatment courses with sulfonamides are complicated by a hypersensitivity syndrome. The skin eruption is usually morbilliform or an erythroderma, but a severe bullous reaction like SJS or TEN may develop. Patients with this syndrome are often slow acetylators unable to detoxify the toxic and immunogenic hydroxylamine metabolites generated during the metabolism of the sulfonamides. Patients with sulfonamide hypersensitivity syndrome may develop antibodies that recognize microsomal proteins to which the reactive hydroxylamine metabolite of the sulfonamides bind. Sulfonamide hypersensitivity syndrome is treated with topical treatments appropriate for the skin eruption, and systemic steroids for systemic compli-

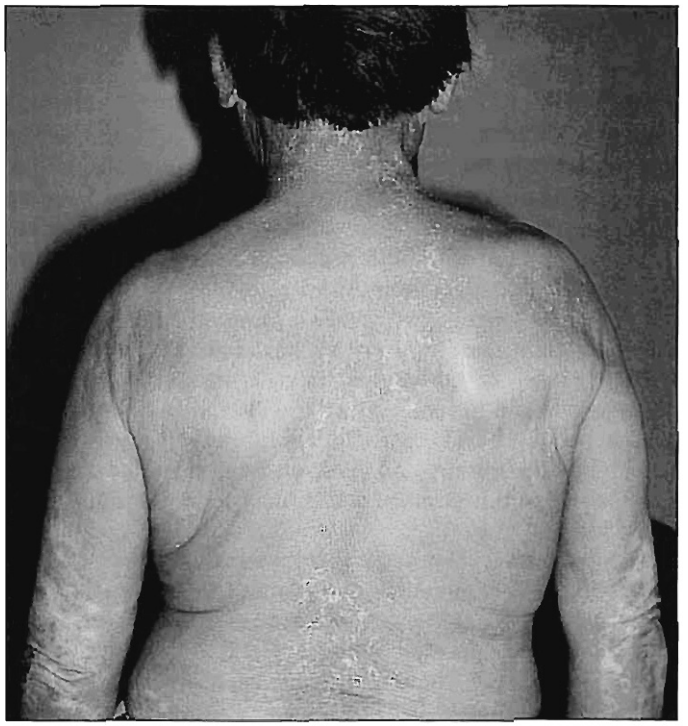

Fig. 6-31 Allopurinol hypersensitivity syndrome.

cations, as outlined above for anticonvulsant hypersensitivity syndrome.

Allopurinol Hypersensitivity Syndrome Allopurinol hypersensitivity syndrome typically occurs in persons with preexisting renal failure. Often, affected patients are treated unnecessarily for asymptomatic hyperuricemia. Weeks to months (average 7 weeks) after the allopurinol is begun, the patient develops a morbilliform eruption (50% of cases) that often evolves to an exfoliative erythroderma (20%) (Fig. 6-31). Bullous eruptions, including TEN (25% of cases) may also occur. Associated with the dermatitis is fever, eosinophilia, sometimes hepatitis, and typically worsening of renal function. This syndrome may be steroid responsive, but is extremely slow to resolve, frequently lasting for months after allopurinol has been stopped. About 25% of patients die as a consequence of this syndrome. Deaths may occur from severe skin disease (TEN), hepatic necrosis, and even delayed myocardial infarction. Pancreatitis and subsequent insulin-dependent diabetes may occur as a complication of the syndrome. Dialysis does not appear to accelerate the resolution of the eruption, suggesting that if a drug metabolite is responsible, it is not dialyzable. It has been suggested that adjusting the allopurinol dose to compensate for the patient's impaired renal function might reduce the risk of developing this reaction.

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Drug-Induced Pseudolymphoma

At times, exposure to medication may result in cutaneous inflammatory patterns that resemble lymphoma, most frequently mycosis fungoides. The finding of atypical lymphocytes within inflammatory infiltrates is common in many inflammatory dermatoses, including drug reactions, and this alone is insufficient to diagnose pseudolymphoma. The overall histology must be consistent with the diagnosis of lymphoma. These true pseudolymphoma reactions are uncommon or rare. The most frequent setting in which they occur is that of a hypersensitivity syndrome as described

above, in which, uncommonly, the histology may resemble cutaneous T-cell lymphoma. Usually, other features such as keratinocyte necrosis and dermal edema help to distinguish these reactions from true lymphoma. Importantly, T-cell receptor gene rearrangements in the skin and blood may be positive in these drug-induced cases, representing a potential pitfall for the unwary physician. More rarely, medications may induce plaques or nodules, usually in elderly white men after many months of treatment. Lymphadenopathy and circulating Sézary cells may also be present. Pseudolymphoma resolves with discontinuation of the medication. The medication groups primarily responsible are anticonvulsants, sulfa drugs (including thiazide diuretics), dapsone, and antidepressants. Vaccinations can also induce pseudolymphoma.

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Urticaria/Angioedema

Medications may induce urticaria by immunologic and nonimmunologic mechanisms. In either case, clinically the lesions are pruritic wheals or angioedema. Urticaria may be part of a more severe anaphylactic reaction with bronchospasm, laryngospasm, or hypotension. Immediate hypersensitivity skin testing and sometimes RAST tests are useful in evaluating risk for these patterns of reaction.

Aspirin and the NSAIDs are the most common causes of nonimmunologic urticarial reactions. They alter prostaglandin metabolism, enhancing degranulation of mast cells. They may therefore also exacerbate chronic urticaria of other causes. The nonacetylated salicylates (trilisate and salsalate) do not cross-react with aspirin in patients experiencing bronchospasm and may be safe alternatives. Other agents causing nonimmunologic urticaria include radiocontrast material, opiates, tubocurarine, and polymyxin B. Pretesting does not exclude the possibility of anaphylactoid reaction to radiocontrast material. The use of low-osmolarity radiocontrast material and pretreatment with antihistamines, systemic steroids, and in those with a history of asthma, theophylline, may reduce the likelihood of reaction to radiocontrast material.

Immunologic urticaria is most commonly associated with penicillin and related β-lactam antibiotics. It is associated with IgE antibodies to penicillin or its metabolites. Skin testing with penicillin and its major and minor determinants is useful in evaluating patients with a history of urticaria associated with penicillin exposure. If the patient is skin-test positive, an alternative antibiotic must be considered, or the patient be given penicillin in a desensitization protocol. Most patients with a history of penicillin "allergy" are skin-test negative. These patients can be treated with penicillin with a low likelihood of a severe adverse event. If a semisynthetic penicillin is associated with the initial reaction, the patient may be skin-test negative to the standard penicillin-derived reagents and still suffer anaphylaxis. This may be caused by IgE antibodies directed against the acyl side chain, in the case of amoxicillin. Patients with penicillin allergy have an increased rate of reaction to cephalosporins. In the case of cefaclor, half of anaphylactic reactions occur in patients with a history of penicillin allergy. Third-generation cephalosporins are much less likely to induce a reaction in a penicillin-allergic patient than are first- or second-generation ones.

Bupropion is commonly used for depression and smoking cessation. It can induce urticaria, which may be associated with hepatitis and a serum sickness-like syndrome. Two antihistamines, cetirizine and hydroxyzine, may induce urticaria, an apparent paradox which may lead to confusion in the clinical setting.

Angioedema is a known complication of the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II antagonists. Black persons are at nearly five times greater risk than white persons. Lisinopril and enalapril produce angioedema more commonly than captopril. Angioedema typically occurs within a week of starting therapy, but may begin after months of treatment. The episodes may be severe, requiring hospitalization in up to 45% of patients, intensive care in up to 27%, and intubation in up to 18%. One-quarter of patients affected give a history of previous angioedema. Captopril enhances the flare reaction around wheals. The angioedema appears to be dose dependent, as it may resolve with decreased dose. All these factors suggest that the angioedema may represent a consequence of a normal pharmacologic effect of the ACE inhibitors. The blocking of kininase II by ACE inhibitors may increase tissue kinin levels, enhancing urticarial reactions and angioedema. Although this is dose dependent, ACE inhibitor users with one episode of angioedema have a 10-fold risk of a second episode, and the recurrent episodes may be more severe.

Red Man Syndrome

The intravenous infusion of vancomycin is frequently complicated, especially if the infusion is rapid, by a characteristic reaction called "red man syndrome." At any time during the infusion, a macular eruption appears initially on the back of the neck, sometimes spreading to the upper trunk, face, and arms. Angioedema has been described. There is associated pruritus and "heat" as well as hypotension. The hypotension may be severe enough to cause cardiac arrest. The reaction is caused by elevated blood histamine. Red man syndrome can be prevented in most patients by reducing the rate of infusion of the antibiotic, or by pretreatment with H_1 and H_2 antihistamines. While typically reported with vancomycin, similar "anaphylactoid" reactions have been seen with ciprofloxacin, amphotericin B, rifampin, imfliximab, and teicoplanin.

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Photosensitivity Reactions (Photosensitive Drug Reactions)

Medications may cause phototoxic, photoallergic, and lichenoid reactions, and photodistributed telangiectasias, as well as pseudoporphyria. The mechanisms of photosensitivity are discussed in Chapter 3. In many cases the mechanism for drug-induced photosensitivity is unknown. Most medication-related photosensitivity is triggered by radiation in the UVA range, partly for two reasons. First, most photosensitizing drugs have absorption spectra in the UVA and short-visible range (315–430 nm), and second, UVA penetrates into the dermis where the photosensitizing drug is present. The most common causes of photosensitivity are NSAIDs, trimethoprim–sulfamethoxazole, thiazide diuretics and related sulfonylureas, quinine and quinidine, phenothiazines, and certain tetracyclines; numerous other medications in many classes induce photosensitivity less commonly.

Phototoxic reactions are related to the dose of both the medication and the UV irradiation. They potentially could occur in anyone if sufficient thresholds are reached, and do not require prior exposure or participation by the immune system. Persons of higher skin types are at lower risk to develop phototoxic eruptions in some studies. There is individual variation in the amount of photosensitivity created by a standard dose of medication, independent of serum concentration. This remains unexplained, but reflects the clinical setting, where interindividual variability in development of phototoxic eruptions is seen. Reactions can appear from hours to days after to exposure. Tetracyclines (especially demeclocyline), amiodarone, and the NSAIDs are common culprits. The reaction may present as immediate burning with sun exposure (amiodarone, chlorpromazine) or exaggerated sunburn (fluroquinolone antibiotics, chlorpromazine, amiodarone, thiazide diuretics, quinine, tetracyclines) (Fig. 6-32). Hyperpigmentation may complicate phototoxic reactions and may last for many months. Treatment may include dose reduction and photoprotection, with a sunblock with strong coverage through the whole UVA spectrum (such as Mexoryl).

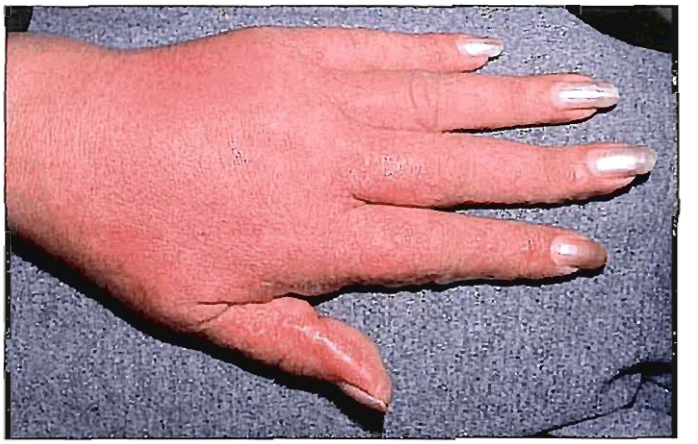

Fig. 6-32 Photosensitivity drug eruption.

Photoallergic reactions are typically eczematous, pruritic, and may first appear weeks to months after drug exposure. They involve the immune system. Unfortunately, in the case of photoallergy to systemic medications, photopatch testing is infrequently positive and of limited clinical value. In general, photoallergic reactions are not as drug dose dependent as phototoxic reactions. Photosensitivity both of the phototoxic and photoallergic types may persist for months to years after the medication has been stopped. Photosensitivity reactions to various drugs are discussed individually below, emphasizing the characteristic patterns seen with each medication group.

Amiodarone photosensitivity develops in up to 75% of treated patients, and occurs after a cumulative dose of 40 g. A reduced minimal erythema dose (MED) to UVA, but not UVB, occurs, and gradually returns to normal between 12 and 24 months after stopping the medication. Stinging and burning may occur as soon as 30 min after sun exposure. Less commonly, a dusky, blue–red erythema of the face and dorsa of the hands occurs. At times papular reactions are also seen. Desquamation, as seen following sunburn, is not observed following amiodarone photosensitivity reactions. This reaction may be dose dependent and acute burning may be relieved by dose reduction. Narrow-band UVB may desensitize patients with persistent phototoxicity after stopping amiodarone.

NSAIDs, especially piroxicam, are frequently associated with photosensitivity. The characteristic reaction is a vesicular eruption of the dorsa of the hands, sometimes associated with a dyshidrosiform pattern on the lateral aspects of the hands and fingers. In severe cases even the palms may be involved. Histologically, this reaction pattern shows intraepidermal spongiosis, exocytosis, and perivascular inflammatory cells—a pattern typical of photoallergy. However, this reaction may occur on the initial exposure to the medication, and phototoxicity tests in animals and man have been negative. Patients with photosensitivity to piroxicam may also react to thiosalicylic acid, a common sensitizer in thimerosal. Half of patients having a positive patch test to thimerosal with no prior exposure to piroxicam are photopatch-test positive to piroxicam. This suggests that piroxicam reactions seen on initial exposure to the medica-

tion may be related to sensitization during prior thimerosal exposure. Topical exposure to ketoprofen (Orudis gel) can lead to a photoallergic contact dermatitis, and contamination of personal objects may lead to persistence despite stopping the use of the product.

Sulfonamide antibiotics, related hypoglycemic agents, and the sulfonylurea diuretics may all be associated with photosensitivity reactions. These agents may all cross-react. In addition, patients may tolerate one of the medications from this group, but when additional members of the group are added, clinical photosensitivity occurs. The typical pattern is erythema, scale, and in chronic cases, lichenification and hyperpigmentation.

Fluoroquinolone antibiotics are frequently associated with photosensitivity reactions. Sparfloxacin is highly photosensitizing; enoxacin, ciprofloxacin, and sitafloxacin are mildly photosensitizing; and levofloxacin rarely if ever causes photosensitivity.

Photodistributed lichenoid reactions have been reported most commonly from thiazide diuretics, quinidine, and NSAIDs, but also occur from diltiazem and clopidogrel bisulfate. They present as erythematous patches and plaques. Sometimes, typical Wickham's stria are observed in the lesions. Histologically, photodistributed lichenoid reactions are often indistinguishable from idiopathic lichen planus. Marked hyperpigmentation may occur, especially in persons of higher skin types (IV–VI), especially in diltiazem-induced cases. The lichenoid nature of the eruption may not be clinically obvious, and histology is required to confirm the diagnosis. This hyperpigmentation may persist for months.

Photodistributed telangiectasias are a rare complication of calcium-channel blockers (nifedipine, felodipine, and amlodipine). UVA appears to be the action spectrum. Cefotaxime has also been reported to produce this reaction. Corticosteroids, oral contraceptives, isotretinoin, interferons (IFNs), lithium, thiotixene, lithium, methotrexate, and other medications may induce telangiectasias, but not via photosensitivity.

Pseudoporphyria is a photodistributed bullous reaction clinically and histologically resembling porphyria cutanea tarda. Patients present with blistering on sun-exposed skin of the face and hands, and skin fragility. Varioliform scarring occurs in 70% of patients. Facial scarring is especially common in children with pseudoporphyria. Hypertrichosis is very rarely found; dyspigmentation and sclerodermoid changes are not reported. Porphyrin studies are normal. The blistering usually resolves gradually once the offending medication is stopped. However, skin fragility may persist for years. Naproxen is the most commonly reported cause. Up to 12% of children with juvenile idiopathic arthritis treated with NSAIDs may develop pseudoporphyria. Pseudoporphyria has also been reported to other NSAIDs (oxaprozin, nabumetone, ketoprofen, mefanamic acid [but not piroxicam]), tetracycline, furosemide, nalidixic acid, isotretinoin, acetretin, 5-fluorouracil, bemetanide, dapsone, oral contraceptives, refecoxib, celecoxib, cyclosporin, and pyridoxine. Sun-bed exposure and even excessive sun exposure can produce pseudoporphyria. Cases in women outnumber men by 24:1. Some women with sunbed-induced pseudoporphyria are on oral contraceptives. Patients on dialysis may develop pseudoporphyria, and N-acetylcysteine in doses up to 600 mg twice a day may lead to improvement in these cases. Histologically, a pauci-inflammatory subepidermal vesicle is seen. Direct immunofluorescence may show immunoglobulin and complement deposition at the dermoepidermal junction and perivascularly, as seen in porphyria cutanea tarda.

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Anticoagulant-Induced Skin Necrosis

Both warfarin and heparin induce lesions of cutaneous necrosis, albeit by different mechanisms. Obese, postmenopausal women are predisposed, and lesions tend to occur in areas with abundant subcutaneous fat such as the breast, abdomen, or buttocks.

Warfarin necrosis occurs 3 to 5 days after therapy is begun, and a high initial dose increases the risk. It occurs in 1 in 10,000 persons treated with warfarin. Lesions begin

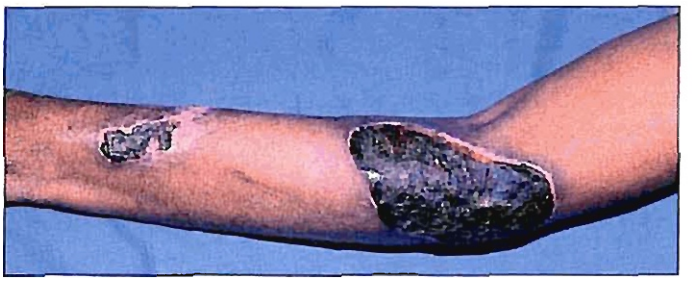

Fig. 6-33 Warfarin necrosis.

as red, painful plaques that become necrotic (Fig. 6-33). Priapism can complicate warfarin necrosis. Hereditary or acquired deficiency of protein C, and less commonly protein S, antithrombin III, or factor V Leiden and lupus anticoagulant syndrome are associated. Early in warfarin treatment the serum levels of the vitamin K-dependent antithrombotic protein C falls. Since the half-life of antithrombotic protein C is shorter than those for the vitamin K-dependent prothrombotic factors II, X and IX, an acquired state of reduced protein C level occurs before the clotting factors are reduced. This creates a temporary prothrombotic state. This is more likely to occur if the levels of protein C are already low, if other antithrombotic proteins are deficient, or the patient has an associated hypercoagulable state. This explains why the syndrome does not always recur with gradual reinstitution of warfarin, and has been reported to resolve with continued warfarin treatment. Histologically, noninflammatory thrombosis with fibrin in the subcutaneous and dermal vessels is seen. Treatment is to stop the warfarin, administer vitamin K to reverse the warfarin, and begin heparin or low molecular weight heparin. Administration of purified protein C can rapidly reverse the syndrome, as well as associated priapism. Untreated, the reaction can be fatal.

Heparin induces necrosis both at the sites of local injections and in a widespread pattern when infused intravenously. Local reactions are the most common. Heparin can also induce local allergic reactions at injection sites, which are distinct from the necrosis syndrome. Independent of its method of delivery, lesions present as tender red plaques that undergo necrosis, usually 6 to12 days after the heparin treatments are started. Bovine heparin appears to be more likely to cause the reaction, but it can occur with porcine heparin and even fractionated low molecular weight heparin. Both low- and high-dose heparin therapy can produce the syndrome. Even the heparin used for dialysis may be associated with cutaneous necrosis, simulating calciphylaxis. Some necrotic reactions to local injections, and most disseminated reactions occurring with intravenous heparin, are associated with heparin-induced thrombocytopenia. A heparin-dependent antiplatelet antibody is found. This causes both the thrombocytopenia and aggregation of platelets in vessels, causing thrombosis (white clot syndrome). The antibody may appear up to 3 weeks after the heparin has been discontinued, so the onset of the syndrome may be delayed. Histologically, fibrin thrombi are less reproducibly found in affected tissues, since the vascular thrombosis is the result of platelet aggregation, not protein deposition. The process may produce not only infarcts in the skin but may also cause arterial thrombosis of the limbs, heart, lung, and brain, resulting in significant morbidity or mortality. The syndrome must be recognized immediately in anyone receiving heparin with late-developing thrombocytopenia. The treatment is to stop the heparin and treat with warfarin if anticoagulation is still required.

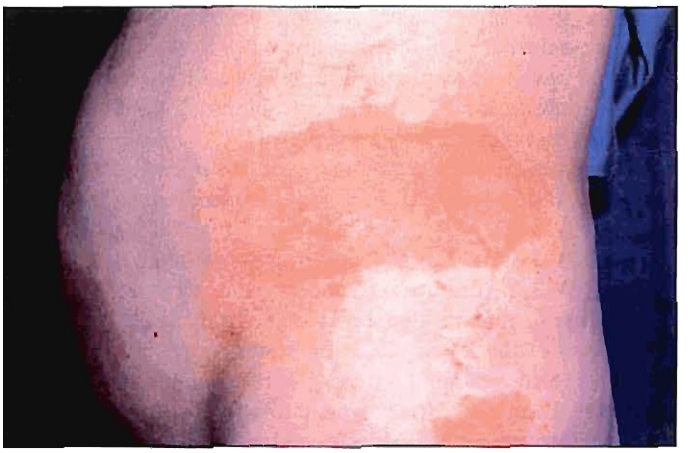

Fig. 6-34 Vitamin K allergy.

Patients with cancer, an acquired prothrombotic state, are at increased risk for deep venous thrombosis. If they are treated with heparin and develop heparin-induced thrombocytopenia, they are at extreme risk for the development of a prothrombotic state if treated with warfarin. In this setting, digital and limb gangrene has occurred in the face of normal peripheral pulses and super-therapeutic anticoagulation by standard measures (INR). The consumptive coagulopathy induced by the cancer is the underlying trigger.

Vitamin K Reactions

Several days to 2 weeks after injection of vitamin K, an allergic reaction at the site of injection may occur (Fig. 6-34). Most affected persons have liver disease and are being treated for elevated prothrombin times. The lesions are pruritic, red patches or plaques that can be deep-seated, involving the dermis and subcutaneous tissue. There may be superficial vesiculation. Lesions occur most commonly on the posterior arm and over the hip or buttocks. Plaques on the hip tend to progress around the waist and down the thigh, forming a "cowboy gunbelt and holster" pattern. Generalized eczematous small papules may occur on other skin sites in severe reactions. These reactions usually persist for 1 to 3 weeks, but may persist much longer, or resolve only to spontaneously recur. On testing, patients with this pattern of reaction are positive on intradermal testing to the pure vitamin K_1.

In Europe, a second pattern of vitamin K reaction has been reported. Subcutaneous sclerosis with or without fasciitis appears at the site of injections many months after vitamin K treatment. There may have been a preceding acute reaction as described above. Peripheral eosinophilia may be found. These pseudoscleroedermatous reactions have been termed *Texier's disease*, and last several years.

Injection Site Reactions

In addition to allergic reactions, as described with vitamin K, cutaneous necrosis may occur at sites of medication injections. These are of two typical forms—those associated with intravenous infusions and those related to intra-

muscular injections. Pharmacologic agents that extravasate into tissue during intravenous infusion may cause local tissue necrosis resulting from inherent tissue-toxic properties. These include chemotherapeutic agents, calcium salts, radiocontrast material, and nafcillin.

Intramuscular injections may produce a syndrome called *embolia cutis medicamentosa*, *Livedoid dermatitis*, or *Nicolau syndrome*. Immediately after injection there is local intense pain and the overlying skin blanches (ischemic pallor). Within minutes to hours the site develops an erythematous macule that evolves into a livedoid violaceous patch with dendrites. This becomes hemorrhagic, then ulcerates, often forming a deep ulcer of many centimeters in diameter. Eventually (over weeks to months) the ulcer heals with an atrophic scar. Muscle and liver enzymes may be elevated, and neurologic symptoms and sequelae occur in a third of patients. The circulation of the limb may be affected, rarely leading to amputation. This syndrome has been seen with injection of many unrelated agents, including NSAIDs, local anesthetics, corticosteroids, antibiotics, IFN-α, sedatives, and Depo-Provera. It appears to be caused by periarterial injection leading to arterial thrombosis. Treatment is conservative: dressing changes, debridement, bed rest, and pain control. Surgical intervention is rarely required.

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Acute Generalized Exanthematous Pustulosis

Acute generalized exanthematous pustulosis (AGEP), also known as *toxic pustuloderma* and *pustular drug eruption*, is a not uncommon cutaneous reaction pattern that in 90% of cases is related to medication administration. The eruption is of sudden onset and appears an average of 5 days (2.5 days in antibiotic-induced cases) after the medication is started—in 50% of cases within the first 24 h. In France, β-lactams were the cause in 44%, macrolides in 17%, and mercury in 13%. Nutritional chromium supplementation and the ingestion of urushiol-flavored chicken have also caused AGEP. Many other medications have been implicated, but interestingly, sulfonamides have uncommonly been reported to cause this reaction (in contrast to erythema multiforme major). Infections due to viruses and parasites are rare causes. In 5% of cases, no trigger can be identified. AGEP should be distinguished from the generalized pustulation that occurs in the evolution of anticonvulsant hypersensitivity syndrome. Seventeen percent of patients have a prior history of psoriasis, and similar cases have been reported as acute psoriasis induced by medications. The course and evolution are different from true pustular psoriasis, although patients with psoriasis may be at increased risk for this form of drug reaction.

Initially there is a scarlatiniform erythema. The eruption evolves and disseminates rapidly, consisting, usually, of more than 100 nonfollicular pustules less than 5 mm in diameter (Fig. 6-35). Rarely the eruption may remain localized, usually to the face and neck. The Nikolsky sign may be positive and widespread superficial desquamation occurs after a few days. Edema of the face, purpura, and atypical target lesions, as in erythema multiforme, may appear in the background, making distinction from erythema multiforme major difficult in some cases. Mucous membranes, usually the oral mucosa, are involved in 22%. Fever is universal, with neutrophilia in 90% and eosinophilia in 30%. Liver function tests are usually normal. Once the inciting agent is discontinued or removed, the eruption resolves within 15 days without sequelae. Histologically, early lesions show marked papillary edema, neutrophil clusters in the dermal papillae, and perivascular eosinophils. There may be an associated leukocytoclastic vasculitis. Well-developed lesions show intraepidermal or subcorneal spongiform pustules. If there is a background of erythema multiforme clinically, the histologic features of erythema multiforme may be superimposed. The presence of eosinophils and the marked papillary edema help to distinguish this eruption from pustular psoriasis.

Patch testing with the suspected agent may reproduce a pustular eruption on an erythematous base at 48 h in about 50% of cases. Patch testing rarely will result in a recrudescence of AGEP. AGEP is mediated by T-cells, which produce high levels of CXCL8 (interleukin-8) and granulocyte-

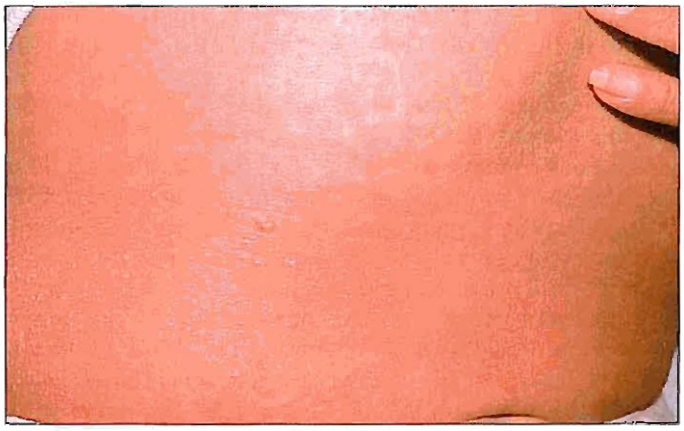

Fig. 6-35 Acute generalized exanthematous pustulosis.

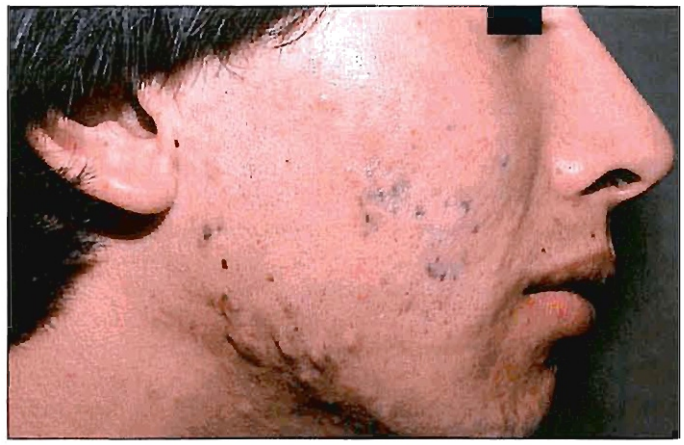

Fig. 6-36 Minocycline hyperpigmentation.

macrophage colony-stimulating factor (GM-CSF). CXCL8 is also produced by keratinocytes in lesions of AGEP.

The diagnosis of AGEP is usually straightforward in typical cases. In cases with associated targetoid lesions and widespread vesiculation, distinction from erythema multiforme major and TEN may be difficult. The clinical features of rapid onset after exposure (< 5 days), visible pustules (even as a minor component of the eruption), and marked neutrophilia favor the diagnosis of AGEP over erythema multiforme. Frozen-section examination of a skin biopsy will usually confirm the diagnosis of AGEP and exclude the diagnosis of erythema multiforme.

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Drug-Induced Pigmentation

Pigmentation of the skin may occur as a consequence of drug administration. The mechanism may be postinflammatory hyperpigmentation in some cases but frequently is related to actual deposition of the offending drug in the skin.

Minocycline induces many types of hyperpigmentation, which may occur in various combinations in the affected patient. Classically, three types of pigmentation are described. The most common is a blue–black discoloration appearing in areas of prior inflammation, often acne or surgical scars (type I) (Fig. 6-36). It does not appear to be related to the total or daily dose of exposure. In all other types of pigmentation resulting from minocycline the incidence increases with total dose, with approximately 4% of treated patients experiencing hyperpigmentation at a cumulative dose of 100 g. The second type (type II) is the appearance of a similar colored pigmentation on the normal skin of the anterior shins, analogous to that seen in antimalarial-induced hyperpigmentation. It is initially mistaken for ecchymoses, but does not fade quickly. In most cases type I and II minocycline pigmentation occur after 3 months to several years of treatment. Generalized black hyperpigmentation has occurred after several days or a few weeks of treatment in Japanese patients. In type I and II minocycline hyperpigmentation, histologic evaluation reveals pigment granules within macrophages in the dermis, very similar to a tattoo. These granules usually stain positively for both iron and melanin, the usual method for confirming the diagnosis. Calcium may also rarely complex with minocycline, producing a type I clinical pattern. In unusual cases electron microscopy or sophisticated chemical analysis can confirm the presence of minocycline in the granules. The least common type (type III) is generalized, muddy brown hyperpigmentation, accentuated in sun-exposed areas. Histologic examination reveals only increased epidermal and dermal melanin. This may represent the consequence of a low-grade photosensitivity reaction.

In addition to the skin, minocycline type I and II pigmentation may also involve the sclera, conjunctiva, bone, thyroid, ear cartilage, nailbed, oral mucosa, and permanent

teeth. Contrasted with tetracycline staining of the teeth, which is usually related to childhood or fetal exposure, is brown, and is accentuated on the gingival third, minocycline hyperpigmentation occurs in adults, is gray or gray–green, and is most marked in the midportion of the tooth. Most patients with affected teeth do not have hyperpigmentation elsewhere. Cutaneous hyperpigmentation from minocycline fades slowly and the teeth may remain pigmented for years. The blue–gray pigmentation of the skin may be improved with the Q-switched ruby laser.

Chloroquine, hydroxychloroquine, and quinacrine all may cause a blue–black pigmentation of the face, extremities, ear cartilage, oral mucosa, and nails. Pretibial hyperpigmentation is the most common pattern and is very similar to that induced by minocycline. The gingiva or hard palate may also be discolored. Quinidine may also rarely cause such a pattern of hyperpigmentation. Quinacrine is yellow and is concentrated in the epidermis. Generalized yellow discoloration of the skin and sclera (mimicking jaundice) occurs reproducibly in patients but fades within 4 months after stopping the drug. In dark-skinned patients this color is masked and not so significant cosmetically. Histologically, in both forms of pigmentation, pigment granules are present within macrophages in the dermis.

Amiodarone after 3 to 6 months causes photosensitivity in 30% to 57% of treated patients. In 1% to 10% of patients, a slate-gray hyperpigmentation develops in the areas of photosensitivity. The pigmentation gradually fades after the medication is discontinued. Histologically, periodic acid-Schiff positive yellow–brown granules are seen within the cytoplasm of macrophages in the dermis. Electron microscopy reveals membrane-bound structures resembling lipid-containing lysosomes. It responds to treatment with the Q-switched ruby laser.

Clofazimine treatment is reproducibly complicated by the appearance of a pink discoloration that gradually becomes reddish-blue or brown and is concentrated in the lesions of patients with Hansen's disease. This pigmentation may be very disfiguring and is a major cause of noncompliance with this drug in the treatment of Hansen's disease. Histologically, a periodic acid-Schiff positive brown, granular pigment is variably seen within foamy macrophages in the dermis. This has been called "drug-induced lipofuscinosis."

Zidovudine causes a blue or brown hyperpigmentation that is most frequently observed in the nails. The lunula may be blue or the whole nail plate may become dark brown. Diffuse hyperpigmentation of the skin, pigmentation of the lateral tongue, and increased tanning are less common. It occurs in darkly pigmented persons, is dose dependent, and clears after the medication is discontinued. Hydroxyurea causes a very similar pattern of hyperpigmentation.

Chlorpromazine, thioridazine, imipramine, and clomipramine may cause a slate-gray hyperpigmentation in sun-exposed areas after long periods of ingestion. Frequently, corneal and lens opacities are also present, so all patients with hyperpigmentation from these medications should have an ophthalmologic evaluation. The pigmentation from the phenothiazines fades gradually over years, even if the patient is treated with another phenothiazine. The corneal, but not the lenticular, changes also resolve. Imipramine hyperpigmentation has been reported to disappear within a year. Histologically, in sun-exposed but not sun-protected skin, numerous refractile golden-brown granules are present within macrophages in the dermis along with increased dermal melanin. The slate-gray color comes from a mixture of the golden-brown pigment of the drug and the black color of the melanin viewed in the dermis.

The heavy metals gold, silver, and bismuth produce blue to slate-gray hyperpigmentation. Pigmentation occurs after years of exposure, predominantly in sun-exposed areas, and is permanent. Zinc and silver may also tattoo the skin in areas of injury. Bismuth also pigments the gingival margin. Histologically, granules of the metals are seen in the dermis and around blood vessels. Arsenical melanosis is characterized by black, generalized pigmentation or by a pronounced truncal hyperpigmentation that spares the face, with depigmented scattered macules that resemble raindrops.

Periocular hyperpigmentation occurs in patients treated with prostaglandin analogs for glaucoma. These agents cause pigmentation of the iris. Eyelash length also increases. Bimatoprost may induce pigmentary changes more quickly than latanoprost. The periocular hyperpigmentation may gradually resolve when the medications are discontinued.

Pigmentary changes induced by chemotherapeutic agents are discussed later is this chapter.

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Vasculitis and Serum Sickness-Like Reactions

True leukocytoclastic vasculitis can be induced by many medications, but these events are rare, except in the case of

propylthiouracil. True serum sickness is caused by foreign proteins such as antithymocyte globulin. They are caused by circulating immune complexes. In the case of true serum sickness there is a tendency for purpuric lesions to be accentuated along the junction between palmoplantar and glabrous skin (Wallace line).

Serum sickness-like reactions refer to adverse reactions that have similar symptoms to serum sickness, but in which immune complexes are not found. The use of cefaclor for the treatment of an upper respiratory infection or otitis media in children is complicated by a specific hypersensitivity reaction in 3.4% of cases beginning about 1 week into cefaclor therapy. Affected children are usually younger than 6 years old (median age 32 months). The onset is from hours to 2 weeks (mean 6 days) after treatment is begun. This reaction presents in the skin with urticarial plaques that may progress to have dusky centers (misdiagnosed as erythema multiforme). Pruritus is common, as well as acral edema and swollen, painful joints of the hands and feet. The mucous membranes are spared. The eruption usually rapidly resolves without sequelae once the cefaclor is discontinued. In about 5% of patients prolonged sequelae of joint swelling or persistent urticarial reaction may persist for 1 to 2 months, usually not requiring medical intervention. Children may be rechallenged without recurrence, or more severe symptomatology may occur on re-exposure. It is unclear whether children suffering a serum sickness-like reaction have increased risk of adverse reactions to β-lactam antibiotics. In vitro testing may document enhanced lymphocyte toxicity in affected patients, suggesting a metabolic basis similar to anticonvulsant hypersensitivity syndrome. A history of drug allergy is common in children and family members of children who develop serum sickness-like reactions to antibiotics.

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Fixed Drug Reactions

Fixed drug reactions are common. Fixed drug eruptions are so named because they recur at the same site with each exposure to the medication. In most patients, six or fewer lesions occur, frequently only one. Uncommonly, fixed eruptions may be multifocal with numerous lesions. They may present anywhere on the body, but half occur on the oral and genital mucosa. Fixed eruptions represent 2% of all genital ulcers evaluated at clinics for sexually-transmitted diseases (Fig. 6-37), and are not infrequent in young boys.

Clinically, a fixed eruption begins as a red patch that soon evolves to an iris or target lesion identical to erythema multiforme, and may eventually blister and erode. Lesions of the genital and oral mucosa usually present as erosions. Most lesions are 1 to several cm in diameter, but larger plaques may occur, resembling cellulitis. Characteristically, prolonged or permanent postinflammatory hyperpigmentation results, although a nonpigmenting variant of a fixed drug eruption is recognized. With repeated or continued ingestion of the offending medication, new lesions may be added, sometimes eventuating in a clinical picture similar to drug-induced erythema multiforme major. Histologically, an interface dermatitis occurs with intraepidermal and subepidermal vesicle formation, necrosis of keratinocytes, and a mixed superficial and deep infiltrate of neutrophils, eosinophils, and mononuclear cells. Pigment incontinence is usually marked, correlating with the pigmentation resulting from fixed drug eruptions. As biopsies are generally performed during the acute stage of a recurrence, the stratum corneum is normal. Papillary dermal fibrosis and deep perivascular pigment incontinence are commonly present from prior episodes. This contrast between a normal stratum corneum (suggesting an acute process) and chronic dermal changes is virtually pathognomonic of fixed drug eruption.

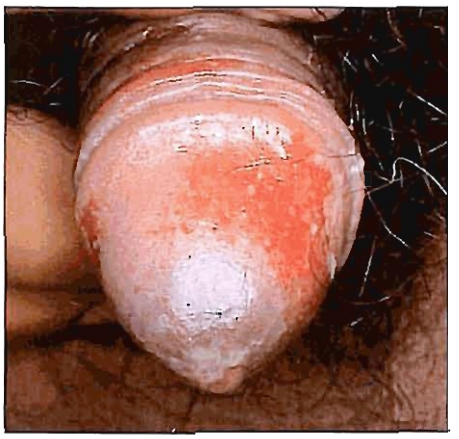

Fig. 6-37 Fixed drug eruption presenting as a broad-based superficial penile erosion.

Medications inducing fixed drug eruptions are usually those taken intermittently. Many of the NSAIDs, especially pyrazolone derivatives, paracetamol, naproxen, oxicams, and mefenamic acid cause fixed drug eruption, with a special predilection for the lips. Sulfonamides, trimethoprim, or the combination are now responsible for the majority of genital fixed drug eruptions. Barbiturates, tetracyclines, phenolphthalein (in laxatives), acetaminophen, ceterizine, celecoxib, dextromethophan, hydroxyzine, lamotrigine, phenylpropanolamine, erythromycin, and Chinese and Japanese herbs are other possible causes. The risk of developing a fixed drug eruption has been linked to HLA-B22. Patch tests with various concentrations of the offending medication can reproduce the lesion on affected but not unaffected skin. Tape stripping the skin before applying the suspected medication in various vehicles may increase the likelihood of a positive patch test. This technique appears to be most useful in pyrazolone derivative-related reactions that are reproduced in 85% or more of cases.

Occasionally, fixed drug reactions do not result in long-lasting hyperpigmentation. The so-called nonpigmenting fixed drug eruption is distinctive. It is characterized by large, tender, often symmetrical erythematous plaques that resolve completely within weeks, only to recur on reingestion of the offending drug (Fig. 6-38). Pseudoephedrine hydrochloride is by far the most common culprit. The baboon syndrome, where the buttocks, groin, and axilla are preferentially involved, is considered a nonpigmenting fixed drug eruption by some.

Lesions of a fixed drug eruption contain intraepidermal CD8+ T-cells with the phenotypic markers of effector memory T-cells. These skin-resident T-cells rapidly produce IFN-γ on exposure to the offending medication.

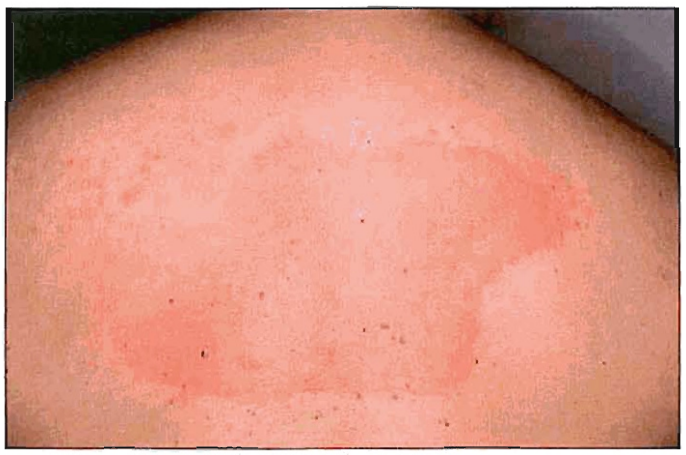

Fig. 6-38 Fixed drug eruption, nonpigmenting variant due to pseudoephedrine.

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Lichenoid Reactions

Lichenoid reactions can be seen with many medications, including gold (Fig. 6-39), hydrochlorothiazide, NSAIDs, aspirin, D-penicillamine, captopril, quinidine, proton pump inhibitors, and the antimalarials. Hepatitis B immunization may trigger a lichenoid eruption. Reactions may be photodistributed (lichenoid photoeruption) or generalized, and those drugs causing lichenoid photoeruptions may also induce more generalized ones. In either case, the lesions may be plaques (very occasionally with Wickham striae), small papules, or exfoliative erythema. Photolichenoid reactions favor the extensor extremities, including the dorsa of the hands. Oral involvement is less common in lichenoid drug reactions than in idiopathic lichen planus but can occur. It appears as either plaques or erosions. The lower lip is frequently involved in photolichenoid reactions. The nails may also be involved. Histologically, there is inflammation along the dermoepidermal junction, with necrosis of keratinocytes and a dermal infiltrate composed primarily of lymphocytes. Eosinophils are useful if present, but are not common in photolichenoid reactions. The histology is often very similar to idiopathic lichen planus, and a clinical correlation is required to determine if the lichenoid eruption is drug induced.

Lichenoid reactions may be restricted to the oral mucosa, especially if induced by dental amalgam. In these cases the lesions are topographically related to the dental fillings or to metal prostheses, and mercury or gold will produce positive patch tests in up to two-thirds of these patients. Amalgam replacement will result in resolution of the oral lesions in these cases. Patients with cutaneous lesions of lichen planus and oral lesions do not improve with amalgam removal. An

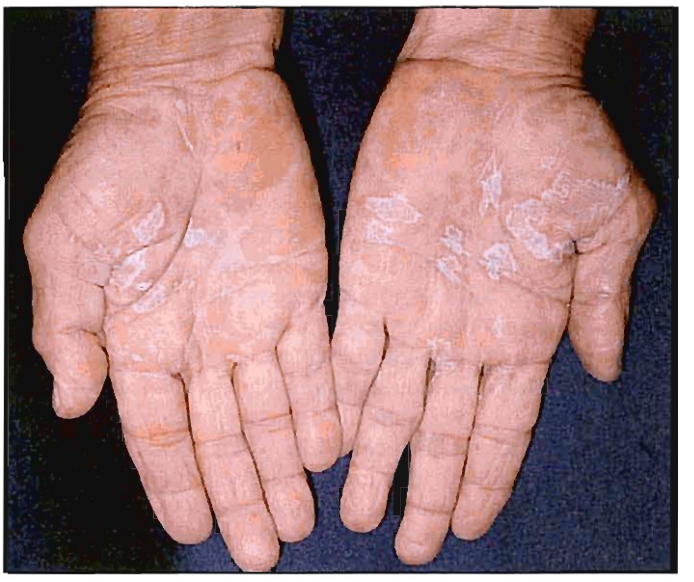

Fig. 6-39 Lichenoid drug eruption due to gold.

unusual form of eruption is the "drug-induced ulceration of the lower lip." Patients present with a persistent erosion of the lower lip that is tender but not indurated. It is induced by diuretics and resolves slowly once they are discontinued.

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Bullous Drug Reactions (Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis)

Skin blistering may complicate drug reactions in many ways. Medications may induce known autoimmune bullous diseases such as pemphigus (penicillamine) or linear IgA disease (vancomycin). Acute generalized exanthematous pustulosis may be so extensive as to cause a positive Nikolsky sign, and have a background of purpura and targetoid lesions, simulating erythmea multiforme. Pseudoporphyria and other photodermatoses from drugs may form bullae. Cytokines may produce widespread bullous eruptions, perhaps through physiologic mechanisms. The term *bullous drug reaction*, however, most commonly refers to a drug reaction in the erythema multiforme group (for a complete discussion of other forms of erythema multiforme see Chapter 7).

These are fortunately uncommon reactions to medications, with an incidence of 0.4 to 1.2 per million person-years for TEN and 1.2 to 6.0 per million person-years for SJS. Drug-induced erythema multiforme is usually more extensive than that induced by infectious agents but at times the distinction may be difficult. The more severe the reaction, the more likely it is to be drug induced (50% of cases of SJS and 80% of cases of TEN). The exact definitions of SJS and TEN remain arbitrary as a result of overlap in some cases. The following definitions are useful to classify cases: SJS has less than 10% body surface area (BSA) involved, cases with 10% to 30% are SJS-TEN overlap cases, and more than 30% BSA erosion is called TEN. SJS and TEN probably represent parts of a disease spectrum based on the following: they are most commonly induced by the same medications; patients initially presenting with SJS may progress to extensive skin loss resembling TEN; the histologic findings are indistinguishable; and both are increased by the same magnitude in HIV infection. Mycoplasma is a common cause of SJS in children and may closely resemble drug-induced SJS.

More than 100 medications have been reported to cause SJS and TEN. Common inciting medications are trimethoprim–sulfamethoxazole (1–3 in 100,000), Fansidar-R, sulfadoxine plus pyrimethamine (10 in 100,000), nevirapine, lamotrigine (1 in 1000 adults and 3 in 1000 children) and carbamazepine (14 in 100,000). Antibiotics (especially long-acting sulfa drugs and penicillins), other anticonvulsants, anti-inflammatories (NSAIDs), and allopurinol are also frequent causes. If the inciting drug has a short half-life, and the drug is promptly stopped, the mortality is reduced from 26% to 5%. This suggests that the use of agents with short half-lives and the prompt discontinuation of the medication when the first signs of an adverse reaction appear may be very important ways to reduce the mortality from TEN.

Fever and influenza-like symptoms often precede the eruption by a few days. Skin lesions appear on the face and trunk and rapidly spread (usually within 4 days) to their maximum extent. Initial lesions are macular and may remain so, followed by desquamation, or may form atypical targets with purpuric centers that coalesce, form bullae, then slough (Fig. 6-40). Virtually always two or more mucosal surfaces are also eroded, the oral mucosa and conjunctiva being most frequently affected. There may be photophobia, difficulty with swallowing and rectal erosions, painful urination, and cough, indicative of ocular, alimentary, urinary, and respiratory tract involvement, respectively.

A skin biopsy is usually performed. Frozen-section analysis may lead to a rapid diagnosis. This is to exclude other diseases and to confirm the diagnosis. Independent of the extent of the slough, the clinical morphology (atypical targets versus simple erythema), or the clinical diagnosis (SJS versus TEN), the histology is similar. There is a lymphocytic infiltrate at the dermoepidermal junction with necrosis of keratinocytes that at times may be full thickness. The infiltrate may be marked or very scant. Paraneoplastic pemphigus also shows changes of erythmea multiforme and may be excluded with direct immunofluorescence. Patients with graft-versus-host disease may also demonstrate a TEN-like picture with identical histology.

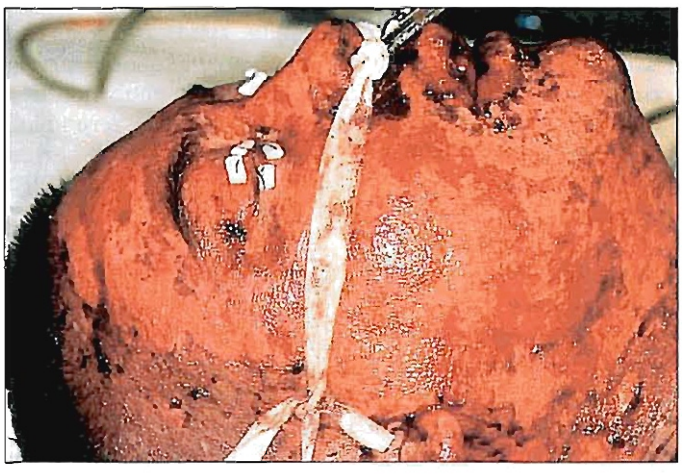

Fig 6-40 Toxic epidermal necrolysis.

Management of these patients is similar to an extensive burn. They suffer fluid and electrolyte imbalances, bacteremia from loss of the protective skin barrier, hypercatabolism, and sometimes acute respiratory distress syndrome. Survival is improved if patients are cared for in a specialized "burn unit." Nutritional support is critical. Patients who are very ill or with more than 30% to 50% loss of epidermis should be transferred for such care.

IVIG is now frequently used to manage the more severe adult and pediatric patients with bullous drug eruptions (TEN). It has also been used to prevent SJS due to radiocontrast dye. The proposed mechanism of action of IVIG in this condition is by stopping keratinocyte apoptosis through blockade of the death receptor FAS (CD 95). Soluble Fas ligand was elevated in the blood of one patient with TEN, and its level correlated with BSA involvement. Imfliximab has also been reported to arrest rapidly progressive TEN in a single dose of 5 mg/kg. The presumed mechanism is by blocking tumor necrosis factor (TNF).

The role of immunosuppressive therapy is very controversial in severe bullous drug eruptions. The benefit of immunosuppressives would be to stop the process very quickly and thereby reduce the ultimate amount of skin lost. Once most of the skin loss has occurred, immunosuppressives only add to the morbidity and perhaps mortality of the disorder. In children, this adverse effect has been documented, probably since their mortality from severe bullous drug eruptions is low. Because the condition evolves rapidly (average 4 days to maximum extent), very early treatment would be required to observe benefit. Patients have developed TEN while undergoing systemic corticosteroid therapy in moderate-to-high doses (40–60 mg of prednisone equivalent daily). Perhaps the therapeutic benefit is not seen at this range, but at higher doses, as is suggested by anecdotal reports of benefit with more potent immunosuppressive regimens. If immunosuppressive treatment is considered, it should be used as soon as possible, given as a short trial to see if the process may be arrested, and then tapered rapidly to avoid the risk of immunosuppression in a patient with substantial loss of skin. As with burns, the patient's age, severity of underlying disease, and extent of skin loss are the most important factors determining the outcome rather than the use of immunosuppressive agents.

In patients who survive, the average time for epidermal regrowth is 3 weeks. The most common sequelae are ocular scarring and vision loss. A sicca-like syndrome may also result. Rarely, complications include cutaneous scarring, eruptive melanocytic lesions, and nail abnormalities. Transient, widespread verrucous hyperplasia, resembling confluent seborrheic keratoses has also been reported. Mortality averages about 5% for patients with SJS and 30% for patients with TEN.

Radiation-Induced Erythema Multiforme

If phenytoin is given prophylactically in neurosurgical patients who are receiving whole-brain radiation therapy and systemic steroids, an unusual reaction occurs. As the dose of steroids is being reduced, erythema and edema initially appear on the head in the radiation ports. This evolves over 1 or 2 days to lesions with the clinical appearance and histology of erythema multiforme. The eruption spreads caudad and mucosal involvement may occur, eventuating in full-blown SJS. A similar syndrome has been reported with the use of amifostine during radiation for head and neck cancers. This syndrome can rarely be seen with radiation therapy alone.

"Urticarial Erythema Multiforme"

"Urticarial erythema multiforme" is an unusual reaction virtually always associated with antibiotic ingestion. The skin lesions consist of urticarial papules and plaques, some of which clear centrally forming annular lesions, but no true iris lesions. Lesions can be distinguished from true urticaria in that they are fixed for days. Pruritus is common. In contrast to true erythema multiforme, the annular lesions are not dusky in the center, but rather clear to normal skin. Bullae are absent, and mucous membranes are not involved. Rarely, hypotension may occur, suggesting mast cell products are important in the production of this eruption. Histologically, there is a superficial and deep dermal infiltrate containing eosinophils with dermal edema. The epidermis is uninvolved. Response to systemic steroids is usually dramatic, with clearing in 48 to 72 h. This condition is best classified as a variant of urticaria rather than erythema multiforme.

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HIV Disease and Drug Reactions

HIV-infected patients, especially those with helper T-cell counts between 25 and 200, are at increased risk for the development of adverse reactions to medications. Morbilliform reactions to trimethoprim–sulfamethoxazole occur in 45% or more of AIDS patients being treated for *Pneumocystis carinii* pneumonia. In two-thirds of patients without life-threatening reactions, trimethoprim–sulfamethoxazole treatment can be continued with simple conservative support, and the eruption may resolve. Associated hepatitis or neutropenia may require discontinuation of the drug. A similar increased rate of reaction to amoxicillin–clavulanate in HIV is also seen. If the dermatitis is treatment limiting, but the eruption is not life-threatening, low-dose rechallenge/desensitization may be attempted. It is successful in 65% to 85% of patients in the short term, and higher than 50% in the long term. In fact, initial introduction of trimethoprim–sulfamethoxazole for prophylaxis by dose escalation reduces the rate of adverse reactions as well. However, rechallenge at full dose may have the same rate of recurrent eruptions as does introduction by dose escalation. Although low-dose rechallenge is usually safe, severe, acute reactions including marked hypotension may occur. Although most adverse reactions occur in the first few days of rechallenge, adverse reactions may appear months after restarting trimethoprim–sulfamethoxazole, and may be atypical in appearance. The mechanism of this increased adverse reaction to trimethoprim–sulfamethoxazole is unknown.

Severe bullous reactions, SJS, and TEN are between 100 and 1000 times more common per drug exposure in patients with AIDS. These reactions are usually caused by sulfa drugs, especially long-acting ones, but may be caused by many agents. Nevirapine, a non-nucleoside reverse-transcriptase inhibitor, had been associated with a high rate of severe drug eruptions including SJS/TEN. Most of these adverse reactions are cutaneous and occur in the first 6 weeks of treatment. This high rate of reaction can be reduced by starting with a lower lead-in dose, and by concomitant treatment with prednisone during the induction period. Fixed drug eruptions are also frequently seen in patients with HIV infection.

Acyclovir, nucleoside and non-nucleoside reverse transcriptase inhibitors (except nevirapine), and protease inhibitors are uncommon causes of adverse drug reactions. Many reactions attributed to these agents may actually be coexistent HIV-associated pruritic disorders, especially folliculitis, which are very common in patients with AIDS.

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Adverse Reactions to Chemotherapeutic Agents

Chemotherapeutic agents can cause adverse reactions by multiple potential mechanisms. Adverse reactions may be related to toxicity either directly to the mucocutaneous surfaces (alopecia) or to some other organ system, and reflected in the skin, such as purpura resulting from thrombocytopenia. Being organic molecules in many cases, they can act as allergens inducing classic immunologic reactions. In addition, since they are inherently immunosuppressive, they can cause skin reactions associated with alterations of immune function. Some of these patterns may be overlapping and clinically difficult to distinguish. For example, oral erosions may occur as a toxic effect of chemotherapy and also by immunosuppression-associated activation of herpes simplex virus.

Dermatologists are rarely confronted with the relatively common acute hypersensitivity reactions seen during infusion of chemotherapeutic agents. These reactions resemble type I allergic reactions, with urticaria and hypotension. Although in only some cases are the type I reactions IgE mediated, they can be prevented with premedication with systemic steroids and antihistamines in most cases.

Numerous macular and papular eruptions have been described with chemotherapeutic agents as well. Many of these occur at the time of the earliest recovery of the bone marrow, as lymphocytes return to the peripheral circulation. They are associated with fever. Horn et al have termed this phenomenon *cutaneous eruptions of lymphocyte recovery*. Histologically, these reactions demonstrate a nonspecific superficial perivascular mononuclear cell infiltrate, composed primarily of T-lymphocytes. Treatment is not required and the eruption spontaneously resolves.

Radiation Enhancement and Recall Reactions

Radiation dermatitis, in the form of intense erythema and vesiculation of the skin, may be observed in radiation ports.

Administration of many chemotherapeutic agents, during or in close proximity to the time of radiation therapy, may induce an enhanced radiation reaction. However, in some cases, months to years following radiation treatment the administration of a chemotherapeutic agent may induce a reaction within the prior radiation port with features of radiation dermatitis. This phenomenon has been termed "radiation recall." It has been reported with numerous chemotherapeutic agents, high-dose IFN-α, and simvastatin. Not only the skin, but internal structures such as the gut may be affected. A similar reaction of reactivation of a sunburn after methotrexate therapy also occurs. Exanthems restricted to prior areas of sunburn are not true radiation recall.

Chemotherapy-Induced Acral Erythema (Palmoplantar Erythrodysesthesia Syndrome) This is a relatively common syndrome induced by many chemotherapeutic agents, most frequently 5-fluorouracil (5-FU), doxorubicin, and cytosine arabinoside. The reaction may occur in as many as 40% of treated patients. The reaction is dose dependent, and may appear with bolus short-term infusions or low-dose, long-term infusions. It may present days to months after the treatments are started. It is probably a direct toxic effect of the chemotherapeutic agents on the skin. The large number of sweat glands on the palms and soles that may concentrate the chemotherapeutic agents may explain the localization of the toxicity.

The initial manifestation is often dysesthesia or tingling of the palms and soles. This is followed in a few days by painful, symmetric erythema and edema most pronounced over the distal pads of the digits. The reaction may spread to the dorsal hands and feet, and can be accompanied by a morbilliform eruption of the trunk, neck, scalp and extremities. Over the next several days the erythema becomes dusky, develops areas of pallor, blisters, desquamates, then re-epithelializes. The desquamation is often the most prominent part of the syndrome. Blisters developing over pressure areas of the hands and feet are a variant of this syndrome. The patient usually recovers without complication, although rarely full-thickness ischemic necrosis occurs in the areas of blistering.

The histopathology is nonspecific, with necrotic keratinocytes and vacuolar changes along the basal cell layer. Acute graft-versus-host disease is in the differential diagnosis. Histologic evaluation may not be useful in the acute setting to distinguish these syndromes. Most helpful are gastrointestinal or liver findings of graft-versus-host disease.

Most cases require only local supportive care. Cold compresses and elevation are helpful, and cooling the hands during treatment may reduce the severity of the reaction. Modification of the dose schedule can be beneficial. Pyridoxine decreases the pain of 5-FU-induced acral erythema.

Neutrophilic Eccrine Hidradenitis Neutrophilic eccrine hidradenitis is discussed in Chapter 33.

Chemotherapy-Induced Hyperpigmentation Many chemotherapeutic agents (especially the antibiotics bleomycin, doxorubicin, and daunorubicin) and the alkylating agents (cyclophosphamide and busulfan) cause various patterns of cutaneous hyperpigmentation. Adriamycin (doxorubicin) causes marked hyperpigmentation of the nails, skin, and tongue. This is most common in black patients and appears in locations where constitutional hyperpigmentation is sometimes seen. Hydroxyurea can also cause this pattern of hyperpigmentation. It is very similar to zidovudine-associated pigmentation seen in pigmented persons. Cyclophosphamide causes transverse banding of the nails or diffuse nail hyperpigmentation beginning proximally. Bleomycin and 5-FU cause similar transverse bands. Busulfan and 5-FU induce diffuse hyperpigmentation that may be photoaccentuated.

Bleomycin induces characteristic flagellate erythematous urticarial wheals associated with pruritus within hours or days of infusion (Fig. 6-41). Lesions continue to appear for days to weeks. While investigators have not always been able to induce lesions, the pattern strongly suggests scratching is the cause of the erythematous lesions. A similar characteristic pattern of flagellate hyperpigmentation occurs following bleomycin treatment. It may have been preceded by the erythematous reaction or simply pruritus. Bleomycin hyperpigmentation may be accentuated at areas of pressure, strongly supporting trauma as the cause of the peculiar pattern.

5-FU, and less commonly other chemotherapeutic agents, may produce a serpentine hyperpigmentation overlying the veins proximal to an infusion site. This represents postinflammatory hyperpigmentation from a direct cytotoxic effect of the chemotherapeutic agent.

Exudative Hyponychial Dermatitis Nail toxicity is common (26–40%) during chemotherapy for breast cancer, especially if docataxel is in the chemotherapeutic regimen. Subungual hemorrhage, subungual abscesses, paronychia, subungual hyperkeratosis, and onychomadesis all occur. In its most severe form, severe exudation and onycholysis may result. All these reactions probably represent various degrees of toxicity to the nailbed. Capecitabine has caused a similar reaction.

Scleroderma-Like Reactions to Taxanes Patients treated with docetaxel or paclitaxel may develop an acute,

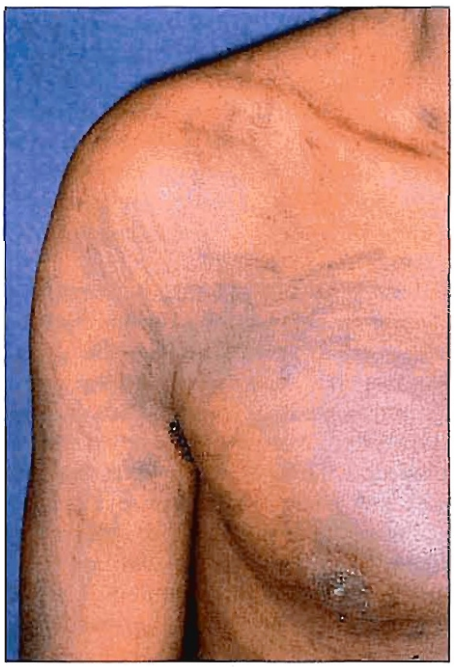

Fig. 6-41 Flagellate hyperpigmentation, bleomycin.

diffuse, infiltrated edema of the extremities and head. This occurs after one to several courses of the taxane. The affected areas evolve over months to become sclerotic and at times painful. Flexion contractures of the palm and digits and large joints may occur. Biopsies of the initial lesion show lymphangiectasia and a diffuse infiltration with mononuclear cells in the superficial dermis. Late fibrotic lesions demonstrate marked dermal fibrosis.

Adverse Reactions to Cytokines

Cytokines, which are normal mediators of inflammation or cell growth, are increasingly used in the management of malignancies and to ameliorate the hematologic complications of disease or its treatment Skin toxicity is a common complication of the use of these agents. Many of these agents cause local inflammation and/or ulceration at the injection sites in a large number of the patients treated. More widespread papular eruptions are also frequently reported, but these have been poorly studied in most cases and are of unclear pathogenesis.

Granulocyte colony-stimulating factor (G-CSF) has been associated with the induction of several neutrophil-mediated disorders, most commonly Sweet syndrome or bullous pyoderma gangrenosum. These occur about a week after cytokine therapy is initiated and are present despite persistent neutropenia in peripheral blood. A rare complication of G-CSF is a thrombotic and necrotizing panniculitis. Both G-CSF and granulocyte–macrophage (GM)-CSF may exacerbate leukocytoclastic vasculitis. IFN-α and -γ, and G-CSF have been associated with the exacerbation of psoriasis.

Interleukin-2 (IL-2) commonly causes diffuse erythema followed by desquamation, pruritus, mucositis (resembling aphthosis), glossitis, and flushing. While the majority of erythema reactions with IL-2 treatment are mild to moderate, some may be quite severe. Erythroderma with blistering or TEN-like reactions can occur, and be dose limiting. Administration of iodinated contrast material within 2 weeks of IL-2 therapy will be associated with a hypersensitivity reaction in 30% of cases. Fever, chills, angioedema, urticaria, and hypotension may occur. Subcutaneous injections of IL-2 can lead to injection-site nodules or necrosis. Histologically, a diffuse panniculitis with noninflammatory necrosis of the involved tissue is present.

Adverse Reactions to Biologic Agents

Imatinib (Gleevec) is used to treat chronic myelogenous leukemia. Cutaneous adverse events occur in more than 80% of patients. These include edema and pruritus without dermatitis. In addition, exanthematous and psoriasiform skin lesions, AGEP, erythema nodosum, small vessel vasculitis, exaggerated sunburn, SJS, acneiform eruption, and a graft-versus-host-like reaction can occur. Higher doses are associated with increased risk of a skin eruption and edema with over 90% of patients on doses higher than 600 mg/day developing a rash. This high rate of reaction suggests a pharmacologic rather than an allergic causality. Eruptions respond to stopping the medication. Gradual reintroduction may be tolerated in some patients. Diffuse hypopigmentation and lightening of the hair can also occur without the development of a dermatitis.

Infliximab for the treatment of rheumatologic disorders has been associated with the appearance of round, erythematous macules, papules, and plaques which tend to resolve with hyperpigmentation. Histologically the lesions demonstrated an interface dermatitis. Clinical diagnosis in these cases was erythema multiforme or lichenoid dermatitis. Patch tests were positive in one patient suggesting an allergic basis, but in another, etanercept triggered an identical eruption suggesting a pharmacologic effect. In one patient the infliximab therapy was continued with no recurrence of the eruption.

Injection site reactions (ISRs) are common with etanercept therapy for rheumatologic disease, with 20% to 40% of patients developing ISR. ISRs present as erythematous, mildly swollen plaques, appearing 1 to 2 days after the injection. Pruritus occurs in 20% of cases. ISR is most common early in the treatment course (median number of injections was four), and stops appearing with continued treatment. Individual lesions resolve over 2 to 3 days. Recall ISR (reappearance of the eruption at a site of a previous ISR) occurs in 40% of patients. This adverse reaction appears to be mediated by CD8+ T-cells. Cytokine therapy with TNF and IFN-α, -β, and -γ also cause ISRs.

Eleven percent of patients treated for rheumatoid arthritis with etanercept develop new antinuclear antibodies (ANAs) and 15% anti-double-stranded DNA (dsDNA) antibodies. Anti-Sm antibodies can also occur. Similarly, patients treated with infliximab may develop new ANAs, anti-dsDNA (14%), and anticardiolipin antibodies. A small number of these patients will develop drug-induced lupus erythematosus 2 to 18 months after starting treatment. Cutaneous lesions are common in these cases, and may resemble SCLE or DLE (photosensitivity, skin eruption). Systemic symptoms and findings may allow the diagnosis of systemic lupus erythematosus to be made. Renal and neurologic disease appears to be uncommon. Women are favored (86%) with a mean age of 50. Uncommon complications include vasculitis, cryoglobulinemia, pleuropericarditis, antiphospholipid syndrome (complicated by myocardial infarction). This form of drug-induced lupus erythematosus resolves within 1 to 4 months of drug withdrawal.

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Mercury

Mercury may induce multiple cutaneous syndromes. The classic syndrome is acrodynia, also known as *calomel disease*, *pink disease*, and *erythredemic polyneuropathy*. Acrodynia is caused by mercury poisoning, usually in infancy. The skin changes are characteristic and almost pathognomonic. They consist of painful swelling of the hands and feet, sometimes associated with considerable itching of these parts. The hands and feet are also cold, clammy, and pink or dusky red. The erythema is usually blotchy but may be diffuse. Hemorrhagic puncta are frequently evident. Over the trunk a blotchy macular or papular erythema is usually present. Stomatitis and loss of teeth may occur. Constitutional symptoms consist of moderate fever, irritability, marked photophobia, increased perspiration, and a tendency to cry most of the time. There is always moderate upper respiratory inflammation with soreness of the throat. There may be hypertension, hypotonia, muscle weakness, anorexia, and insomnia.

Albuminuria and hematuria are usually present. The diagnosis is made by finding mercury in the urine.

An exanthema may occur from inhalation of mercury vapors or absorption by direct contact. A diffuse, symmetrical erythematous morbilliform eruption in the flexors and proximal extremities begins within a few days of exposure. Accentuation in the groin and medial thighs produces a "baboon syndrome" appearance. The eruption burns or itches, and small follicular pustules appear. Extensive desquamation occurs with resolution. Old broken thermometers or the application of mercury-containing creams and herbal medications are potential sources. In Haiti elemental mercury is applied to surfaces for religious purposes and may result in contamination of those coming in contact.

Mercury is also a possible cause of foreign-body granulomas and hyperpigmentation at the sites of application. An eruption of 1- to 2-mm minimally pruritic papules and papulovesicles on the palms (all patients) and soles, arms, and trunk has also been ascribed to levels of mercury in the blood at near the upper limits considered to be safe. Treatment with a seafood-free diet and chelation with succimer led to resolution of the eruption in some patients. Nummular dermatitis improved in two mercury patch-test positive patients when their dental amalgam was removed.

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Bromoderma

Bromides produce distinctive follicular eruptions, acneiform, papular or pustular. Exudative plaques studded with pustules may develop, resembling Sweet syndrome or an orthopox virus infection. Histologically the lesions show epidermal hyperplasia with intraepidermal neutrophilic abscesses. There is rapid involution of the lesions on cessation of bromide ingestion. Excessive cola or soft-drink ingestion, or the ingestion of bromine-containing medications (ipratropium bromide, dextromethorphan hydrobromide, Medecitral) may be the cause of a bromoderma.

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Iododerma

Iodides may cause a wide variety of skin eruptions. The most common sources of exposure are oral and intravenous contrast materials, and when iodides are used to treat thyroid disease. The most common type is the acneiform eruption with numerous acutely inflamed follicular pustules, each surrounded by a ring of hyperemia. Bullous lesions are also common and may become ulcerated and crusted. The eruption may involve the face, upper extremities, trunk, and even the buccal mucosa. Acne vulgaris and rosacea are unfavorably affected by iodides. Acute iododerma may follow intravenous radiocontrast studies in patients with renal failure. The lesions may be associated with severe leukocytoclastic vasculitis, intraepidermal spongioform pustules, and suppurative folliculitis. Iodine is removed slowly by hemodialysis. The lesions respond to prednisone.

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Drug-Induced Autoimmune Diseases

Lupus Erythematosus Hydralazine- and procainamide-induced systemic lupus erythematosus is rarely associated with skin lesions. This form of drug-induced lupus erythematosus (DILE) is associated with a positive ANA, homogenous pattern, and antihistone antibodies. Numerous medications have been reported to produce cutaneous lesions characteristic of subacute cutaneous lupus erythematosus (SCLE). Hydrochlorthiazide, diltiazem (and other calcium-channel blockers), and terbinafine are reported to have triggered numerous cases. These patients may also be ANA positive and have antihistone antibodies, but in addition have positive anti-SSA antibodies. Cutaneous lesions are photosensitive, but not photodistributed, annular or papulosquamous plaques. Chilblain-like lesions are rarely seen. Treatment is as for SCLE, with sun avoidance, and topical and systemic steroids as required. Drug withdrawal results in resolution over weeks to months. The positive serologies may decrease as the eruption improves. Etanercept can produce both classic drug-induced SLE and drug-induced SCLE (see above).

Hydroxyurea Dermopathy Chronic use of hydroxyurea for chronic myelogenous leukemia, thrombocythemia, or psoriasis may be associated with the development of cutaneous lesions characteristic of dermatomyositis. Scaly, linear erythema of the dorsal hands, accentuated over the knuckles is noted. There may be marked acral atrophy and telangiectasia. Elbow and eyelid involvement, characteristic of dermatomyositis may also be seen. Biopsy shows vacuolar degeneration of the basal cells and an interface lymphocytic infiltrate. The skin lesions tend to improve over months, although the atrophy may not improve.

Linear IgA Bullous Dermatosis Linear IgA disease is frequently associated with medication exposure, especially vancomycin. Men and women are equally affected, and the eruption usually begins within 2 weeks of vancomycin therapy. Clinical morphology is variable and can include flaccid or tense bullae, vesicles, erythematous papules or plaques, and targetoid papules. TEN or severe SJS may be simulated, but mucosal involvement is not universal (30–45%) and conjunctival involvement is uncommon (10%). Treatment is to stop the offending drug and to give dapsone at 100 to 200 mg daily, as needed.

Leukotriene Receptor Antagonist-Associated Churg-Strauss Syndrome Asthma patients being treated with leukotriene receptor antagonists may develop a syndrome

resembling Churg-Strauss. It occurs 2 days to 10 months after the leukotriene receptor antagonist has been started. Features of the syndrome include peripheral eosinophilia, pulmonary infiltrates, and less commonly neuropathy, sinusitis, and cardiomyopathy. Skin lesions occur in about half the patients and are usually purpuric and favor the lower legs. Histologically the skin lesions show leukocytoclastic vasculitis with significant tissue eosinophilia. Antibodies to neutrophilic cytoplasmic antigens (ANCA) with myeloperoxidase specificity may be positive. Withdrawal of the leukotriene receptor antagonist therapy may lead to improvement, but systemic therapy with prednisone and cyclophosphomide may be required. The neuropathy may be permanent. The pathogenesis of this drug-induced syndrome is unknown. Some cases occur as steroids are tapered, but others have occurred in steroid naïve asthmatics. Unopposed leukotriene B4 activity, a potent chemoattractant for eosinophils and neutrophils, may explain the clinical findings.

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Adverse Reactions to Corticosteroids

Cutaneous reactions may result from topical, intralesional, subcutaneous, or systemic delivery of corticosteroids.

Topical Application The prolonged topical use of corticosteroid preparations may produce distinctive changes in the skin. The appearance of these side effects is dependent on three factors: the strength of the steroid, the area to which it is applied, and the individual's predisposition to certain side effects. Atrophy, striae, telangiectasia, skin fragility, and purpura are the most frequent changes seen. The most striking changes of telangiectasia are seen in fair-skinned individuals who use fluorinated corticosteroids on the face. The changes in the skin are enhanced by occlusion. When these side effects occur, the strength of the steroid should be reduced or substituted with pimecrolimus or tacrolimus. Weekly pulse dosing of a potent topical steroid can also reduce the incidence of side effects. Adjunctive measures to reduce steroid requirement could include addition of topical doxepin, pramoxine, or menthol and camphor to the regimen. Usually the telangiectases disappear in a few months after corticosteroid applications are stopped.

When corticosteroid preparations are applied to the face over a period of weeks or months, persistent erythema with telangiectases, and often small pustules, may occur (Fig. 6-42). Perioral dermatitis and rosacea are in some cases

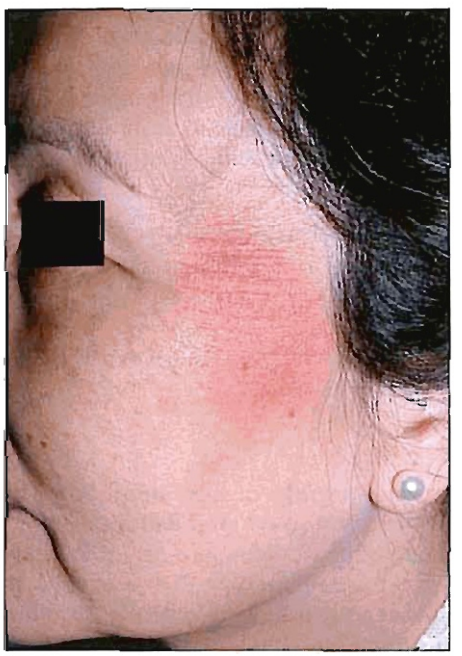

Fig. 6-42 Persistent erythema and telangiectasias due to chronic topical steroid application.

caused by the use of topical corticosteroids. Steroid rosacea has been reported from long-term use of 1% hydrocortisone cream. For this reason, the authors do not recommend chronic topical steroid preparations of any strength in the adjunctive treatment of rosacea.

Repeated application of corticosteroids to the face, scrotum or vulva may lead to marked atrophy of these tissues. These tissues become "addicted" to the topical steroid, so that withdrawing the topical steroid treatment results in severe itching or burning and intense erythema. Topical application of corticosteroids can produce epidermal atrophy with hypopigmentation. If used over large areas, sufficient topical steroids may be absorbed to suppress the hypothalamic pituitary axis. This may affect the growth of children with atopic dermatitis and has led to Addisonian steroid dependency and also Cushing syndrome. Atopic children with more than 50% body surface area involvement have short stature. This may be related to their increased use of potent topical steroids. In addition, bone mineral density is reduced in adults with chronic atopic dermatitis severe enough to require corticosteroid preparations stronger than hydrocortisone.

Injected Corticosteroids Intralesional injection of corticosteroids is valuable in the management of many dermatoses. The injection of corticosteroids may produce subcutaneous atrophy at the site of injection (Fig. 6-43). The injected corticosteroid may also migrate along lymphatics, causing not only local side effects but also linear atrophic hypopigmented hairless streaks. These may take years to resolve. These complications are best avoided by injecting directly into the lesion, not into the fat, and using only the minimal concentration and volume required.

Intramuscular steroid injections should always be given into the buttocks with a long needle (at least 1 1/2 inches in adults). Injection of corticosteroids into the deltoid muscle sometimes causes subcutaneous atrophy. The patient becomes aware of the reaction by noticing depression and depigmentation at the site of injection. There is no pain, but it is bothersome cosmetically. The patient may be assured that this will fill in but it may take several years to do so.

Systemic Corticosteroids Prolonged use of corticosteroids may produce numerous changes of the skin. In addition, they have a profound effect on the metabolism of many tissues, leading to predictable, and sometimes preventable, complications. Intramuscular injections are not a safer delivery method than oral administration.

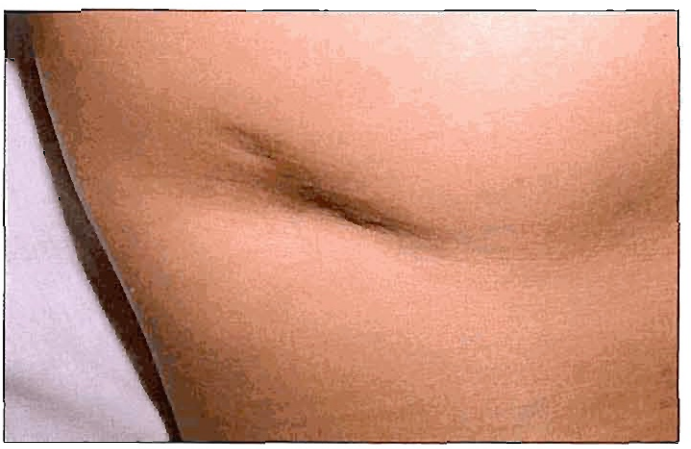

Fig. 6-43 Fat atrophy due to superficial corticosteroid injection.

Pupura and Ecchymosis

The skin may become thin and fragile. Spontaneous tearing may occur from trivial trauma. Purpura and ecchymoses are especially seen over the dorsal forearms in many patients over the age of 50. It is aggravation of actinic purpura.

Cushingoid Changes

The most common change is probably the alteration in fat distribution. Buffalo hump, facial and neck fullness, increased supraclavicular and suprasternal fat, gynecomastia, protuberant or pendulous abdomen, and flattening of the buttocks may occur. Aggressive dietary management with reduction in carbohydrate and caloric intake may ameliorate these changes.

Steroid Acne

Small, firm follicular papules on the forehead, cheeks, and chest may occur. Even inhaled corticosteroids for pulmonary disease can cause acne. Steroid acne can persist as long as the corticosteroids are continued. The management is similar to acne vulgaris with topical preparations and oral antibiotics.

Striae

These may be widely distributed, especially over the abdomen, buttocks, and thighs.

Other Skin Changes

There may be generalized skin dryness (xerosis); the skin may become thin and fragile; keratosis pilaris may develop; persistent erythema of the skin in sun-exposed areas may occur, and erythromelanosis may rarely occur.

Hair Changes

Hair loss occurs in about half of patients on long-term corticosteroids in large doses. There may be thinning and brittle fracturing along the hair shaft. There may be increased hair growth on the bearded area and on the arms and back with fine vellus hairs.

Systemic Complications

Hypertension, cataracts, aseptic necrosis of the hip, and osteoporosis are potential consequences of therapy with systemic steroids. Bone loss can occur early in the course of corticosteroid therapy, so it should be managed preemptively. Effective management can reduce steroid-induced osteoporosis. All patients with anticipated treatment courses longer than 1 month should be supplemented with calcium and vitamin D (1.0–1.5 g calcium and 400–800 U cholecalciferol a day). Smoking should be stopped and alcohol consumption minimized. Bone mineral density can be accurately measured at baseline via DEXA scan, and followed during corticosteroid therapy. Hypogonadism, which contributes to osteoporosis, can be treated in men and women with testosterone or estrogen, respectively. Calcitonin and bisphosphonates may be added to the management if necessary.

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CHAPTER

7 Erythema and Urticaria

FLUSHING

Flushing presents with transient erythema, usually localized to the face, neck, and upper trunk. Menopausal flushing may be associated with perspiration, as is that induced by high ambient temperature, fever, or consumption of hot or spicy food and beverages. Flushing associated with medications, histamine or serotonin is generally dry.

Menopausal flushing may be age related, induced by oophorectomy or medication (tamoxifen, leuprolide acetate), and may begin long before menses cease. Men may also experience climacteric flushing following surgery or antiandrogen therapy (flutamide).

Blushing, or emotional flushing, may be either emotionally or physiologically induced. Simple facial redness may occur in individuals with translucent skin and is called *anatomically predisposed blushing*.

Intense flushing may be associated with rosacea. In patients with rosacea, spicy foods, alcohol and hot beverages are frequent triggers for flushing. Drugs associated with flushing include niacin, calcium-channel blockers, cyclosporin, chemotherapeutic agents, vancomycin, bromocriptine, intravenous contrast material, sildenafil and related drugs for erectile dysfunction, and high-dose methylprednisolone. Reduced-to-absent methylnicotinate-induced flushing has been noted in patients with schizophrenia. This lack of flushing in response to methylnicotinate has been used for diagnostic psychiatric testing. Flushing after induction of general anesthesia with agents such as thiopental and muscle relaxants is more common in patients prone to blushing. It appears to be neuronally mediated, rather than related to histamine release. Endogenous vasoactive substances are associated with flushing in carcinoid syndrome, mastocytosis, medullary thyroid carcinoma, and pheochromocytoma.

Food-associated flushing may be caused by capsaicin (red pepper), sodium nitrate, or alcohol. Sulfites are found in wine, dried fruit, prepared foods, and fresh grapes and potatoes. Ciguatera or scombroid fish poisoning is a form of histamine-related food poisoning, caused by histamine within the flesh of the fish.

Individuals who flush without an identifiable cause should be investigated for dietary triggers and subtle manifestations of rosacea. Urine catecholamines, and serotonin and histamine metabolites should be measured if an endogenous cause is suspected. Many cases of flushing remain idiopathic. These patients may be managed with avoidance of dietary triggers and by sipping iced water to break the flush. Menopausal flushing responds to low-dose estrogen given orally or transdermally. The Women's Health Initiative studies concerning hormone replacement therapy (HRT) suggest that breast cancer risk is increased by combinations of estrogen and progestogen taken for longer than 5 years. There is little evidence that this is true for estrogen alone. Unopposed estrogen can increase the risk of endometrial carcinoma in premenopausal women. HRT does not appear to lower the risk of cardiac events, and the risks of long-term therapy often outweigh the benefits. Short-term HRT may still be very helpful in the management of perimenopausal flushing.

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ERYTHEMAS

The term *erythema* means blanchable redness (hyperemia) of the skin. A number of reactive skin conditions are referred to as erythemas. These include toxic erythemas related to viral and bacterial infections, erythema multiforme (EM), erythema nodosum, and the gyrate (figurate) erythemas.

Erythema Palmare

Erythema palmare, persistent palmar erythema, is usually most marked on the hypothenar areas, and is associated with an elevated level of circulating estrogen. Cirrhosis, hepatic metastases, and pregnancy are common causes.

Generalized Erythema

Generalized erythema may be caused by medications, bacterial toxins, or viral infection. It is often uneven in distribution, being most noticeable on the chest, proximal extremities, and face. In general, these reactions are self-limited and resolve when the offending medication is stopped or the associated infection is treated or resolves. Specific exanthems associated with bacterial or viral infections are discussed in Chapters 14 and 19.

Erythema Toxicum Neonatorum

Erythema toxicum neonatorum occurs in the majority of healthy full-term newborns, usually on the second or third

day. Because it is so common, dermatologists are usually consulted only for the most florid or atypical cases. Characteristically, the broad erythematous flare is much more prominent than the small follicular papule or pustule it surrounds. Lesions involve the face, trunk, and proximal extremities, and appear only rarely on the soles or palms. There may be confluent erythema on the face. Fever is absent and the eruption generally disappears by the 10th day. It must be distinguished from miliaria, bacterial folliculitis, neonatal herpes, and scabies. When the rash is a typical, smears of the pustules demonstrating eosinophils are adequate to confirm the diagnosis. Rarely, a biopsy will be required, demonstrating a folliculitis containing eosinophils and neutrophils.

Erythema Multiforme

In 1860, von Hebra first described erythema exudativum multiforme. The original disease described by von Hebra is now called *erythema multiforme minor* or *herpes simplex-associated erythema multiforme* (HAEM). It is strongly associated with a preceding herpetic infection. In contrast, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) usually represent adverse reactions to medications (see Chapter 6). There is, however, overlap in this spectrum of diseases, with herpes being causative in 6% to 10% of cases of SJS, and in some series up to 25% caused by mycoplasma. As treatment and prognosis are related in part to the inciting agent, it is useful to classify EM as follows:

- Herpes simplex-associated EM (HAEM)
- Chronic oral EM
- Mycoplasma-induced EM/SJS (see Chapter 6)
- Contact dermatitis-induced EM (see Chapter 6)
- Drug-induced EM (see Chapter 6)
- Radiation-induced EM (see Chapter 6)
- Idiopathic

Clinical Features

EM minor is a self-limited, recurrent disease, usually of young adults, occurring seasonally in the spring and fall, with each episode lasting 1 to 4 weeks. The individual clinical lesions begin as sharply marginated, erythematous macules, which become raised, edematous papules over 24 to 48 h. The lesions may reach several centimeters in diameter. Typically, a ring of erythema forms around the periphery, and centrally the lesions become flatter, more purpuric, and dusky. This lesion is the classic "target" or "iris" lesion with three zones—central dusky purpura; an elevated, edematous, pale ring; and surrounding macular erythema (Figs 7-1 to 7-3). The central area may be bullous. Typical targets are best observed on the palms and soles. Lesions generally appear symmetrically and acrally, with initial involvement most frequently on the dorsal hands. The dorsal feet, extensor limbs, elbows, knees, palms and soles typically become involved. In about 10% of cases more widespread lesions occur on the trunk. Koebner's phenomenon or photoaccentuation may be observed. Mucosal involvement occurs 25% of the time and is usually limited to the oral mucosa (Figs 7-4 and 7-5). Oral lesions may appear as indurated plaques, target lesions or erosions. An atypical variant of HAEM has been described in women. It consists of outbreaks of unilateral or segmental papules and plaques that may be few in number or solitary. Lesions may be up to 20 cm in diameter. The plaques are erythematous and evolve to have a dusky center, which desquamates. Subcutaneous nodules resembling erythema nodosum may be simultaneously present. Histologic examination shows features of EM, and herpes simplex virus (HSV) DNA is identified in the lesions by polymerase chain reaction (PCR). Acyclovir suppression prevents

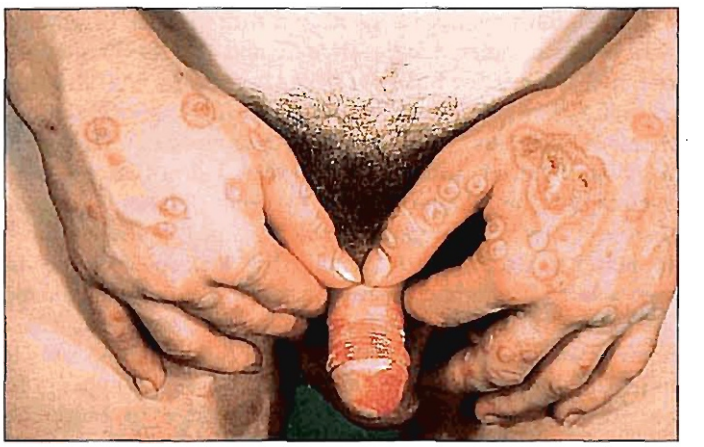

Fig. 7-2 Erythema multiforme involving the dorsal hands and penis. (Courtesy of Brooke Army Medical Center)

Fig. 7-1 Erythema multiforme, target lesions.

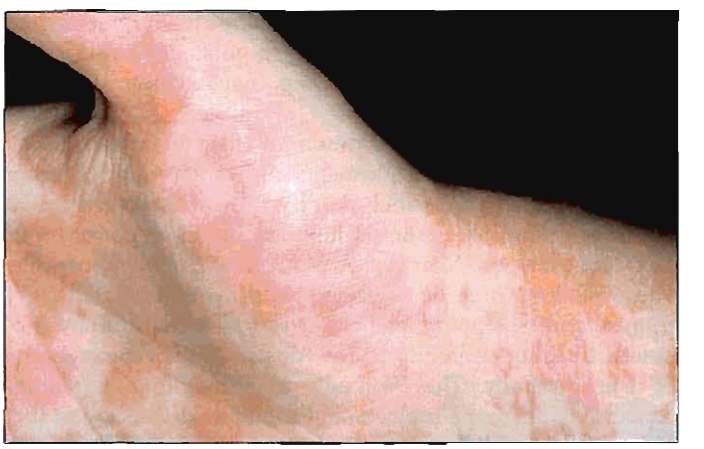

Fig. 7-3 Erythema multiforme, target lesions.

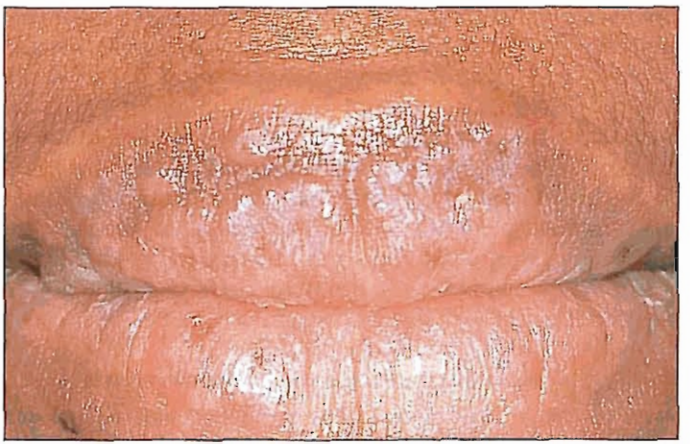

Fig. 7-4 Erythema multiforme involving the lips.

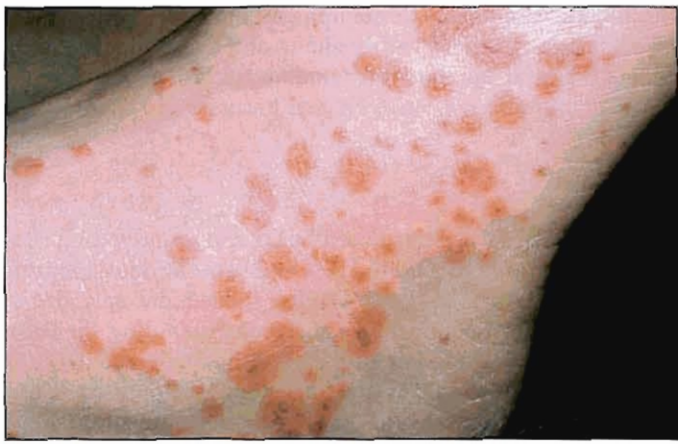

Fig. 7-6 Atypical target lesion in Stevens-Johnson syndrome.

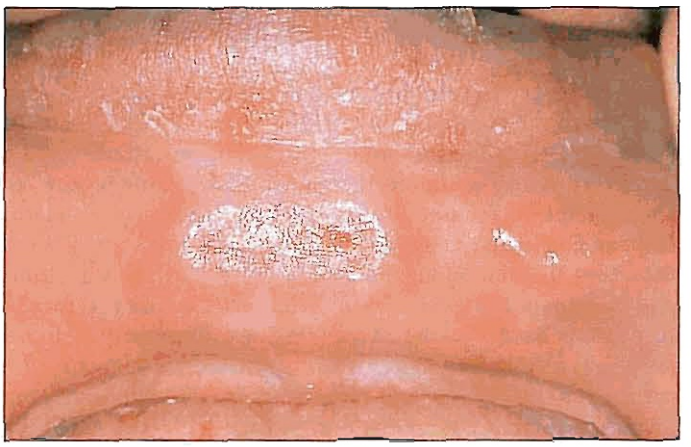

Fig. 7-5 Mucosal lesions of erythema multiforme.

the lesions, and prednisone therapy seems to increase the frequency of attacks.

Mycoplasma-induced SJS is frequently accompanied by a febrile prodrome. The eruption occurs at all ages; it begins diffusely or on the trunk and mucous membranes. The individual lesions are flat, erythematous, or purpuric macules that form incomplete "atypical targets" (Fig. 7-6). Lesions tend to become confluent. Mucous membrane disease is prominent and multiple mucous membranes are generally involved.

Etiologic Factors Typical EM minor is usually associated with a preceding orolabial HSV infection. HAEM lesions appear 1 to 3 weeks (average 10 days) after the herpes outbreak. Episodes of EM minor may not follow every episode of herpes, and some EM outbreaks will not be preceded by a clinically recognizable herpetic lesion. Using PCR and in situ hybridization techniques, HSV DNA and antigens have been found in the lesions of EM minor. The majority of "idiopathic" cases of EM minor are associated with recurrent HSV, and may be successfully treated with suppressive antiviral regimens. SJS is associated with medications and *Mycoplasma* infections. The most common implicated drugs are sulfonamides and other antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), allopurinol, and anticonvulsants (see Chapter 6).

Pathogenesis

Activated T-lymphocytes are present in lesions of EM, with cytotoxic or suppressor cells more prominent in the epidermis and helper T-cells in the dermis. EM minor is linked to HLA type HLA-DQ3.

Histopathology

The histologic features are similar in all entities within the spectrum, from EM minor to TEN, and are not predictive of etiology. The extent of epidermal involvement depends on the duration of the lesion and where in the lesion the biopsy is taken. All lesions are characterized by cellular necrosis, and the concept of dermal EM is no longer accepted.

Biopsies of EM demonstrate a normal basket-weave stratum corneum, suggesting an acute process which has not had time to produce abnormal keratin. Vacuolar interface dermatitis is present, with vacuoles and foci of individual cell necrosis out of proportion to the number of lymphocytes. With time, the necrosis becomes confluent. The dermal infiltrate is largely mononuclear and tends to be primarily around the upper dermal vessels and along the dermoepidermal junction. Leukocytoclastic vasculitis is not observed. Eosinophils may sometimes be present, but are rarely prominent. The presence of eosinophils is not predictive of the etiology. Histologically, EM must be distinguished from fixed drug eruption (which often has a deeper infiltrate, eosinophils and neutrophils, papillary dermal fibrosis, and melanophages around post-capillary venules), graft-versus-host disease (which typically has a more compact stratum corneum and epithelial disorder resembling Bowen's disease), pityriasis lichenoides (which characteristically has a lymphocyte in every vacuole, erythrocyte extravasation, and neutrophil margination within dermal vessels) and lupus erythematosus (which has compact hyperkeratosis, a deeper periadnexal infiltrate, dermal mucin, and basement membrane zone thickening).

Differential Diagnosis

When characteristic target lesions are present, the diagnosis is established clinically. When bullae are prominent, EM must be distinguished from bullous arthropod reactions and autoimmune bullous diseases (pemphigus if mucous membrane involvement is prominent, and bullous pemphigoid if lesions are small and erythema prominent at the periphery of

the bulla). Paraneoplastic pemphigus may produce atypical target lesions, mucosal involvement, and a vacuolar interface dermatitis, and appear very similar to EM major. Use of direct immunofluorescence may be necessary to exclude this possibility.

Treatment

Treatment of EM is determined by its cause and extent. EM minor is generally related to HSV, and prevention of herpetic outbreaks is central to control of the subsequent episodes of EM. A sunscreen lotion and sunscreen-containing lip balm should be used daily on the face and lips to prevent UVB-induced outbreaks of HSV. If this does not prevent recurrences or if genital HSV is the cause, chronic suppressive doses of an oral antiviral drug (acyclovir, valacyclovir, or famciclovir) may be used. This will prevent recurrences in up to 90% of HSV-related cases. Intermittent treatment with systemic antivirals or the use of topical antivirals is of little benefit in preventing HSV-associated EM. In patients whose condition fails to respond adequately to antiviral suppression, dapsone may occasionally be helpful. It should be noted that most cases of EM minor (HAEM) are self-limited and symptomatic treatment may be all that is required. Symptoms related to oral lesions often respond to topical mixtures containing lidocaine, benadryl, and kaolin. In extensive cases of EM minor, systemic steroids have been used, but because they theoretically may reactivate HSV, they are best given concurrently with an antiviral drug. The response to systemic corticosteroids is often disappointing. For patients with widespread EM unresponsive to the above therapies, management is as for severe drug-induced EM (see Chapter 6).

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Oral Erythema Multiforme A unique subset of EM is limited to or most prominent in the oral cavity. Clinically, patients are otherwise well, 60% are female, with a mean age of 43 years. The minority (about one-quarter) have recurrent, self-limited, cyclical disease. The oral cavity is the only site of involvement in 45%, in 30% there is oral and lip involvement, and in 25% the skin is also involved. All portions of the oral cavity may be involved, but the tongue, gingiva, and buccal mucosa are usually most severely affected. Lesions are almost universally eroded, with or without a pseudomembrane. There are no well-designed trials of treatment for this subgroup, but the treatments listed above for EM minor are commonly used. Mixtures containing lidocaine, benadryl, and kaolin are helpful for symptomatic relief. They are best used in a "swish and spit" fashion, and patients should be warned to chew carefully as the anesthetic effect may dampen their gag reflex.

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Gyrate Erythemas: Figurate, Annular, and Circinate

The gyrate erythemas are characterized by clinical lesions that are round, ring-like, polycyclic or arcuate. The primary lesions are erythematous and slightly elevated. There may be a trailing scale, as in erythema annulare centrifugum. In some of these diseases the lesions are transient and migratory and in some they are fixed. Gyrate erythemas often represent the cutaneous manifestations of various infectious and malignant diseases or drug reactions. Certain diseases in this group have specific causes and are discussed in those chapters (erythema marginatum of rheumatic fever; the carrier state of chronic granulomatous disease; and erythema migrans, which is cutaneous borreliosis).

Erythema Annulare Centrifugum Erythema annulare centrifugum (EAC) is the most common gyrate erythema. It is characterized by annular or polycyclic lesions that grow slowly (2–3 mm/day), rarely reaching more than 10 cm in diameter. Characteristically, there is a trailing scale at the inner border of the annular erythema (Fig. 7-7). The surface is typically devoid of crusts or vesicles, although atypical cases with telangiectasia and purpura have been described. Lesions commonly occur on the trunk and proximal extremities. Mucosal lesions are absent.

Histologically, the epidermis will show mild focal spongiosis and parakeratosis. Within the superficial dermis and at times the deep dermis, lymphocytes are organized tightly around the blood vessels in a pattern described as a "coat sleeve" arrangement. Histologically, the gyrate erythemas are divided into the superficial and deep types, but these histologic types do not correlate with etiology.

EAC tends to be recurrent over months to years, waxing and waning in severity. Most cases eventually subside spontaneously. While active, the eruption is sometimes responsive to topical steroids. Topical macrolide therapy and topical calcipotriol have also been reported to be successful.

The majority of cases are idiopathic. Some cases are clearly associated with dermatophytosis or the ingestion of molds, such as those in blue cheese. Other foods, such as tomatoes, are sometimes implicated, and a dietary journal may be helpful. Medications are implicated in some cases, and internal cancer has been found. Laboratory tests should

Fig. 7-7 Erythema annulare centrifugum.

be dictated by the physical examination and associated signs and symptoms. In one study of 66 patients, 48% were found to have an associated cutaneous fungal infection such as tinea pedis, and 13% to have internal malignancies.

The differential diagnosis includes those conditions that can have annular configuration, including granuloma annulare, secondary syphilis, tinea, subacute cutaneous lupus erythematosus sarcoidosis, Hansen's disease, erythema marginatum, erythema migrans, annular urticaria, and mycosis fungoides. Histologic examination, clinical features, and basic laboratory examinations will usually allow these diseases to be excluded.

Erythema Gyratum Repens Erythema gyratum repens (EGR) is a rare disease that is striking and unique in appearance. Lesions consist of undulating wavy bands of slightly elevated erythema with trailing scale over the entire body. Lesions migrate rapidly (up to 1 cm/day) and are characteristically concentric, giving the skin a "wood grain" appearance (Fig. 7-8).

Pruritus may be severe and blood eosinophilia is often found. In more than 80% of cases, an underlying malignancy is found. Lung cancer is the most common associated malignancy, although a wide range of neoplasms has been described. The skin eruption precedes the detection of the malignancy by an average of 9 months. Given the high frequency of malignant disease, patients with EGR should have extensive evaluations to exclude internal malignancy. If the carcinoma is removed, the lesions clear. Otherwise, the eruption is generally resistant to treatment, although a tumor-associated case responsive to cetirizine has been reported. Rarely, EGR may be associated with pulmonary tuberculosis, a preexisting papulosquamous disorder or drug therapy. These cases respond to treatment of the underlying condition or discontinuation of the implicated medication.

Annular Erythema of Infancy Peterson and Jarratt reported a case of 3 months' duration in a 6-month-old boy; lesions were transitory (36–48 h), and the eruption stopped without treatment at age 11 months. They called it *annular erythema of infancy*. A similar case, with more persistent lesions, was reported in a 6-month-old girl; it lasted 11 months without treatment. This condition appears to be exceedingly rare.

Fig. 7-8 Erythema gyratum repens.

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Necrolytic Migratory Erythema (Glucagonoma Syndrome) Necrolytic migratory erythema is a rare syndrome that is usually associated with an islet cell tumor of the pancreas. The eruption occurs in periorificial, flexural, intertriginous, and acral areas, and closely resembles the lesions associated with zinc or other micronutrient deficiency. Annular and arcuate erythematous lesions coalesce to form large plaques with necrosis and slough of the superficial epidermis, followed by erosion or crusting. The condition is poorly responsive to topical therapy with corticosteroid and antifungal medications.

Histologically, findings identical to zinc deficiency and other nutritional deficiencies are seen. There is irregular acanthosis with parakeratosis and crust. The upper third of the epidermis demonstrates pallor and ballooning degeneration of keratinocytes.

Most patients are ill at the presentation of the eruption, with hyperglycemia, anemia, weight loss, diarrhea, atrophic glossitis, and angular cheilitis. Additional laboratory findings may include a low serum zinc level and hypoaminoacidemia. Glucagon levels are elevated. Standard scans of the pancreas may be normal, but angiography will usually detect the neoplasm. Radiolabeled octreotide scans may be useful if the tumor has somatostatin receptors.

The cause of the syndrome is unknown, since some cases are not associated with glucagon-secreting tumors. Amino acid, zinc, and essential fatty acid supplementation has improved the eruption without lowering glucagon levels, suggesting these secondary consequences of hyperglucagonemia are the actual cause of the eruption.

Removal of the tumor leads to resolution. Unfortunately, in more than half the cases, metastases have already occurred at the time of diagnosis. In these patients streptozotocin or octreotide may be used.

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EOSINOPHILIC CELLULITUS (WELLS SYNDROME)

In 1971, Wells described four patients with acute onset of plaques resembling cellulitis that persisted for many weeks. Wells syndrome occurs at all ages and pruritus is common. The condition is typically recurrent, and rarely, the duration of individual episodes may be prolonged. Degranulation of dermal eosinophils produces the flame figures seen in histologic sections. These consist of dermal collagen with adherent eosinophil granules. Eosinophilic panniculitis may also be present.

It is unclear whether Wells syndrome is a distinct disorder sui generis, or a reaction pattern to many possible allergic stimuli. Many (perhaps most) cases represent arthropod reactions. It has also been associated with onchocerciasis, intestinal parasites, varicella, mumps, immunization, drug reactions, myeloproliferative diseases, atopic diathesis, hypereosinophilic syndrome, the Churg–Strauss syndrome, and fungal infection. Expression of the α chain of the IL-2 receptor (CD25) on eosinophils appears to be important in determining the extent of eosinophil degranulation and the degree of tissue damage in eosinophil-mediated disorders, including Wells syndrome. Treatment includes topical and intralesional corticosteroids, oral antihistamines, minocycline, ultraviolet (UV)B, PUVA, dapsone, and low-dose prednisone. Any triggering factor, such as arthropod bites, should be eliminated.

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REACTIVE NEUTROPHILIC DERMATOSES

Like the gyrate erythemas, the reactive neutrophilic dermatoses tend to follow certain stimuli, such as acute upper respiratory infections, or are associated with underlying diseases, such as inflammatory bowel disease and hematologic malignancy. Some of the neutrophilic dermatoses share common triggers, and clinical features may overlap. Patients may exhibit the simultaneous or sequential appearance of two or more of the conditions. In some cases, it may be difficult to firmly establish the diagnosis as one or the other of these disorders. For these reasons, it is clinically useful to think of these diseases as forming a spectrum of conditions expressed in certain individuals by a group of stimuli with various overlapping morphologies.

Erythema Nodosum

Erythema nodosum (EN) is the most commonly diagnosed form of inflammatory panniculitis, with most cases occurring in young adult women. The eruption consists of bilateral, symmetrical, deep, tender, bruise-like nodules, 1 to 10 cm in diameter, located pretibially (Fig. 7-9). Initially the skin over the nodules is red, smooth, slightly elevated, and shiny. The onset is generally acute, frequently associated with malaise, leg edema, and arthritis or arthralgias. Over a few days, the lesions flatten, leaving a purple or blue–green color resembling a resolving bruise. The natural history is for the nodules to last a few days or weeks, appearing in crops, and then to slowly involute.

EN is a reactive process. Specific causes, histopathology, and other features of EN are discussed in Chapter 23. The disorder is grouped with the other neutrophilic dermatoses because it shares common triggers, and the acute phase of

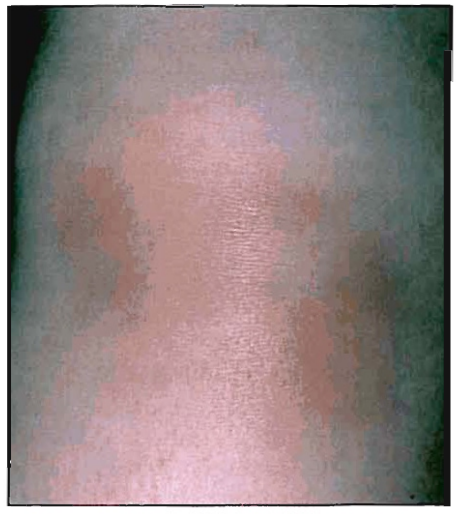

Fig. 7-9 Erythema nodosum.

the disorder is characterized by neutrophils within subcutaneous septae.

Sweet Syndrome (Acute Febrile Neutrophilic Dermatosis)

Since its first description in 1964 by Dr Robert Sweet, as a recurrent febrile dermatosis in women, the spectrum of this syndrome has expanded. Sweet syndrome primarily affects adults, and females outnumber males by about 3:1. In younger adults, female predominance is marked, but in persons older than 50 years of age, the sex ratio is more equal, as cases associated with malignancy have a sex ratio of 1:1. In children, males and females are equally affected. In Europe, cases are more common in the spring and fall. Four subtypes of Sweet syndrome have been described, based on their pathogenesis: the classic type (71%); cases associated with neoplasia (11%); cases associated with inflammatory disease (16%); and cases associated with pregnancy (2%).

The clinical features of all four subtypes are similar, although dusky bullous and necrotic lesions that overlap with pyoderma gangrenosum are more common in patients with associated leukemia. The primary skin lesion is a sharply marginated, rapidly extending, tender, erythematous or violaceous, painful, elevated plaque, 2 to 10 cm in diameter. Lesions may appear intensely edematous (Fig. 7-10) or merely indurated (Fig. 7-11). They typically involve the face, neck, upper trunk, and extremities. They may burn, but do not itch. The surface of the plaques may develop vesiculation or pustulation as a result of an intense dermal inflammatory infiltrate and accompanying dermal edema. Localized Sweet syndrome has been used to describe cases in which lesions are present only on the face, usually the cheeks. Pathergy and koebnerization after trauma or UVB uncommonly occur.

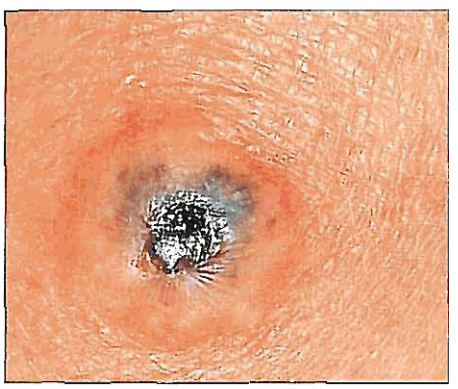

Fig. 7-10 Sweet syndrome, intensely edematous lesion.

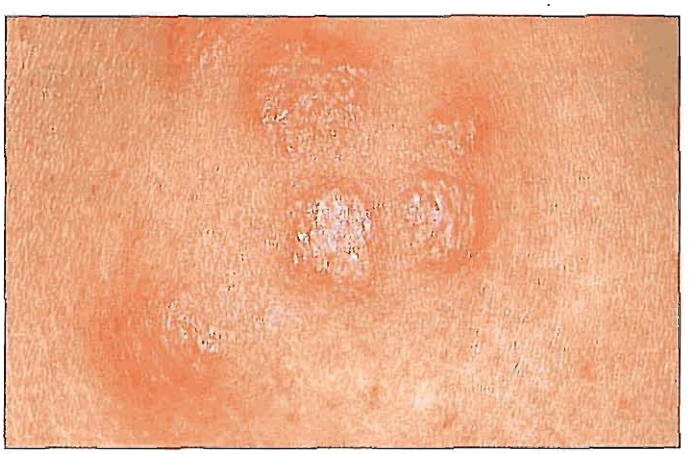

Fig. 7-11 Sweet syndrome, erythematous lesions.

More than three-quarters of patients have systemic findings. The most common is fever, occurring in 50% to 80% of patients. Arthritis, arthralgias, or myalgias occur in one- to two-thirds of cases. Conjunctivitis or episcleritis occurs in about 30% of cases. Oral lesions resembling aphthae occur in 2% or 3% of classic cases but in 10% or more of those associated with hematologic malignancy. Cough, dyspnea, and pleuritis may represent pulmonary involvement. Pulmonary infiltrates and effusions are often seen on chest x-rays of such patients. Rarely, there may be cardiac, renal, hepatic, intestinal, and neurologic involvement. Multifocal sterile osteomyelitis may occur.

Laboratory findings include an elevated sedimentation rate (90%), neutrophilia (70%), leukocytosis (60%), and a left shift (increased bands; 50%). Antineutrophilic cytoplasmic antibodies have been reported. In most cases, an attack lasts 3 to 6 weeks and then resolves. Recurrences may be seen with the same precipitating cause, such as upper respiratory infection. Persistent cases, with new lesions erupting before the old lesions resolve, may continue for many years.

The hallmark of Sweet syndrome is a nodular and diffuse dermal infiltrate of neutrophils with karyorrhexis and massive papillary dermal edema. Leukocytoclastic vasculitis may be present focally, and this does not exclude a diagnosis of Sweet syndrome. Upper dermal edema may be so intense as to form subepidermal bullae.

The majority of cases of Sweet syndrome follow an upper respiratory tract infection and are therefore acute and self-limited. Other associated conditions include infections with *Yersinia*, toxoplasmosis, histoplasmosis, salmonellosis, tuberculosis, tonsillitis or vulvovaginal infections. Sweet syndrome has been reported is association with inflammatory bowel disease, and overlaps with the bowel bypass or "blind loop" syndrome. Cases have also been associated with peripheral ulcerative keratitis and Behçet syndrome.

Hematologic malignancies or solid tumors are present in about 10% of reported cases. Sweet syndrome often presents early in the course of the cancer, when therapy is more efficacious. Associated malignancies are usually hemoproliferative and include leukemias (usually acute myelogenous), lymphomas, anemias, or polycythemias. Solid tumors are of any type but are most commonly genitourinary, breast (in women), or gastrointestinal (in men). Anemia is found in 93% of men and 71% of women with malignancy-associated Sweet syndrome. Thrombocytopenia is seen in half. Solitary or ulcerative lesions are more frequently associated with malignancy.

Pregnancy-associated Sweet syndrome typically presents in the first or second trimester with lesions on the head, neck, and trunk, and less commonly on the upper extremities. Lower-extremity lesions resembling EN may occur. The condition may resolve spontaneously or clear with topical or systemic steroids. It may recur with subsequent pregnancies but there does not seem to be any risk to the fetus.

Medications such as granulocyte colony-stimulating factor have been associated with Sweet-like reactions in the skin. Lesions may occur at the site of injection or at distant sites. Oral contraceptives, trimethoprim–sulfamethoxazole, and

minocycline have also been implicated. All-*trans*-retinoic acid causes terminal differentiation of some leukemic clones, and is used to treat promyelocytic leukemia. After about 2 weeks of treatment, Sweet-like syndrome lesions may appear. Initially these skin lesions may contain immature blasts, making it difficult to distinguish them from leukemia cutis. Later the lesions contain more mature neutrophils. Induction of the skin lesions appears to be related to the desired pharmacologic effect of the medication.

Classic diagnostic criteria for Sweet syndrome exclude cases with histologic evidence of leukocytoclastic vasculitis. However, as focal vasculitis may occur in Sweet syndrome, the criteria have been modified. The two major criteria are the presence of red edematous plaques and a biopsy demonstrating neutrophils, karyorrhexis, and marked papillary dermal edema. Minor criteria include associated symptoms or conditions, laboratory findings, and response to therapy. Patients should have both of the major and two of the minor criteria for diagnosis (Box 7-1). EM can be distinguished by its typical morphology and histologic features. Clinically, both diseases can have red plaques, and central vesiculation can occur. True target lesions are not seen in Sweet syndrome. Bowel-bypass syndrome has skin lesions that on histologic examination are identical to those of Sweet syndrome; fever and arthritis also accompany this condition. Although it is easy to distinguish classic EN from Sweet syndrome, these two conditions share many features. They occur most often in young adult women and frequently follow upper respiratory infections. They may be associated with pregnancy, underlying malignancy, and inflammatory bowel disease. In both, fever and arthritis may occur, along with leukocytosis with neutrophilia. There are many reports of simultaneous or sequential EN and Sweet syndrome in the same patient.

Sweet syndrome has considerable overlap with pyoderma gangrenosum. Both are associated with similar diseases, especially inflammatory bowel disease and hematologic malignancy. In early lesions their histologies are virtually identical. In general, pyoderma gangrenosum lesions are chronic and ulcerative; they begin as papulopustules rather than plaques. Patients with pyoderma gangrenosum usually do not have the associated systemic symptoms or abnormal laboratory findings that are seen with Sweet syndrome. Solitary lesions that begin like Sweet syndrome may vesiculate and form superficial ulcerations—so-called bullous Sweet or bullous pyoderma gangrenosum. Similarly, disseminated vesiculopustular forms of pyoderma gangrenosum with systemic symptoms may closely resemble Sweet syndrome. Sweet syndrome also occurs in patients with Behçet syndrome, another disorder with cutaneous and mucosal lesions often containing neutrophils.

A search for an underlying cause should be undertaken, especially in persons over the age of 50 and those with anemia, thrombocytopenia, or lesions that are bullous or necrotic. The standard treatment is systemic corticosteroids (approximately 1 mg/kg/day oral prednisone). This will result in resolution of fever and skin lesions within days. Potassium iodide has been reported to be effective. Colchicine, dapsone, doxycycline, clofazimine, and NSAIDs may be helpful in chronic or refractory disease. Medication should be continued for several weeks to prevent relapse.

Box 7-1 *Revised diagnostic criteria for the diagnosis of* Sweet syndrome*

Major criteria

1. Abrupt onset of erythematous plaques or nodules, *occasionally with vesicles, pustules, or bullae*
2. Nodular and diffuse neutrophilic infiltration in the dermis with karyorrhexis and massive papillary dermal edema

Minor criteria

1. Preceded by a respiratory infection, gastrointestinal tract infection, or vaccination *or* associated with:
   - Inflammatory disease or infection
   - Myeloproliferative disorders or other malignancy
   - Pregnancy
2. Malaise and fever (>38° C)
3. ESR >20 mm; C-reactive protein positive; peripheral leukocytosis, and left shift
4. Excellent response to treatment with systemic corticosteroids

*Both major and two minor criteria are needed for diagnosis.

Neutrophilic Dermatosis (Pustular Vasculitis) of the Dorsal Hands

Lesions of neutrophilic dermatosis of the dorsal hands present as edematous, pustular or ulcerative nodules or plaques localized to the dorsal hands (Fig. 7-12). Histologically, papillary dermal edema and a nodular and diffuse neutrophilic infiltrate with karyorrhexis are noted. As in Sweet syndrome, leukocytoclastic vasculitis may be present. Individual flares respond to prednisone and dapsone, but recurrences are common. As the clinical appearance, tendency to relapse, response to treatment, and histologic features overlap with those of Sweet syndrome and pyoderma gangrenosum, this condition illustrates the close relationship of the various neutrophilic dermatoses. It is best considered a localized variant of Sweet syndrome or pyoderma gangrenosum.

Neutrophilic Eccrine Hidradenitis

Neutrophilic eccrine hidradenitis is discussed in Chapter 33.

Marshall Syndrome

This rare syndrome is characterized by skin lesions resembling Sweet syndrome, which are followed by acquired

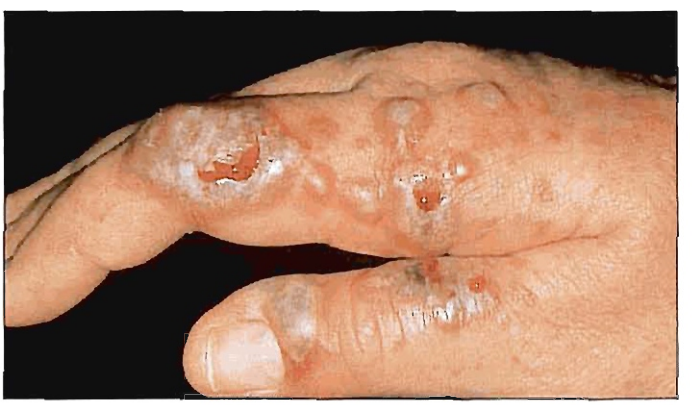

Fig. 7-12 Neutrophilic dermatosis of the dorsal hands.

cutis laxa. Cases occur primarily in children. Small red papules expand to urticarial, targetoid plaques with hypopigmented centers. Histologic evaluation of the skin lesions usually shows a neutrophilic dermatosis virtually identical to Sweet syndrome. Occasionally, an eosinophilic infiltrate will be found. The lesions resolve with destruction of the elastic tissue at the site, producing soft, wrinkled, skin-colored, protuberant, plaques that can be pushed in to the dermis. Elastic tissue in other organs may also be affected, especially the heart and lungs. Some cases may be associated with α_1-antitrypsin deficiency.

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Pyoderma Gangrenosum

Brunsting is credited with the initial clinical description of pyoderma gangrenosum (PG) in 1930. Classic PG begins as an inflammatory pustule with a surrounding halo that enlarges and begins to ulcerate. A primary lesion may not always be seen, and a substantial proportion of lesions appear at sites of trauma (pathergy). Satellite violaceous papules may appear just peripheral to the border of the ulcer and break down to fuse with the central ulcer. Fully developed lesions are painful ulcers with sharply marginated, undermined, blue to purple borders (Fig. 7-13). PG most commonly occurs in adults aged 40 to 60 years, and typically presents on the lower extremities and trunk. Lesions heal with characteristic thin, atrophic scars. "Malignant pyoderma" is no longer used as a diagnosis, according to the investigators at the Mayo Clinic who originally described it. Although ulcerative PG may occur on the head and neck, most cases described originally as malignant pyoderma are cANCA (antibodies to neutrophilic cytoplasmic antigens) positive, and represent cutaneous presentations of Wegener granulomatosis. Pustular PG consists of pustular lesions that generally do not progress to ulcerative lesions. This forme fruste of PG is often seen in patients with inflammatory bowel disease. Pyostomatitis vegetans and subcorneal pustular dermatosis are two other pustular neutrophilic diseases reported in association with PG, sometimes in patients with IgA gammopathy.

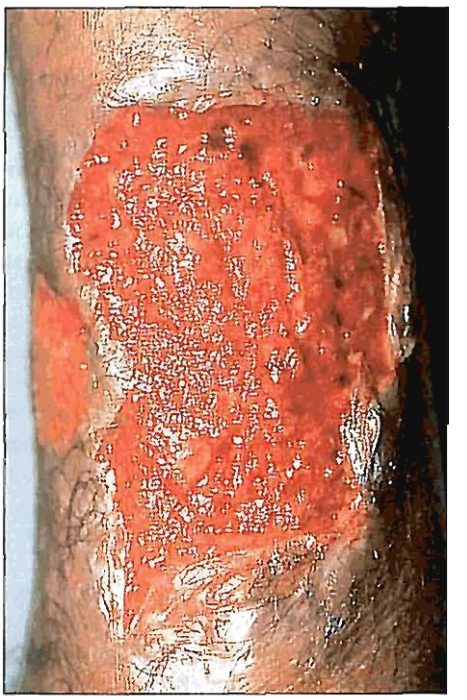

Fig. 7-13 Enlarging ulcer of pyoderma gangrenosum.

"Bullous" PG is more superficial and less destructive than the ulcerative type. These lesions have considerable overlap with what has been called *bullous Sweet syndrome* and are usually seen in patients with leukemia or polycythemia vera. These red plaques become dusky and develop superficial erosions. They are not deep, usually are not undermed, and are less painful than ulcerative PG.

"Vegetative" PG is the least aggressive form of PG. It is synonymous with "superficial granulomatous pyoderma." Lesions present as cribriform chronic superficial ulcerations usually of the trunk. They enlarge slowly and have elevated, granulomatous borders and clean bases. They are rarely painful, generally respond to relatively conservative treatments, and are usually not associated with underlying systemic disease. PG is rare in children. More than 40% of these patients have underlying inflammatory bowel disease, and

another 18% have leukemia. An association of childhood acquired immunodeficiency syndrome (AIDS) and PG has been documented. About one-quarter of children with PG have no underlying disease. Genital and head and neck lesions are not uncommon in children.

Overall, approximately 50% of patients with PG have an associated disease. The most common is inflammatory bowel disease, both Crohn's and ulcerative colitis. Between 1.5% and 5% of patients with inflammatory bowel disease develop PG. The two diseases may flare together or run an independent course. Surgical removal of the diseased intestine may lead to complete remission of PG, or lesions may persist or first appear after removal of the affected bowel. Most patients with PG and inflammatory bowel disease have involvement of the colon. The ulcerative and pustular types of PG are most commonly seen in patients with associated inflammatory bowel disease.

Many other associated conditions have been reported. Leukemia (chiefly acute or chronic myelogenous leukemia), myeloma, monoclonal gammopathy (chiefly IgA), polycythemia vera, myeloid metaplasia, chronic active hepatitis, hepatitis C, human immunodeficiency virus (HIV) infection, systemic lupus erythematosus, pregnancy, PAPA syndrome, and Takaysu arteritis are among the many diseases seen in conjunction with PG. PAPA syndrome is discussed with the other autoinflammatory disorders (see below). More than one-third of PG patients have arthritis, most commonly an asymmetrical, seronegative, monoarticular arthritis of the large joints. Monoclonal gammopathy, usually IgA, is found in 10% of PG patients. Children with congenital deficiency of leukocyte-adherence glycoproteins (LAD) develop PG-like lesions.

Early biopsies of PG show a suppurative folliculitis. The affected follicle is often ruptured. As the lesions evolve, they demonstrate suppurative inflammation in the dermis and subcutaneous fat. Massive dermal edema and epidermal neutrophilic abscesses are present at the violaceous undermined border. These features are not diagnostic and infectious causes must still be excluded.

The clinical picture of PG, in the classic ulcerative form, is very characteristic. Because there are no diagnostic serologic or histologic features, however, PG remains a diagnosis of exclusion. Multiple infections, including mycobacteria, deep fungi, gummatous syphilis, synergistic gangrene, and amebiasis must be excluded with cultures and special studies. Other disorders frequently misdiagnosed as PG include vascular occlusive or chronic venous disease, vasculitis, cancer, and exogenous tissue injury including factitial disease.

PG may be misdiagnosed as a spider bite if there is only a solitary lesion on an extremity. Spider bites tend to evolve more rapidly and may be associated with other systemic symptoms or findings, such a disseminated intravascular coagulation. Various forms of cutaneous large-vessel vasculitis may produce similar clinical lesions and are excluded by histologic evaluation and ancillary studies, such as ANCA and antiphospholipid antibodies tests.

The most difficult diagnosis to exclude is factitial disease. The clinical lesions may be strikingly similar, evolving from small papulopustules to form ulcerations that do not heal. Histologic evaluation will often simply show suppurative dermatitis, since the injected or applied caustic substance may not be identifiable (urine, disinfectants, drain cleaner). Even the most experienced clinician may misdiagnose factitial disease as PG.

Management of PG is challenging. The initial step is to classify the lesion by type. Underlying conditions should be sought, even if no symptoms are found. Treatment of underlying inflammatory bowel disease may lead to improvement. In general, the vegetative type will respond to topical or local measures. The treatment is determined by the severity of the disease and by its rate of progression. In rapidly progressive cases, aggressive early management may reduce morbidity.

Local treatment includes compresses or whirlpool baths, followed by the use of ointment or hydrophilic occlusive dressings. In mild cases, application of potent topical steroidal medications, intralesional steroid injections, or topical 4% cromolyn or tacrolimus may be beneficial, although pathergy may sometimes be seen at sites of injection. Hyperbaric oxygen therapy has been successful in some patients. Systemic steroids can be very effective. Initial doses are in the range of 1 mg/kg or higher. If control is achieved, the dose may be rapidly tapered. If steroid reduction is not possible, a steroid-sparing agent may be added. In cases that are unresponsive to oral corticosteroids, the use of pulse methylprednisolone may be beneficial.

In general, when the disease is aggressive and use of steroidal medications does not lead to rapid resolution, an immunosuppressive agent is added. Azathioprine, cyclophosphamide, and chlorambucil have been effectively used; however, cyclosporin and infliximab result is faster healing and are the immunosuppressives of choice for PG. The lesions often respond dramatically to these agents, including many that have not responded adequately to corticosteroid therapy. Initial doses of cyclosporin of approximately 5 mg/kg/day are effective in most cases. In failures, the dose can be raised to 10 mg/kg/day. The response is independent of any underlying cause. Infliximab is given as intravenous infusions in doses of about 5 mg/kg every few weeks. In very aggressive, rapidly progressive cases, consideration should be given to starting cyclosporin or infliximab treatment early to gain control of the disease. Adalinumab has also been used.

Tacrolimus and mycophenolate mofetil are also effective in some cases, but experience with these agents is much more limited. Sulfapyridine, sulfasalazine, salicylazosulfapyridine, and dapsone may be helpful, either as single agents or in combination with corticosteroids. Clofazimine in doses of 200 to 400 mg/day has been useful in some patients. Minocycline and rarely other antibiotics have anecdotally been successful. Epidermal allo- or auto-grafts may be applied soon after the disease is controlled. Pathergy is rarely noted at the donor site when patients are on adequate immunosuppressive therapy.

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AUTOINFLAMMATORY SYNDROMES

The autoinflammatory syndromes are a group of inherited disorders characterized by bouts of inflammation and periodic fevers. Inflammatory skin lesions are often prominent manifestations, especially acne, PG, and erysipelas- and urticaria-like lesions.

Familial Mediterranean fever (FMF) is an autosomal-recessive syndrome characterized by recurrent attacks of fever, peritonitis, pleuritis, arthritis, and erysipelas-like erythema. It is caused by mutation in the MEFV gene which produces pyrin, but a significant number of patients with a similar phenotype lack a detectable gene defect. Incomplete penetrance is common and many patients with paired mutations lack symptoms or have attenuated symptoms. Colchicine is the mainstay of treatment for these patients and it can reduce the risk of associated amyloidosis. Thalidomide has been reported as successful in a colchicine-resistant patient. Recently, an herbal remedy (a combination of *Andrographis paniculata Nees* with *Eleutherococcus senticosus Maxim*, *Schizandra chinensis Bail*, and *Glycyrrhiza glabra L* extracts) was shown to be effective in a small double-blind, randomized, placebo-controlled study.

The *PAPA syndrome* is an autosomal-dominant syndrome characterized by pyogenic arthritis, PG, and acne, and is caused by proline serine threonine phosphatase-interacting protein (PSTPIP1) or CD2-binding protein 1 (CD2BP1) mutations. PSTPIP1/CD2BP1, a tyrosine-phosphorylated protein involved in cytoskeletal organization, interacts with pyrin, the gene product important in the pathogenesis of FMF.

The *tumor necrosis factor (TNF) receptor associated periodic syndrome (TRAPS)* is similar to FMF, but shows autosomal-dominant inheritance, longer attacks, and a lack of response to colchicine. TRAPS is associated with mutations in the TNFRSF1A gene resulting in decreased serum-soluble TNF receptor. The *hyper IgD syndrome (HIDS)*, associated with mutations in the mevalonate kinase (MVK) gene leading to MVK deficiency, also presents with hereditary periodic fever.

Cryopyrin, the product of the CAIS1 locus, is associated with *familial cold urticaria (familial cold autoinflammatory syndrome)*, an autosomal-dominant syndrome characterized by fever, rash, conjunctivitis, and arthralgia elicited by generalized exposure to cold. The defect has been mapped to a 10-cM region on chromosome 1q44. The same gene and product are associated with the *Muckle-Wells syndrome* and *chronic infantile neurologic cutaneous and articular syndrome (CINCA)*. The Muckle-Wells syndrome is an autosomal-dominant syndrome associated with acute febrile inflammatory episodes comprising abdominal pain, arthritis, urticaria, and multiorgan amyloidosis. Patients with the CINCA syndrome have fever, chronic meningitis, uveitis, sensorineural hearing loss, urticarial skin rash, and a deforming arthritis. They may also have dysmorphic facial appearance, clubbing of the fingers, mild mental retardation and papilledema. The *Blau syndrome*, an autosomal-dominant syndrome with arthritis, uveitis, granulomatous inflammation, and camptodactyly, is associated with mutations in the NOD2/CARD15 gene, which also predisposes to Crohn's disease.

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URTICARIA (HIVES)

Urticaria is a vascular reaction of the skin characterized by the appearance of wheals, generally surrounded by a red halo or flare and associated with severe itching, stinging, or pricking sensations. These wheals are caused by localized edema. Clearing of the central region may occur and lesions may coalesce, producing an annular or polycyclic pattern (Fig. 7-14). Subcutaneous swellings (angioedema) may accompany the wheals. Angioedema may target the gastrointestinal and respiratory tracts, resulting in abdominal pain, coryza, asthma, and respiratory problems. Respiratory tract involvement can produce airway obstruction. Anaphylaxis and hypotension may also occur.

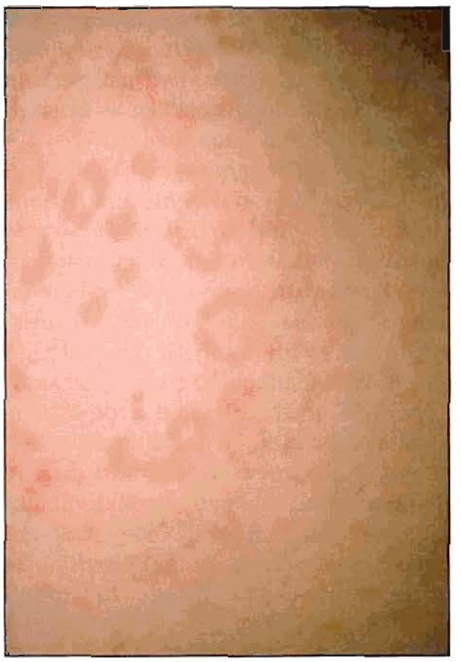

Fig. 7-14 Annular and polycyclic urticaria.

Classification

Acute urticaria evolves over days to weeks, producing evanescent wheals that individually rarely last more than 12 h, with complete resolution of the urticaria within 6 weeks of onset. Daily episodes of urticaria and/or angioedema lasting more than 6 weeks is designated chronic urticaria. Chronic urticaria predominantly affects adults and is twice as common in women as in men.

Nonimmunologic mechanisms can produce mast cell degranulation. Common triggers include opiates, polymyxin B, tubocurarine, radiocontrast dye, aspirin, other NSAIDs, tartrazine, and benzoate. More than 50% of chronic urticaria is idiopathic. Physical stimuli may produce urticarial reactions and represent 7% to 17% of cases of chronic urticaria. The physical urticarias include dermatographic, cold, heat, cholinergic, aquagenic, solar, vibratory, and exercise-induced cases. Physical urticaria commonly occurs in patients with chronic urticaria.

Etiologic Factors

Drugs Drugs are probably the most frequent cause of acute urticaria. Penicillin and related antibiotics are the most frequent offenders (see Chapter 6). A frequently overlooked factor is that penicillin sensitivity may become so exquisite that reactions can occur from penicillin in dairy products.

The incidence of aspirin-induced urticaria has fallen, most likely related to the availability of alternative anti-inflammatory agents. Aspirin-sensitive persons tend to have cross-sensitivity with tartrazine, the yellow azo-benzone dye, and other azo dyes, natural salicylates, and benzoic acid and its derivatives. These are common food additives and preservatives. Aspirin exacerbates chronic urticaria in at least 30% of patients.

Patients may have allergic rhinitis or asthma, nasal polyps, and food-induced anaphylaxis. Mite-contaminated wheat flour has been implicated as an allergen. The nature of the association between aspirin intolerance and mite-induced respiratory allergies is unknown.

Food Foods are a frequent cause of acute urticaria, whereas in chronic urticaria food is a less frequent factor. The most allergenic foods are chocolate, shellfish, nuts, peanuts, tomatoes, strawberries, melons, pork, cheese, garlic, onions, eggs, milk, and spices. Food allergens that may cross-react with latex include chestnuts, bananas, passion fruit, avocado, and kiwi. Exposure to safely cooked fish and shellfish parasitized by *Anisakis simplex* can result in angioedema and urticaria, suggesting that some seafood allergies may be related to exposure to parasite antigens.

If the urticaria is acute and recurrent, food allergy may be suggested by a food diary. Serum radioallergosorbent tests (RASTs) can be used to detect specific IgE, and elimination diets can be of benefit in some patients. One such diet permits inclusion of the following: lamb, beef, rice, potatoes, carrots, string beans, peas, squash, apple sauce, tapioca, preserved pears, peaches, or cherries, Ry-Krisp crackers, butter, sugar, tea without milk or lemon, and coffee without cream. This diet is followed for 3 weeks. If urticaria does not occur, then suspected foods are added one by one and reactions observed. It should be noted that potatoes often contain sulfites, and that some patients may be allergic to the foods contained in the above diet. It is best tried only after a careful history.

The use of food challenges, and scratch and intradermal tests can be misleading. False-positive food challenges are common and an offending food may give a negative prick or intradermal test. Moreover, food additives and preservatives may be responsible.

Food Additives Less than 10% of cases of chronic urticaria are caused by food additives. Natural food additives that may be implicated in urticaria include yeasts, salicylates, citric acid, egg, and fish albumin. Synthetic additives include azo dyes, benzoic acid derivatives, sulfite, and penicillin.

Yeast is widely used in foods. When suspected as the causative agent, bread and breadstuffs, sausages, wine, beer, grapes, cheese, vinegar, pickled foods, catsup, and yeast tablets should be avoided.

Foods containing azo dyes and benzoic acid include candy, soft drinks, jelly, marmalade, custards, puddings, various cake and pancake mixes, mayonnaise, ready-made salad dressings and sauces, packaged soups, anchovies, and colored toothpastes. With the exception of sulfite and penicillin, most food additives can be avoided by eating only meat produce and dairy products. Packaged foods are largely off limits.

Infections Acute urticaria may be associated with upper respiratory infections, especially streptococcal infections. The incidence of streptococcal infection in pediatric cases of acute urticaria varies greatly in reported series. The possibility of localized infection in the tonsils, a tooth, the sinuses, gallbladder, prostate, bladder, or kidney should be considered as a possible cause in cases of acute or chronic urticaria. In some patients, treatment with antibiotics for *Helicobacter pylori* has led to resolution of the urticaria.

Chronic viral infections such as hepatitis B and C may cause urticaria. Acute infectious mononucleosis and psittacosis may also be triggering conditions. Helminths may cause urticaria. Among these are ascaris, ankylostoma, strongyloides, filaria, echinococcus, schistosoma, trichinella, toxocara, and liver fluke.

Emotional Stress Persons under severe emotional stress may have more marked urticaria, no matter what the primary cause is. In cholinergic urticaria emotional stress is a particularly well-documented inciting stimulus.

Menthol Rarely, menthol may cause urticaria. It is found in mentholated cigarettes, candy and mints, cough drops, aerosol sprays, and topical medications.

Neoplasms Urticaria has been associated with carcinomas and Hodgkin's disease. Cold urticaria with cryoglobulinemia has been reported associated with chronic lymphocytic leukemia.

Inhalants Grass pollens, house dust mites, feathers, formaldehyde, acrolein (produced when frying with lard or by smoking cigarettes containing glycerin), castor bean or soybean dust, cooked lentils, cottonseed, animal dander, cosmetics, aerosols, pyrethrum, and molds have been known to cause urticaria.

Alcohol Urticaria may be induced by the ingestion of alcohol. The mechanism of alcohol-induced indirect mast cell stimulation is unknown. Wines generally contain sulfites.

Pathogenesis/Histopathology

Capillary permeability results from the increased release of histamine from the mast cells situated around the capillaries. The mast cell is the primary effector cell in urticarial reactions. Other substances besides histamine may cause vasodilation and capillary permeability, and thereby may possibly become mediators of urticaria and angioedema. These include serotonin, leukotrienes, prostaglandins, proteases, and kinins. The major basic protein of eosinophil granules is abnormally high in the blood of more than 40% of patients with chronic urticaria, even when peripheral blood eosinophil counts are normal, and there are extracellular deposits of it in the skin in about the same proportion of patients.

About one-third of patients with chronic idiopathic urticaria have circulating functional histamine-releasing IgG autoantibodies that bind to the high-affinity IgE receptor. Some patients have IgG that does not bind the IgE receptor, but causes mast-cell degranulation. Thyroid autoantibodies are often present in women with chronic idiopathic urticaria, but clinically-relevant thyroid disease is seldom present. Even in those with thyroid disease, treatment of the thyroid disorder generally does not affect the course of the urticaria.

The histopathologic changes in acute urticaria include mild dermal edema and margination of neutrophils within post-capillary venules. Later, neutrophils migrate through the vessel wall into the interstitium, and eosinophils and lymphocytes are also noted in the infiltrate. Karyorrhexis and fibrin deposition within vessel walls are absent, helping to differentiate urticaria from vasculitis.

A subset of patients have long-lasting, refractory lesions and this has been dubbed "neutrophilic urticaria." Lesions in these patients often persist for longer than 24 h, and biospies demonstrate a neutrophil-rich perivascular infiltrate that lacks karyorrhexis or fibrin deposition within vessels walls. Eosinophils and mononuclear cells are noted in varying proportions. Patients with neutrophilic urticara may present with acute urticaria, chronic urticaria or physical urticaria. Lesional skin demonstrates increased expression of TNF-α and IL-3, whereas IL-8 expression is only minor. As neutrophils are commonly present in urticaria in general, it is likely that cases of neutrophilic urticaria represent urticaria with upregulation of some mast cell-derived cytokines.

Diagnosis

Diagnosis of urticaria and angioedema is usually made on clinical grounds. Lesions in a fixed location for more than 24 h suggest the possibility of urticarial vasculitis, the urticarial phase of an immunobullous eruption, EM, granuloma annulare, sarcoidosis, or cutaneous T-cell lymphoma. If individual wheals last for longer than 24 h, a skin biopsy should be performed.

Clinical Evaluation

Laboratory evaluation should be driven by associated signs and symptoms. Random tests in the absence of a suggestive history or physical findings are rarely cost-effective. A practical evaluation is limited to a detailed history (foods, drugs, aspirin, physical causes) and physical examination. Angioedema in the absence of urticaria may be related to hereditary angioedema or an angiotensin-converting enzyme (ACE)-inhibitor. C1 esterase deficiency does not cause hives, only angioedema. If there is a history of sinus difficulties, particularly if there is palpable tenderness over the maxillary or ethmoid sinuses, radiologic sinus evaluation is recommended. In areas where parasitic disease is common, a blood count to detect eosinophilia is an inexpensive screening test with a fair yield. The blood count may be unreliable if the patient has been on a systemic corticosteroid.

In patients with chronic urticaria, a review of medications, including over-the-counter products, supplements, aspirin and other NSAIDs should be obtained. If the history suggests a physical urticaria, then the appropriate challenge test should be used to confirm the diagnosis. Lesions that burn rather than itch, resolve with purpura or last longer than 24 h should prompt a biopsy to exclude urticarial vasculitis.

A directed history and physical examination should elicit signs or symptoms of thyroid disease, connective tissue disease, changes in bowel or bladder habits, vaginal or urethral discharge, other localized infection, jaundice, or risk factors for hepatitis or Lyme disease. Positive findings should prompt appropriate screening tests. Although sinus x-ray films, a Panorex dental film, a streptococcal throat culture, abdominal ultrasonography, and urinalysis with urine culture (in men, with prostatic massage) may reveal the most common occult infections triggering urticaria, positive cases are almost always associated with some signs or symptoms suggestive of the diagnosis. In patients with chronic angioedema, without classic wheals or symptoms of pruritus, a careful drug history and evaluation of C4 level should be ordered. If C4 is low, an evaluation of C1 esterase inhibitor is appropriate.

Anaphylaxis

Anaphylaxis is an acute and often life-threatening immunologic reaction often heralded by scalp pruritus, diffuse erythema, urticaria, or angioedema. Bronchospasm, laryngeal edema, hyperperistalsis, hypotension, and cardiac arrhythmia may occur. Antibiotics, especially penicillins, other drugs, and radiographic contrast agents are the most common

causes of serious anaphylactic reactions. *Hymenoptera* stings are the next most frequent cause, followed by ingestion of crustaceans and other food allergens. Atopic dermatitis is commonly associated with anaphylaxis regardless of origin. Causative agents can be identified in up to two-thirds of cases and recurrent attacks are the rule. Exercise-induced anaphylaxis is often dependent on priming by prior ingestion of a specific food, or food in general.

Treatment

Acute Urticaria The mainstay of treatment of acute urticaria is administration of antihistamines. In adults, nonsedating antihistamines pose a lower risk of psychomotor impairment. If the cause of the acute episode can be identified, avoiding that trigger should be stressed. In patients with acute urticaria that does not respond to antihistamines, systemic corticosteroids are generally effective. Less rebound is seen with a 3-week tapered course of systemic corticosteroid therapy as compared with shorter courses.

For severe reactions, including anaphylaxis, respiratory and cardiovascular support is essential. A 0.3 mL dose of a 1:1000 dilution of epinephrine is administered every 10 to 20 min as needed. In young children, a half-strength dilution is used. In rapidly progressive cases, intubation or tracheotomy may be required. Adjunctive therapy includes intramuscular antihistamines (25–50 mg hydroxyzine or diphenhydramine every 6 h as needed) and systemic corticosteroids (250 mg hydrocortisone or 50 mg methylprednisolone intravenously every 6 h for two to four doses).

Chronic Urticaria The mainstay for treating chronic urticaria is, again, administration of antihistamines. These should be taken on a daily basis; they should not be prescribed to be taken as needed. The patient should be warned about driving an automobile when first-generation antihistamines are used.

Second-generation H_1 antihistamines (cetirizine, famotidine, loratadine, acrivastine, and azelastine) are large, lipophilic molecules with charged side chains that bind extensively to proteins, preventing the drugs from crossing the blood–brain barrier; thus they produce less sedation in most patients. Long-acting forms are available, and the long half-life of these antihistamines and reduced sedation result in improved compliance and efficacy. Cetirizine (Zyrtec) and some of the other second-generation antihistamines can cause drowsiness in some individuals, particularly in higher doses or when combined with other antihistamines. Doxepin, a tricyclic antidepressant with potent H_1 antihistaminic activity, may be useful and can be added to the existing antihistamine. Doxepin is frequently dosed at bedtime, so much of the drowsiness and dry mouth are gone by morning.

In stubborn cases, dosages of antihistamines that exceed drug labeling are sometimes required. Even second-generation antihistamines may become sedating at higher doses. Fexofenadine is generally well tolerated, even at doses that exceed product labeling. The combination of H_1 and H_2 antihistamines, such as hydroxyzine and cimetidine or ranitidine, may be effective in some cases. Cimetidine or ranitidine should not be used alone for treatment of urticaria, as they may interfere with feedback inhibition of histamine release. Other second-line treatments include phototherapy, calcium-channel antagonists (nifedipine), antimalarial medications, dapsone, gold, azathioprine, low-dose cyclosporin, terbutaline, and methotrexate. Unfortunately, although systemic corticosteroids are effective in suppressing most cases of chronic urticaria, their long-term side effects make their extended use impractical. As soon as the corticosteroid is stopped, hives recur. In addition, if an infection is the trigger, this could be exacerbated by long-term steroid therapy. Topical corticosteroids, topical antihistamines, and topical anesthetics have no role in the management of chronic urticaria.

For local treatment, tepid or cold tub baths or showers may be freely advocated. Topical camphor and menthol can provide symptomatic relief. Sarna lotion contains menthol, phenol, and camphor. In about one-third of cases of chronic idiopathic urticaria, patients have autoantibodies that bind to high-affinity IgE receptors. Such patients may require more aggressive management to include chronic immunosuppressive therapy, plasmapheresis, or intravenous immunoglobulin (IVIG).

Other Uriticarial Variants

Angioedema Angioedema is an acute, evanescent, circumscribed edema that usually affects the most distensible tissues, such as the eyelids, lips, lobes of the ears, and external genitalia, or the mucous membranes of the mouth, tongue, or larynx. The swelling occurs in the deeper parts of the skin or in the subcutaneous tissues and as a rule is only slightly tender, with the overlying skin unaltered, edematous, or, rarely, ecchymotic. There may be a diffuse swelling on the hands, forearms, feet, and ankles. Frequently the condition begins during the night and is found on awakening.

There are two distinct subsets of angioedema. The first is considered a deep form of urticaria and may be observed as solitary or multiple sites of angioedema alone or in combination with urticaria. The action of histamine or similar substances creates vasomotor lability, and pruritus may be a significant feature. The second, angioedema associated with C1 esterase inhibitor deficiency, is not associated with hives and there is no pruritus. Symptoms of pain predominate.

Angioedema may be related to ACE inhibitors.

Hereditary Angioedema Also known as *Quincke edema*, hereditary angioedema (HAE) was originally described and named by Osler in 1888. HAE characteristically appears in the second to fourth decade. Sudden attacks of angioedema occur as frequently as every 2 weeks throughout the patient's life, lasting for 2 to 5 days. Swelling is typically asymmetrical, and urticaria or itching does not occur. The presentation may overlap with that of the autoinflammatory syndromes.

Patients may experience local swelling in subcutaneous tissues (face, hands, arms, legs, genitals, and buttocks); abdominal organs (stomach, intestines, bladder) mimicking surgical emergencies; and the upper airway (larynx) that can be life-threatening. There is little response to antihistamines, epinephrine, or steroids. The mortality rate is high, with death often caused by laryngeal edema. Gastrointestinal edema is manifested by nausea, vomiting, and severe colic, and it may simulate appendicitis so closely that appendectomy is mistakenly performed. The factors that trigger attacks are minor trauma, surgery, sudden changes of temperature, or sudden emotional stress.

Inherited in an autosomal-dominant fashion, HAE is estimated to occur in 1 in 50,000 to 150,000 persons. There are three phenotypic forms of the disease. Type I is characterized by low antigenic and functional plasma levels of a normal C1 esterase inhibitor protein (C1-EI). Type II is characterized by the presence of normal or elevated antigenic levels of a dysfunctional protein. Type III demonstrates normal C1-EI function and normal complement. It has been described only in female members of affected families. Criteria for type III include a long history of recurrent attacks of skin swelling, abdominal pain or upper airway obstruction; absence of urticaria; familial occurrence; normal C1-EI and C4 concentrations; and failure of treatment with antihistamines, corticosteroids, and C1-EI concentrate.

The screening test of choice for types I and II is a C4 level. C4 will be low (< 40% of normal) as a result of continuous activation and consumption. In addition to depressed C4 levels, patients with types I and II also have low C1, C1q, and C2 levels. If the clinical picture and screening tests are positive, a titer of C1-EI should be ordered. C1-EI is a labile protein and sample decay is common. A low C1-EI in the presence of normal C4 levels should raise the suspicion of sample decay, rather than true HAE.

The treatment of choice for acute HAE types I and II is replacement therapy with concentrates or fresh frozen plasma. Short-term prophylaxis (e.g. for patients undergoing dental care, endoscopy, or intubation for surgery) can be obtained from stanozolol, an attenuated androgen. Estrogens in oral contraceptives, in contrast, may precipitate attacks. Antifibrinolytic tranexamic acid, a drug related to ε-aminocaproic acid, has been used to treat acute and chronic disease. Type III does not respond to C1-EI replacement, but may respond to danazol.

Acquired C1 Esterase Inhibitor Deficiency Some patients present with symptoms indistinguishable from HAE, but with onset after the fourth decade of life and lacking a family history. As in HAE, there is no associated pruritus or urticaria. This condition is subdivided into acquired angioedema-I and -II, and an idiopathic form. Acquired angioedema-I is a rare disorder associated with lymphoproliferative diseases. These associations include lymphomas (usually B-cell), chronic lymphocytic leukemia, monoclonal gammopathy, myeloma, myelofibrosis, Waldenström macroglobulinemia, and breast carcinoma. Some patients have detectable autoantibodies to C1-EI.

Acquired angioedema-II is an extremely rare disease defined by the presence of autoantibodies to C1-EI. It is important to realize that autoantibodies directed against C1-EI may also be found in acquired angioedema-I, particularly in patients with B-cell lymphomas, so the diagnosis of acquired angioedema-II is made only when no such underlying condition exists.

The pathophysiology of acquired angioedema-I is unknown but may be related to increased catabolism of C1-EI, since many patients with the disorder have been shown to produce normal amounts of C1-EI. In acquired angioedema-II, hepatocytes and monocytes are able to synthesize normal C1-EI; however, a subpopulation of B-cells secretes autoantibodies to the functional region of the C1-EI molecule.

Management of acute attacks in acquired angioedema-I is directed toward replacement of C1-EI with concentrates or fresh-frozen plasma. Some patients develop progressive resistance to the infusions. Antifibrinolytic agents such as aminocaproic acid or tranexamic acid may be beneficial, and are more effective than antiandrogen therapy. Synthetic androgens, such as danazol, may be helpful in angioedema-I; however, androgens are ineffective in treating patients with acquired angioedema-II, stressing the importance of identifying these patients. Immunosuppressive therapy has been shown to be effective in the treatment of acquired angioedema-II by decreasing autoantibody production. Systemic corticosteroids may be temporarily effective. Plasmapheresis is another consideration.

Episodic Angioedema with Eosinophilia Episodic angioedema or isolated facial edema may occur with fever, weight gain, eosinophilia, and elevated eosinophil major basic protein. The disorder is not uncommon, and there is no underlying disease. Increased levels of IL-5 have been documented during periods of attack. Treatment options include administration of systemic steroidal medications, antihistamines, and IVIG.

Schnitzler Syndrome The rare disorder Schnitzler syndrome is a combination of chronic, non-pruritic urticaria, fever of unknown origin, disabling bone pain, hyperostosis, increased erythrocyte sedimentation rate, and monoclonal IgM gammopathy. Pruritus is not generally a feature. The age of onset ranges from 29 to 77 years, without gender predilection. In some cases the IgM gammopathy progresses to neoplasia, especially Waldenström macroblobulinemia. Effective therapy has not been determined, although the bone pain and urticarial lesions respond to systemic corticosteroids in some patients.

Physical Urticarias Specific physical stimuli are the cause of approximately 20% of all urticarias. They occur most frequently in persons between the ages of 17 and 40. The most common form is dermatographism followed by cholinergic and cold urticaria. Several forms of physical urticaria may occur in the same patient. Physical urticarias, particularly dermatographism, delayed pressure, cholinergic, and cold urticaria, are frequently found in patients with chronic idiopathic urticaria.

Dermatographism

Dermatographism is a sharply localized edema or wheal with a surrounding erythematous flare occurring within seconds to minutes after the skin has been stroked (Fig. 7-15). It affects 2% to 5% of the population. Dermatographism may arise spontaneously after drug-induced urticaria and persist for months. It has also been reported to be associated with the use of the H_2 blocker famotidine. It may occur in hypo- and hyper-thyroidism, infectious diseases, diabetes mellitus, and during onset of menopause. It may be a cause of localized or generalized pruritus. Antihistamines suppress this reaction. The addition of an H_2 antihistamine may be of benefit.

Cholinergic Urticaria

Cholinergic urticaria, produced by the action of acetylcholine on the mast cell, is characterized by minute, highly pruritic, punctate wheals or papules 1 to 3 mm in diameter

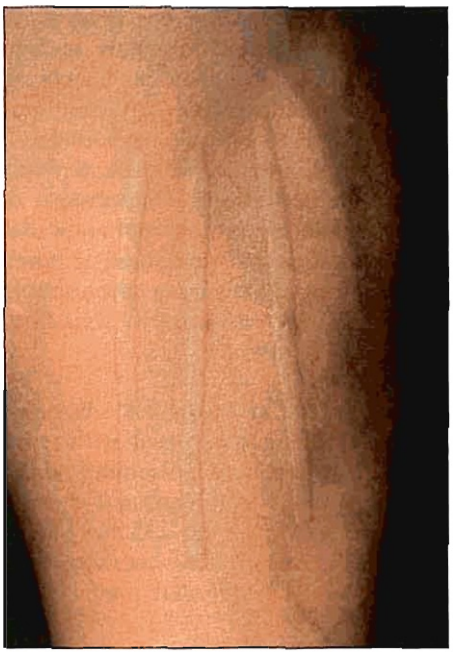

Fig. 7-15 Dermatographism.

Fig. 7-16 Cholinergic urticaria, small papules with surrounding large erythematous flare.

and surrounded by areas of erythema (Fig. 7-16). These lesions occur primarily on the trunk and face. The condition spares the palms and soles. Lesions persist for 30 to 90 min and are followed by a refractory period of up to 24 h. Bronchospasm may occur. Familial cases have been reported.

The lesions may be induced in the susceptible patient by exercise, emotional stress, increased environmental temperature, or intradermal injection of nicotine picrate or methacholine. Sometimes an attack may be aborted by rapid cooling of the body, as by taking a cold shower. A refractory period with no lesions occurs for approximately 24 h after an attack. Cholinergic dermatographism is noted in some patients.

Treatment with antihistamines is often effective if dosage is adequate. Attenuated androgens, such as danazol, may be of benefit in refractory cases. Provocative tests include exercise, a warm bath to raise core temperature by 0.7 to 1.0° C (1.2 to 1.8° F), or a methacholine skin test.

Adrenergic Urticaria

Urticaria may be attributable to norepinephrine. The eruption consists of small (1–5 mm) red macules and papules with a pale halo, appearing within 10 to 15 min after emotional upset, coffee or chocolate. Serum catecholamines, norepinephrine, dopamine, and epinephrine may rise markedly during attacks, whereas histamine and serotonin levels remain normal. Propranolol in a dosage of 10 mg four times a day is effective; atenolol has been ineffective. A provocative test consists of intradermal administration of 3 to 10 ng of norepinephrine.

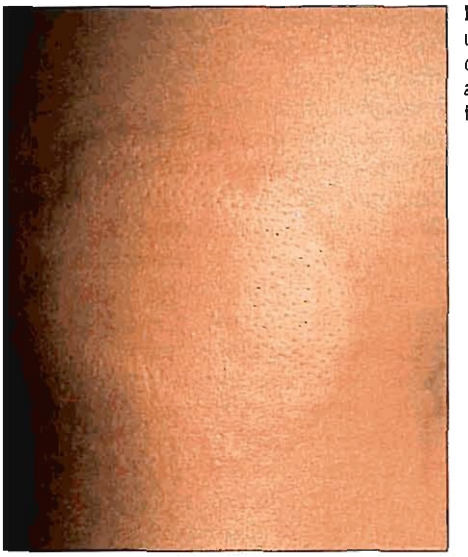

Fig. 7-17 Cold urticaria after an ice cube had been applied to the site for 3 min.

Cold Urticaria

Exposure to cold may result in edema and whealing on the exposed areas, usually the face and hands. The urticaria does not develop during chilling, but on rewarming. This *heterogenous group of disorders is classified into primary* (essential), secondary, and familial cold urticaria.

Primary (essential) cold urticaria is not associated with underlying systemic diseases or cold reactive proteins. *Symptoms are usually localized to the areas of cold exposure* although respiratory and cardiovascular compromise may develop. Fatal shock may occur when these persons go swimming in cold water or take cold showers. This type of cold urticaria usually begins in adulthood. *It is usually* ice-cube test positive (Fig. 7-17).

The treatment of primary cold urticaria is with doxepin in doses from 25 mg at bedtime to 50 mg twice a day, or cyproheptadine 4 mg three times a day. Good therapeutic responses to the second-generation antihistamines acrivastine and cetirizine have been reported, and these agents are less likely to result in sedation. Cetirizine and zafirlukast in combination are more effective than either drug given alone. Ketotifen may also be effective. Although this drug is not marketed in the US, patients in southern states have been known to obtain it in Mexico. Corticosteroid medications are ineffective.

Desensitization by repeated, increased exposures to cold has been effective in some cases. In one report, successful desensitization was induced in an 18-year-old patient with severe cold urticaria. Tolerance in a small area of the skin occurred by repeated applications of an ice cube at 30-min intervals for 7 h, followed by forearm immersion in cold water hourly for 4 h. The other limbs were then treated one at a time, and finally the trunk. After a week, the patient was able to tolerate whole-body immersion in cold water for

5 min without urticaria. He maintained this "desensitization" with a 5-min cold shower every 12 h. He was free from urticaria for 6 months, continuing his daily cold showers. This sort of regimen is only suitable in rare cases. There is some tendency for cold urticaria to disappear after months, although about 50% of patients have symptomatic disease for years.

As a provocative test, a plastic-wrapped ice cube is applied to the skin for 5 to 20 min. If no wheal develops, the area should be fanned for an additional 10 min. The use of a combination of cold and moving air is, in some cases, more effective in reproducing lesions than is cold alone. The provocative test is not performed if secondary cold urticaria is being considered.

Secondary cold urticaria is associated with an underlying systemic disease, such as cryoglobulinemia. Other associations include cryofibrinogenemia, multiple myeloma, secondary syphilis, hepatitis, and infectious mononucleosis. Patients may have headache, hypotension, laryngeal edema, and syncope. An ice-cube test is not recommended, since it can precipitate vascular occlusion and tissue ischemia.

Familial cold urticaria is grouped with the other autoinflammatory syndromes. The lesions produce a burning sensation rather than itching. They may have cyanotic centers and surrounding white halos, and last for 24 to 48 h. They may be accompanied by fever, chills, headache, arthralgia, myalgia, and abdominal pain. A prominent feature is leukocytosis, which is the first observable response to cold. Familial cold urticaria will yield a negative result to an ice-cube test. Stanozolol therapy has been shown to be effective in treating three of eight patients.

Heat Urticaria

Within 5 min after the skin has been exposed to heat above 43° C (109.4° F), the exposed area begins to burn and sting and becomes red, swollen, and indurated. This rare type of urticaria may also be generalized and is accompanied by cramps, weakness, flushing, salivation, and collapse. Heat desensitization may be effective. As a provocative test, apply a heated cylinder, 50 to 55° C (122–131° F), to a small area of skin of the upper body for 30 min.

Solar Urticaria

Solar urticaria appears soon after unshielded skin is exposed to sunlight. It is classified by the wavelengths of light that precipitate the reaction. Visible light can trigger solar urticaria, and sunblocks may not prevent it. Treatment is sun avoidance, sunscreens, antihistamines, repetitive phototherapy, and PUVA. (Solar urticaria is reviewed more extensively in Chapter 3.)

Pressure Urticaria (Delayed Pressure Urticaria)

Pressure urticaria is characterized by the development of swelling with pain that occurs 3 to 12 h after local pressure has been applied. It occurs most frequently on the feet after walking and on the buttocks after sitting. It is unique in that there may be a latent period of as much as 24 h before lesions develop. Arthralgias, fever, chills, and leukocytosis can occur. The pain and swelling last for 8 to 24 h. Pressure urticaria may be seen in combination with other physical urticarias. As a provocative test, a 15-lb weight is applied to the skin for 20 min and the area inspected after 4 to 8 h.

The combination of montelukast and an antihistamine has been used effectively. Systemic corticosteroids are often therapeutic, but are generally unsuitable for long-term use. High-dose IVIG is effective in some cases refractory to other treatment.

Exercise-Induced Urticaria

Although both cholinergic urticaria and exercise urticaria are precipitated by exercise, they are distinct entities. Raising the body temperature passively will not induce exercise urticaria, and the lesions of exercise urticaria are larger than the tiny wheals of cholinergic urticaria. Urticarial lesions appear 5 to 30 min after the start of exercise. Anaphylaxis may be associated. Atopy is common in these patients and some have documented food allergy. Avoiding these allergens may improve symptoms.

Therapy with H_1 and H_2 antihistamines may be partially effective. Self-injectable epinephrine kits are recommended for those rare patients with episodes of anaphylaxis manifesting respiratory symptoms. Exercise is a provocative test.

Vibratory Angioedema

Vibratory angioedema, a form of physical urticaria, may be an inherited autosomal-dominant trait, or it may be acquired after prolonged occupational vibration exposure. Dermatographism, pressure urticaria, and cholinergic urticaria may occur in affected patients. Plasma histamine levels are elevated during attacks. The appearance of the angioedema is usually not delayed. The treatment is antihistamines. As a provocative test, laboratory vortex vibration is applied to the forearm for 5 min.

Aquagenic Urticaria

This rare condition is elicited by water or seawater at any temperature. Pruritic wheals develop immediately or within minutes at the sites of contact of the skin with water, irrespective of temperature or source, and clear within 30 to 60 min. Sweat, saliva, and even tears can precipitate a reaction. Aquagenic urticaria may be familial in some cases or associated with atopy or cholinergic urticaria. Systemic symptoms have been reported to include wheezing, dysphagia, and respiratory distress. The pathogenesis is unknown but may be associated with water-soluble antigens that diffuse into the dermis and cause histamine release from sensitized mast cells.

Whealing may be prevented by pretreatment of the skin with petrolatum. Many antihistamines have been effective. PUVA appears to prevent skin lesions but may not prevent the symptoms of pruritus. The provocative test is to apply water compresses (35° C [95° F]) to the skin of the upper body for 30 min.

Galvanic Urticaria

Galvanic urticaria has been described after exposure to a galvanic device used to treat hyperhidrosis. The relationship of this condition to other forms of physical urticaria remains to be established.

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CHAPTER

8 Connective Tissue Diseases

Lupus erythematosus (LE), dermatomyositis, scleroderma, rheumatoid arthritis, Sjögren syndrome, eosinophilic fasciitis, mixed connective tissue disease, and relapsing polychondritis are classified as connective tissue diseases. Basic to them all is a complex array of autoimmune responses that target or affect collagen or ground substance.

LUPUS ERYTHEMATOSUS

LE may manifest as a systemic disease or in purely cutaneous forms. Significant overlap occurs and chronic skin lesions do not equate with purely cutaneous disease. Chronic discoid lesions may be seen in patients with severe systemic lupus erythematosus (SLE). A number of patients with verrucous LE or lupus panniculitis have systemic disease, and most patients with subacute cutaneous LE have at least some systemic symptoms, although most do not meet the current American College of Rheumatology (ACR) criteria for SLE. Cutaneous manifestations of LE are classified as in Box 8-1.

Chronic Cutaneous Lupus Erythematosus

Discoid Lupus Erythematosus Discoid lupus erythematosus (DLE) generally occurs in young adults, with women outnumbering men 2:1. Lesions begin as dull red macules or indurated plaques that develop an adherent scale, and evolve with atrophy, scarring, and pigment changes (Fig. 8-1). In darker skinned individuals, lesions typically demonstrate areas of both hyper- and de-pigmentation. In lighter skinned patients, the plaques may appear gray or have little pigment alteration. The hyperkeratosis characteristically extends into patulous follicles, producing carpet tack-like spines on the undersurface of the scale. These spines have been called carpet tacks or *langue au chat* (cat's tongue).

Very small lesions of DLE may be mistaken for actinic keratoses. Some early discoid lesions are very superficial, resembling mild seborrheic dermatitis. Others may be brightly erythematous or even urticarial. Sometimes erythema is minimal, especially in scalp lesions. This may produce the clinical appearance of a noninflammatory alopecia, although a biopsy demonstrates deep nodular and perifollicular lymphoid infiltrates.

Localized Discoid Lupus Erythematosus

Discoid lesions are usually localized above the neck. Favored sites are the scalp, bridge of the nose, malar areas, lower lip, and ears. The concha of the ear and external canal are frequently involved. Some patients present with periorbital edema and erythema. On the scalp most lesions begin as erythematous patches or plaques that evolve into white, often depressed, hairless patches. Perifollicular erythema and the presence of easily extractable anagen hairs are signs of active disease and are helpful in monitoring the response to therapy. Scarred areas may appear completely smooth, or may demonstrate dilated follicular openings in the few remaining follicles. Itching and tenderness are common and may rarely be severe. On the lips lesions may be gray or red and hyperkeratotic. They may be eroded and are usually surrounded by a narrow, red inflammatory zone. In one study, 24% of DLE patients had mucosal involvement of the mouth, nose, eye, or vulva. Rarely, aggressive squamous cell carcinoma arises in long-standing lesions of DLE.

Box 8-1 Classification of cutaneous manifestations of lupus erythematosus

I. Chronic cutaneous LE
A. Discoid LE
   1. Localized
   2. Disseminated
B. Verrucous (hypertrophic) LE (Behçet): usually acral and often lichenoid
C. Lupus erythematosus—lichen planus overlap
D. Chilblain LE
E. Tumid lupus
F. Lupus panniculitis (LE profundus)
   1. With no other involvement
   2. With overlying discoid LE
   3. With systemic LE

II. Subacute cutaneous LE
A. Papulosquamous
B. Annular
C. Syndromes commonly exhibiting similar morphology
   1. Neonatal LE
   2. Complement deficiency syndromes
   3. Drug induced

III. Acute cutaneous LE: localized or generalized erythema or bullae, generally associated with SLE

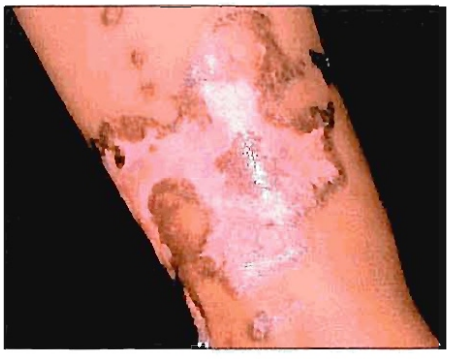

Fig. 8-1 Dyspigmentation and scarring of discoid lupus erythematosus.

Generalized Discoid Lupus Erythematosus

Generalized DLE is less common than localized DLE. All degrees of severity are encountered. Most often the thorax and upper extremities are affected in addition to the head and neck. The scalp may become quite bald with striking patterns of hyper- and de-pigmentation. Diffuse scarring may involve the face and upper extremities. Laboratory abnormalities, such as an elevated sedimentation rate, elevated antinuclear antibodies, single-stranded (ss)DNA antibodies or leukopenia are more common with this form of LE than with localized DLE.

The course of DLE is variable, but 95% of cases confined to the skin at the outset will remain so. Progression from purely cutaneous DLE to SLE is uncommon. However, patients with SLE frequently have discoid lesions. These patients generally have systemic involvement early in the course of their disease, rather than evolving from chronic cutaneous LE to SLE. Fever and arthralgia are common in patients with SLE and discoid lesions. In patients with systemic symptoms, abnormal laboratory tests, such as elevation of antinuclear antibodies (ANAs), antibodies to double-stranded (ds)DNA and C1q, leukopenia, hematuria, and proteinuria help to identify patients with SLE and give an indication of prognosis.

Childhood Discoid Lupus Erythematosus

Among children with DLE a lack of female predominance, a low frequency of photosensitivity, and a higher progression to SLE have been noted. In most other respects, the clinical presentation and course are similar to those in adults.

Histology

The epidermis is usually thin with effacement of the rete ridge pattern. Compact hyperkeratosis without parakeratois is characteristic, and follicular plugging is typically prominent. Hydropic degeneration of the basal layer of the epidermis and follicular epithelium results in pigmentary incontinence. A patchy perivascular and periadnexal lymphoid inflammatory infiltrate occurs in the superficial and deep dermis. The infiltrate characteristically surrounds vessels, follicles, and the eccrine coil. Increased mucin is often present, and may be visible as deposition of a blue to amphophilic substance between collagen bundles, or merely as a widening of the space between the bundles. Thickening of the basement membrane zone may be prominent.

The histology varies with the stage of the lesion. Acute lesions show only patchy lymphoid inflammation and vacuolar interface dermatitis. Lesions established for several months begin to show hyperkeratosis, basement membrane thickening, and dermal mucin. Chronic, inactive lesions show atrophy, with postinflammatory pigmentation and scarring throughout the dermis. At this stage, the inflammatory infiltrate is sparse to absent. Pilosebaceous units, except for "orphaned" arrector muscles, are destroyed. At this stage, the dermis appears fibrotic, but an elastic tissue stain can still distinguish the diffuse dermal scar of lupus from the focal wedge-shaped superficial scars of lichen planopilaris or folliculitis decalvans. Direct immunofluorescence (DIF) testing of lesional skin is positive in more than 75% of cases, providing that the lesions have been active for at least several months. Transporting specimens in normal saline may result in a higher yield than freezing or Michel's transport medium, if the specimen can reach the lab within 24 h. Early lesions usually have negative or nonspecific immunofluorescent findings, whereas established lesions usually demonstrate strong continuous granular deposition of immunoglobulin and complement located at the dermoepidermal junction. Uninvolved skin is negative, and the biopsy should always be from lesional skin of a well established inflammatory lesion.

Differential Diagnosis

DLE must often be differentiated from seborrheic dermatitis, rosacea, lupus vulgaris, sarcoidosis, drug eruptions, actinic keratosis, Bowen's disease, lichen planus, tertiary syphilis, polymorphous light eruption, and lymphocytic infiltration (Jessner). Immunoglobulin deposits distinguish DLE from the latter conditions. LE also demonstrates predominantly CD4+ lymphocytes, whereas Jessner's infiltrate may be composed largely of CD8+ lymphocytes. Seborrheic dermatitis does not show atrophy, alopecia, or dilated follicles, and has greasy, yellowish scale without follicular plugs. Acral, lip, and scalp lesions of chronic cutaneous LE may demonstrate lichenoid dermatitis histologically. In these cases, the presence of continuous granular immunoglobulin in addition to cytoid bodies is a helpful distinguishing feature.

In rosacea, atrophy does not occur and pustules are nearly always found. Apple-jelly nodules (granulomas) are seen with diascopy in lupus vulgaris. Sunlight-sensitizing agents, such as sulfonamides, may produce lesions similar to LE, as phototoxic reactions demonstrate vacuolar interface dermatitis. It may be necessary to differentiate syphilis and sarcoid by biopsy and serologic testing. Polymorphous light eruption (PMLE) is distinguished by the absence of scarring and the presence of intensely edematous plaques and papules. DIF is generally negative or nonspecific in PMLE.

Verrucous (Hypertrophic) Lupus Erythematosus

Non-pruritic papulonodular lesions may occur on the arms (Fig. 8-2) and hands, resembling keratoacanthoma or hypertrophic lichen planus (LP). Some of these patients have

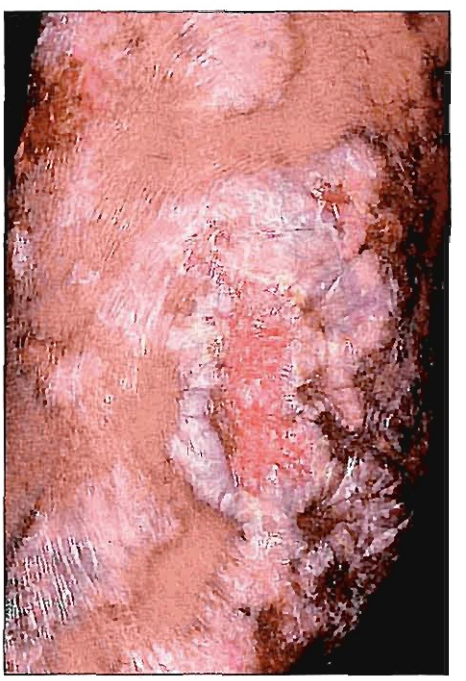

Fig. 8-2
Hypertrophic lupus erythematosus, indurated hyperkeratotic plaques with ulceration.

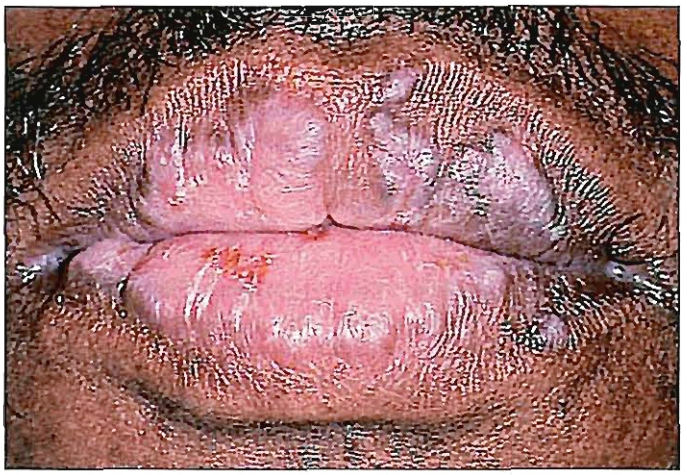

Fig. 8-3 Lip involvement in hypertrophic lupus erythematosus.

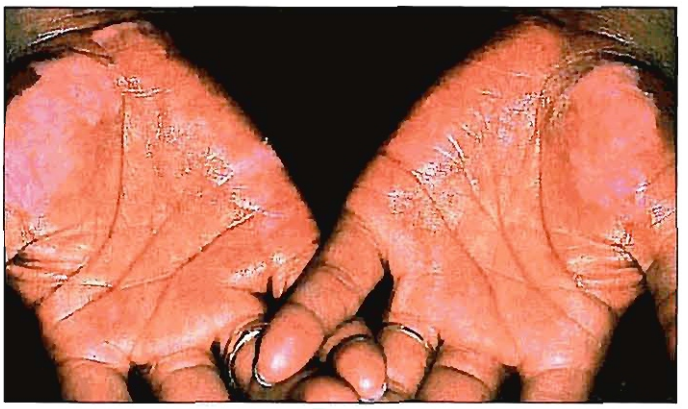

Fig. 8-4 Characteristic palmar involvement in lupus lichen planus overlap syndrome.

SLE, while some have only cutaneous involvement. The lips (Fig. 8-3) and scalp may also demonstrate lesions that resemble LP or lichen planopilaris (LPP). Histologic sections of these lesions typically demonstrate a lichenoid dermatitis, and a careful examination for other characteristic skin lesions of LE or LP, as well as DIF testing, may be critical in establishing a diagnosis. Basement membrane zone thickening, dermal mucin, eccrine coil involvement, and subcutaneous nodular lymphoid infiltrates are features of LE that are not found in LP. DIF may demonstrate continuous granular immunoglobulin deposition in cases of lichenoid LE. In cases where only cytoid bodies are present, they tend to be restricted to the dermoepidermal junction rather than extending deep into the follicle or fibrous tract remnants. Shaggy fibrin may be seen in both LPP and LE, but tends to extend deep into the follicle in cases of LPP.

Lupus Erythematosus–Lichen Planus Overlap Syndrome In addition to the cases of hypertrophic LE with lichenoid histology discussed above, there are patients with a true overlap syndrome with features of both LE and LP. The lesions are usually large, atrophic, hypopigmented, red or pink patches and plaques. Pigment abnormalities become prominent over time, and fine telangiectasia and scaling are usually present. The extensor aspects of the extremities and midline back are typically affected. Prominent palmoplantar involvement is characteristic and tends to be the most troublesome feature for these patients (Fig. 8-4). Nail dystrophy and anonychia may occur. Scarring alopecia and oral involvement have been noted in some patients. The histology of individual lesions has features of LP and/or LE. DIF usually suggests the former, but immuofluorescence may demonstrate a continuous granular deposition of immunoglobulin. Response to treatment is poor, though potent topical corticosteroids, dapsone, thalidomide or isotretinoin may be effective. Some patients require immunosuppressive therapy with agents such as mycophenolate mofetil or azathioprine. It should also be noted that antimalarials can occasionally produce a lichenoid drug eruption in patients with LE.

Chilblain Lupus Erythematosus Chilblain LE (Hutchinson) is a chronic, unremitting form of LE with the fingertips, rims of ears, calves, and heels affected, especially in women. It is usually preceded by DLE on the face. Systemic involvement is sometimes seen. Mimicry of sarcoidosis may be striking. Cryoglobulins and antiphospholipid antibody should also be sought.

Tumid Lupus Erythematosus Tumid LE is a rare, but distinctive entity. Patients present with edematous erythematous plaques, usually on the trunk. Histologically, the lesions demonstrate a patchy superficial and deep perivascular and periadnexal lymphoid infiltrate that frequently affects the eccrine coil. Dermal mucin deposition is typical and may be striking. The lesions generally respond readily to antimalarials. Tumid LE shares may features with reticular erythematous mucinosis, and some authorities consider them to be closely related entities.

Lupus Erythematosus Panniculitis (Lupus Erythematosus Profundus) Patients with this type of LE develop subcutaneous nodules that are commonly firm, sharply defined, and nontender. The proximal extremities are usually involved. Usually the overlying skin is normal, but overlying discoid or tumid lesions may occur. Some cases are discovered incidentally when an unrelated lesion is biopsied. The lesions may heal with deep depressions from loss of the panniculus. LE panniculitis is characteristically chronic and occurs most often in women between the ages of 20 and 45. Many patients have DLE at other sites, or less typically in the overlying skin.

Histologic sections demonstrate lymphoid nodules in the subcutaneous septae, necrosis of the fat lobule, and fibrinoid or hyaline degeneration of the remaining lipocytes. Lipomembranous change, resembling frost on a window pane, is more typical of stasis panniculitis (lipodermatosclerosis), but may be noted focally in LE panniculitis. The overlying epidermis may show basal liquefaction and follicular plugging, or may be normal. It is not uncommon to see dermal lymphoid nodules or vertical columns of lymphoid cells in fibrous tract remnants. Dermal mucin may be prominent and dermal collagen hyalinization (resembling that seen in morphea) may be present. Continuous granular deposition of immunoglobulin and C3 may be seen at the dermoepidermal junction. In active cases, abundant fibrin is usually noted in the panniculus.

The most important entity to consider in the differential diagnosis is subcutaneous panniculitis-like lymphoma.

Important clues include the presence of lipocytes rimmed by atypical lymphocytes, and the presence of constitutional symptoms. Erythrophagocytosis may be present focally, and T-cell clonality can usually be demonstrated. The infiltrate may be CD8 dominant or may label strongly for CD56 (as in natural killer cell lymphoma) or CD30 (as in anaplastic lymphoma). CD5 and CD7 expression may be reduced (abherrent loss of pan-T-markers). Unfortunately, T-cell clonality, erythrophagocytosis, CD8 predominance, and loss of CD5 or CD7 may also be seen in cases of LE panniculitis that respond to antimalarials or corticosteroids and do not progress to clinical lymphoma. Taken together, these data suggest that some cases of lymphoma may be virtually indistinguishable from LE panniculitis or that some cases of LE panniculitis represent an abortive lymphoid dyscrasia.

Subacute Cutaneous Lupus Erythematosus

Sontheimer, Thomas, and Gilliam in 1979 described a clinically distinct subset of cases of LE to which they gave the name *subacute cutaneous lupus erythematosus (SCLE)*. Patients are most often white women aged 15 to 40. SCLE patients make up approximately 10% to 15% of the LE population. Lesions are scaly and evolve as polycyclic annular lesions (Fig. 8-5) or psoriasiform plaques. The lesions vary from red to pink with faint violet tones. The scale is thin and easily detached, and telangiectasia or dyspigmentation may be present. Follicles are not involved, the lesions tend to be transient or migratory, and there is no scarring. Lesions tend to occur on sun-exposed surfaces of the face and neck, the V portion of the chest and back, and the sun-exposed areas of the arms. Photosensitivity is prominent in about half of patients. Concomitant DLE is present in 20% of cases.

Roughly three-quarters of patients have arthralgia or arthritis, 20% have leukopenia, and 80% have a positive antinuclear antigen (ANA) test (usually in a particulate pattern). Roughly a third of patients meet the American Rheumatism Association (ARA) criteria for a diagnosis of SLE. The majority of cases have antibodies to Ro/SSA antigen, and most are positive for HLA-DR3. La/SSB may also be present and many patients have overlap features with Sjögren syndrome. The disease generally runs a mild course, and renal, central nervous system (CNS), or vascular complications are unusual. Most cases respond to sun protection and antimalarial agents. Drug-induced SCLE is most commonly related to hydrochlorothiazide, but may also be seen with angiotensin-converting enzyme (ACE) inhibitors, calcium-channel blockers, interferons (IFNs), anticonvulsants, griseofulvin glyburide piroxicam, penicillamine, spironolactone, and statins.

Histopathology

Vacuolar interface dermatitis is a universal finding in active lesions. Mild hyperkeratosis and parakeratosis may be present. Chronic changes of DLE, such as follicular plugging, basement membrane zone thickening, and heavy lymphoid aggregates are usually lacking. Dermal mucin is variable. DIF is positive in lesions in only about one-third of cases. A dustlike particulate deposition of IgG in epidermal nuclei of Ro-positive patients may be present and is a helpful diagnostic finding.

Neonatal Lupus Erythematosus

Most infants with neonatal lupus are girls, born to mothers who carry the Ro/SSA antibody. These infants have no skin lesions at birth, but develop them during the first few weeks of life. Annular erythematous macules (Fig. 8-6), and plaques may appear on the head (Fig. 8-7) and extremities. Perioccular involvement (raccoon eyes) may be prominent. With time, the lesions fade and become atrophic. Telangiectasia or dermal mucinosis in an acral papular pattern may be the predominant findings in some cases. Telangiectatic macules or angiomatous papules may be found in sun-protected sites such as the diaper area, may occur independent of active lupus skin lesions, and may be persistent. The skin lesions usually resolve spontaneously by 6 months of age, and usually heal without significant scarring, although atrophy may be present. Dyspigmentation and persistent telangiectasias may remain for months to years. Half of the mothers are asymptomatic at the time of delivery, although many will subsequently develop arthralgia, Sjögren syndrome or other mild systemic findings.

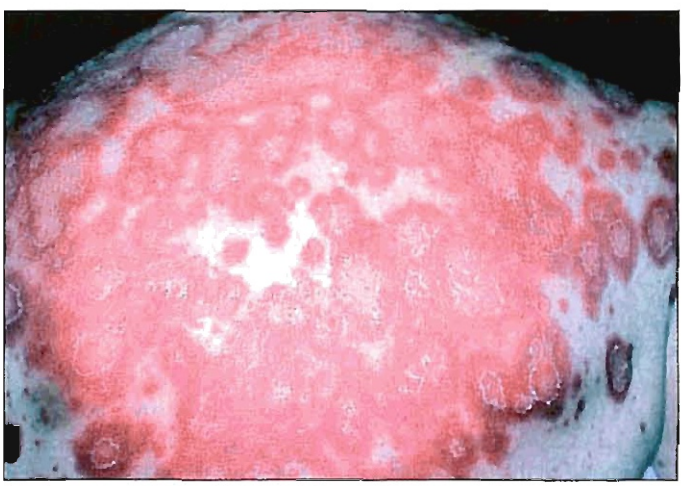

Fig. 8-5 Annular lesions of subacute cutaneous lupus erythematosus.

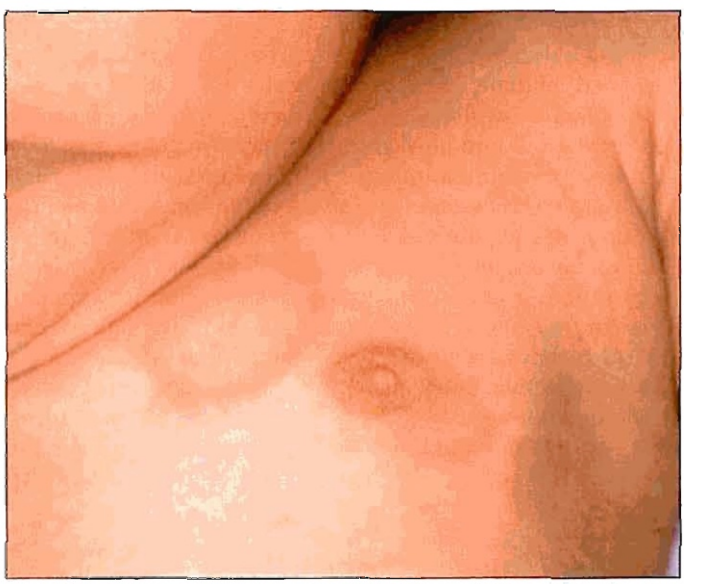

Fig. 8-6 Annular erythematous lesions of neonatal lupus erythematosus.

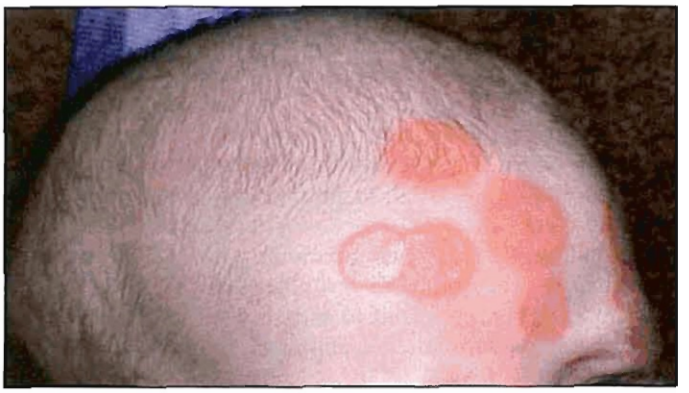

Fig. 8-7 Indurated coalescing lesions of neonatal lupus erythematosus.

Although the skin lesions are transient, half the patients have an associated isolated congenital heart block, usually third degree, which is permanent. Some infants have only this manifestation of LE, and for cardiac lesions alone there is no female predominance. In children with cutaneous involvement, thrombocytopenia and hepatic disease may occur as frequently as cardiac disease.

There is a strong association with Ro/SSA autoantibody. Nearly all mothers, and hence nearly all infants, are positive for this antibody, although some mothers are also positive for La/SSB and some with only U1RNP antibodies have been described. Infants with only U1RNP antibodies have not developed heart block. There is linkage to HLA-Dr3 in the mother. The risk that a second child will have neonatal LE is approximately 25%. Japanese infants apparently differ in that they may express anti-dsDNA antibodies and 8% progress to SLE. In unselected women with anti-Ro antibodies, only 1% to 2% will have an infant with neonatal LE.

Complement Deficiency Syndromes

Although deficiency of many complement components may be associated with LE-like conditions, deficiencies of the early components, especially C2 and C4, are most characteristic. Many such cases are found to have photosensitivity annular SCLE lesions and Ro/SSA antibody formation. Patients with C4 deficiency often have hyperkeratosis of the palms and soles. Heterozygous deficiency of either complement component C4A or C4B has a frequency of approximately 20% in white populations. Homozygous deficiency of both is rare, and affected patients may present with SLE with mesangial glomerulonephritis, membranous nephropathy, and severe skin lesions. Although frequently asymptomatic, homozygous C2 deficiency can cause severe infections, SLE, and atherosclerosis.

Systemic Lupus Erythematosus

Young to middle-aged women are predominantly affected with SLE, manifesting a wide range of symptoms and signs. Skin involvement occurs in 80% of cases and is often helpful in arriving at a diagnosis. Its importance is suggested by the fact that four of the ACR's 11 criteria for the diagnosis of SLE are mucocutaneous findings. The diagnostic criteria are as follows:

- Malar rash
- Discoid rash
- Photosensitivity
- Oral ulcers (21%)
- Arthritis
- Proteinuria >0.5 g/day or casts
- Neurologic disorders (seizures or psychosis in the absence of other known causes)
- Pleuritis/pericarditis
- Blood abnormalities (including hemolytic anemia, leukopenia, thrombocytopenia)
- Immunologic disorders such as anti-dsDNA antibody, anti-Sm, antiphospholipid antibodies (based on IgG or IgM anticardiolipin antibodies, lupus anticoagulant or a false-positive serologic test for syphilis known for at least 6 months)
- Positive ANA blood test

For identification of patients in clinical studies, a patient may be said to have SLE if four or more of the above criteria are satisfied, serially or simultaneously. It is important to note that many patients present with autoantibodies, arthralgia, and constitutional signs, but do not meet ACR criteria for SLE. With time, patients may evolve to meet all criteria.

Cutaneous Manifestations

The characteristic butterfly facial erythema seen in patients with SLE is a common manifestation of acute cutaneous LE. The eruption usually begins on the malar area and the bridge of the nose. There may be associated edema. The ears and chest may also be the sites of early lesions. Biopsies at all sites show interface dermatitis and a scant perivascular lymphoid infiltrate. The eruption may last from a day to several weeks, and resolves without scarring. There may be more widespread erythema in some cases.

Bullous lesions of LE (BLE) (Fig. 8-8) occur as single or grouped vesicles or bullae, often widespread, with a predilection for sun-exposed areas. Rarely, they may itch. Most sets of published criteria require that patients with BLE meet ACR criteria for SLE, but patients exist who have identical bullous lesions and fewer than four ACR criteria. ACR criteria are critical to ensure that patients with similar severity are enrolled in clinical trials, but they sometimes fall short in the evaluation of a given patient. Histologically, neutrophils accumulate at the dermoepidermal junction and within dermal papillae. In bullous lesions, there is a subepidermal bulla containing neutrophils. Fluorescence with

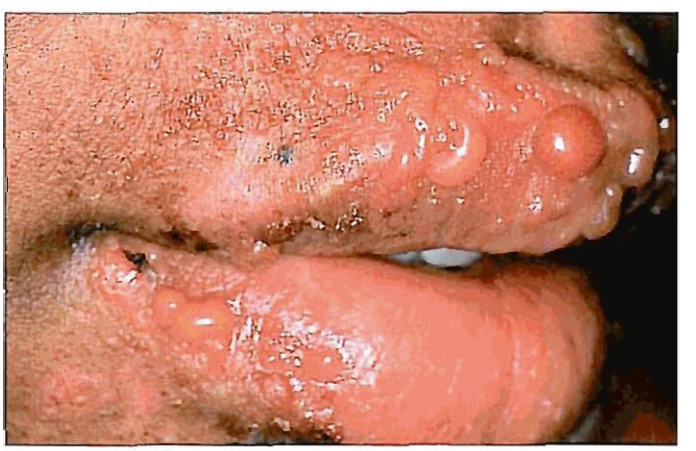

Fig. 8-8 Bullous lupus erythematosus.

IgG, IgM, IgA, or C3 is commonly present in a granular or linear pattern at the basement membrane zone on DIF testing. They are found in or below the lamina densa on immunoelectron microscopy. Most of these patients are HLA-DR2 positive. The recognition of this subset as a distinct one is made clear by its often dramatic therapeutic response to dapsone. Epidermolysis bullosa acquisita is histopathologically and immunopathologically identical since both diseases are mediated by circulating antibodies against type VII collagen. Dapsone is usually ineffective in epidermolysis bullosa acquisita. Bullous lesions may also occasionally arise as a result of liquifactive degeneration of the basal cell layer or full-thickness epidermal necrosis resembling toxic epidermal necrolysis.

A variety of vascular lesions occur in 50% of cases of SLE. Often the fingertips or toes show edema, erythema, or telangiectia. Nailfold capillary loops in LE are more likely to show wandering glomeruloid loops, whereas dermatomyositis and scleroderma capillary loops demonstrate symmetrical dilatation and dropout of vessels. Capillary loops in the Osler-Weber-Rendu syndrome demonstrate ectasia of half of the capillary loop. Erythema multiforme-like lesions may predominate; this has been termed *Rowell syndrome*. Rarely, toxic epidermal necrolysis may be associated with lupus.

In addition to periungual telangiectasia, red or spotted lunulae may be present in patients with SLE. The palms, soles, elbows, knees, or buttocks may become persistently erythematous or purplish, sometimes with overlying scale. Diffuse, nonscarring hair loss is common. Short hairs in the frontal region are referred to as *lupus hairs* (Fig. 8-9). These hairs result from a combination of chronic telogen effluvium and increased hair fragility.

Mucous membrane lesions are seen in 20% to 30% of SLE patients. Conjunctivitis, episcleritis, and nasal and vaginal ulcerations may occur. Oral mucosal hemorrhages, erosions, shallow angular ulcerations with surrounding erythema, and gingivitis occur commonly. Erythema, petechiae, and ulcerations may occur on the hard palate.

Multiple eruptive dermatofibromas have been described in SLE. Leg ulcers, typically deeply punched out, and with very little inflammation, may be seen on the pretibial or malleolar areas. Many of these patients present with a livedoid pattern and many have an antiphospholipid antibody. Sneddon syndrome is composed of livedo reticularis and strokes related to a hyalinizing vasculopathy.

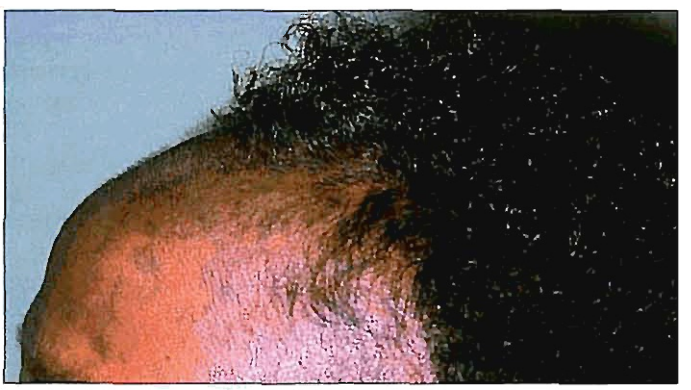

Fig. 8-9 Lupus hair, short miniaturized hairs affecting the anterior hairline.

Calcinosis cutis is uncommon but may be dramatic. Also seen infrequently are plaque-like or papulonodular depositions of mucin. These reddish-purple to skin-colored lesions are often present on the trunk and arms or head and neck. Finally, a symmetrical papular eruption of the extremities may occur. These skin-colored to erythematous lesions with a smooth, ulcerated, or umbilicated surface may show vasculitis or, in older lesions, a palisaded granulomatous inflammation. These occur in patients with SLE, rheumatoid arthritis, or other immune complex-mediated disease. This eruption has been referred to as palisaded neutrophilic and granulomatous dermatitis of immune complex disease.

Systemic Manifestations

Most organs can be involved; the symptoms and findings are often due to immune complex disease, especially vasculitis. The earliest changes noted may be transitory or migratory arthralgia, often with periarticular inflammation. Fever, weight loss, pleuritis, adenopathy, or acute abdominal pain may occur. Arthralgia is often the earliest abnormality and may remain the sole symptom for some time. Ninety-five percent of SLE patients will manifest this symptom. Arthralgia, deforming arthropathy, and acute migratory polyarthritis resembling rheumatoid arthritis may all occur as manifestations of SLE. Avascular necrosis of the femoral head has been observed. Although this is a known complication of systemic corticosteroid therapy, it has occurred also in patients with SLE who have never had corticosteroids.

Thrombosis in vessels of various sizes and thromboembolism may be a recurring event. It may be attributed to a plasma constituent paradoxically called *lupus anticoagulant (LA)* because it causes prolonged coagulation studies in vitro, but thrombosis in vivo. The finding of a lupus anticoagulant is usually associated with antiphospholipid antibodies. These may be anticardiolipin antibodies, but other types of antiphospholipid antibodies (antiphosphatidylserine, antiphosphatidylinositol, and antiphosphatidylethanolamine) may occur. Antiphospholipid antibodies and elevated homocysteine may each increase the risk of thrombosis. Antiphopholipid antibodies are associated with early-onset organ damage. Many, but not all, patients have a false-positive blood test for syphilis. In one study, inflammatory lesions of SLE and infections were the most common causes of death during the initial 5 years of disease, while thromboses were the most common cause of death after the first 5 years.

Renal involvement may be of either nephritic or nephrotic type, leading in either case to chronic renal insufficiency with proteinuria and azotemia. Active nephritis is unlikely in the absence of anti-dsDNA. Both anti-dsDNA antibody and anti-C1q antibody are of relatively high specificity for active nephritis. Hypercholesterolemia and hypoalbuminemia may occur. Immunoglobulin and complement components have been found localized to the basement membrane of glomeruli, where vasculitis produces the characteristic "wire-loop" lesion.

Myocarditis is indicated by cardiomegaly and gallop rhythm, but the electrocardiographic changes are usually not specific. Pericarditis (the most frequent cardiac manifestation) and endocarditis also occur. Raynaud phenomenon occurs in about 15% of patients; these individuals have less renal disease and consequently lower mortality.

The CNS may be involved with vasculitis, manifested by hemiparesis, convulsions, epilepsy, diplopia, retinitis, choroiditis, psychosis, and other personality disorders. Livedo reticularis is a marker for patients at risk for CNS lesions (Sneddon syndrome, see above).

Idiopathic thrombocytopenic purpura is occasionally the forerunner of SLE. Coombs-positive hemolytic anemia, neutropenia, and lymphopenia are other hematologic findings. Gastrointestinal involvement may produce symptoms of nausea, vomiting, and diarrhea. Frequently the intestinal wall and the mesenteric vessels show vasculitis. Pulmonary involvement with pleural effusions, interstitial lung disease, and acute lupus pneumonitis may be present. Sjögren syndrome (keratoconjunctivitis sicca) and Hashimoto thyroiditis are associated with SLE. Overlap with any of the connective tissue diseases may be seen, and occurs in approximately 25% of patients. Muscular atrophy may accompany extreme weakness so that dermatomyositis may be suspected. Myopathy of the vacuolar type may produce muscular weakness, myocardial disease, dysphagia, and achalasia of the esophagus. Steroid myopathy may also occur. The serum aldolase level may be elevated with a normal creatine phosphokinase.

A history of exposure to excessive sunlight before the onset of the disease or before an exacerbation is sometimes obtained. Some patients may suffer only mild constitutional symptoms for weeks or months, but immediately after exposure to strong sunlight they may develop the facial eruption and severe disease complications.

Hydralazine, procainamide, sulfonamides, penicillin, anticonvulsants, minocycline, and isoniazid have been implicated as causes of drug-induced LE. Most drug-induced lupus is associated with a positive ANA test, antihistone antibodies, and sometimes serositis. Penicillamine induces (or unmasks) true SLE, and etanercept has produced a range of findings, including SLE.

Childhood Systemic Lupus Erythematosus The onset of childhood SLE occurs between the ages of 3 and 15, with girls outnumbering boys 4:1. The skin manifestations may be the typical butterfly eruption on the face and photosensitivity. In addition, there may be morbilliform, bullous, purpuric, ulcerating, or nodose lesions. The oral mucosa is frequently involved.

Skin eruptions may be associated with joint, renal, neurologic, and gastrointestinal disease. Weight loss, fatigue, hepatosplenomegaly, lymphadenopathy, and fever are other manifestations. Pediatric patients with SLE and antiphospholipid antibodies, specifically lupus anticoagulants, are at high risk of developing thromboembolic events.

Pregnancy Women with LE may have successful pregnancies, although there might be difficulty in conceiving, and miscarriages occur with greater frequency, especially among those with antiphospholipid antibodies. The course of pregnancy may be entirely normal, with remission of the LE, or the symptoms of LE may become worse. Risk of fetal death is increased in women with a previous history of fetal loss and anticardiolipin or anti-Ro antibodies. Low-dose aspirin is often used in the former instance. For the patient with these antibodies but without a history of previous fetal loss, the risk of fetal loss or neonatal lupus is low. In most cases, the pregnancy itself is well tolerated, although a flare of SLE may occur during the postpartum period. Several studies have failed to demonstrate a clinically significant association between oral contraceptive use and flares of SLE. There is a high incidence of thromboses in women with antiphospholipid antibodies and oral contraceptives containing second- or third-generation progestogens may induce a higher risk.

Etiology A family history of connective tissue disease is a strong risk factor for all forms of LE. HLA and gene linkage studies suggest a strongly heritable component, and some skin lesions of LE follow lines of Blaschko, suggesting postzygotic mutation or loss of heterozygosity for a genetic locus. The C-reactive protein (CRP) response is defective in patients with flares of SLE, and the gene locus for CRP maps to 1q23.2 within an interval linked with SLE. Gene polymorphisms in APRIL, a member of the tumor necrosis factor (TNF) family, have also been linked with SLE. Strong linkage has been found with SLE at 5p15.3, 1q23, 1q31, 11q14, 12q24, and 16q12, as well as other candidate sites. Linkage differs in different ethnic groups and different clinical subsets of lupus. Taken together, these data suggest polygenetic susceptibility to LE.

Both ultraviolet (UV)B and UVA can upregulate antigen expression and cytokines, and cause release of sequestered antigens and free radical damage. All of these mechanisms may contribute to photosensitivity and UV-induced flares of systemic disease.

Several aspects of the altered immune response are worth particular attention. T-suppressor-cell function is reduced in patients with LE. Overproduction of γ-globulins by B-cells and reduced clearance of immune complexes by the reticuloendothelial system may contribute to complement-mediated damage. Externalization of cellular antigens, such as Ro/SSA in response to sunlight, may lead to cell injury by way of antibody-dependent cellular cytotoxicity.

HLA-Dr4 individuals, who are slow acetylators, are predisposed to develop hydralazine-induced LE. Antibody to the histone complex H2A–H2B is closely associated with disease. In most drug-induced LE, antibodies are directed against histones. Exceptions include penicillamine and etanercept, which may induce or unmask native disease with anti-dsDNA antibodies. Drugs implicated in SCLE are listed earlier in this chapter. L-Canavanine, an amino acid found in alfalfa sprouts and tablets, can also induce or worsen SLE. There is little credible data regarding other possible aggravating dietary factors, but some reports have implicated excess calories, excess protein, high fat (especially saturated and omega-6 polyunsaturated fatty acids), excess zinc, and excess iron. Well designed studies are needed. Cigarette smoking is associated with increased disease activity in SLE, and can interfere with the effects of antimalarial drugs.

Laboratory Findings

There may be hemolytic anemia, thrombocytopenia, lymphopenia, or leukopenia; the erythrocyte sedimentation rate (ESR) is usually markedly elevated during active disease, Coombs test may be positive, there is a biologic false-positive test for syphilis, and a rheumatoid factor may be present. Levels of IgG may be high, the albumin-to-globulin ratio is reversed, and the serum globulin is increased, espe-

cially the γ-globulin or α_2 fraction. Albumin, red blood cells, and casts are the most frequent findings in the urine.

Immunologic Findings

1. *ANA test.* This is positive in 95% of cases of SLE. Human substrates, such as Hep-2 or KB tumor cell lines, are far more sensitive than mouse substrates. ANA pattern has some correlation with clinical subsets, such as a shrunken peripheral pattern in SLE with renal disease, a fine particulate pattern in subacute cutaneous LE, and a homogeneous pattern with antihistone antibodies.
2. *Lupus erythematosus cell test.* This is specific but not very sensitive and has been deleted from the ACR criteria.
3. *Double-stranded DNA.* Anti-dsDNA, anti-native DNA. Specific, but not very sensitive. Indicates high risk of renal disease, and correlates with a shrunken peripheral ANA pattern and positive DIF in sun-protected skin.
4. *Anti-Sm antibody.* Sensitivity less than 10% but with very high specificity.
5. *Antinuclear ribonucleic acid protein (anti-nRNP).* Very high titers are present in mixed connective tissue disease. Lower titers may be seen in SLE.
6. *Anti-La antibodies.* Common in SCLE and Sjögren syndrome, occasionally found in SLE.
7. *Anti-Ro antibodies.* Found in about 25% of SLE and 40% of Sjögren cases. More common in patients with SCLE (70%), neonatal LE (95%), C2- and C4-deficient LE (50–75%), late-onset LE (75%), and Asian patients with LE (50–60%). Photosensitivity may be striking, and externalization of the antigen is seen after UV exposure.
8. *Serum complement.* Low levels indicate active disease, often with renal involvement.
9. *Lupus band test.* Direct cutaneous immunofluorescence. Continuous granular deposits of immunoglobulins and complement along the dermoepidermal junction occur in more than 75% of well established lesions of DLE. In SLE, it is commonly positive in sun-exposed skin. A positive test in normal protected skin correlates with the presence of anti-dsDNA antibodies and renal disease. The test is seldom performed, as the same population of patients can be detected with anti-dsDNA antibodies.
10. *Anti-ssDNA antibody.* Sensitive but not specific. Many are photosensitive. An IgM isotope seen in DLE may identify a subset of patients at risk for developing systemic symptoms.
11. *Antiphospholipid antibodies.* Both the anticardiolipin antibody and the lupus anticoagulant are subtypes of these. They are associated with a syndrome that includes venous thrombosis, arterial thrombosis, spontaneous abortions, and thrombocytopenia. Livedo reticularis is a frequent skin finding and nonfading acral microlivedo, small cyanotic pink lesions on the hands and feet, is a subtle clue to the presence of these antibodies. Antiphospholipid antibodies may occur in association with lupus, other connective tissue disease, or as a solitary event. In the latter case it is referred to as the *primary antiphospholipid syndrome.*

Differential Diagnosis

SLE must be differentiated from dermatomyositis, erythema multiforme, polyarteritis nodosa, acute rheumatic fever, rheumatoid arthritis, pellagra, pemphigus erythematosus (Senear-Usher syndrome), drug eruptions, hyperglobulinemic purpura, Sjögren syndrome, necrotizing angiitis, and myasthenia gravis. In SLE there may be fever, arthralgia, weakness, lassitude, diagnostic skin lesions, an increased ESR, cytopenias, proteinuria, immunoglobulin deposition at the dermoepidermal junction, and a positive ANA test. Biopsies of skin lesions and involved kidney may also be diagnostic.

Treatment

Some general measures are important for all patients with LE. Exposure to sunlight must be avoided, and a high sun-protection factor (SPF) sunscreen should be used daily. Photosensitivity is frequently present even if the patient denies it, and all patients must be educated about sun avoidance and sunscreen use. The patient should also avoid exposure to excessive cold, to heat, and to localized trauma. Biopsies and scar revision will often provoke a flare of the disease. Women with SLE have an increased risk of osteoporosis, independent of the use of corticosteroids. Bone density should be monitored, and calcium and vitamin D supplementation should be considered. Some women will benefit from bisphosphonate therapy, especially if corticosteroids are used. The most rapid bone loss with corticosteroid therapy occurs at the onset of treatment, so bisphosphonate therapy should not be delayed. Patients who will be treated with immunosuppressive agents should receive a tuberculin skin test as well as a thorough physical examination. Aggressive treatment is often necessary for discoid lesions and scarring alopecia. The slowly progressive nature of these lesions, and the lack of systemic involvement, may lead to inappropriate therapeutic complacency. The result is slow, progressive disfigurement.

Local Treatment The application of potent or superpotent topical corticosteroids is beneficial. Occlusion may be necessary and may be enhanced by customized vinyl appliances (especially for oral lesions) or surgical dressings. Tape containing corticosteroid (Cordran) is sometimes helpful. The single most effective local treatment is the injection of corticosteroids into the lesions. Triamcinolone acetonide, 2.5 to 10 mg/mL, is infiltrated into the lesion through a 30-gauge needle at intervals of 4 to 6 weeks. No more than 40 mg of triamcinolone should be used at one time. Steroid atrophy is a valid concern, but so is the atrophy and scar produced by the disease. The minimal intralesional dose needed to control the disease should be used; but when the response is poor, it is generally better to err on the slightly more aggressive side of treatment than to undertreat. Topical macrolactams (topical calcineurin inhibitors) may also be useful as second-line topical therapy.

Systemic Treatment The safest class of systemic agents for LE is the antimalarials. Retinoids are second-line agents and are particularly helpful in treating hypertrophic LE. Systemic immunosuppressive agents are often required to manage the systemic manifestations of LE, and are third-line systemic agents for cutaneous LE. Thalidomide can be effec-

tive but its use is limited by the risk of teratogenicity and neuropathy. Dapsone is the drug of choice for bullous systemic LE, and may be effective in some cases of SCLE and DLE. Oral prednisone is generally reserved for acute flares of disease.

Antimalarials

Hydroxychloroquine (Plaquenil), at a dose equal to or less than 6.5 mg/kg/day, has an excellent safety profile, and is generally used as first-line systemic therapy in most forms of cutaneous LE. If no response occurs after 3 months, another agent should be considered. Chloroquine (Aralen) is effective in a dose of 250 mg/day for an average adult, but is difficult to procure. Quinacrine (Atabrine), 100 mg/day, may be added to hydroxychloroquine, since this adds no increased risk of retinal toxicity. Quinacrine is also difficult to procure and carries a higher risk of disfiguring pigmentation than the other antimalarials. Systemic treatment can sometimes be reduced or stopped during the winter months.

Ocular toxicity is rare with doses of hydroxychloroquine equal to or less than 6.5 mg/kg/day. Ophthalmologic consultation should be obtained before, and at 4- to 6-month intervals during, treatment. Constriction of visual fields to a red object and paracentral scotomas are rare at the recommended dose, but even a small risk of loss of vision must be taken seriously. The finding of any visual field defect or pigmentary abnormality is an indication to stop antimalarial therapy.

Other reported side effects with antimalarials include erythroderma, erythema multiforme, purpura, urticaria, nervousness, tinnitus, abducens nerve paralysis, toxic psychoses, leukopenia, and thrombocytopenia. Antimalarials, except in very small doses, will exacerbate skin disease or cause hepatic necrosis in patients with porphyria cutanea tarda. They may also worsen or induce psoriasis. Quinacrine produces a yellow discoloration of the skin and conjunctivae. Quinacrine has also been known to produce blue–black pigmentation of the hard palate, nailbeds, cartilage of the ears, alae nasi, and sclerae. Other antimalarials may also rarely produce a blue–black pigmentation of skin. Bullous erythema multiforme, lichenoid drug eruption, nausea, vomiting, anorexia, and diarrhea may develop. Aplastic anemia has rarely been noted in long-term therapy. A patient's brown or red hair may turn light blond.

Corticosteroids

Systemic corticosteroids are highly effective for widespread or disfiguring lesions, but disease activity often rebounds quickly when the drug is discontinued. Because of long-term side effects, corticosteroid treatment should be limited to short (generally 3 weeks or less) courses to treat flares of disease or to obtain initial control while antimalarial therapy is being initiated. In cases with renal or neurologic involvement, corticosteroids should be administered in doses adequate to control the disease, while treatment with a steroid-sparing regimen is initiated. Treatment with 1000 mg/day intravenous methylprednisolone for 3 days, followed by oral prednisone, 0.5 to 1 mg/kg/day, is effective in quickly reversing most clinical and serologic signs of activity of lupus nephritis. In general, the corticosteroid dose should be optimized to the lowest possible that controls symptoms and laboratory abnormalities.

Immunosuppressive Therapy

Aggressive treatment protocols with agents such as pulse cyclophosphamide (with hydration and MESNA to prevent bladder toxicity) have greatly improved the outcome of renal LE. Other immunosuppressive agents, including azathioprine, methotrexate, and mycophenolate mofetil are often employed as steroid-sparing agents for refractory cutaneous disease.

Other Therapy Isotretinoin therapy, in doses of 1 mg/kg/day may be effective, especially in hypertrophic or lichenoid lesions of LE. Rapid relapse may be noted when the drug is discontinued. Dapsone, clofazimine, acitretin, IFN-α 2a, auranofin (oral gold), high-dose intravenous γ-globulin, and thalidomide have all been reported as effective in anecdotal use or limited trials. Pulsed dye laser has been shown to be effective for some erythematous lesions of cutaneous LE, but should be used cautiously, as it may also cause flares of disease. Flares of disease are also common with surgical modalities used to improve scarring or alopecia. Anti-CD20 monoclonal antibody (rituximab) has been used successfully to treat life-threatening refractory SLE with renal and CNS involvement, as well as for hypocomplementemic urticarial vasculitis related to LE. Although lupus is a photosensitive disorder, UVA-1 therapy appears to be a useful adjuvant treatment modality in some patients.

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DERMATOMYOSITIS

Dermatomyositis (DM) is typically characterized by inflammatory myositis and skin disease, although amyopathic DM (DM with subclinical or absent myopathy) also occurs. Muscle involvement without skin changes is called *polymyositis (PM)*. With or without skin lesions, weakness of proximal muscle groups is characteristic.

Skin Findings

Usually the disease begins with erythema and edema of the face and eyelids. Eyelid involvement (Fig. 8-10) may be characterized by pruritic and scaly pink patches, edema, and pinkish-violet (heliotrope) discoloration or bullae. Pruritic scaly pink patches are often seen in amyopathic DM. Edema

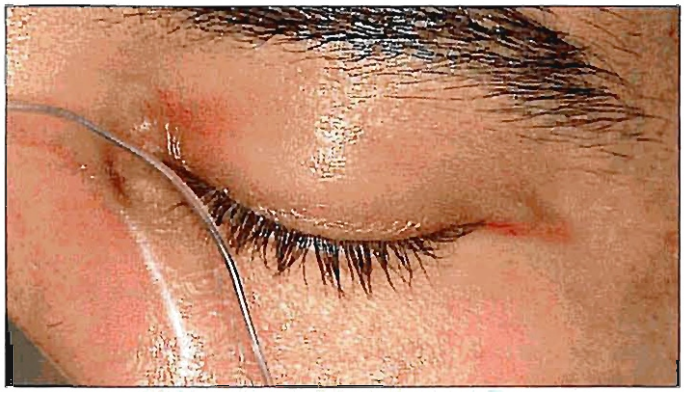

Fig. 8-10 Heliotrope rash in a patient with dermatomyositis.

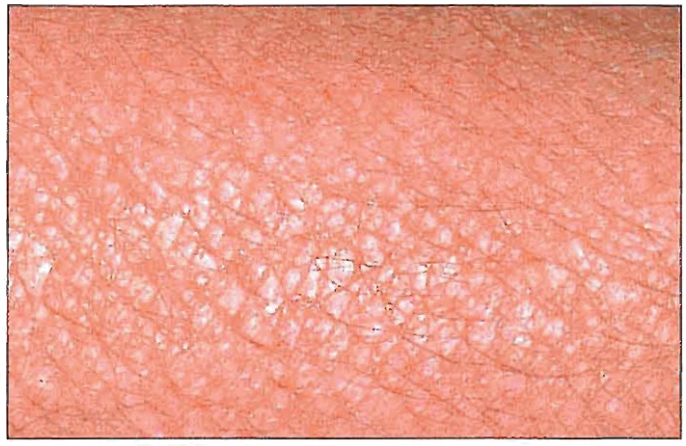

Fig. 8-11 Atrophic coalescing lesions of dermatomyositis on the arm.

and pinkish-violet discoloration are often signs of inflammation in the underlying striated orbicularis oculi muscle, rather than the skin itself. In such cases, the eyelids may be tender to the touch. Bullous DM may portend a poor prognosis, and patients often have severe inflammatory myopathy or lung disease.

Other skin changes include erythema, scaling, and swelling of the upper face, often with involvement of the hairline and eyebrows. Extensor surfaces of the extremities are often pink, red or violaceous with an atrophic appearance (Fig. 8-11) or overlying scale. The similarity to psoriasis can be striking, and patients may suffer severe flares of DM if they are inappropriately treated with phototherapy for presumed psoriasis. Photosensitivity to natural sunlight is common as well. Firm, slightly pitting edema may be seen over the shoulder girdle, arms, and neck. Associated erythema and scale (with or without poikiloderma) over the shoulder regions is known as the *shawl sign*. Pruritus may be severe in some cases, and is much more common in DM than in psoriasis or LE.

Over time, more widespread skin changes are typically seen. Skin lesion become more prominent on the neck, thorax, shoulders, and arms. Characteristic areas include the nape of neck, upper chest (V) pattern, and upper back, neck, and shoulder (shawl) pattern. Occasionally, a flagellate pattern mimicking bleomycin-induced linear edematous streaks or erythroderma may be seen.

On the hands, telangiectatic vessels often become prominent in the proximal nailfolds. Enlarged capillaries of the nailfold appear as dilated, sausage-shaped loops with adjacent avascular regions (Fig. 8-12), similar to those changes observed in scleroderma. There may be cuticular overgrowth with an irregular frayed appearance. A pink to reddish purple atrophic (Fig. 8-13) or scaling eruption often occurs over the knuckles, knees, and elbows (Gottron's sign). Flat topped, polygonal, violaceous papules over the knuckles (Gottron's papules) (Fig. 8-14) are less common, but are highly characteristic of DM. Hyperkeratosis, scaling, fissuring, and hyperpigmentation over the fingertips, sides of the thumb, and fingers with occasional involvement of the palms is referred to as *mechanic's hands* and has been reported in 70% of patients with antisynthetase antibodies. Intermittent fever, malaise, anorexia, arthralgia, and marked weight loss are commonly present at this stage.

Telangiectasia and erythema may become more pronounced with time. Mottled hyper- and hypo-pigmentation,

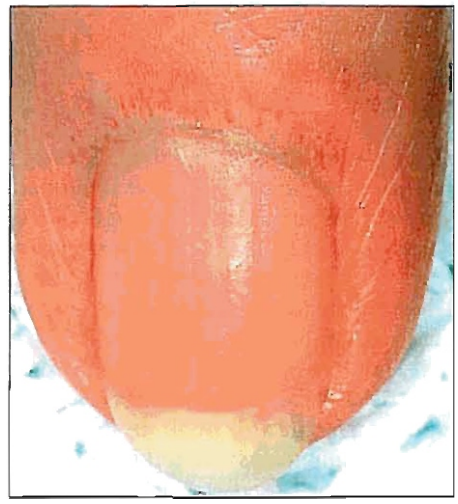

Fig. 8-12 Dilated vessels and avascular regions of the proximal nailfold.

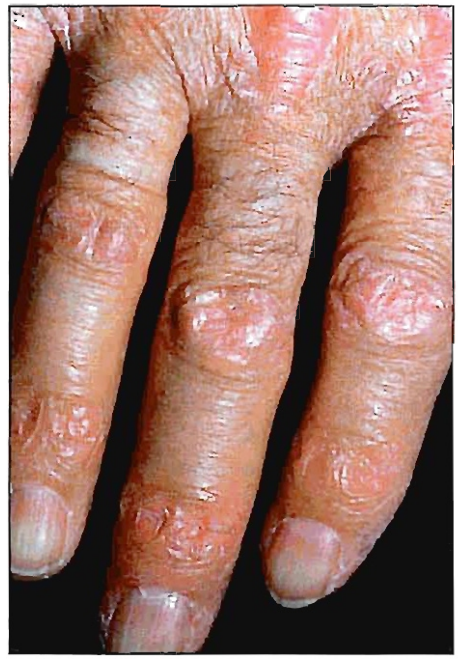

Fig. 8-13 Atrophic lesions of dermatomyositis involving the knuckles.

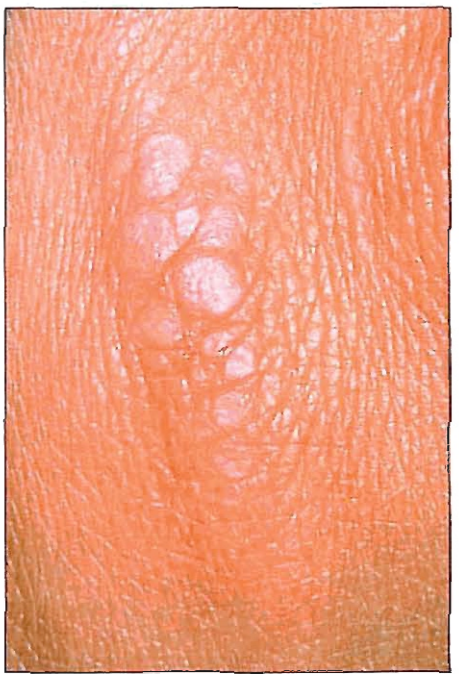

Fig. 8-14 Gottron's papules appear as pink, flat-topped polygonal shiny papules over the knuckles.

atrophy, and telangiectasia (poikiloderma) eventually develop in many patients. In some patients with disease remission, the residual hyperpigmentation simulates the bronze discoloration of Addison's disease. Rarely, large, persistent ulcerations in flexural areas or over pressure points may develop. Ulceration in early stages of disease has been reported to be associated with a higher incidence of cancer and a poor prognosis, but the authors have seen many patients with ulcerative DM without associated cancer. In later stages, ulceration may merely be a manifestation of pressure or trauma to atrophic areas. Rarely, DM may be associated with clinical findings of pityriasis rubra pilaris (Wong variant of DM).

Calcium deposits in the skin and muscles occur in more than half of children with DM; this occurs rather infrequently in adults. Calcification is related to duration of disease activity and its severity. Calcinosis of the dermis, subcutaneous tissue, and muscle occurs mostly on the upper half of the body around the shoulder girdle, elbows, and hands. Ulcerations and cellulitis are frequently associated with this debilitating and disabling complication of DM.

Muscle Changes

In severe cases early and extensive muscular weakness occurs, with acute swelling and pain. The muscle weakness is seen symmetrically, most frequently involving the shoulder girdle and sometimes the pelvic region, as well as the hands. The patients may notice difficulty in lifting even the lightest objects. They may be unable to raise their arms to comb their hair, and rising from a chair may be impossible without "pushing off" with the arms. Patients often complain of pain in the legs when standing barefoot or of being unable to climb stairs. Difficulty in swallowing, talking, and breathing, caused by weakness of the involved muscles, may be noted early in the disease. Some patients with severe diaphragmatic disease require mechanical ventilation. Cardiac failure may be present in the terminal phase of the disease.

Skin involvement commonly precedes muscle involvement, but some patients have typical skin findings of DM but never develop clinically apparent muscle involvement. These cases have been termed *amyopathic DM* or *DM sine myositis*. It is common, however, for muscle inflammation to be present but not symptomatic. Muscle enzymes (to include both creatinine kinase and aldolase), electromyogram (EMG), and magnetic resonance imaging (MRI) may be required to detect subtle involvement.

Diagnostic Criteria

The following criteria are commonly used to define DM/PM:

- Skin lesions
- Heliotrope rash (red–purple edematous erythema on the upper palpebra)
- Gottron's papules or sign (red–purple flat-topped papules, atrophy or erythema, on the extensor surfaces and finger joints)
- Proximal muscle weakness (upper or lower extremity and trunk)
- Elevated serum creatine kinase or aldolase level
- Muscle pain on grasping or spontaneous pain
- Myogenic changes on EMG (short-duration, polyphasic motor unit potentials with spontaneous fibrillation potentials)
- Positive anti-Jo-1 (histadyl tRNA synthetase) antibody
- Nondestructive arthritis or arthralgias
- Systemic inflammatory signs (fever: >37° C at axilla, elevated serum CRP level or accelerated erythrocyte sedimentation rate (ESR) of >20 mm/h by the Westergren method)
- Pathologic findings compatible with inflammatory myositis

Patients with the first criterion and four of the remaining criteria have DM. Patients lacking the first criterion but with at least four of the remaining criteria have PM. Some patients with DM have little evidence of myopathy and drug eruptions may mimic the characteristic rash. In particular, hydroxyurea has been associated with a DM-like eruption.

Associated Diseases

DM may overlap with other connective tissue diseases. Sclerodermatous changes are the most frequently observed. This is called *sclerodermatomyositis*. Antibodies such as anti-Ku and anti-PM/scl may be present in this subgroup. Mixed connective tissue disease (associated with high anti-ribonucleoprotein [RNP]), rheumatoid arthritis, lupus erythematosus, and Sjögren syndrome may occur concomitantly. DM may be associated with interstitial lung disease, which is frequently the cause of death. The presence of anti-Jo-1 antibody, as well as other antisynthetase antibodies, such as anti-PL-7, anti-PL-12, anti-DJ, and anti-EJ, correlates well with the development of pulmonary disease. Even those patients without anti-Jo-1 should routinely be screened for interstitial lung disease, as up to 69% of patients with interstitial lung disease are seronegative for the anti-Jo-1 antibody in published reports.

Neoplasia with Dermatomyositis In adults, malignancy is frequently associated with DM. The malignancy is discovered before, simultaneously, or after the DM in almost equal proportions. Factors associated with malignancy include age, constitutional symptoms, rapid onset of DM, the lack of Raynaud phenomenon, and a grossly elevated ESR or creatine kinase level. Malignancy is most frequently seen in

patients in the fifth and sixth decades of life. Routine "age appropriate screening" may be inadequate to uncover a significant number of malignancies. In addition to history and physical examination, a stool hemoccult test, mammography, pelvic exam, chest x-ray, and computed tomographic (CT) scans of the abdominal, pelvic, and thoracic areas may be indicated. Periodic rescreening may be of value, but the appropriate interval for screening has not been established. The presence of leukocytoclastic vasculitis might indicate a higher potential for malignancy.

Childhood Dermatomyositis

Several features of childhood dermatomyositis differ from the adult form. Two childhood variants exist. The more common *Brunsting type* has a slow course, progressive weakness, calcinosis, and steroid responsiveness. Calcinosis may involve intermuscular fascial planes or be subcutaneous. The second type, the *Banker type*, is characterized by a vasculitis of the muscles and gastrointestinal tract, rapid onset of severe weakness, steroid unresponsiveness, and a high death rate. Internal malignancy is seldom seen in children with either type, but insulin resistance may be present.

Etiology

There is mounting evidence that muscle findings in DM are related to humoral immunity, a vasculopathy mediated by complement deposition, lysis of endomysial capillaries and resulting muscle ischemia. In contrast, PM and inclusion-body myositis are related to clonally expanded CD8+ cytotoxic T-cells invading muscle fibers and causing necrosis via the perforin pathway. The initial immune response in DM is an IFN-α/-β-induced cascade with secondary stimulation of IFN-γ. Many autoantibodies may be present in DM, some of which are disease specific and can identify specific subgroups. In addition to the antisynthetase antibodies previously discussed, the anti-Mi-2 antibody is present in some patients with acute onset of classic DM and a good prognosis. An association with bovine collagen dermal implants has been reported, but may reflect a referral bias, rather than a true statistical association.

Both healthy individuals and children with juvenile DM may demonstrate persistence of maternal microchimerism, but the incidence is higher in children with juvenile DM. This has also been demonstrated in patients with other connective tissue diseases such as scleroderma. The finding may be an epiphenomenon, or may be part of a pathogenic alloimmune response. An inherited predisposition has been demonstrated, and studies of juvenile DM gene expression have shown DQA1*0501 in 85% of patients.

Viral or bacterial infections may produce an abnormal immune response. Epitopes of group A β-hemolytic streptococcal M protein have sequence homology with myosin, and can elicit both cell-mediated cytotoxicity and TNF-α production when incubated with mononuclear cells from children with active juvenile DM. The TNF-α-308A allele is associated with increased TNF-α synthesis in juvenile DM patients, and is associated with increased thrombospondin-1 (an antiangiogenic agent) and small vessel occlusion. In adults with PM and DM, endothelial damage occurs early. Pathogenic factors in adults include interleukin (IL)-1α, transforming growth factor (TGF)-β, and myoblast production of IL-15.

Incidence

DM is relatively rare. It is twice as prevalent in women as in men and four times as common in black as in white patients. There is a bimodal peak, the smaller one seen in children and the larger peak in adults between the ages of 40 and 65.

Histopathology

The histologic changes in DM are similar to those of LE. The two may be indistinguishable, although lesions of DM have more of a tendency to become atrophic. Lesions typically demonstrate thinning of the epidermis, hydropic degeneration of the basal layer, basement membrane thickening, papillary dermal edema, and a perivascular and periadnexal lymphocytic infiltrate in the superficial and deep dermis with increased dermal mucin. Scattered melanophages are present in the superficial dermis. As compared with LE, DM shows less eccrine coil involvement and fewer vertical columns of lymphocytes in fibrous tract remnants. Subcutaneous lymophoid nodules and panniculitis are rarely seen in DM. Characteristic changes are found in the muscles. The deltoid, trapezius, and quadriceps muscles seem to be almost always involved, and are good biopsy sites. Muscle bundles demonstrate lymphoid inflammation and atrophy which preferentially affects the periphery of the muscle bundle. Muscle biopsy is directed to those areas found to be most tender or in which EMG demonstrates myopathy. MRI is a useful aid in identifying active sites for muscle biopsy, and may obviate the need for biopsy in some cases. The MRI short transition interval recovery (STIR) images are best. They can be used to localize disease and longitudinally assess results of treatment.

Laboratory Findings

The serum levels of creatinine kinase are elevated in most patients. Aldolase, lactic dehydrogenase, and transaminases are other indicators of active muscle disease. There may be leukocytosis, anemia with low serum iron, and an increased ESR. Positive ANA tests are seen in 60% to 80% of patients if a human diploid substrate is used; 35% to 40% have myositis-specific antibodies.

Cutaneous DIF is positive in at least one-third of cases, with a higher yield in well established (at least 3–6 months old) lesions. Cytoid bodies are commonly seen, although continuous granular staining with IgG, IgM, and IgA may be seen.

X-ray studies with barium swallow may show weak pharyngeal muscles and a collection of barium in the pyriform sinuses and valleculae. MRI of the muscles is an excellent way to assess activity of disease noninvasively.

EMG studies for diagnosis show spontaneous fibrillation, polyphasic potential with voluntary contraction, short duration potential with decreased amplitude, and salvos of muscle stimulation.

Differential Diagnosis

DM must be differentiated from erysipelas, SLE, angioedema, drug eruptions, and erythema multiforme. Aldosteronism, with adenoma of adrenal glands and hypokalemia, may also cause puffy heliotrope eyelids and face.

Treatment

Prednisone is the mainstay of acute treatment, at doses beginning with 1 mg/kg/day until the severity decreases and

muscle enzymes are almost normal. The dosage is reduced with clinical response. The aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) and creatinine phosphokinase return to normal levels as remission occurs. Methotrexate and azathioprine are commonly used as steroid-sparing agents, and should be started early in the course of treatment to reduce steroid side effects. Some data favor methotrexate as a steroid-sparing agent, but because of the increased risk of interstitial lung disease with methotrexate, some authors avoid this agent in patients with pulmonary disease or anti-Jo-1 antibodies. Mycophenolate mofetil has a favorable safety profile and should be considered as an alternative agent. If patients do not respond adequately to the combination of prednisone and methotrexate, mycophenolate mofetil or azathioprine, a trial of intravenous immunoglobulin (IVIG) (1 g/kg/day for 2 days each month), cyclosporin, or tacrolimus may be beneficial. IVIG has been associated with thromboembolic events, including deep venous thrombosis, pulmonary embolism, myocardial infarction, and stroke, and this risk must be weighed against the benefits of the drug. Anti-TNF-α treatment with infliximab has proved a rapidly effective therapy for some patients with myositis. Etanercept has also been used. Because etanercept therapy has resulted in signs of lupus in some patients, patients should be monitored carefully. Cyclophosphamide is generally reserved for refractory cases.

In severe juvenile DM, pulse intravenous methylprednisone (30 mg/kg/day) or high-dose prednisone have been reported as highly effective. Patients who fail to respond within 6 weeks should be started on an alternative agent such as methotrexate. Onset of calcinosis is associated with delays in diagnosis and treatment, as well as longer disease duration. Calcinosis related to DM has been treated with aluminum hydroxide, diphosphonates, diltiazem, probenecid, colchicine, low doses of warfarin, and surgery with variable, but usually poor, results.

The skin lesions may respond to systemic therapy; however, its response is unpredictable and skin disease may persist despite involution of the myositis. Because DM is photosensitive, sunscreens with high SPF (>30) should be used daily, and patients should be counseled about sun avoidance. Topical steroids may be helpful in some patients. Antimalarials, such as hydroxychloroquine given in doses of 200 to 400 mg/day (2–5 mg/kg/day in children), has been shown to be useful in abating the eruption of DM; however, adverse cutaneous reactions are common. Non–life-threatening cutaneous reactions occur in approximately one-third of patients and up to one-half of those who react to hydroxychloroquine will also react to chloroquine.

Prognosis

Major causes of death are cancer, ischemic heart disease, and lung disease. Independent risk factors include failure to induce clinical remission, white blood cell count above 10,000/mm^3, temperature greater than 38° C at diagnosis, older age, shorter disease history, and dysphagia. Early aggressive therapy in juvenile cases is associated with a lower incidence of disabling calcinosis cutis.

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SCLERODERMA

Scleroderma is characterized by the appearance of circumscribed or diffuse, hard, smooth, ivory-colored areas that are immobile and give the appearance of hidebound skin. It occurs in both localized and systemic forms. Cutaneous types may be categorized as morphea (localized, generalized, profunda, atrophic, and pansclerotic types) or linear scleroderma (with or without melorheostosis or hemiatrophy). Progressive systemic sclerosis and the Thibierge-Weissenbach syndrome (commonly referred to as the *CREST syndrome*) are the two types of systemic scleroderma.

Cutaneous Types

Localized Morphea This form of scleroderma is twice as common in women as in men and occurs in childhood as well as in adult life. It presents most often as macules or plaques a few centimeters in diameter, but also may occur as bands or in guttate lesions or nodules. Rose or violaceous macules may appear first, followed by smooth, hard, somewhat depressed, yellowish-white or ivory lesions. They are most common on the trunk but also occur on the extremities.

The margins of the areas are generally surrounded by a light violaceous zone or by telangiectases. Within the patch skin elasticity is lost, and when it is picked up between the thumb and index finger it feels rigid. The follicular orifices may be unusually prominent, leading to a condition that resembles pigskin. In guttate morphea multiple small, chalk-white, and flat or slightly depressed macules occur over the chest, neck, shoulders, or upper back. The lesions are not very firm and may be difficult to separate clinically from guttate lichen sclerosus et atrophicus.

Morphea-Lichen Sclerosus et Atrophicus Overlap There are patients who present with both lesions of morphea and lichen sclerosus et atrophicus (LSA). They are commonly women with widespread morphea who have typical LSA lesions either separated from morphea or overlying morphea. When the changes are seen above dermal changes of morphea, the characteristic inflammatory lymphoid band of LSA is lacking, suggesting that the superficial homogenization is really a manifestation of morphea rather than representing a separate disease process.

Generalized Morphea Widespread involvement by indurated plaques with pigmentary change characterizes this variety. Muscle atrophy may be present, but there is no visceral involvement. Patients may loose their wrinkles as a result of the firmness and contraction of skin. Spontaneous involution is less common with generalized morphea than with localized lesions.

Atrophoderma of Pasini and Pierini In 1923, Pasini described a peculiar form of atrophoderma now thought to be in the spectrum of morphea. The disease consists of brownish-gray, oval, round or irregular, smooth atrophic lesions depressed below the level of the skin with a well demarcated, sharply sloping border. Some of the appearance of depression is an optical illusion related to the color change. Atrophoderma occurs mainly on the trunk of young individuals, predominately females. The lesions are usually asymptomatic, and may measure 20 cm or more in diameter. Linear atrophoderma of Moulin is a related condition that follows lines of Blaschko.

Biopsies of atrophoderma demonstrate a reduction in the thickness of the dermal connective tissue. Some widening and hyalinization of collagen bundles may be noted. Because the changes may be subtle, a biopsy should include normal-appearing skin so that a comparison may be made.

Pansclerotic Morphea This variant is manifested by sclerosis of the dermis, panniculus, fascia, muscle, and at times, bone. There is disabling limitation of motion of joints.

Morphea Profunda Morphea profunda involves deep subcutaneous tissue, including fascia. There is clinical overlap with eosinophilic fasciitis, eosinophilia myalgia syndrome, and the Spanish toxic oil syndrome. The latter two conditions were related to contaminants found in batches of tryptophan or cooking oil. Unlike eosinophilic fasciitis, morphea profunda shows little response to corticosteroids and tends to run a more chronic debilitating course.

Linear Scleroderma These linear lesions (Fig. 8-15) may extend the length of the arm or leg, and may follow lines of Blaschko. The condition often begins during the first decade of life. Lesions may also occur parasagittally on the frontal scalp and extend part way down the forehead (en coup de sabre). The Parry-Romberg syndrome, which manifests as progressive hemifacial atrophy, epilepsy, exophthalmos, and alopecia, may be a form of linear scleroderma. When the lower extremity is involved, there may be associated spina bifida, faulty limb development, hemiatrophy, or flexion contractures. Melorheostosis, seen in roentgenograms as a dense linear cortical hyperostosis, may occur. At times linear lesions of the trunk merge into more generalized involvement. Generally, the only type that shows spontaneous improvement is the childhood type involving the extremities. Physical therapy of the involved limb is of paramount importance to prevent contractures and frozen joints.

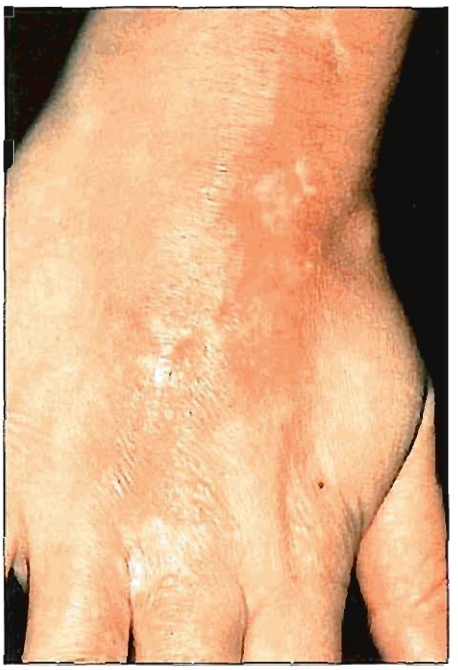

Fig. 8-15 Linear scleroderma presents with induration and pigmentary change.

Systemic Types

CREST Syndrome *This variant of systemic scleroderma* has the most favorable prognosis, owing to the usually limited systemic involvement. Patients with the syndrome develop calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia. *Patients* may present with sclerodactyly, severe heartburn or telangiectatic mats. The mats tend to have a smooth outline, in contrast to the mats of the Osler-Weber-Rendu syndrome, which tend to exhibit an irregular outline with more radiating vessels. This form of scleroderma generally lacks serious renal or pulmonary involvement. Anticentromere antibodies are highly specific for the CREST syndrome, being positive in 50% to 90% of cases and only 2% to 10% of patients with progressive sclerosis.

Progressive Systemic Sclerosis Progressive systemic sclerosis (PSS) is a generalized disorder of connective tissue in which there is thickening of dermal collagen bundles, and fibrosis and vascular abnormalities in internal organs. Raynaud phenomenon is the first manifestation of PSS in more than half the cases. Other patients present with "woody edema" of the hands. The heart, lungs, gastrointestinal tract, kidney, and other organs are frequently involved. Women are affected three times more commonly than men, with the peak age of onset being between the third and fifth decade.

Classic criteria include either proximal sclerosis or two or all of the following: 1) sclerodactyly; 2) digital pitting scars *of the fingertips or loss of substance of the distal finger pad*; and 3) bilateral basilar pulmonary fibrosis. Localized forms of scleroderma must be excluded. These criteria have been shown to be 97% sensitive and 98% specific for the diagnosis. *The ACR has proposed an expanded list of criteria*, including:

1. Skin changes: tightness, thickening, and nonpitting induration, sclerodactyly, proximal scleroderma; changes proximal to the metacarpophalangeal or metatarsophalangeal joints, and affecting other parts of the extremities, face, neck, or trunk (thorax or abdomen), digital pitting, loss of substance from the finger pad, bilateral firm but pitting finger or hand edema, abnormal skin pigmentation (often "pepper and salt"). The changes are usually bilateral, symmetrical and almost always include sclerodactyly.
2. Raynaud phenomenon: at least two-phase color change in fingers and often toes consisting of pallor, cyanosis, and reactive hyperemia.
3. Visceral manifestations: bibasilar pulmonary fibrosis not attributable to primary lung disease, lower (distal) esophageal dysphagia, lower (distal) esophageal dysmotility, colonic sacculations.

Skin Findings

In the earlier phases of scleroderma the affected areas are erythematous and swollen. Patients are frequently misdiagnosed as having carpal tunnel syndrome and may even have positive EMGs. Raynaud phenomenon is often present, and suggests the correct diagnosis. Over time, sclerosis supervenes. The skin becomes smooth, yellowish, and firm, and shrinks so that the underlying structures are bound down. The earliest changes often occur insidiously on the face and hands, and in more advanced stages these parts become hidebound, so that the face is expressionless, the mouth is *constricted, and* the hands are clawlike. The skin of the face appears drawn, stretched, and taut, with loss of lines of expression. The lips are thin, contracted, and radially furrowed, the nose appears sharp and pinched, and the chin may be *puckered. Barnett described the "neck sign" as a ridging* and tightening of the neck on extension, which occurs in 90% of patients with scleroderma.

The disease may remain localized to the hands and feet for long periods (acrosclerosis). *The fingers become semiflexed,* immobile, and useless, the skin over them being hard, inelastic, incompressible, and pallid. The terminal phalanges are boardlike and indurated. Mizutani described the "round fingerpad sign." The fingers lose the normal peaked contour, but rather appear as a rounded hemisphere when viewed from the side. This process may lead to loss of pulp on the distal digit. Trophic ulcerations and gangrene may occur on the tips of the fingers and knuckles, which may be painful or insensitive. Pterygium inversum unguis (Fig. 8-16), in which the distal part of the nailbed remains adherent to the ventral surface of the nail plate, may be seen in scleroderma and LE, or may be idiopathic. Dilated, nailfold capillary loops are present in 75% of systemic scleroderma patients. Symmetrically dilated capillaries are seen adjacent to avascular areas. This differs from the nailfold capillaries of the Osler-Weber-Rendu syndrome which typically have dilatation of only one-half of the loop and no avascular areas. Nailfold capillary hemorrhage in two or more fingers is highly specific for scleroderma and correlates with the anticentromere antibody.

Keloid-like nodules may develop on the extremities or the chest, and there may be a widespread diffuse calcification of the skin as shown by radiographs. A diffuse involvement of the chest may lead to a cuirass-like restraint of respiration. Late in the course of the disorder, hyper- or de-pigmented spots or a diffuse bronzing may be present. The most characteristic pigmentary change is a loss of pigment in a large *patch with perifollicular pigment retention within it.* Perifollicular pigmentation may appear in response to UV light

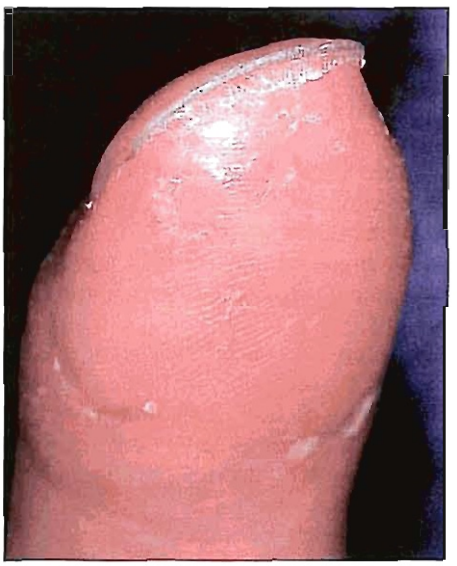

Fig. 8-16 Pterygium inversum unguis in progressive systemic sclerosis.

exposure. Pigment may also be retained over superficial blood vessels. The affected areas become hairless and atrophy is often associated with telangiectasia. Bullae and ulcerations may develop, especially on the distal parts of the extremities.

Internal Involvement

PSS may involve most of the internal organs. Esophageal involvement is seen in more than 90% of patients. The distal two-thirds are affected, leading to dysphagia and reflux esophagitis. Small intestinal atonia may lead to constipation, malabsorption, or diarrhea. Pulmonary fibrosis with arterial hypoxia, dyspnea, and productive cough may be present. Progressive nonspecific interstitial fibrosis, with bronchiectasis and cyst formation, is the most frequent pathologic change. Pulmonary hypertension and right-sided heart failure are ominous signs, occurring in 5% to 10% of patients. The cardiac involvement produces dyspnea and other symptoms of congestive heart failure. Sclerosis of the myocardium also produces conduction changes and may result in arrhythmia. Pericarditis, hypertension, and retinopathy may be present.

The skeletal manifestations include articular pain, swelling, and inflammation. Polyarthritis may be the first symptom in systemic sclerosis. There is limitation of motion, as a result of skin tautness, followed by ankylosis and severe contractual deformities. The hand joints are involved most frequently. There may be resorption and shortening of the phalanges, and narrowing of the joint spaces. Osteoporosis and sclerosis of the bones of the hands and feet may occur, as well as decalcification of the vault of the skull.

Childhood PSS has identical cutaneous manifestations. Raynaud phenomenon is less frequent, while cardiac wall involvement is more common and is responsible for half the deaths. Renal disease is unusual. Familial scleroderma rarely occurs.

Prognosis

The course of PSS is variable. Renal disease accounts for some early mortality, but pulmonary disease remains the major cause of death. The patient's age at disease onset is a significant risk factor for pulmonary arterial hypertension. Cardiac disease also correlates with a poor prognosis, while gastrointestinal involvement contributes mainly to morbidity. ANA patterns predict different subsets of disease with varying prognosis. Anticentromere antibodies correlate with CREST syndrome and a good prognosis, while Scl-70 and ANA correlate with a poorer prognosis.

Laboratory Findings

ANA testing is positive in more than 90% of patients with systemic scleroderma. As noted above, several of these antibodies identify specific clinical subsets of patients. The antinucleolar pattern is considered most specific for scleroderma, and when present as the only pattern, it is highly specific for scleroderma. When antibodies to such nucleolar antigens as RNA polymerase I and fibrillarin are present, diffuse sclerosis, generalized telangiectasia, and internal organ involvement are often seen. The homogeneous ANA pattern is seen in those patients with PM–Scl antibodies, the marker for PM–scleroderma overlap. The true speckled or anticentromere pattern is sensitive and specific for the CREST variant. Patients with antibodies to Scl-70 tend to have diffuse truncal involvement, pulmonary fibrosis, and digital pitted scars, but a lower incidence of renal disease. Antibodies to nuclear RNP are found in patients with Raynaud phenomenon, polyarthralgia, arthritis, and swollen hands. Very high RNP titers define mixed connective tissue disease. These patients are fairly homogeneous and the term is not synonymous with connective tissue overlap. Anti-ssDNA antibodies are common in linear scleroderma.

Radiographic Findings

The gastrointestinal tract is commonly involved. The esophagus may have decreased peristalsis and dilation. Esophagograms and esophageal manometry may be helpful. In early esophageal involvement, a barium swallow in the usual upright position may be reported as normal. If the patient is supine, however, barium will often be seen to pool in the flaccid esophagus. The stomach may be dilated and atonic, resulting in delayed emptying time. Involvement of the small intestine may cause extreme dilation of the duodenum and jejunum, producing a characteristic roentgenographic picture of persistently dilated intestinal loops long after the barium has passed through. Colonic or small intestinal sacculations may be present.

Histology

Systemic and localized forms of scleroderma show similar histologic changes, although lymphoid infiltrates tend to be heavier in the acute phase of morphea. In the acute phase there is a perivascular lymphocytic infiltrate with plasma cells that is heaviest at the junction of the dermis and subcutaneous fat. Collagen bundles become hyalinized and the space between adjacent bundles is lost. Loss of CD34+ dermal dendritic cells is an early finding.

Dermal sclerosis typically results in a rectangular punch biopsy specimen. As the dermis replaces the subcutaneous tissue, eccrine glands appear to be in the midportion of the thickened dermis. The subcutaneous fat is quantitatively reduced and adventitial fat (the fat that normally surrounds the adnexal structures on the trunk) is lost. Collagen abuts directly on the adnexal structures. Elastic fibers in the reticular dermis may be prominent and stain bright red, and the papillary dermis may appear pale and edematous. In advanced lesions, the inflammatory infiltrate may be

minimal. Pilosebaceous units are absent, and eccrine glands and ducts are compressed by surrounding collagen.

On DIF testing of skin the nucleolus may be stained in the keratinocytes if antinucleolar circulating antibodies are present, and a "pepper-dot" epidermal nuclear reaction pattern may be seen in CREST patients who have anti-centromere antibodies in their serum.

Differential Diagnosis

Myxedema is softer and associated with other signs of hypothyroidism. Diabetic scleredema tends to be erythematous and affects the central back in a pebbly pattern. Scleromyxedema begins with discrete papules, but may assume an appearance very similar to systemic sclerosis. A paraprotein is typically present. Sclerodactyly may be confused with digital changes of leprosy and syringomyelia. Eosinophilic fasciitis is more steroid responsive. The skin is thickened, edematous, and erythematous, and has a coarse peau d'orange appearance, as opposed to its sclerotic, taut appearance in scleroderma. The hands and face are usually spared in eosinophilic fasciitis, and when the arms are involved, the blood vessels draw inward when the arms are raised, producing a "dry riverbed appearance."

In vitiligo the depigmentation is the sole change in the skin, and sclerosis is absent. Scleroderma in the atrophic stage may closely resemble acrodermatitis chronica atrophicans (ACA), but ACA shows more attenuation of collagen fibers and a diffuse lymphohistiocytic infiltrate. Lyme titers may be positive.

Dermal fibrosis is a major feature of chronic sclerodermoid graft-versus-host disease, porphyria cutanea tarda, phenylketonuria, carcinoid syndrome, juvenile-onset diabetes, progeria, and the Werner, Huriez, and Crow-Fukase (POEMS) syndromes. Occupational exposure to silica, epoxy resins, polyvinyl chloride, and vibratory stimuli (jackhammer or chain saw) may produce sclerodermoid conditions. Chemicals such as polyvinyl chloride, bleomycin, isoniazid, pentazocine, valproate sodium, epoxy resin vapor, vitamin K (after injection), contaminated Spanish rapeseed oil (toxic oil syndrome), contaminated tryptophan (eosinophilia–myalgia syndrome), nitrofurantoin, and hydantoin may also induce various patterns of fibrosis. The "stiff skin syndrome," also known as *congenital fascial dystrophy*, is characterized by stony-hard induration of the skin and deeper tissues of the buttocks, thighs, and legs, with joint limitation and limb contractures. The disease begins in infancy.

Pathogenesis

The pathogenesis of scleroderma and morphea involves vascular damage, autoimmune mechanisms, and possibly microchimerism resulting in alloimmune graft-versus-host reactions. *Borrelia afzelli* and *Borrelia garinii* are related to the development of morphea-like lesions in some cases. Other environmental agents may be involved. Epidemiologic studies support the role of organic solvents and certain chemicals. In women, there is an association with teaching and working in the textile industry.

The immune mechanisms involved are complex. Up-regulated proteins and mRNAs include monocyte chemoattractant protein-1, pulmonary and activation-regulated chemokine, macrophage inflammatory protein-1, IL-8, and TGF-β (although the latter has not correlated well in some studies). These factors may stimulate extracellular matrix production, TGF-β production and activation, and chemoattraction of T-cells. Various target antigens have been proposed, including a protein termed "protein highly expressed in testis" (PHET), which is ectopically overexpressed in scleroderma dermal fibroblasts. Serum antibodies to a recombinant PHET fragment have been detected in 9 (8.4%) of 107 scleroderma patients, but in none of 50 SLE patients or 77 healthy controls. The presence of anti-PHET antibodies was associated with diffuse cutaneous scleroderma and lung involvement

Expression of CD40 is increased on fibroblasts in lesional skin, and ligation of CD40 by recombinant human CD154 results in increased production of IL-6, IL-8, and monocyte chemoattractant protein-1 in a dose-dependent manner. These phenomena are not shown in normal fibroblasts with the addition of CD154.

Lesion skin of early-stage scleroderma contains T-cells preferentially producing high levels of IL-4. CD4+ Th2-like cells can inhibit collagen production by normal fibroblasts and the inhibition is mediated by TNF-α. The inhibition is dominant over the enhancement induced by IL-4 and TGF-β. To be inhibitory, Th2 cells require activation by CD3 ligation. Th2 cells are less potent than T-helper 1 (Th1) cells in inhibiting collagen production by normal fibroblasts, and fibroblasts from involved skin are resistant to inhibition. Because Th2 cells reduce type I collagen synthesis through the effect of TNF-α, TNF-α blockade by new biologics should be approached with caution.

Treatment

Although effective treatment is available for many of the visceral complications of scleroderma, treatment for the skin disease remains unsatisfactory. Spontaneous improvement may be seen in some children and in some cases of localized scleroderma. Physical therapy emphasizing range of motion for all joints as well as the mouth is important. Exposure to cold is to be avoided, and smoking is forbidden. Among patients with scleroderma, smokers are three to four times more likely than never-smokers to incur digital vascular complications.

Vasodilating drugs (calcium-channel blockers, angiotensin II receptor antagonists, topical nitrates, and prostanoids) remain the mainstay of medical therapy for Raynaud phenomenon. Antioxidants, such as vitamin C, have been used, but the data are mixed. Both sildenafil (Viagra) and intravenous or inhaled iloprost are useful in the treatment of both pulmonary hypertension and Raynaud phenomenon. Ginkgo biloba has been shown to have some efficacy in a double-blinded trial. Oral L-arginine has reversed digital necrosis in some patients with Raynaud phenomenon and improved symptoms in others. Calcium-channel blockers, such as nifedipine (Procardia XL), 30 to 60 mg/day, are commonly used as first-line therapy. Some patients who experience worsening of esophageal reflux with nifedipine do better with diltiazem (Cardizem CD), 120 to 180 mg/day. Topical nitroglycerin and simple hand warming on a regular basis may also be effective.

Cyclophosphamide has shown some promising results in the treatment of cutaneous disease, improving skin scores, maximal oral opening, flexion index, forced vital capacity (FVC) and carbon monoxide diffusing capacity (DLCO).

Results with cyclophosphamide have been superior to those obtained with D-penicillamine. Oral methotrexate or cyclophosphamide have been used with prednisolone in some trials. Oral cyclophosphamide must be given in the morning with vigorous hydration. Many rheumatologists prefer intravenous pulse cytoxan with MESNA and hydration to reduce bladder toxicity. In some trials, scleroderma has been largely unresponsive to most immune-modulating therapies except for intravenous cyclophosphamide, which has sometimes been used together with antithymocyte globulin and hematopoietic stem cell infusion. Immune ablation and hematopoietic stem cell rescue has been used for some severe autoimmune diseases, including scleroderma, but the procedure is associated with greater than 10% mortality, and increased renal and pulmonary toxicity as well as parenchymal fibrosis have been reported in patients with scleroderma. This treatment should still be considered experimental.

Phototherapy and photochemotherapy especially with UVA1 have also shown some efficacy, at least for localized scleroderma (morphea). Methotrexate may have some efficacy for the skin thickening of diffuse scleroderma, although better trials are needed. Widespread morphea has been treated with oral calcitriol and calcipotriene may have some efficacy as a topical agent. Halofuginone, an inhibitor of collagen type I synthesis, can decrease collagen synthesis in the tight skin mouse and murine graft-versus-host disease. Application of halofuginone caused a reduction in skin scores in a pilot study with scleroderma patients. CO_2 laser vaporization has produced remission of symptoms in cutaneous calcinosis of CREST syndrome. Some data suggest that minocycline may be effective in the control of calcinosis in systemic sclerosis.

Although there is strong evidence that the ACE inhibitors are disease modifying for scleroderma renal crisis, better randomized controlled trials are still needed. Epoprostenol is used to treat pulmonary hypertension in scleroderma, based largely on evidence that it can be life-saving in the treatment of primary pulmonary hypertension. Other promising drugs for visceral involvement include bosentan (for pulmonary hypertension), cyclophosphamide (for alveolitis), IFN-γ (for interstitial pulmonary fibrosis), intravenous prostaglandins (for vascular disease), and sildenafil (for pulmonary hypertension and Raynaud phenomenon).

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EOSINOPHILIC FASCIITIS

In 1974, Lawrence Shulman described a disorder that he called *diffuse eosinophilic fasciitis*. Classically, patients had engaged in strenuous muscular activity for a few days or weeks before the acute onset of weakness, fatigability, and pain and swelling of the extremities. The prodrome was followed by severe induration of the skin and subcutaneous tissues of the forearms and legs. A favorable response to corticosteroids was noted. Since the initial description, environmental exposures have been reported as possible triggers for the syndrome, including L-tryptophan contaminated with 1,1′-ethylidenebis, *Borrelia*, and exposure to trichloroethylene. Some consider this disease to be a variant of scleroderma. Polycythemia vera and multiple myeloma have been associated in a limited number of patients, suggesting that some cases may represent a paraneoplastic phenomenon.

The skin is commonly edematous and erythematous, with a coarse peau d'orange appearance, most noticeable inside the upper arms, thighs, or flanks. The hands and face are usually spared. When the patient holds the arms laterally or vertically, linear depressions occur within the thickened skin. This "groove sign" or "dry riverbed sign" (Fig. 8-17) follows the course of underlying vessels. This contrasts with scleroderma, in which the skin remains smooth and taut. Limitation of flexion and extension of the limbs and contracture may develop, and patients are often unable to stand fully erect. In contrast to scleroderma, Raynaud phenomenon is usually absent. Associated systemic abnormalities have included carpal tunnel syndrome, peripheral neuropathy, seizures, posterior ischemic optic neuropathy, pleuropericardial effusion, pancytopenia, anemia, antibody-mediated hemolytic anemia, thrombocytopenia, Sjögren syndrome, lymphadenopathy, pernicious anemia, and IgA nephropathy. Detected cytokine abnormalities are similar to those in atopic patients, but with a striking elevation of TGF-β1. The ESR is generally increased and hypergammaglobulinemia is common. Increased production of IL-5 and clonal populations of circulating T-cells have been reported.

Biopsy shows a patchy lymphohistiocytic and plasma cell infiltrate in the fascia and subfascial muscle with massive thickening of the fascia and deep subcutaneous septae. Peripheral blood eosinophilia of 10% to 40% is the rule, but eosinophils may or may not be present in the affected fascia. The inflammatory infiltrate is mainly composed of macrophages and lymphocytes, often with a CD8+ T-lymphocyte predominance. Few eosinophils are typically present in tissue, although they may be numerous in some cases. Cytotoxic CD8+ T-lymphocytes may be demonstrated by granzyme B staining. MHC Class I antigens are upregulated in muscle fibers, but MHC class II antigens are not usually expressed by muscle fibers. C5b9 membrane attack complex (MAC) deposits are generally not detected. CT and MRI have both been used to demonstrate fascial thickening, and may obviate the need for biopsy in some cases.

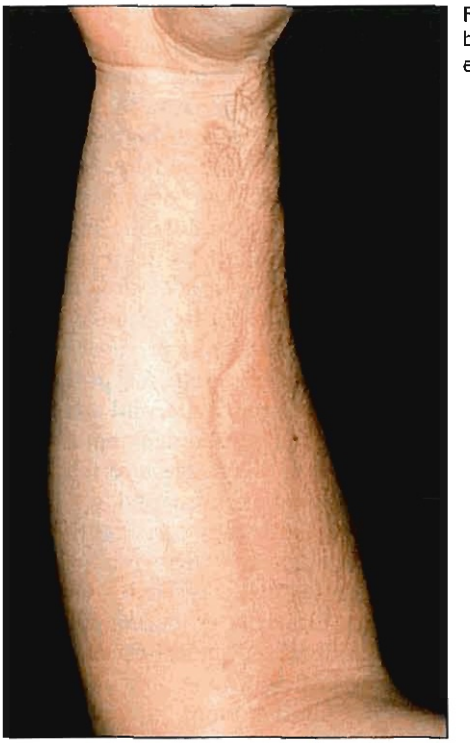

Fig. 8-17 Dry river bed sign in eosinophilic fasciitis.

The response to systemic corticosteroids is generally excellent. In responders, complete recovery is usual within 1 to 3 years. Some patients have also demonstrated a response to histamine blockers, including hydroxyzine and cimetidine. Patients with a prolonged course unresponsive to systemic steroids are being recognized with increasing frequency. Many of these poorly responsive cases overlap with morphea profunda. In refractory cases, plaquenil, cyclosporin, PUVA, bath PUVA, extracorporeal photochemotherapy, and other immunosuppressive regimens have been used with variable success. The increased synthesis of IL-5 may be blocked by IFN-α, suggesting a possible role for IFN in the treatment of this disorder.

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MIXED CONNECTIVE TISSUE DISEASE

Mixed connective tissue disease (MCTD) has overlapping features of scleroderma, SLE, and DM, and high antiRNP antibodies. Patients often have severe arthralgia, swelling of the hands, tapered fingers, Raynaud phenomenon, abnormal esophageal motility, pulmonary fibrosis, and muscle pain, weakness, and tenderness. Hyperglobulinemia and lymphadenopathy are present in some cases. MCTD is a distinct disorder with a characteristic serologic marker. The term is not synonymous with "overlap syndrome," a combination of diseases where each disease complies with the diagnostic criteria for that disorder. MCTD is also not synonymous with undifferentiated connective tissue disease (UCTD)—patients with connective tissue disease who have not yet developed a defined disease. Only about 4% of patients with UCTD go on to develop MCTD.

The ANA test typically demonstrates a particulate pattern in MCTD, reflecting the high titers of nuclear RNP antibodies (anti-RNP antibodies). This ANA pattern generally persists through periods of remission and is a valuable diagnostic test. In addition, particulate epidermal nuclear IgG deposition on DIF study of skin is a distinctive finding in MCTD. Anti-TS1-RNA antibodies appear to define a subpopulation with predominance of lupus-like clinical features. Lung disease may be a cause of death in patients with MCTD. The pulmonary disease has many similarities to that seen in DM or scleroderma, but differences in pathogenesis may exist. Pulmonary lavage usually demonstrates a significantly higher CD4:CD8 ratio with more CD4+ lymphocytes in MCTD patients than in PM–DM patients. MCTD patients have a significantly lower percentage of CD71+ alveolar macrophages as compared with scleroderma patients.

For acute treatment, corticosteroids (such as prednisone at a daily dose of 1 mg/kg) are effective for inflammatory features such as arthritis and myositis. Like LE, MCTD may be associated with an independent risk of osteoporosis, and the long-term morbidity associated with corticosteroid treatment can be significant. Bisphosphonate therapy and therapy with a steroid-sparing agent should be considered early. In general, the LE features of MCTD are the most likely to improve with therapy, while the scleroderma features are the least likely to improve. Generally the prognosis is better than that of scleroderma, largely related to the lower incidence of renal disease.

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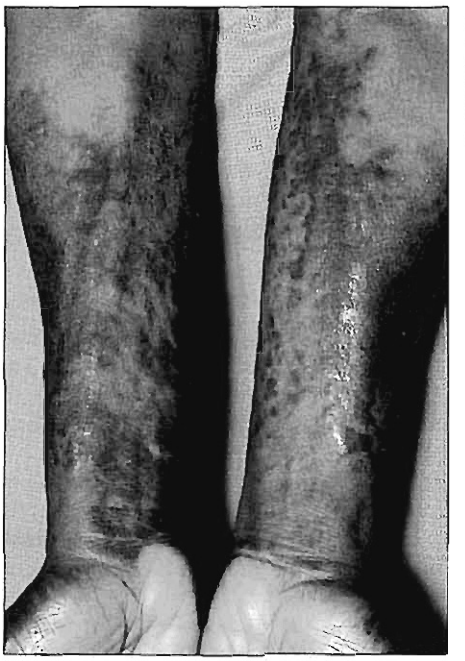

Fig. 8-18
Hyperpigmented sclerotic plaques of nephrogenic fibrosing dermopathy.

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NEPHROGENIC FIBROSING DERMOPATHY

Nephrogenic fibrosing dermopathy (NFD) is a newly recognized fibrosing skin condition that resembles scleromyxedema histologically. It usually develops in patients with renal insufficiency on hemodialysis, although it has been noted in patients with acute renal failure who had never undergone dialysis. Clinical findings include thickened sclerotic or edematous papules and plaques involving the extremities (Fig. 8-18) and trunk. Yellow scleral plaques have been described. Soft tissue calcification is rare, but may be extensive when it occurs. Clinically, the condition differs from scleromyxedema by the lack of involvement of the face, absence of plasma cells, and lack of paraproteinemia. Systemic involvement is generally absent, but may occur with fibrosis and calcification of the diaphragm, psoas muscle, renal tubules, and rete testes.

Circulating antiphospholipid antibodies have been noted in some patients. Histologic sections demonstrate plump bipolar spindle cells, many new collagen bundles and increased mucin. With time, thickened collagen bundles become prominent in the reticular dermis. Myofibroblasts have been noted in lesional skin. Immunohistochemical staining for CD34 and procollagen in the spindle cells of NFD suggests that many of the dermal cells of NFD may represent circulating fibrocytes recruited to the dermis. The CD34 positivity in NFD contrasts with the loss of CD34+ cells in morphea.

Effective therapy remains elusive. Topical retinoids, steroids, and vitamin D analogs are not effective. Immunosuppressive therapy appears to be of little benefit: in three cases that have evolved after liver transplantation, treatment with basiliximab, mycophenolate mofetil, calcineurin inhibitor, and prednisone did not stop the development of "woody" skin induration of the distal extremities, erythematous papules, and contractures. Various forms of phototherapy and thalidomide show some promise.

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SJÖGREN SYNDROME (SICCA SYNDROME)

Keratoconjunctivitis sicca and xerostomia are commonly associated with rheumatoid arthritis and other connective tissue diseases. Dry eyes and mouth may occur as *primary Sjögren syndrome*. Most patients are aged 50 or older and more than 90% are women. Sjögren syndrome is a chronic autoimmune disorder characterized by lymphocytic infiltration of the exocrine glands, particularly the salivary and lacrimal glands. One-third of patients present with extraglandular manifestations, such as vasculitis.

Xerostomia (mouth dryness) may produce difficulty in speech and eating, increased tooth decay, thrush, and decreased taste (hypogeusia). Patients frequently suck on sour candies to stimulate what little salivary secretions remain, and those unfamiliar with the condition may blame the habit of sucking lemon drops for the ensuing tooth decay. Rhinitis sicca (dryness of the nasal mucous membranes) may induce nasal crusting and decreased olfactory acuity (hyposmia). Vaginal dryness and dyspareunia may develop. Dry eyes are painful, feel gritty or scratchy, and produce discharge and blurry vision. Fatigue is a prominent symptom. In addition there may be laryngitis, gastric achlorhydria, thyroid enlargement resembling Hashimoto thyroiditis, malignant lymphoma, thrombotic thrombocytopenic purpura, painful distal sensory axonal neuropathy; and splenomegaly.

Skin manifestations of Sjögren syndrome include vasculitis, xerosis, pruritus, and annular erythema. Decreased sweating occurs. Asian patients have been described who develop erythematous, indurated, annular dermal plaques primarily on the face. This is different from the annular lesions of SCLE, which show epidermal change and histologic changes of lupus. Patients may also present with an overlap of Sjögren syndrome and LE. A common finding in these patients is Ro (SSA) antibody positivity. SCLE patients with Sjögren syndrome have a worse prognosis than patients with SCLE unassociated with Sjögren syndrome.

Patients with Sjögren syndrome and cutaneous vasculitis also have a high prevalence of peripheral or CNS vasculitis. Cutaneous vasculitis may present as purpura of the legs, which may be palpable or nonpalpable. Sjögren vasculitis accounts for most patients with Waldenström benign hypergammaglobulinemic purpura. Approximately 30% of benign hypergammaglobulinemic purpura patients will have or will develop Sjögren syndrome, and a high percentage have SSA and SSB antibodies. Other cutaneous vascular manifestations are urticarial vasculitis, digital ulcers, and petechiae. Histologically, a leukocytoclastic vasculitis is found at the level of the post-capillary venule with expansion of the vascular wall, fibrin deposition and karyorrhexis, but no necrosis of the endothelium.

Labial salivary gland biopsy from inside the lower lip is regarded by many as the most definitive test for Sjögren syndrome. Typically, there is a dense lymphocytic infiltrate with many plasma cells and fewer histiocytes in aggregates within minor salivary glands. More than one focus of 50 or more lymphocytes is typically present per 4 mm^2 of the tissue biopsy. Lymphoepithelial islands predominate early, while glandular atrophy predominates in the late stages. At this stage, few lymphoid aggregates are present. Xerostomia is diagnosed by the Schirmer test and reflects diminished glandular secretion from the lacrimal glands. Imaging studies are also helpful.

Classically, the diagnosis is made when there is objective evidence for two of the following three major criteria:

1. *Xerophthalmia*
2. Xerostomia
3. An associated autoimmune, rheumatic, or lymphoproliferative disorder

These criteria may be too restrictive, as patients are increasingly being identified with predominantly extraglandular disease. The lack of sicca symptoms or anti-SSA or -SSB antibodies does not exclude Sjögren syndrome. Numerous serologic abnormalities are associated with Sjögren syndrome or its associated conditions. Antibodies to fodrin, a major component of the membrane cytoskeleton of most eukaryotic cells, is present in some populations with primary and secondary Sjögren syndrome. IgA and IgG antibodies against α-fodrin are detected in 88% and 64%, respectively in some studies. In other populations, fodrin antibodies are less helpful. Eighty percent of patients have anti-Ro/SSA antibodies; half as many have anti-La/SSB antibodies. The rheumatoid factor is commonly positive, and an elevated ESR, serum globulin, and CRP, and high titers of IgG, IgA, and IgM are common. Cryoglobulins may be demonstrated.

The aquaporin family of water channels (proteins freely permeated by water but not protons) appears to be important targets in the pathogenesis of Sjögren syndrome. Both duct and secretory cells are targets for the activation of CD4+ T-cells. IL-12 and IFN-γ are upregulated. It appears

that Th1 cytokines mediate the functional interactions between antigen-presenting cells and CD4+ T-cells in early lesions.

Patients with Sjögren syndrome are predisposed to the development of lymphoreticular malignancies, especially non-Hodgkin B-cell lymphoma. Both malignant and non-malignant extraglandular lymphoproliferative processes occur. Cases of pseudolymphoma have the potential for regression, or for progression to overt B-cell lymphoma.

The differential diagnosis of Sjögren syndrome includes sarcoidosis, lymphoma, amyloidosis, and human immunodeficiency virus (HIV) disease. The latter produces diffuse infiltrative lymphocytosis syndrome (DILS), which is characterized by massive parotid enlargement; prominent renal, lung, and gastrointestinal manifestations; and a low frequency of autoantibodies.

Treatment for Sjögren syndrome has largely been symptomatic, but disease-modifying therapy is also becoming a reality. Artificial lubricants are helpful for eye symptoms, as well as oral, nasal, and vaginal dryness. Topical lubricants are helpful for xerosis. In hot climates, patients with impaired sweating must be counseled to avoid heat stroke. Pharmacologic agents, such as pilocarpine and cevimeline, are helpful to stimulate salivation. These agents may also have a role in the treatment of dry eyes. Topical cyclosporin A looks promising for local treatment of Sjögren syndrome, as does topical human IFN therapy for oral lesions. In all trials, the mechanical stimulation by the lozenge may play a significant role in the improvement of symptoms. This is reflected in a high placebo response. Acid maltose lozenges are cheaper and remain useful for symptomatic relief. For patients with systemic disease, biologic TNF inhibitors such as infliximab are promising. Pilocarpine, in doses of 10 mg/day, has been shown to have a beneficial effect on subjective eye symptoms, as well as improvement of rose bengal staining. An increase in tear production, as measured by the Schirmer-I test, was not substantiated. Gene therapy also looks promising, at least in animal models. IL-10 genes can be transferred via adenovirus vectors, and can have disease-modifying effects in the salivary glands of a mouse model.

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RHEUMATOID ARTHRITIS

The majority of skin manifestations of rheumatoid arthritis (RA) are consequences of neutrophil-mediated injury. There may be annular erythemas, purpura, bullae, shallow ulcers, and gangrene of the extremities. Many diseases have been reported to occur in association with RA, such as erythema elevatum diutinum, pyoderma gangrenosum, Felty syndrome, IgA vasculitis, linear IgA disease, Sjögren syndrome, bullous pemphigoid, and yellow nail syndrome. Treatment of RA with disease-modifying drugs has reduced the burden of destructive disease for patients with this disorder. Biologic agents are being used with increasing frequency, although older drugs like methotrexate still have a role. Of interest to dermatologists, extracts from the Rhus family of plants have been shown to have some benefit in limited studies.

Rheumatoid Nodules

Subcutaneous nodules (Fig. 8-19) are seen in 20% to 30% of patients. They may arise anywhere on the body but most

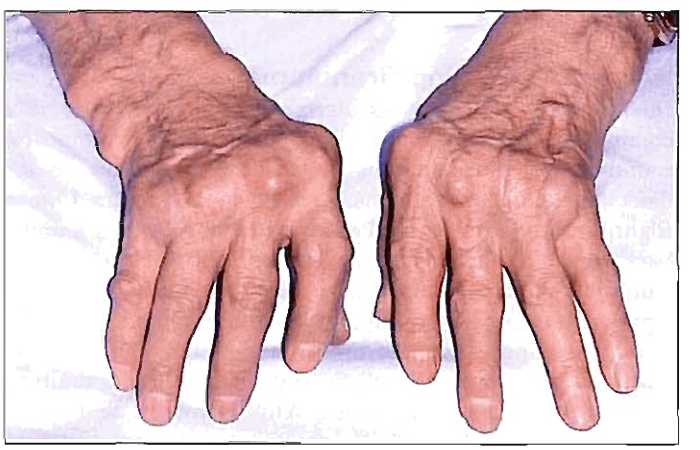

Fig. 8-19 Rheumatoid nodules.

frequently are found over the bony prominences, especially on the extensor surface of the forearm just below the elbow and the dorsal hands. The lesions are nontender, firm, skin-colored, round nodules, which may or may not be attached to the underlying tissue. Frequently they are attached to the fibrous portions of the periarticular capsule, or they may be free in the subcutaneous tissue. Rheumatoid nodules can easily be mistaken for xanthomas because of a yellow color (pseudoxanthomatous variant). They also occur in 5% to 7% of patients with SLE, especially around small joints of the hands. Rheumatoid factor may or may not be present. Histologic examination of the rheumatoid nodule shows intensely staining foci of fibrin surrounded by histiocytes in palisade arrangement. Neutrophils and neutrophilic debris may be noted in association with the fibrin, and with time, the surrounding histiocytes are replaced by fibrosis.

Rheumatoid nodules are differentiated from Heberden nodes, which are tender, hard, bony exostoses on the dorsolateral aspects of the distal interphalangeal joints of patients with degenerative joint disease. Nodules or tophi of gout are characterized by masses of feathery urate crystals surrounded by a chronic inflammatory infiltrate often containing foreign body giant cells.

Rare patients present with multiple ulcerated nodules and high rheumatoid factors, but no active joint disease. This variant of rheumatoid disease without destructive joint disease is designated *rheumatoid nodulosis*.

Rheumatoid Vasculitis

Peripheral vascular lesions appear as typical features of RA. These are localized purpura, cutaneous ulceration, and gangrene of the distal parts of the extremities (Fig. 8-20). Additionally, papular lesions located primarily on the hands have been described as rheumatoid papules. These show a combination of vasculitis and palisading granuloma formation. A rheumatoid factor is typically present. Peripheral neuropathy is frequently associated with the vasculitis. The presence of rheumatoid nodules may help to distinguish these lesions of vasculitis from SLE, polyarteritis nodosa, Buerger's disease, and the dysproteinemias.

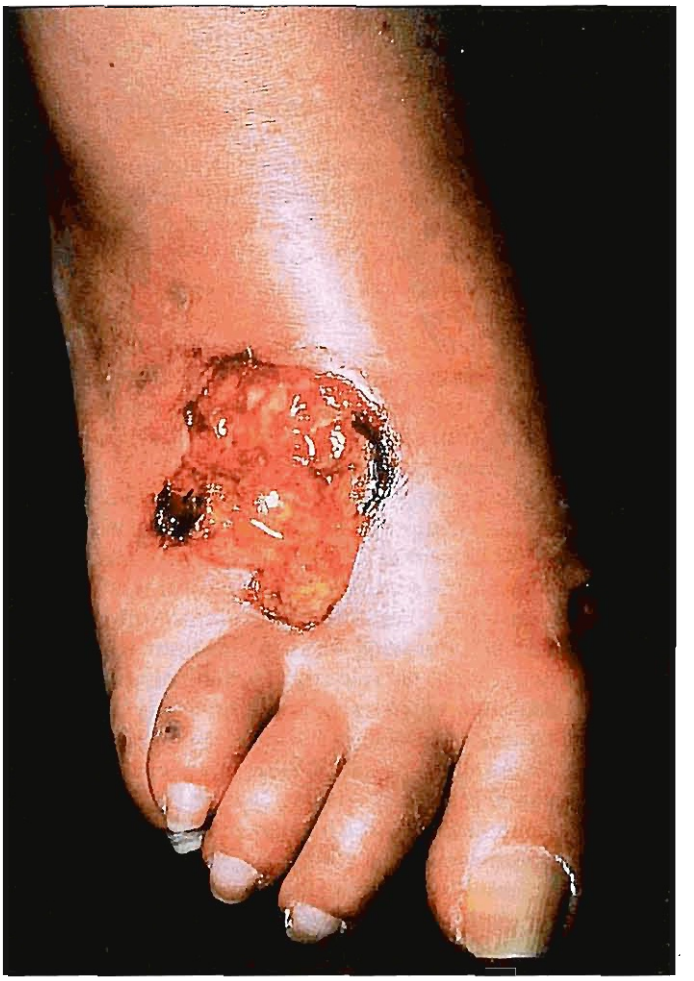

Fig. 8-20 Rheumatoid vasculitis frequently results in ulceration.

Rheumatoid Neutrophilic Dermatosis

Chronic urticaria-like plaques (Fig. 8-21) characterized histologically by a dense neutrophilic infiltrate have been described in patients with debilitating RA. The differential diagnosis includes erythema elevatum diutinum and Sweet syndrome.

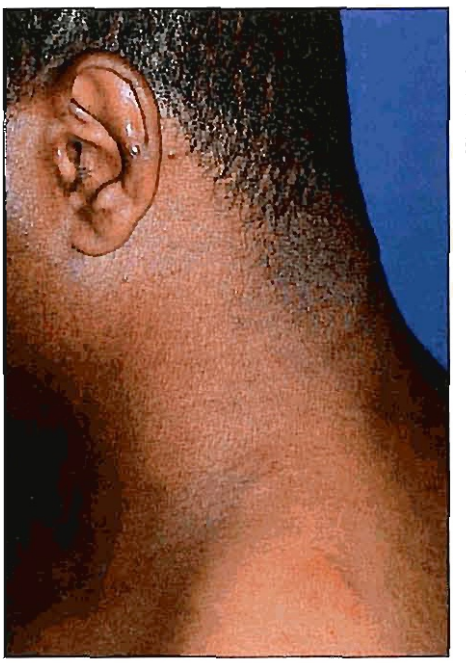

Fig. 8-21 Rheumatoid neutrophilic dermatosis presents with urticarial plaques.

Related Palisading Granulomas

Interstitial granulomatous dermatitis with arthritis is a condition that most commonly presents with symmetrical round-to-oval erythematous or violaceous plaques on the flanks, axillae, inner thighs, and lower abdomen. Linear, slightly red or skin-colored cords extending from the upper back to the axilla may occur. The presence of these linear bands has been called the *rope sign*. When the lesions resolve they may leave behind hyperpigmentation and a slightly wrinkled appearance. Arthritis may occur before, concurrently or after the eruption, and tends to affect multiple joints of the upper extremities. While serologic findings of connective tissue disease are common, most patients do not have a well-defined associated condition. A moderate-to-dense inflammatory infiltrate is seen through the reticular dermis composed of mostly histiocytes distributed interstitially around discrete bundles of sclerotic collagen. Variable numbers of neutrophils and/or eosinophils are seen. Mucin, necrobiosis, vascultitis, and vacuolar change is usually absent

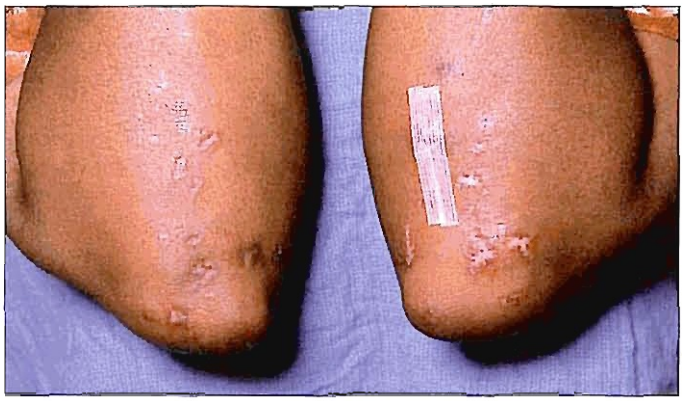

Fig. 8-22 Palisaded neutrophilic and granulomatous dermatitis often involves the extensor surfaces with erosion or ulceration of the lesions.

or mild. The eruption is usually asymptomatic and may spontaneously involute after many months or years. If therapy is required, methotrexate, etanercept, cyclosporin or steroids are needed.

Palisaded neutrophilic and granulomatous dermatitis is usually associated with a well-defined connective tissue disease (lupus erythematosus or RA most commonly). It often presents with eroded or ulcerated symmetrically distributed umbilicated papules or nodules on the elbows (Fig. 8-22), knuckles, and knees. The biopsy may reveal leukocytoclastic vasculitis and collagen degeneration in early lesions or palisaded granulomatous infiltrates with dermatofibrosis and scant neutrophilic debris in older lesions.

Methotrexate-induced popular eruption appears in patients with rheumatic diseases during treatment with this medication. They present with erythematous indurated papules, usually located on the proximal extremities. Histopathologic examination reveals an inflammatory infiltrate composed of histiocytes interstitially arranged between collagen bundles of the dermis, intermingled with few neutrophils. At times, small rosettes composed of clusters of histiocytes surrounding a thick central collagen bundle are present in the deep reticular dermis.

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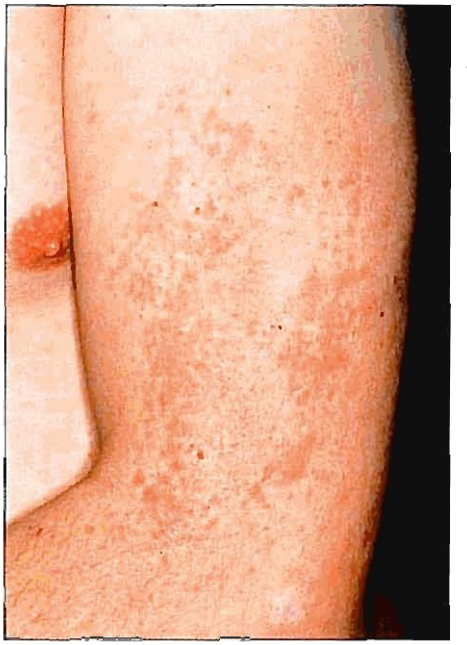

Fig. 8-23 Evanescent eruption of Still's disease.

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JUVENILE RHEUMATOID ARTHRITIS (JUVENILE IDIOPATHIC ARTHRITIS)

Juvenile RA is not a single disease but a group of disorders characterized by arthritis and young age of onset. The subset called *Still's disease* accounts for only 20% of the patients. It shows skin manifestations in some 40% of young patients ranging in age from 7 to 25 years. An eruption consisting of evanescent, non-pruritic, salmon-pink, macular or papular lesions on the trunk and extremities (Fig. 8-23) may precede the onset of joint manifestations by many months. The systemic symptoms of fever and serositis usually recur over weeks each afternoon. Most remit permanently by adulthood. Steroid-sparing agents are useful to decrease steroid-associated toxicity. The dose–response curve for methotrexate plateaus with parenteral administration of 15 mg/m^2/week. The full therapeutic effect may not be evident for 12 months. Refractory disease has been treated with pulse methylprednisolone and cyclophosphamide.

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RELAPSING POLYCHONDRITIS

Relapsing polychondritis is characterized by intermittent episodes of inflammation of the articular and nonarticular cartilage eventuating in chondrolysis and collapse of the involved cartilage. The course of the disease is chronic and variable, with episodic flares. Both sexes are equally

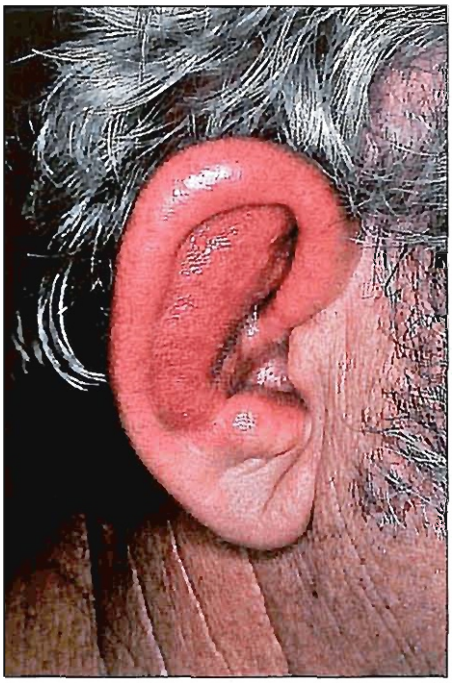

Fig. 8-24 Relapsing polychondritis characteristically involves cartilaginous portions of the ear but spares the lobe.

affected, with the usual age at onset being in the fourth to fifth decade. Dissolution of the cartilage involves the ears, nose, and respiratory tract. During bouts of inflammation, the bright red involvement of the ears is confined to the cartilaginous portion while the ear lobes remain conspicuously normal (Fig. 8-24). The affected areas are swollen and tender. There may be conductive deafness as a result of the obstruction produced by the swollen cartilage. The nasal septal cartilage is similarly involved to produce rhinitis, with crusting and bleeding and, eventually, a saddle-nose deformity. Involvement of the bronchi, larynx, and epiglottis produces hoarseness, coughing, and dyspnea. Migratory arthralgia and atypical chest pain is often present. Patients evaluated for chest pain are often released without treatment and with a diagnosis of costochrondritits. Ocular disease most often presents as conjunctivitis, scleritis, or iritis. Perforation of the globe may occur. The MAGIC syndrome is a combination of Behçet's disease and relapsing polychondritis (mouth and genital ulcers with inflamed cartilage).

Autoimmune mechanisms appear to be responsible for this disease. Cell-mediated immunity to cartilage has been demonstrated in vitro, with a degree of response correlated with disease activity. IgG anti-type-II collagen antibodies have been documented, again in titers corresponding with disease activity. Elevations in ESR, CRP levels, and urinary type II collagen neoepitope levels correlate with disease activity.

Limited data suggest that serum levels of Th1 cytokines (IFN-γ, IL-12, and IL-2) may correlate better with disease activity than those of Th2 cytokines (IL-4, IL-5, IL-6, and IL-10).

Histologically, a predominantly neutrophilic infiltrate is noted in the perichondrium. Varying degrees of chondrolysis may be present. DIF often demonstrates a lupus-like continuous granular band of immunoglobulin and complement in the perichondrium.

Dapsone, 100 mg once or twice a day for an adult, reduces the frequency of flares, but is usually inadequate to control the disease. Systemic corticosteroids should be used to treat acute flares, but most patients require a steroid-sparing immunosuppressive drug. Azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide, and TNF-α inhibitors have been used. Endobronchial ultrasonography has been used to facilitate the diagnosis and estimate the size of the involved airway for placement of stents.

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CHAPTER

9 Mucinoses

Within the dermis is a fibrillar matrix, termed *ground substance*, which is composed of proteoglycans and glycosaminoglycans. These acid mucopolysaccharides, produced by fibroblasts, are highly hygroscopic, binding about 1000 times their own volume in water. They are critical in holding water in the dermis and are responsible for dermal volume and texture. Normally, the sulfated acid mucopolysaccharide chondroitin sulfate and heparin are the primary dermal mucins. In certain diseases, fibroblasts produce abnormally large amounts of acid mucopolysaccharides, usually hyaluronic acid. These acid mucopolysaccharides (mucin) accumulate in large amounts in the dermis, and may be visible as pale blue granular or amorphous material between collagen bundles. They are often not visualized with hematoxylin eosin stains, since the water they bind is removed in processing, so the presence of increased mucin is suspected by the presence of large empty spaces between the collagen bundles. They can be detected by special stains, such as colloidal iron, alcian blue, and toluidine blue. Incubation of the tissue with hyaluronidase eliminates the staining, confirming the presence of hyaluronic acid.

Increased dermal mucin may result from many diseases and is a normal component of wound healing. The mucinoses are those diseases in which the production of increased amounts of mucin is the primary process. Mucin may also accumulate in the skin as a secondary phenomenon, such as when it is present in lupus erythematosus, dermatomyositis, Degos' disease, granuloma annulare, cutaneous tumors, or after therapies such as PUVA or retinoids. Mucin deposits in the skin are also prominent features of eosinophilia–myalgia syndrome and toxic oil syndrome and may herald the onset of scleroderma. The genetic diseases in which mucin accumulates as a result of inherited metabolic abnormalities are termed the *mucopolysaccharidoses* (see Chapter 25). Myxedema and pretibial myxedema are reviewed in Chapter 24.

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LICHEN MYXEDEMATOSUS

The terminology used to describe disorders in the disease group known as *lichen myxedematosus* (LM) has been confusing. Rongioletti and Rebora have introduced a useful classification system for this group of disorders. A generalized form, scleromyxedema, is accompanied by a monoclonal gammopathy and may have systemic involvement. Five localized forms are recognized, these being characterized by a lack of a monoclonal antibody and systemic disease. Finally, patients may have disease that does not fit into these subsets, and their condition is termed atypical or intermediate in type. Thyroid disease should not account for the findings in any category.

Generalized Lichen Myxedematosus

Scleromyxedema affects adults of both sexes and appears from ages 30 to 80. It is chronic and progressive. The primary lesions are multiple waxy, 2- to 4-mm, dome-shaped or flat-topped papules (Fig. 9-1). They may coalesce into plaques (Fig. 9-2) or be arranged in linear array. Less commonly, urticarial, nodular, or even annular lesions are seen. The

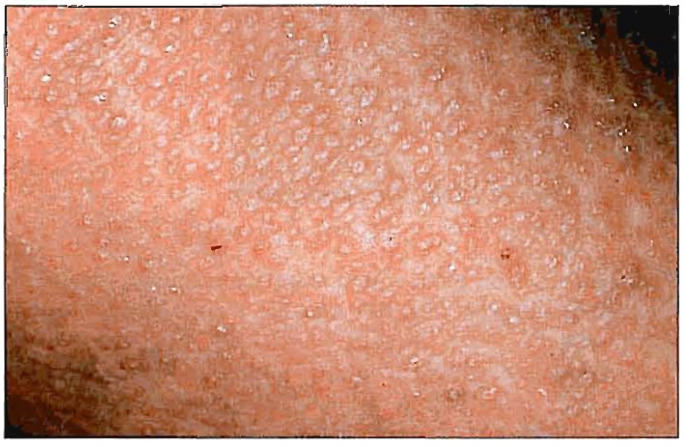

Fig. 9-1 Shiny papules of early scleromyxedema.

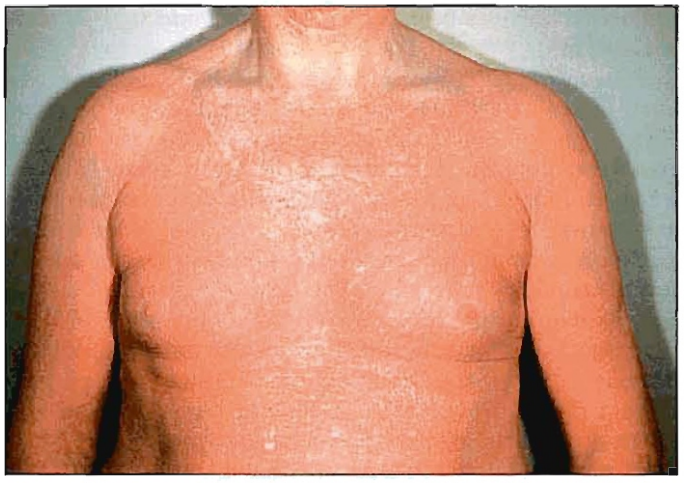

Fig. 9-2 Scleromyxedema.

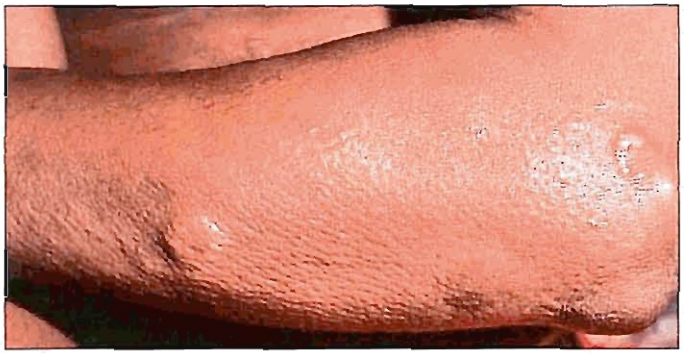

Fig. 9-3 Scleromyxedema. (Courtesy of Marshall Guill, MD)

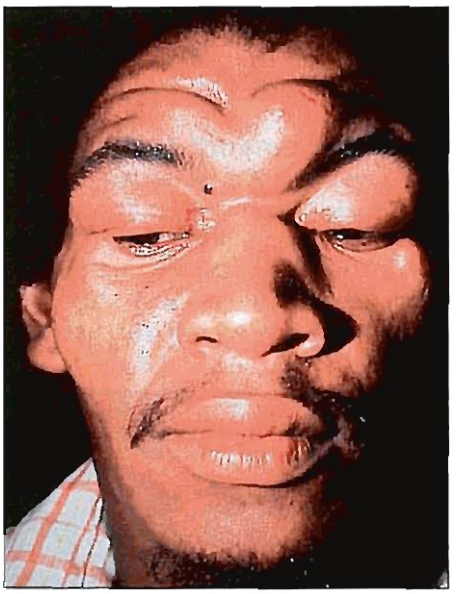

Fig. 9-4 Scleromyxedema. (Courtesy of Marshall Guill, MD)

dorsal hands, face, elbows, and extensor extremities are most frequently affected (Fig. 9-3 and Fig. 9-4). Mucosal lesions are absent.

A diffuse infiltration develops leading to woody sclerosis of the skin (Fig. 9-5). A reduced range of motion of the mouth, hands, and extremities may follow. On the glabella and forehead, coalescence of lesions leads to the prominent furrowing of a "leonine facies" (Fig. 9-6). At the proximal interphalangeal joint, induration surrounding a centrally depressed area has been termed the *doughnut sign*. Pruritus may occur.

Scleromyxedema not infrequently is associated with visceral disease. Gastrointestinal involvement is most frequent. Dysphagia resulting from involvement of the esophagus is most common, but the stomach or intestine may also be affected. Pulmonary complications with dyspnea caused by restrictive or obstructive disease are the second most common visceral problem. Proximal muscle weakness with an inflammatory myopathy or a nonspecific vacuolar change may occur. Carpal tunnel syndrome occurs in 10% of patients. Arthralgias or inflammatory arthritis is not uncommon. Peripheral neuropathies and central nervous system (CNS) disturbances, including confusion, dizziness, dysarthria, ascending paralysis, seizures, syncope, and coma, can occur. The latter has been termed the *dermatoneuro syndrome*. Visceral disease can be fatal.

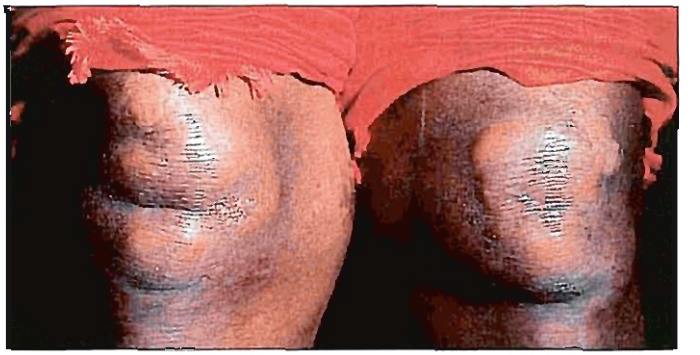

Fig. 9-5 Scleromyxedema. (Courtesy of Marshall Guill, MD)

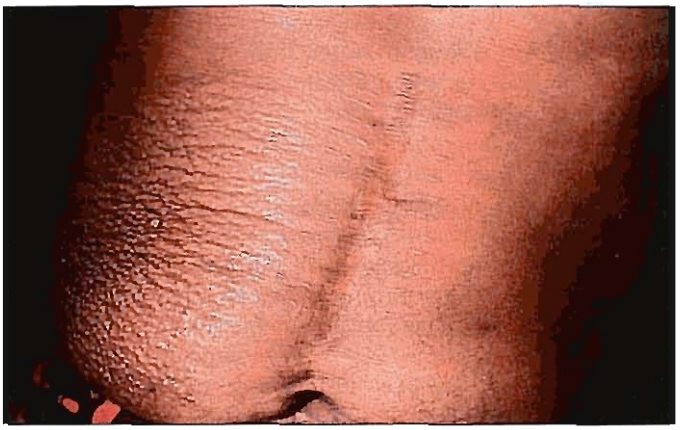

Fig. 9-6 Scleromyxedema. (Courtesy of Marshall Guill, MD)

Criteria for inclusion in this disease category include mucin deposition, fibroblast proliferation and fibrosis, normal thyroid function tests, and the presence of a monoclonal gammopathy. Approximately 10% of patients do not have this latter finding on initial evaluation. The gammopathy is usually an IgG-λ type, suggesting an underlying plasma cell dyscrasia. Bone marrow may be normal or reveal increased numbers of plasma cells or frank myeloma.

Clinical and histologic features are usually diagnostic. Skin biopsies of early papular lesions demonstrate a proliferation of fibroblasts with mucin and many small collagen fibers. The papules generally appear more fibrotic than mucinous. Over time, fibroblast nuclei become less numerous and collagen fibers become thickened.

Many of the clinical findings seen in scleromyxedema are also found in systemic scleroderma, including cutaneous sclerosis, Raynaud phenomenon, dysphagia, and carpal tunnel syndrome. This distinction in some cases may be difficult without a biopsy. Other infiltrative disorders, such as amyloidosis, must be excluded. Association with hepatitis C has been reported frequently. Nephrogenic fibrosing dermopathy presents with skin thickening in the setting of renal failure (Fig. 9-7). In its earliest form, it includes mucin along with collagen deposition with a proliferation of CD34+ cells in the dermis. The first report by Cowper et al was termed a scleromyxedema-like illness associated with renal failure. The clinical findings are dominated by fibrosis, so this entity is fully discussed in Chapter 8.

Treatment of scleromyxedema is difficult. Physical therapy is indicated. Moderate doses of systemic steroids are not usually helpful, but high doses may temporarily arrest progressive visceral disease. Retinoids, plasmapheresis,

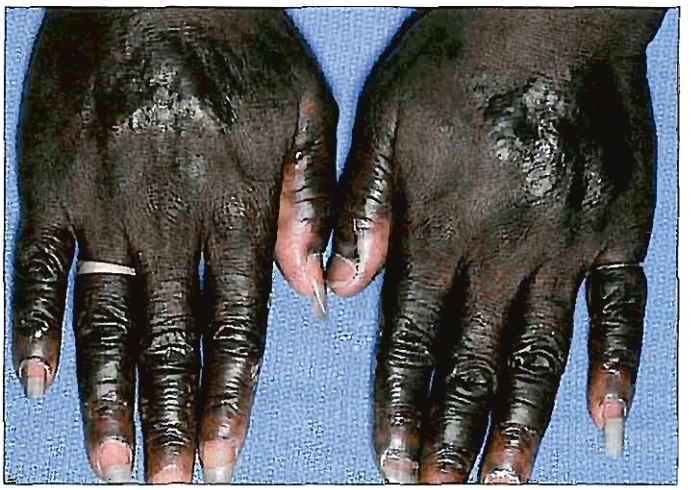

Fig. 9-7 Nephrogenic fibrosing dermopathy.

extracorporeal photochemotherapy, intravenous immunoglobulins, Grenz ray and electron beam therapy, PUVA, thalidomide, interferon (IFN)-α, cyclosporin, topical dimethyl sulfoxide, and topical and intralesional hyaluronidase and corticosteroids have all produced improvement in the skin of selected patients. Many others, however, have not benefited and visceral disease is not affected. One patient treated with high-dose pulse dexamethasone, high-dose melphalan, and autologous stem cell transplant obtained complete remission of the cutaneous and internal disease. UVB and IFN-α have exacerbated scleromyxedema.

Many patients have been treated with immunosuppressive agents, especially melphalan or cyclophosphamide with or without plasma exchange. Temporary remission of progressive visceral disease may occur. These short-term benefits must be weighed against the increase in malignancies and septic complications that may lead to death in as many as 30% of melphalan-treated patients. One patient has responded to 2-chlorodeoxyadenosine, but had severe, short-term, neurologic complications from the treatment.

Occasional patients are reported who spontaneously remit even after many years of disease; however, scleromyxedema remains a therapeutic challenge, and the overall prognosis is poor.

Localized Lichen Myxedematosus

The localized variants of LM lack visceral involvement or an associated gammopathy. As a group, they are benign, but often persistent. No therapy is reliably effective in any of the localized forms of lichen myxedematosus. Since there is no gammopathy, visceral involvement or associated thyroid disease in any of the variants, often no treatment is needed. Shave excision or CO_2 ablation are options for individual lesions, and spontaneous resolution may occur in all varieties.

Discrete Papular Lichen Myxedematosus Discrete papular lichen myxedematosus is characterized by the occurrence of waxy, 2- to 5-mm firm flesh-colored papules, usually confined to the limbs or trunk. The papules may have an erythematous or yellowish hue, may coalesce into nodules or plaques, and may number into the hundreds. Nodules may occasionally be the predominant lesion

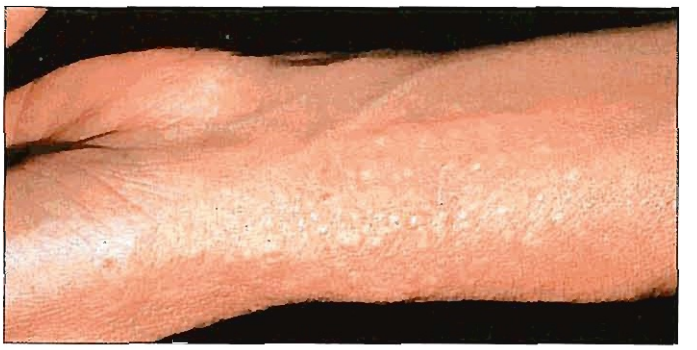

Fig. 9-8 Acral persistent papular mucinosis.

present, with few or absent papules. The underlying skin is not indurated and there is no associated gammopathy or internal involvement. Biopsy reveals the presence of mucin in the upper and mid dermis. Fibroblast proliferation is variable, but collagen deposition is minimal. The slow accumulation of papules is the usual course, without the development of a gammopathy or internal manifestations. Occasional cases may spontaneously involute.

Many patients with acquired immunodeficiency syndrome (AIDS) have been reported with mucinous papules, usually widespread, unassociated with a paraprotein. It is virtually always seen in advanced human immunodeficiency virus (HIV) disease in patients with multiple infectious complications of HIV disease. These lesions may occur in association with an eczematous dermatitis or on normal skin. If associated with an eczematous dermatitis, the lesions often clear if the eczema is controlled. Those cases occurring on normal skin may respond to systemic retinoid therapy. At times spontaneous remission occurs. The authors have also seen one case of a patient with acquired immunodeficiency syndrome (AIDS) and true scleromyxedema with visceral involvement and two patients have been reported with acral persistent papular mucinosis.

Acral Persistent Papular Mucinosis Patients with acral persistent papular mucinosis have few to 100, bilaterally symmetrical, 2- to 5-mm, flesh-colored papules localized to the hands and wrists (Fig. 9-8). The knees, calves or elbows may also be involved in a minority of patients. The face and trunk are spared. Women outnumber men by 5:1. The course is of persistence and slow progression. Two involved sisters have been reported. Histologically there is a collection of upper dermal mucin with minimal or no increase in fibroblasts.

Self-Healing Papular Mucinosis Self-healing papular mucinosis occurs in a juvenile and an adult form. The juvenile variant, also called *self-healing juvenile cutaneous mucinosis*, is a rare, but distinct disorder, characterized by the sudden onset of skin lesions and polyarthritis. Children, most commonly between the ages of 5 and 15, are affected. Familial cases are reported. Skin lesions are ivory-white papules of the head, neck, trunk, and typically the periarticular regions; deep nodules on the face and periarticular sites; and hard edema of the periorbital area and face. An acute arthritis affects the knees, elbows, and hand joints. In the adult form, papular lesions occur, usually without the associated joint symptoms (Fig. 9-9). Histology of the skin

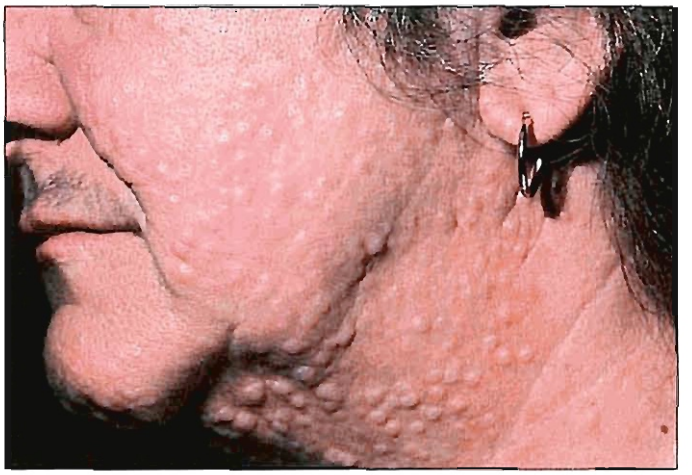

Fig. 9-9 Self-healing papular mucinosis.

lesions reveals dermal mucin with little fibroblastic proliferation or collagen deposition. Although the initial presentation is worrisome, the prognosis is excellent with spontaneous resolution without sequelae over several months.

Papular Mucinosis of Infancy This is also referred to as *cutaneous mucinosis of infancy* and is a rare syndrome that occurs at birth or within the first few months of life. Skin-colored or translucent, grouped or discrete, 2- to 8-mm papules develop on the trunk or upper extremities, especially the back of the hands. Biopsies show very superficial upper dermal mucin without proliferation of fibroblasts. Existing lesions remain static; new lesions continue to gradually accumulate. Similar lesions may sometimes be noted in association with neonatal lupus erythematosus.

Atypical or Intermediate Lichen Myxedematosus

The cutaneous mucinoses are all relatively uncommon. In a literature dominated by case reports, individual patients have been found who do not fit well into the above scheme, e.g. patients with acral persistent papular mucinosis who have had a papaprotein exist, and others with apparently classic scleromyxedema have none.

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SCLEREDEMA

Scleredema is a skin disease characterized by a stiffening and hardening of the subcutaneous tissues, as if they were infiltrated with paraffin. It occurs in two forms—with and without diabetes mellitus. In a large series of 33 patients, one-quarter had a sudden onset following an upper respiratory infection, typically caused by streptococcus. One-third had clinically identical lesions, but the onset was more insidious and there was no documented preceding infection. In 35% the disease was associated with diabetes mellitus and had a different clinical pattern.

In cases not associated with diabetes, females outnumber males by 2:1. The age at onset is from childhood through adulthood. Skin tightness and induration begins on the neck and/or face, spreading symmetrically to involve the arms, shoulders, back, and chest. The distal extremities are spared. There may be difficulty opening the mouth or eyes, and a masklike expression as a result of the infiltration. The involved skin, which is waxy white and of woodlike consistency, gradually transitions into normal skin with no clear demarcation. Associated findings occur in variable numbers of patients and can include dysphagia caused by tongue and upper esophageal involvement, cardiac arrhythmias, and an associated paraprotein, usually an IgG type. Myeloma may be present. There may be pleural, pericardial, or peritoneal effusion. In about half the patients in whom the condition follows an infection, spontaneous resolution will occur in months to a few years. The others have a prolonged course. Therapy is generally of no benefit, but patients may live with the disease for many years. Cyclosporin, UVA1, pulsed dexamethasone, and extracorporeal photophereis have been reported to be beneficial in individual patients.

In the second group, which in most dermatologists' experience is the more common, there is an association with late-onset, insulin-dependent diabetes. Men outnumber

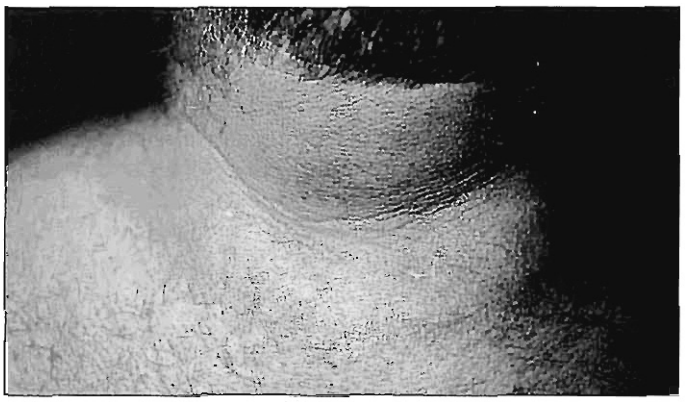

Fig. 9-10 Scleredema.

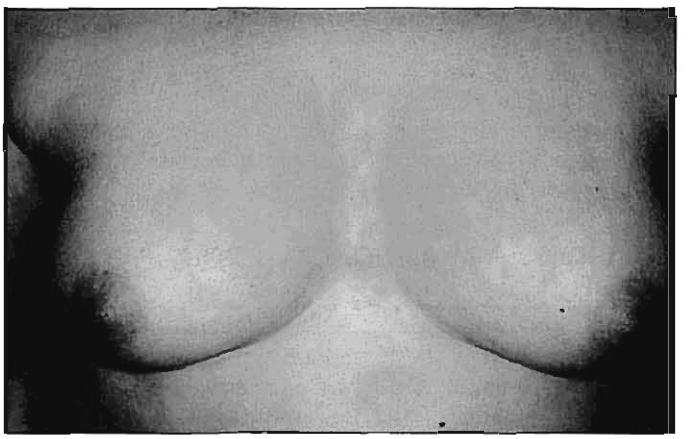

Fig. 9-11 Reticulated erythematous mucinosis.

women by 10:1. Affected men tend to be obese. The lesions are of insidious onset and long duration, presenting as woody induration and thickening of the skin of the mid upper back, neck, and shoulders (Fig. 9-10). There is a sharp step-off from the involved to the normal skin. Persistent erythema and folliculitis may involve the affected areas. The associated diabetes is of long duration and is difficult to control. Further, patients have frequently suffered complications of their diabetes, such as nephropathy, atherosclerotic disease, retinopathy, and neuropathy. Control of the diabetes does not affect the course of the scleredema. No paraprotein is detected, and visceral involvement is not seen. Lesions are persistent and usually unresponsive to treatment. Intravenous penicillin, electron beam alone or in combination with photon irradiation, low-dose methotrexate, and bath-PUVA have each been effective in different case reports.

The histology of both forms is identical. The skin is dramatically thickened, with the dermis often expanded two- to three-fold. There is marked fibrosis without the hyalinization seen in scleroderma. The thickened dermal collagen may be separated by clear spaces that contain hyaluronic acid. The amount of mucin is variable and usually only prominent in early lesions. In late lesions, fibrosis is the sole finding, and the amount of mucin is scant.

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RETICULAR ERYTHEMATOUS MUCINOSIS (REM SYNDROME, PLAQUE-LIKE CUTANEOUS MUCINOSIS)

Reticular erythematous mucinosis (REM) favors women in the third and fourth decades of life. The eruption frequently appears after intense sun exposure. Clinical lesions are erythematous plaques or reticulated patches that are several centimeters in diameter, and are most common in the midline of the chest and back (Fig. 9-11). Evolution is gradual. Photosensitivity is common; lesions may be induced with UVB. Onset or exacerbation with oral contraceptives, menses, and pregnancy are other features. Serologic tests for lupus erythematosus are negative.

Histologically, there are varying degrees of lymphocytic infiltration around dermal vessels, and deposits of mucin in the dermis. Direct immunofluorescence is negative. Treatment with antimalarials is successful in most cases. The pulsed dye laser has led to resolution in two patients.

Lesions of REM have also been reported to occur on the face, arms, abdomen, and groin. When evaluating patients with mucinous smooth-surfaced erythematous lesions it is important to consider the possibility of connective tissue disease. Plaque-like or papulonodular lesions in sites away from the central chest and back may infrequently herald the development of systemic lupus erythematosus, discoid lupus erythematosus, dermatomyositis or scleroderma.

Tumid lupus erythematosus is a subset of chronic cutaneous lupus that is characterized by erythematous papules, nodules, and plaques that most often involve the face, extensor aspects of the arms, shoulders, V of the neck, and upper back. Histology is identical to REM. It is photoinducable and responsive to antimalarials. While serologic abnormalities occur in a small percentage of patients, this is usually a skin-limited condition. Thus, there is considerable overlap with REM and some authors consider the two to be closely related or identical.

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FOLLICULAR MUCINOSIS (ALOPECIA MUCINOSA)

In 1957, Pinkus applied the name *alopecia mucinosa* to a series of patients with inflammatory plaques with alopecia characterized histologically by mucinous deposits in the outer root sheaths of the hair follicles. The plaques may be simply hypopigmented or erythematous and scaly, eczematous, or composed of flesh-colored, follicular papules (Fig. 9-12). There may be only one lesion, especially on the head and neck, or multiple lesions may be present. The plaques are firm and coarsely rough to the palpating finger. They are distributed mostly on the face (Fig. 9-13), neck, and scalp but may appear on any parts of the body. Itching may or may not be present. Alopecia occurs regularly in lesions on the scalp and frequently in lesions located elsewhere. Some papules show a comedo-like black central dot that corresponds to a broken hair or the mucin itself. These may cause the surface of a patch to look like keratosis pilaris. Sensory dissociation, with hot–cold perception difficulties or anesthesia to light touch, has been reported in some lesions, with a resultant misdiagnosis of leprosy.

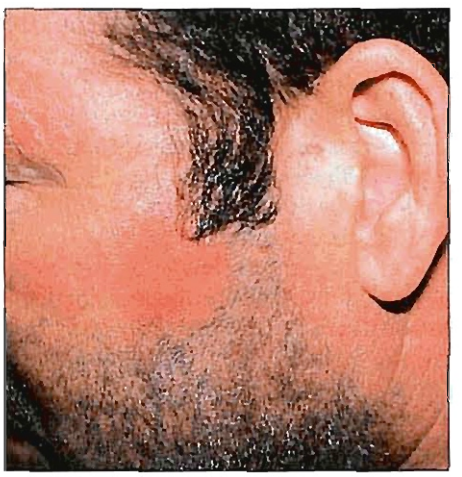

Fig. 9-12 Alopecia mucinosa.

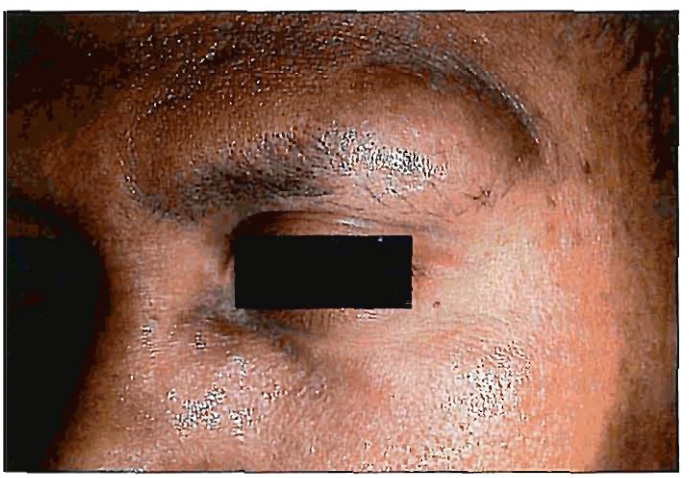

Fig. 9-13 Alopecia mucinosa.

The term *alopecia mucinosa* may be used to describe the disease process, and follicular mucinosis to describe the histologic features. The disease may be skin-limited and benign (primary follicular mucinosis) or may be associated with follicular mycosis fungoides. When lesions are solitary or few in number and cluster on the head and neck of individuals younger than 40 years of age, the condition usually follows a benign, chronic course, even in cases where the infiltrate is found to be clonal in nature. Widespread lesions in an older patient, however, will usually be found to be cutaneous T-cell lymphoma (CTCL) at initial presentation or will progress to lymphoma within 5 years. These two subsets are not exclusive, however, and no clinical or histologic criteria absolutely distinguish them in the absence of diagnostic findings of CTCL.

Histologically, follicular mucinosis demonstrates large collections of mucin within cells of the sebaceous gland and outer root sheath. The mucin typically stains as hyaluronic acid. A mixed dermal infiltrate is present. When the condition occurs in association with cutaneous T-cell lymphoma, the perifollicular infiltrate is atypical but not generally epidermotropic, and a considerable admixture of eosinophils and plasma cells is present. The additional finding of the presence of syringolymphoid hyperplasia should raise concern that lymphoma is or will become evident. T-cell receptor gene rearrangement studies that indicate clonity are also supportive but do not alone predict an aggressive course.

Spontaneous involution of primary follicular mucinosis may occur, especially in young children. Topical corticosteroids have produced varying degrees of improvement. Dapsone, PUVA, radiation therapy, IFN-α 2b, minocycline, isotretinoin, and indomethacin have been reported to be effective in individual cases. Follicular mycosis fungoides, with or without associated mucin, is more refractory to treatment and has a worse prognosis than classic CTCL.

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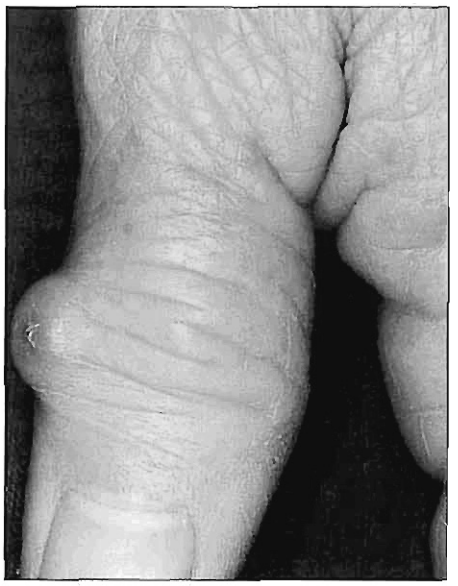

Fig. 9-14 Myxoid cyst.

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CUTANEOUS FOCAL MUCINOSIS

Focal mucinosis is characterized by a solitary nodule or papule. Lesions are asymptomatic and usually occur on the face, neck, trunk, or extremities. They appear in adulthood. Histologically, the lesion is characterized by a loose dermal stroma containing large quantities of mucin together with numerous dendritic-shaped fibroblasts. The clinical appearance is not distinctive and may at times be suggestive of a cyst, a basal cell carcinoma, or a neurofibroma. The treatment is surgical excision.

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MYXOID CYSTS

These lesions occur most commonly on the dorsal or lateral terminal digits of the hands but may also occur on the toes. They present as solitary, 5- to 7-mm, opalescent or skin-colored cysts (Fig. 9-14). They may occur as asymptomatic swellings of the proximal nailfold, as subungual growths, or over the distal interphalangeal joint. They contain a clear, viscous, sticky fluid that may spontaneously drain. These cysts do not have an epithelial lining but a compacted fibrous wall.

When a myxoid cyst is present beneath the proximal nailfold, a characteristic groove may be formed in the nail plate by pressure of the lesion on the nail matrix (Fig. 9-15).

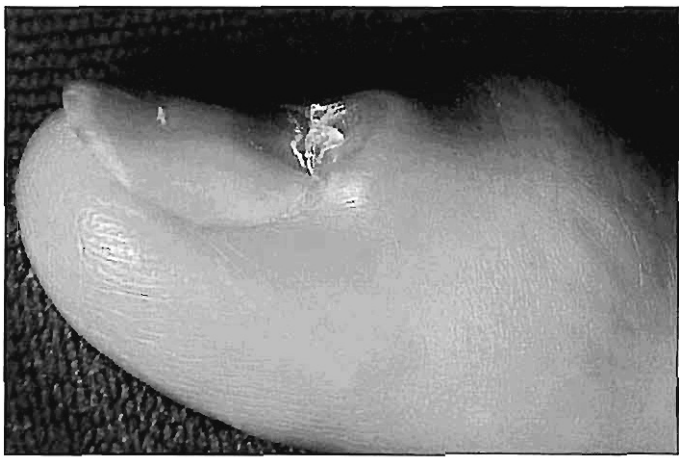

Fig. 9-15 Distortion of nail distal to a synovial cyst.

Those located beneath the nail cause a transverse nail curvature, a red or blue discoloration of the lunula is common, and nail integrity is typically compromised, leading to distal or longitudinal splitting or onycholysis. The diagnosis can be confirmed by magnetic resonance imaging (MRI) or surgical exploration. Myxoid cysts are typically found over the dorsal digit, between the distal joint, and over the proximal nailfold. If a cyst overlies the nailfold, a groove will result. Women are more frequently affected, and osteoarthritis is frequently present in the adjacent distal interphalangeal joint.

Treatment depends on the site of the cyst. The repeated puncture technique for the two accessible types may achieve a cure rate of up to 70%, but multiple punctures (> 40) may be required. This technique may be complicated by local tissue or joint infection. Intralesional steroids may be injected into the tissue after draining the cyst. Destruction by cryotherapy, CO_2 laser ablation, curettage, or fulguration are alternatives with similar cure rates, but these result in scarring.

Surgical approaches that reflect the skin overlying the cyst and either excise or tie off the communication to the joint, which may be visualized by injecting the cyst with methylene blue, have a cure rate of over 90%.

A recently recognized association of multiple myxoid cysts is with connective tissue disease. Young children, even infants, may present with multiple myxoid cysts as the initial manifestation of juvenile rheumatoid arthritis. An adult with systemic sclerosis also developed multiple myxoid cysts.

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CHAPTER

10 Seborrheic Dermatitis, Psoriasis, Recalcitrant Palmoplantar Eruptions, Pustular Dermatitis, and Erythroderma

SEBORRHEIC DERMATITIS

Clinical Features

Seborrheic dermatitis, also known as *seborrheic eczema*, is common, occurring in 2% to 5% of the population. It is a chronic, superficial, inflammatory disease with a predilection for the scalp, eyebrows, eyelids, nasolabial creases (Fig. 10-1), lips, ears, sternal area, axillae, submammary folds (Fig. 10-2), umbilicus, groins, and gluteal crease. The disease is characterized by scaling on an erythematous base. The scale often has a yellow, greasy appearance. Itching may be severe. Dandruff (pityriasis sicca) represents a mild form of seborrheic dermatitis. An oily type, pityriasis steatoides, is accompanied by erythema and an accumulation of thick crusts.

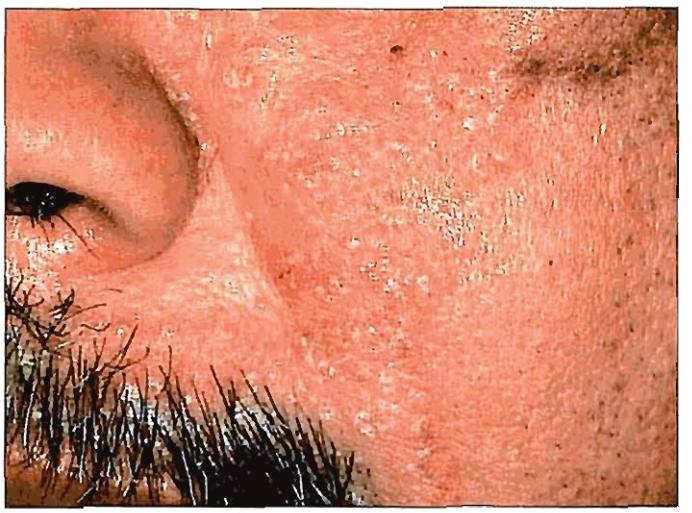

Fig. 10-1 Seborrheic dermatitis involving the cheek, nasolabial fold, and mustache.

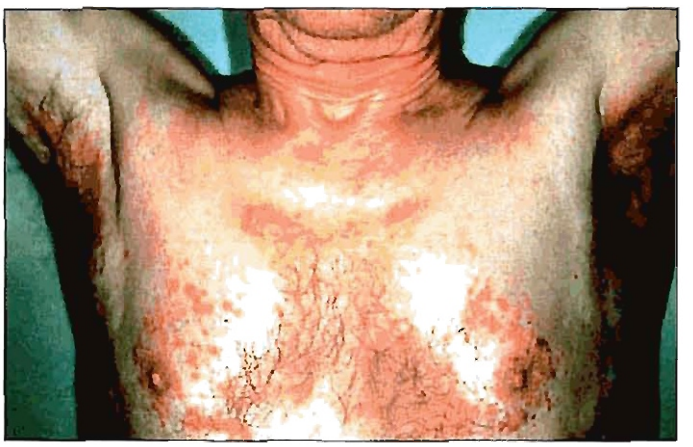

Fig. 10-2 Seborrheic dermatitis involving the chest and axillae.

Other types of seborrheic dermatitis on the scalp include arcuate, polycyclic or petaloid patches, and psoriasiform, exudative or crusted plaques. The disease frequently spreads beyond the hairy scalp to the forehead, ears, postauricular regions, and neck. On these areas the patches have convex borders and are reddish-yellow or yellowish. In dark-skinned individuals, arcuate and petaloid lesions commonly involve the hairline. In extreme cases the entire scalp is covered by a greasy, dirty crust with an offensive odor. In infants, yellow or brown scaling lesions on the scalp with accumulated adherent epithelial debris is called *cradle cap*.

Erythema and scaling are often seen in the eyebrows. The lids may show yellowish-white, fine scales and faint erythema. The edges of the lids may be erythematous and granular (marginal blepharitis), and the conjunctivae may be injected. If the glabella is involved, fissures in the wrinkles at the inner end of the eyebrow may accompany the fine scaling. In the nasolabial creases and on the alae nasi, there may be yellowish or reddish-yellow scaling macules, sometimes with fissures. In men, folliculitis of the beard area is common.

In the ears, seborrheic dermatitis may be mistaken for an infectious otitis externa. There is scaling in the aural canals, around the auditory meatus, usually with marked pruritus. The postauricular region and skin under the lobe may be involved. In these areas the skin often becomes red, fissured, and swollen. In the axillae the eruption begins in the apices, bilaterally, and later progresses to neighboring skin. This pattern resembles that of allergic contact dermatitis to deodorant, but differs from that of clothing dermatitis (which involves the periphery of the axillae, but spares the vault). The involvement may vary from simple erythema and scaling to more pronounced petaloid patches with fissures. The inframammary folds and the umbilicus may be involved. The presternal area is a favored site on the trunk.

Seborrheic dermatitis is common in the groin and gluteal crease, where its appearance may closely simulate tinea cruris or candidiasis. In these areas, the appearance often overlaps with that of inverse psoriasis. In fact, many of these patients have an overlap of the two conditions (sebopsoriasis or seborrhiasis) in the groin as well as the scalp.

The lesions may also become generalized and progress to a generalized exfoliative erythroderma (erythroderma desquamativum), especially in infants. A minority of these infants will have evidence of immunosuppression. In adults, generalized eruptions may be accompanied by adenopathy and may simulate mycosis fungoides or psoriatic erythroderma.

Seborrheic dermatitis may be associated with or accentuated by several internal diseases. Parkinson's disease is often accompanied by severe refractory seborrheic dermatitis

involving the scalp and face, with waxy, profuse scaling. A unilateral injury to the innervation of the face, or a stroke, may lead to unilateral localized seborrheic dermatitis. Patients with acquired immunodeficiency syndrome (AIDS) have an increased incidence of seborrheic dermatitis. An increased incidence has also been noted in patients who are seropositive for human immunodeficiency virus (HIV), but have not developed other signs of clinical disease. Diabetes mellitus, especially in obese persons; sprue; malabsorption disorders; epilepsy; neuroleptic drugs, such as haloperidol; and reactions to arsenic and gold have all produced seborrheic dermatitis-like eruptions.

Etiology and Pathogenesis

The etiology of this common disorder is complex, but may be related to the presence of the lipophilic yeast *Pityrosporum ovale.* The density of yeast has been correlated with the severity of the disease, and reduction of the yeast occurs with response to therapy. *P. ovale* may also be abundant on the scalps of patients who have no clinical signs of the disease, and the yeast may only be pathogenic in predisposed individuals.

Patients with seborrhoeic dermatitis may show upregulation of interferon (IFN)-γ, expressed interleukin (IL)-6, expressed IL-1α, and IL-4. Expression of cytotoxicity-activating ligands and recruitment of natural killer (NK) cells have also been noted.

Histology

The epidermis demonstrates regular acanthosis with some thinning of the suprapapillary plates. Varying degrees of spongiosis and lymphocyte exocytosis are noted. A characteristic finding is the presence of a focal scale crust adjacent to the follicular ostia.

Differential Diagnosis

Some cases of seborrheic dermatitis bear a close clinical resemblance to psoriasis, and the two conditions may overlap. Psoriasis tends to have more pronounced erythema and heavier silvery scales that peel in layers. Removal of scales in psoriasis may disclose bleeding points (Auspitz sign). This sign is common, but lacks great specificity. Severe itching favors seborrheic dermatitis. Characteristic psoriasis elsewhere (nail pitting, balanitis) may resolve the question. Impetigo of the scalp, especially when associated with pediculosis, may cause difficulty in differentiation. Scalp impetigo can be an indolent crusted dermatosis associated with failure to thrive. Langerhans cell histiocytosis may also resemble seborrheic dermatitis, but typically demonstrates yellow–brown perifollicular papules and groin fissuring. Crusted scabies of the scalp can also be confused with seborrheic dermatitis, and *Trichophyton tonsurans* often produces a subtle seborrheic scale. In subtle cases of tinea, a moist gauze pad rubbed vigorously on the scalp will typically dislodge short broken KOH-positive hairs. This can be the fastest way to make the diagnosis.

Treatment

Agents suitable for use on glabrous skin include corticosteroid creams, gels, sprays and foam. Corticosteroids tend to produce a rapid effect, but on the face even mid-potency corticosteroids can produce steroid rosacea. For this reason, antifungal agents and topical calcinearia inhibitors are often preferred. Ketoconazole, ciclopirox, tacrolimus, and pimecrolimus preparations are all effective. The antifungals are now available in a wide range of vehicles to include foams, gels, and liquids. Bifonazole shampoo has been shown to be effective in treating infants and small children. Topical calcinearia inhibitors may be associated with a burning sensation, especially on moist skin. Patients generally tolerate these agents well after initial treatment with a corticosteroid. When secondary bacterial infection is present, a topical or oral antibiotic may be required. In patients infected with HIV, lithium succinate ointment (Efalith) has been used for facial disease. Lithium gluconate 8% ointment has also been shown to compare favorably with ketoconazole 2% emulsion in healthy adults and was more effective in terms of control of scaling and symptoms. Sodium sulfacetamide products with or without sulfur are effective in some refractory patients.

For scalp disease, selenium sulfide, ketoconazole, tar, zinc pyrithione, fluocinolone, and resorcin shampoos are effective. These agents should usually be used two to three times a week, with a regular shampoo used in between as required. Antifungal foams and gels, as well as corticosteroid solutions, foams, gels and sprays, are all effective. In the treatment of the scalp, ointment or oil preparations are preferred by some black patients.

Itching of the external ear canal usually responds to a topical corticosteroid, calcinearia inhibitors or antifungals such as ketoconazole or ciclopirox. Some patients require the use of a class 1 corticosteroid on weekends to control refractory pruritus. Cortisporin otic suspension can bring about prompt clearing, but contact dermatitis to neomycin may complicate the use of some Cortisporin products. Desonide Otic Lotion (0.05% desonide and 2% acetic acid) is also effective and may be better tolerated than Domeboro otic solution in some patients.

Sodium sulfacetamide drops or ointment may be effective for seborrheic blepharitis. Oral tetracyclines can also be effective, and have been shown to decrease the density of microorganisms in the affected follicles. Steroid preparations are suitable for short-term use, but may induce glaucoma and cataracts. Daily gentle cleansing with a cotton-tipped applicator and baby shampoo in water can reduce symptoms. In severe cases, oral antibiotics or oral antifungals may be combined with topical agents.

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PSORIASIS

Clinical Features

Psoriasis is a common, chronic, and recurrent inflammatory disease of the skin characterized by circumscribed, erythematous, dry, scaling plaques of various sizes. The lesions are usually covered by silvery white lamellar scales (Fig. 10-3). The lesions have a predilection for the scalp, nails, extensor surfaces of the limbs, umbilical region, and sacrum. The eruption is usually symmetrical. The eruption usually develops slowly but may be exanthematous, with the sudden onset of numerous guttate (droplike) lesions. Subjective symptoms, such as itching or burning, may be present and may cause extreme discomfort.

The early lesions are small erythematous macules, which from the beginning are covered with dry, silvery scales. The lesions increase in size by peripheral extension and coalescence. The scales are micaceous, meaning that they peel in layers. They are looser toward the periphery and adherent centrally. When removed, bleeding points appear (Auspitz's sign). Although plaques typically predominate, lesions may be annular or polycyclic. Old patches may be thick and covered with tough lamellar scales like the outside of an oyster shell (*psoriasis ostracea*). Various other descriptive terms have in the past been applied to the diverse appearances of the lesions: *psoriasis guttata*, in which the lesions are the size of water drops; *psoriasis follicularis*, in which tiny, scaly lesions are located at the orifices of hair follicles; *psoriasis figurata, psoriasis annulata*, and *psoriasis gyrata*, in which curved linear patterns are produced by central involution; *psoriasis discoidea*, in which central involution does not occur and solid patches persist; and *psoriasis rupioides*, in which crusted lesions occur, resembling syphilitic rupia. The term *chronic plaque psoriasis* is often applied to stable lesions of the trunk and extremities. Inverse psoriasis predominates in intertriginous areas. Pustular variants of psoriasis may be chronic on the palms and soles, or may be eruptive and accompanied by severe toxicity and hypocalcemia.

Involved nails (Fig. 10-4) can demonstrate distal onycholysis, random pitting (the result of parakeratosis from the proximal matrix), oil spots (yellow areas of subungual parakeratosis from the distal matrix), or salmon patches (nailbed psoriasis). Thick subungual hyperkeratosis may resemble onychomycosis.

Types

Seborrheic-Like Psoriasis Some cases of psoriasis overlap with seborrheic dermatitis. Seborrheic lesions may predominate on the face, under the breasts, and in the scalp, flexures, and axillae. Lesions in these areas are moist and erythematous, with yellow, greasy, soft scales, rather than dry and micaceous scales. Terms such as *sebopsoriasis* and *seborrhiasis* may be used to describe such patients.

Inverse Psoriasis This form selectively and often exclusively involves folds, recesses, and flexor surfaces such as the ears, axillae, groins, inframammary folds, navel, intergluteal crease, penis (Fig. 10-5), lips, and webspaces. Other areas, such as the scalp and nails may be involved.

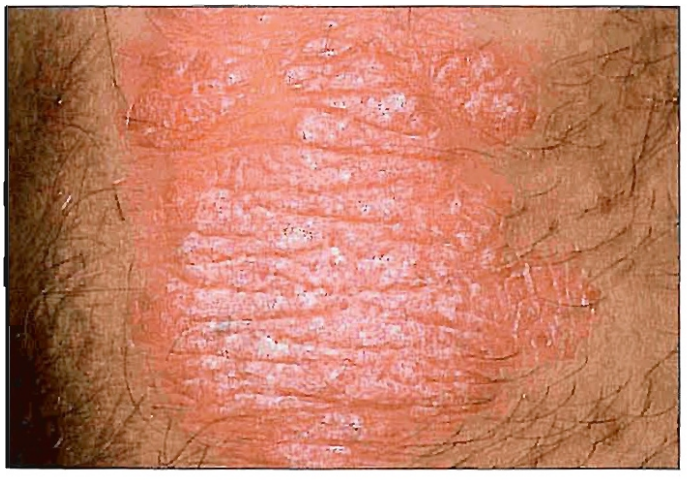

Fig. 10-3 Psoriasis plaque, red plaque with silver scale on the knee.

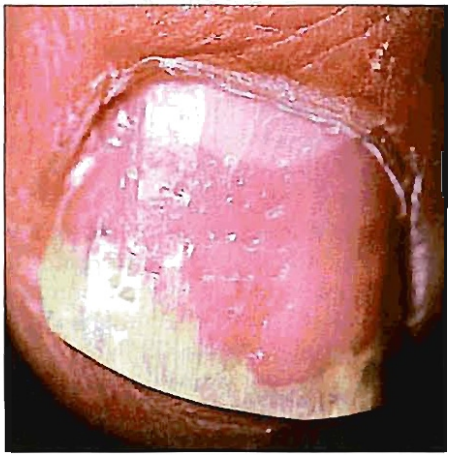

Fig. 10-4 Nail pitting and distal onycholysis in psoriasis.

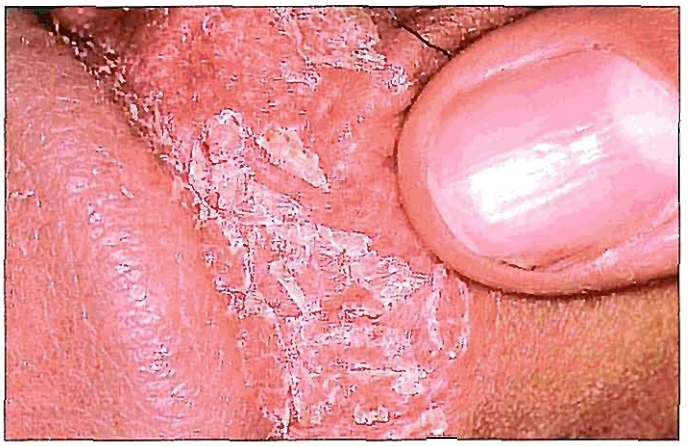

Fig. 10-5 Penile psoriasis with erythema and silver scale.

"Napkin" Psoriasis Napkin psoriasis, or psoriasis in the diaper area, is characteristically seen in infants between 2 and 8 months of age. Lesions appear as brightly erythematous, sharply demarcated patches of skin involving much of the diaper area. The lesions typically clear with topical therapy, but psoriasis may reappear in adulthood.

Psoriatic Arthritis Five clinical patterns of arthritis occur:

1. Asymmetrical distal interphalangeal joint involvement with nail damage (16%)
2. Arthritis mutilans with osteolysis of phalanges and metacarpals (5%)
3. Symmetrical polyarthritis-like rheumatoid arthritis, with claw hands (15%)
4. Oligoarthritis with swelling and tenosynovitis of one or a few hand joints (70%)
5. Ankylosing spondylitis alone or with peripheral arthritis (5%)

Most radiographic findings resemble those in rheumatoid arthritis, but certain findings are highly suggestive of psoriasis. These include erosion of terminal phalangeal tufts (acrosteolysis), tapering or "whittling" of phalanges or metacarpals, "cupping" of proximal ends of phalanges, bony ankylosis, osteolysis of metatarsals, predilection for distal interphalangeal and proximal interphalangeal joints, relative sparing of metacarpal phalangeal and metatarsal phalangeal joints, paravertebral ossification, asymmetrical sacroiliitis, and rarity of "bamboo spine" when the spine is involved. Nearly half the patients with psoriatic arthritis have type HLA-B27.

Rest, splinting, passive motion, and nonsteroidal anti-inflammatory agents (NSAIDs) may provide symptomatic relief, but do not prevent deformity. Methotrexate, cyclosporin, tacrolimus, and biologic agents are disease-modifying drugs that prevent deformity.

Guttate Psoriasis In this distinctive form of psoriasis typical lesions are the size of water drops, 2 to 5 mm in diameter. Lesions typically occur as an abrupt eruption following some acute infection, such as a streptococcal pharyngitis. Guttate psoriasis occurs mostly in patients under age 30. This type of psoriasis usually responds rapidly to broad-band ultraviolet (UV)B at erythemogenic doses. Suberythemogenic doses often have little impact on the lesions. Minimal erythemogenic dose (MED) testing is recommended to allow for appropriately aggressive treatment. Recurrent episodes may be related to pharyngeal carriage of the responsible streptococcus by the patient or a close contact. A course of a semisynthetic penicillin (such as dicloxacillin 250 mg four times a day for 10 days) with rifampin (600 mg/day for an adult) may be required to clear chronic streptococcal carriage.

Generalized Pustular Psoriasis (von Zumbusch) Typical patients have had plaque psoriasis and often psoriatic arthritis. The onset is sudden, with formation of lakes of pus periungually, on the palms, and at the edge of psoriatic plaques. Erythema occurs in the flexures before the generalized eruption appears. This is followed by a generalized erythema and more pustules (Fig. 10-6). Pruritus and intense burning are often present. Mucous membrane lesions are common. The lips may be red and scaly, and superficial ulcerations of the tongue and mouth occur. Geographic or fissured tongue frequently occurs (Fig. 10-7).

The patient is frequently ill with fever, erythroderma, hypocalcemia, and cachexia. A number of cases of acute respiratory distress syndrome associated with pustular and

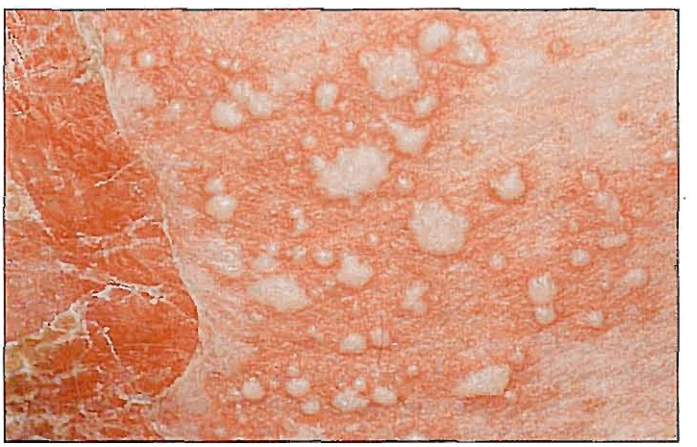

Fig. 10-6 Pustular psoriasis.

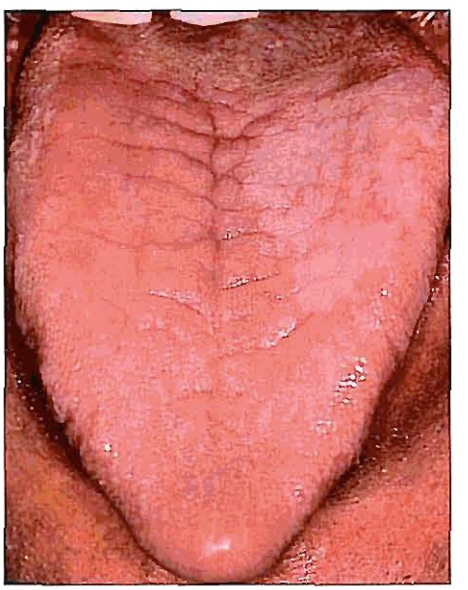

Fig. 10-7 Fissured and geographic tongue in a patient with generalized pustular psoriasis.

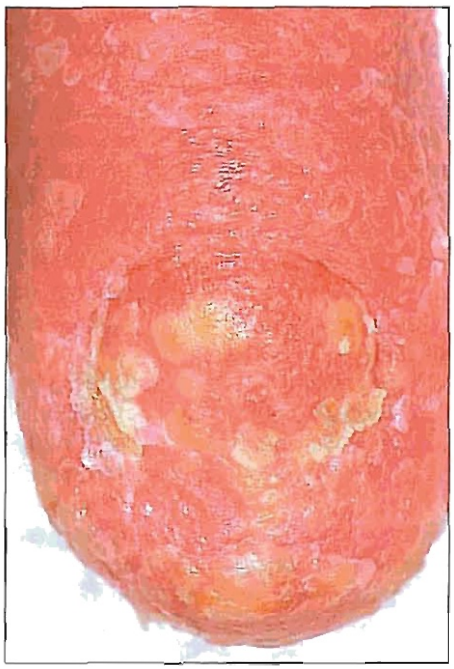

Fig. 10-8 Nailbed involvement in acrodermatitis continua.

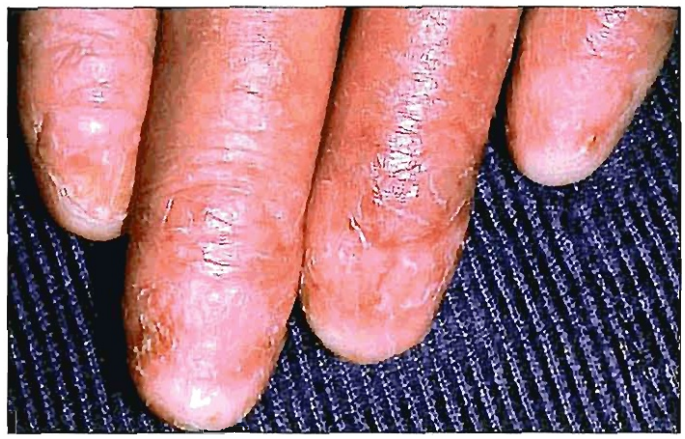

Fig. 10-9 Anonychia in acrodermatitis continua.

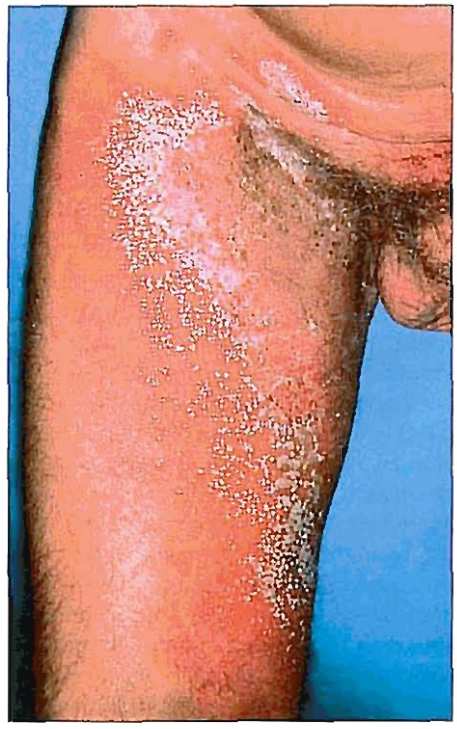

Fig. 10-10 Generalized pustular flare in a patient with acrodermatitis continua.

erythrodermic psoriasis have been reported. Other systemic complications include pneumonia, congestive heart failure, and hepatitis.

Episodes are often provoked by withdrawal of systemic corticosteroids. The authors have also observed a patient whose pustular psoriasis was the presenting sign of Cushing's disease. Other implicated drugs include iodides, coal tar, terbinafine, minocycline, hydroxychloroquine, acetazolamide, and salicylates. There is usually a strong familial history of psoriasis. Generalized pustular psoriasis may occur in infants and children with no implicated drug. It may also occur as an episodic event punctuating the course of localized acral pustular psoriasis.

Acitretin is the drug of choice in this severe disease. The response is generally rapid. Isotretinoin is also effective. Cyclosporin, methotrexate and bilologicals are alternatives. Sometimes dapsone is effective in doses of 50 to 100 mg/day.

Acrodermatitis Continua of Hallopeau Typical patients develop acral erythematous plaques studded with pustules. The nailbeds are heavily involved (Fig. 10-8), and the fingernails float away on lakes of pus resulting in anonychia (Fig. 10-9). Hyperkeratosis often ensues, and the fingertips become increasingly painful, tapering to long keratotic points. Occasionally, patients may develop generalized pustular flares (Fig. 10-10). Acrodermatitis continua is discussed in more detail below.

Impetigo Herpetiformis This term has been applied to generalized pustular psoriasis of pregnancy. Flexural erythema, studded with pustules, often occurs initially, followed by a generalized pustular flare and increasing toxicity. As the patients are pregnant, systemic retinoids are not appropriate. Many patients only respond to delivery, and early delivery should be strongly considered as soon as it is safe for the infant. Alternatively, patients may respond to prednisone at a dose of 1 mg/kg/day. Although systemic corticosteroids are generally contraindicated in plaque psoriasis because they can provoke pustular flares, they have a role in the treatment of impetigo herpetiformis. The corticosteroid can also contribute to neonatal lung maturity.

Keratoderma Blennorrhagica (Reiter Syndrome) Reiter syndrome resembles psoriasis both histologically and clinically, except for its tendency for thicker keratotic lesions. Patients are often positive for HLA-B27 and develop disease after a bout of urethritis or enteritis.

Erythrodermic Psoriasis Patients with psoriasis may develop a generalized erythroderma (Fig. 10-11). Erythrodermic psoriasis is covered in greater detail under exfoliative dermatitis.

Course

The course of psoriasis is unpredictable. It usually begins on the scalp or elbows, and may remain localized in the original region for years. Chronic disease may also be almost entirely

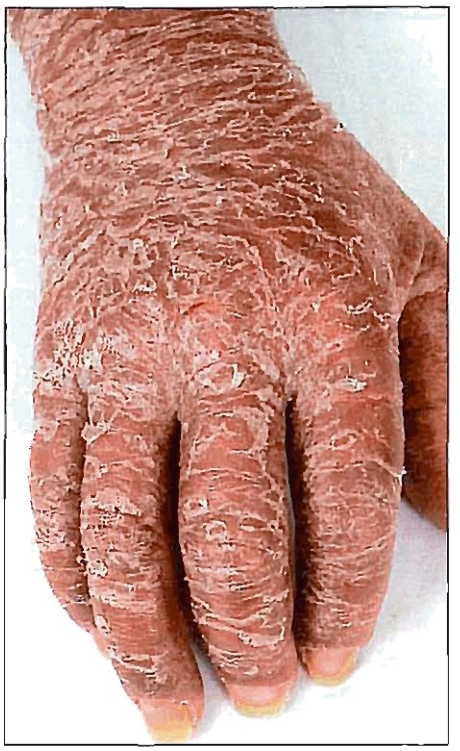

Fig. 10-11
Erythrodermic psoriasis.

limited to the fingernails. Involvement over the sacrum may easily be confused with candidiasis or tinea. Onset may also be sudden and widespread.

Two of the chief features of psoriasis are its tendency to recur and its persistence. The isomorphic response (Koebner's phenomenon) is the appearance of typical lesions of psoriasis at sites of even trivial injury. Lesions may occur at sites of scratches, incisions, and burns. Lesions may first appear after a viral exanthema or following pityriasis rosea. Occasionally a patient receiving phototherapy will experience increased erythema and burning limited to the psoriatic plaques. At the same time, the plaques often enlarge. This phenomenon appears to represent a form of isomorphic response. With a reduction in light dosage, the erythema and burning resolve, and the plaques begin to clear. Woronoff's ring is concentric blanching of the erythematous skin at or near the periphery of a healing psoriatic plaque. It is often the first sign that the patient's psoriasis is responding to phototherapy.

The palms and soles are sometimes exclusively affected, showing discrete erythematous dry scaling patches, circumscribed verrucous thickenings, or pustules on an erythematous base. The patches usually begin in the mid portions of the palms or on the soles, and gradually expand. Psoriasis of the palms and soles is typically chronic and extremely resistant to treatment.

Many studies report an association between hepatitis C and psoriasis, and hepatitis C has also been implicated in psoriatic arthritis. If treatment of psoriasis is to include a potentially hepatotoxic drug, such as methotrexate, a hepatitis C serology should be obtained. It should also be noted that IFN-α, an agent frequently used to treat patients with hepatitis C, can further exacerbate or induce psoriasis. Anti-tumor necrosis factor (TNF)-α therapy shows promise in the treatment of psoriasis, even in the setting of chronic hepatitis C infection.

Inheritance

In a large study of psoriasis in monozygotic twins, heritability was high and environmental influence low. Patients with psoriasis often have relatives with the disease, and the incidence typically increases in successive generations. Multifactorial inheritance is likely. Analysis of population-specific human leukocyte antigen (HLA) haplotypes has provided evidence that susceptibility to psoriasis is linked to the class I and II major histocompatibility complex (MHC) on human chromosome 6. A number of genetic loci are linked to psoriasis, including PSORS1 on chromosome 6 and within the MHC, and PSORS2 on chromosome 17q. It has also been shown that there are two subsets that differ in age of onset and in the frequency of HLA associations. Early onset is type I psoriasis and is associated mostly with -Cw6, -B57, and -DR7. Late onset is type II and this predominantly features -Cw2.

A variety of other HLA associations have been reported. It is believed that any individual who has -B13 or -B17 has a five-fold risk of developing psoriasis. In pustular psoriasis HLA-B27 may be seen, whereas -B13 and -B17 are increased in guttate and erythrodermic psoriasis. In palmoplantar pustulosis, there is an association with HLA-B8, -Bw35, -Cw7, and -DR3. HLA typing is a research tool for population-based studies, but is of limited value in assessing an individual patient.

Epidemiology

Psoriasis occurs with equal frequency in both sexes. One percent to 2% of the US population has psoriasis. It occurs less frequently in the tropics. It is less common in North American and West African black persons. Native Americans and native Fijians rarely have psoriasis. The onset of psoriasis is at a mean age of 27 years, but the range is wide, from the neonatal period to the 70s. Severe emotional stress tends to aggravate psoriasis in almost half of those studied.

In pregnancy there is a distinct tendency for improvement or even temporary disappearance of lesions in the majority of women studied. After childbirth there is a tendency for exacerbation of lesions. Paradoxically, pregnancy is also the milieu for impetigo herpetiformis, and psoriasis may behave differently from one pregnancy to another in the same patient.

A high prevalence of celiac disease has been noted in patients with psoriasis. Lymphoma also occurs with an increased incidence in these patients.

Pathogenesis

Psoriasis is a hyperproliferative disorder, but the proliferation is driven by a complex cascade of inflammatory mediators. T-cells and cytokines play pivotal roles in the pathophysiology of psoriasis. Overexpression of type-1 cytokines such as IL-2, IL-6, IL-8, IL-12, IFN-γ and TNF-α, has been demonstrated, and overexpression of IL-8 leads to the accumulation of neutrophils. The main signal for Th1 development is IL-12, which promotes intracellular IFN-γ production. In animal models, shifting from Th1 to Th2 responses improves psoriasis. IL-4 is capable of inducing Th2 responses and improving psoriasis. Reduced expression of the anti-inflammatory cytokines IL-1RA and IL-10 has been found, and polymorphisms for IL-10 genes correlate with psoriasis. IL-10 is a type 2 cytokine with major influences on immuno-

regulation, inhibiting type 1 proinflammatory cytokine production. Patients on established traditional therapies show rising levels of IL-10 mRNA expression, suggesting that IL-10 may have antipsoriatic capacity.

As discussed above, the response to biologic agents has demonstrated that CD2+ lymphocytes, CD-11a and TNF-α are important in the pathogenesis of psoriasis. IL-15 triggers inflammatory cell recruitment, angiogenesis, and production of inflammatory cytokines, including IFN-γ, TNF-α, and IL-17, all of which are upregulated in psoriatic lesions. An IL-15 monoclonal antibody has been shown to be effective in a mouse model of psoriasis. TGF-β and its receptors are downregulated in psoriatic skin, leading to abnormal cell proliferation. Circulating NK cells are reduced in psoriasis. Specific targets for therapy include TNF-α, leukocyte function-associated antigen-1 (LFA-1)/intercellular adhesion molecule-1 (ICAM-1) binding, and LFA-3/CD2 binding.

Many genes, including CCL-4/MIP-1β, CCL-20/MIP-3α, CXCL-2/GRO-β CXCL-8/IL-8, and CXCR2/IL-8R, demonstrate increased gene expression in psoriatic skin compared with atopic skin. Reduction of CD18 (β(2) integrin) in mice leads to the development of a psoriasiform skin disease. Both CD4+ and CD8+ T-cells are increased in the skin of affected mice, but only depletion of CD4+ T-cells results in disappearance of skin lesions. The stat3 activated mouse is a new model for the study of psoriasis.

Streptococci Streptococci play a role in some patients. Patients with psoriasis report sore throat more often than controls. Beta-hemolytic streptococci of Lancefield groups A, C, and G can cause exacerbation of chronic plaque psoriasis. T-helper 1 (Th-1) cells recognize cell-wall extract isolated from group A streptococci. HLA variation has a significant effect on the immune response to group A streptococci.

Stress Various studies have shown a positive correlation between stress and severity of disease. In almost half of studied patients, stress appears to play a significant role.

Drug-Induced Psoriasis Psoriasis may be induced by beta-blockers, lithium, antimalarials, terbinafine, calcium-channel blockers, captopril, glyburide, granulocyte colony-stimulating factor, ILs, IFNs, and lipid-lowering drugs. Systemic steroids may cause rebound or pustular flares. Antimalarials are associated with erythrodermic flares, but patients traveling to malaria-endemic regions should take appropriate prophylaxis. Often, drugs such as doxycycline or mefloquin are appropriate for the geographic area, but when a quinine derivative offers the best protection, it is generally better to take the prophylactic doses of a quinine derivative than to risk disease and full dose treatment.

Pathology

Histologically, all psoriasis is pustular. The microscopic pustules include spongiform intraepidermal pustules, and Munro microabscesses within the stratum corneum. In early guttate lesions, focal parakeratosis is noted within the stratum corneum. The parakeratotic focus typically has an outline resembling a child's rendition of a sea gull. Neutrophils are generally noted immediately above the focus of parakeratosis, but in some sections, the neutrophils will not be visible as a result of sampling error. In plaque psoriasis, neutrophilic foci are so numerous that they are rarely missed. Neutrophilic microabscesses are generally present at multiple levels in the stratum corneum, generally on top of small foci of parakeratosis. These foci generally alternate with areas of orthokeratotic stratum corneum, suggesting that the underlying spongiform pustules arise in a rhythmic fashion. The granular layer is absent focally, corresponding to areas producing foci of parakeratosis. In well developed plaques, there is regular epidermal acanthosis with long, bulbous rete ridges, thinning over the dermal papillae, and dilated capillaries within the dermal papillae. The last two findings correlate with Auspitz's sign. The stratum corneum may be entirely parakeratotic but still shows multiple small neutrophilic microabscesses at varying levels. Spongiosis is typically scant except in the area immediately surrounding collections of neutrophils.

In pustular psoriasis, geographic tongue and Reiter syndrome, intraepidermal spongiform pustules tend to be much larger. Grossly pustular lesions often have little associated acanthosis. In Reiter syndrome, the stratum corneum is often massively thickened with prominent foci of neutrophils above parakeratosis, alternating with orthokeratosis.

Acral lesions often demonstrate nondiagnostic features histologically. Spongiosis is typically prominent in these lesions and often leads to a differential diagnosis of psoriasis or chronic psoriasiform spongiotic dermatitis. Foci of neutrophils often contain serum and may be interpreted as impetiginized crusting.

On direct immunofluorescence testing, the stratum corneum demonstrates intense fluorescence with all antibodies, complement, and fibrin. This fluorescence may be partially independent of the fluorescent label, as it has been noted in hematoxylin and eosin (H&E)-stained sections and frozen unstained sections. The same phenomenon of stratum corneum autofluorescence has been noted in some cases of candidiasis that demonstrate a psoriasiform histology.

Psoriasis can generally be distinguished from dermatitis by the paucity of edema, the relative absence of spongiosis, the tortuosity of the capillary loops, and the presence of neutrophils above foci of parakeratosis. Neutrophils in the stratum corneum are commonly seen in tinea, impetigo, candidiasis and syphilis, but rarely are found atop parakeratosis alternating with orthokeratosis in a rhythmic fashion. In psoriasiform syphilis the rete are typically long and slender, a vacuolar interface dermatitis is commonly present, dermal blood vessels appear to have no lumen because of endothelial swelling, and plasma cells are present in the dermal infiltrate. About one-third of biopsies of syphilis lack plasma cells, but the remaining characteristics still suggest the correct diagnosis. Psoriasiform lesions of mycosis fungoides exhibit epidermotropism of large lymphocytes with little spongiosis. The lymphocytes are typically larger, darker, and more angulated than the lymphocytes in the dermis. There is associated papillary dermal fibrosis, and the superficial perivascular infiltrate is asymmetrically distributed around the post-capillary venules, favoring the epidermal side (bare underbelly sign).

Clinical Differential Diagnosis

Psoriasis must be differentiated from dermatomyositis, lupus erythematosus, seborrheic dermatitis, pityriasis rosea, lichen planus, eczema, and psoriasiform syphilid. The distribution in psoriasis is on the extensor surfaces, especially of the

elbows and knees, and on the scalp; dermatomyositis shares this distribution whereas lupus erythematosus generally lacks involvement of the extensor surfaces. Patients with dermatomyositis may exhibit a heliotrope sign, atrophy, poikiloderma, and nailfold changes. Advanced lesions of discoid lupus erythematosus often demonstrate follicular hyperkeratosis (carpet tack sign). Seborrheic dermatitis has a predilection for the eyebrows, nasolabial angle, ears, sternal region, and flexures. The scales in psoriasis are dry, white, and shiny, whereas those in seborrheic dermatitis are greasy and yellowish. On removal of the scales in psoriasis there is an oozing of blood from the capillaries (Auspitz's sign), whereas this does not occur in seborrheic dermatitis.

In pityriasis rosea the eruption is located on the upper arms, trunk, and thighs, and the duration is a matter of weeks. Lesions are typically oval and follow skin tension lines. Individual lesions show a crinkling of the epidermis and collarette scaling. A herald patch is frequently noted. Lichen planus chiefly affects the flexor surfaces of the wrists and ankles. Often the violaceous color is pronounced. In darker skinned individuals, the lesions have a tendency to pronounced hyperpigmentation. The nails are not pitted as in psoriasis, but longitudinally ridged, rough, and thickened. Pterygium formation is characteristic of lichen planus.

Hand eczema may resemble psoriasis. In general, psoriatic lesions tend to be more sharply marginated, but at times the lesions are indistinguishable. Psoriasiform syphilid has infiltrated copper-colored papules, often arranged in a figurate pattern. Serologic tests for syphilis are generally positive, but prozone reactions may occur, and the serum may have to be diluted in order to obtain a positive test. Generalized lymphadenopathy and mucous patches may be present.

Treatment

Topical therapy is generally suitable for limited plaques. Localized treatments, such as the eximer laser or other forms of intense pulsed light, may be suitable for limited plaques. Phototherapy remains highly cost-effective for widespread psoriasis. Cyclosporin has a rapid onset of action, but is generally not suitable for sustained therapy. Methotrexate remains the systemic agent against which others are compared. Biologic agents can produce dramatic responses at dramatic expense. Rotating therapeutic agents that have varying toxicities has conceptual appeal, and combination therapy may reduce toxicity and reduce the incidence of neutralizing antibodies to agents such as infliximab.

Topical Treatment

Corticosteroids

Topical application of corticosteroids in creams, ointments, lotions, foams, and sprays is the most frequent prescribed therapy for psoriasis. Class I steroids are suitable for 2-week courses of therapy on most body areas. Therapy can be continued with pulse applications on weekends to reduce the incidence of local adverse effects. On the scalp, corticosteroids in propylene glycol, gel, foam, and spray bases are preferred by most white patients. Black patients may find them drying, and may prefer oil and ointment preparations. Low-to-mid strength creams are preferred in the intertriginous areas and on the face. To augment effectiveness of topical corticosteroids in areas with thick keratotic scale, the area should be hydrated by soaking prior to application, and covered with an occlusive dressing of a polyethylene film (Saran Wrap) or a sauna suit. Unfortunately, there is typically a rapid recurrence of disease when corticosteroid therapy is discontinued. Side effects include epidermal atrophy, steroid acne, miliaria, and pyoderma.

Intralesional injections of triamcinolone are helpful for refractory plaques. Triamcinolone acetonide (Kenalog) suspension 10 mg/mL may be diluted with sterile saline to make a concentration of 2.5 to 5 mg/mL. Good results are also obtained in the treatment of psoriatic nails by injecting triamcinolone into the region of the matrix and the lateral nailfold. A digital block can be performed prior to injection to provide anesthesia. Injections are given once a month until the desired effect is achieved.

Tars

Crude coal tar and tar extracts such as liquor carbonis detergens can be compounded into agents for topical use. Tar bath oils and shampoos are readily available. Oil of cade (pine tar) or birch tar in concentrations of 5% to 10% may also be incorporated into ointments. The odor of all tars may be offensive.

Anthralin

Anthralin is effective, but is irritating and stains skin, clothing, and bedding. To avoid these drawbacks, short-contact anthralin treatment (SCAT) can be helpful, with anthralin washed off after 15 to 30 min. In warmer climates, SCAT is often done outdoors to keep the mess out of the house. Anthralin exerts a direct effect on keratinocytes and leukocytes by suppressing neutrophil superoxide generation and inhibiting monocyte-derived IL-6, IL-8, and TNF-α.

Tazarotene

Tazarotene is a nonisomerizable retinoic acid receptor-specific retinoid. It appears to treat psoriasis by modulating keratinocyte differentiation and hyperproliferation, as well as by suppressing inflammation. Combining its use with a topical corticosteroid and weekend pulse therapy can decrease irritation.

Calcipotriene

Vitamin D_3 affects keratinocyte differentiation partly through its regulation of epidermal responsiveness to calcium. Treatment with the vitamin D analog calcipotriene (Dovonex) in ointment, cream, or solution form has been shown to be very effective in the treatment of plaque-type and scalp psoriasis. Combination therapy with calcipotriene and high-potency steroids may provide greater response rates, fewer side effects, and steroid sparing. Calcipotriene is unstable in the presence of many other topical agents and degrades in the presence of UV light. Monitoring of serum calcium levels in adults is not required.

Macrolactams (calcineurin inhibitors)

Topical macrolactams such as tacrolimus and pimecrolimus are especially helpful for thin lesions in areas prone to atrophy or steroid acne. The burning commonly associated with these agents can be problematic, but may be avoided by prior treatment with a corticosteroid, and by application to dry skin, rather than after bathing.

Salicyclic Acid

Salicylic acid is used as a keratolytic agent in shampoos, creams and gels. It can promote the absorption of other topical agents. Widespread application may lead to salicylate toxicity manifesting with tinnitus, acute confusion, and refractory hypoglycemia, especially in patients with diabetes and those with compromised renal function.

Ultraviolet Light

In most instances sunlight improves psoriasis. However, burning of the skin may cause Koebner's phenomenon and an exacerbation. Artificial UVB light is produced by fluorescent bulbs in broad- or narrow-band spectrums. Maximal effect is usually achieved at minimal erythemogenic doses (MED). Although suberythemogenic doses can be effective, the response is slower than with erythemogenic regimens. As skin type is poorly predictive of MED; MED testing can be useful to ensure adequate dosing. With treatment, a tanning response occurs, and the dose must be increased to maintain efficacy. Maintenance UVB phototherapy after clearing contributes to the duration of remission and is justified for many patients.

Using a monochromator, it has been shown that wavelengths of 254, 280, and 290 nm are ineffective; at 296, 300, 304, and 313 nm there is clearing. Narrow-band UVB (peak emission around 311 nm) has been shown to be more effective in treating psoriasis than broad-band UVB. Erythemogenic doses are not required in order to achieve a response. The response rates are better than 70% and close to those achievable with PUVA therapy.

Goeckerman Technique

The Goeckerman technique remains an effective and cost-effective method of treatment. In its modern form, a 2% to 5% tar preparation is applied to the skin, and a tar bath is taken at least once a day. The excess tar is removed with mineral or vegetable oil, and UV light is given. In psoriasis daycare centers, patients clear in an average of 18 days, and 75% remain free of disease for extended periods. The addition of a topical corticosteroid to the Goeckerman regimen shortens the time required for remission. Phototoxic reactions (tar smarts) may occur as a result of UVA generated by the predominantly UVB bulbs.

Ingram Technique

The Ingram technique consists of a daily coal tar bath in a solution such as 120 mL liquor carbonis detergens to 80 L of warm water. This is followed by daily exposure to UV light for increasing periods. An anthralin paste is then applied to each psoriatic plaque. Talcum powder is sprinkled over the lesions and stockinette dressings are applied. Modern versions of the technique employ SCAT.

PUVA Therapy

High-intensity longwave UV radiation (UVA) given 2 h after ingestion of 8-methoxypsoralen (Oxsoralen-Ultra), twice a week, is highly effective, even in severe psoriasis. Most patients clear in 20 to 25 treatments, but maintenance treatment is needed.

Although PUVA therapy is highly effective, in patients with less than 50% of the skin surface affected, UVB may be as good. Polyethylene sheet bath PUVA is another therapeutic alternative to oral psoralen-UVA. The patient is immersed in a psoralen solution contained in plastic sheeting that conforms to the patient's body.

Oral psoralen can produce cataracts, and protective eyewear must be used. PUVA therapy is a risk factor for skin cancer, including squamous cell carcinoma and melanoma. Arsenic exposure is a more significant cofactor than prior exposure to methotrexate, UVB, or concomitant use of topical tar. Men treated without genital protection are at an increased risk of developing squamous cell carcinomas of the penis and scrotum. Although the risk of cancer is dose related, there is no definitive threshold dose of cumulative PUVA exposure above which carcinogenicity can be predicted.

Surgical Treatment In patients with pharyngeal colonization by streptococci, an excellent response has been reported after tonsillectomy. More effective antibiotic regimens, such as a 10-day course of dicloxacillin combined with rifampin (600 mg/day for an adult) have largely replaced tonsillectomy.

Hyperthermia Local hyperthermia can clear psoriatic plaques, but relapse is usually rapid. Microwave hyperthermia may produce significant complications such as pain over bony prominences and tissue destruction.

Occlusive Treatment Occlusion with surgical tape or dressings can be effective as monotherapy or when combined with topical drugs.

Systemic Treatment

Corticosteroids

The hazards of the injudicious use of systemic corticosteroids must be emphasized. There is great risk of "rebound" or induction of pustular psoriasis when therapy is stopped. Corticosteroid use is generally restricted to unique circumstances, such as impetigo herpetiformis when expeditious delivery is not possible.

Methotrexate

This folic acid antagonist remains the standard against which other systemic treatments are measured. Methotrexate has a greater affinity for dihydrofolic acid reductase than has folic acid. The synthesis of DNA is blocked when dihydrofolic acid reductase is bound and thereby cell division is reduced. Methotrexate may also affect the inflammatory element of psoriasis.

The indications for the use of methotrexate include psoriatic erythroderma, psoriatic arthritis, acute pustular psoriasis (von Zumbusch type), or widespread body surface involvement. Localized pustular psoriasis or palmoplantar psoriasis that impairs normal function and employment may also require systemic treatment.

It is important to make sure that the patient has no history of liver or kidney disease. Methotrexate can be toxic to the liver and decreased renal clearance can enhance toxicity. Other important factors to consider are alcohol abuse, cryptogenic cirrhosis, severe illness, debility, pregnancy, leukopenia, thrombocytopenia, active infectious disease, immunodeficiency, anemia, colitis, and ability to comply

with directions. Serum glutamic oxaloacetic transaminase (SGOT or AST), serum glutamic pyruvic transaminase (SGPT or ALT), bilirubin, serum albumin, creatinine, alkaline phosphatase, complete blood count (CBC), platelet count, hepatitis serology (B and C), HIV antibody, and urinalysis should all be evaluated before starting treatment. Patients with hypoalbuminemia have a higher risk of developing pulmonary complications.

The need for liver biopsy remains controversial. Biopsy is not without risks and is not commonly performed in the setting of methotrexate therapy for rheumatic disease. However, patients with psoriasis have a greater risk of liver disease, and liver biopsies are still recommended for them if treated with methotrexate. In most patients with no risk factors for liver disease, the first liver biopsy should be obtained at approximately 1.0 to 1.5 g of cumulative methotrexate and repeated every subsequent 1.5 to 2.0 g until a total of 4.0 g is reached. The frequency then changes to every 1.0 to 1.5 g cumulative intervals. These recommendations are likely to change as more data are evaluated. Weekly blood counts and monthly liver enzyme assessment are recommended at the onset of therapy or when the dosage is changed. Monitoring of aminoterminal procollagen III peptide may reduce the need for liver biopsy.

Numerous treatment schedules have evolved. The authors recommend either three divided oral doses (12 h apart) weekly, weekly single doses orally, or single weekly subcutaneous injections. The weekly dose varies from 5 mg to more than 50 mg, with most patients requiring 15 to 30 mg a week. Once a single dose exceeds 25 mg, oral absorption is unpredictable and subcutaneous injections are recommended. Mid-week doses can result in severe toxicity and must be avoided. Oral or cutaneous ulceration may be a sign that the patient has taken a mid-week dose. Oral folic acid has been reported to decrease side effects, especially nausea, and doses of 1 to 4 mg/day are used. Oral folic acid is not adequate for the treatment of overdosage and leukovorin must be used in such cases.

Cyclosporin

The therapeutic benefit of cyclosporin in psoriatic disease may be related to downmodulation of proinflammatory epidermal cytokines. The microemulsion formulation Neoral has greater bioavailability and is now standard. Doses of 2 to 5 mg/kg/day generally produce rapid clearing of psoriasis. Unfortunately, the lesions recur rapidly as well, and transition to another form of therapy is required. Treatment durations of up to 6 months are associated with a low incidence of renal complications, but blood pressure and serum creatinine must be monitored, and doses adjusted accordingly. Usually the dose is reduced if the baseline creatinine increases by a third.

Diet

The anti-inflammatory effects of fish oils rich in n-3 polyunsaturated fatty acids have been demonstrated in rheumatoid arthritis, inflammatory bowel disease, psoriasis, and asthma. n-3 and n-6 Polyunsaturated fatty acids affect a variety of cytokines, including IL-1, IL-6, and TNF. Herbal remedies have also been used with variable effects. Many of these products are unpalatable, and their efficacy does not compare favorably to pharmacologic agents.

Oral Antimicrobial Therapy

The association of streptococcal pharyngitis with guttate psoriasis is well established. *Staphylococcus aureus* and streptococci secrete exotoxins that act as superantigens, producing massive T-cell activation. Oral antibiotic therapy for patients with psoriasis infected with these organisms is imperative. The efficacy of antimicrobial agents in other subsets of psoriasis is unclear. Oral bile acid supplementation has been shown to improve psoriasis, presumably by affecting the microflora and endotoxins in the gut. Oral ketoconazole, itraconazole, and other antibiotics have shown efficacy in a limited number of patients with psoriasis.

Retinoids

Oral treatment with the aromatic retinoid ethylester, etretinate is effective in many patients with psoriasis, especially in pustular disease. Because of its long half-life, the drug has been replaced by acitretin. Alcohol ingestion can convert acitretin to etretinate and is strongly discouraged. 13-*Cis*-retinoic acid can also produce good results in some patients with pustular psoriasis. All of these drugs are potent teratogens and elevations in triglycerides may complicate therapy. Combinations of retinoic acids with photochemotherapy can be effective in chronic plaque psoriasis, resulting in lowered cumulative doses of light.

Dapsone

Dapsone use is limited largely to palmoplantar pustulosis or other variants of pustular psoriasis Even in this setting, it is a second- or third-line agent with limited efficacy.

Biologic Agents A number of biologic agents are available that can produce dramatic responses in some patients with psoriasis; all are expensive. Three agents block TNF-α: infliximab is a chimeric monoclonal antibody to TNF-α and requires intravenous infusion; etanercept is a fusion protein of human TNF type II receptor and the Fc region of IgG1; and adalimimab is a recombinant fully human IgG1 monoclonal antibody to TNF-α. Alefacept is a fusion protein of the external domain of LFA-3 and the Fc region of IgG1, and blocks T-cell activation and triggers apoptosis of pathogenic T-cells. Efulizumab is a humanized monoclonal antibody to the CD11a portion of LFA-1, and blocks T-cell activation, binding, and trafficking.

Etanercept provides a good balance of safety and efficacy. Response rates are higher with induction therapy for 12 weeks at doses of 50 mg twice a week. Maintenance therapy is generally given as 50 mg/week. No routine laboratory monitoring is required, but it may be prudent to perform a PPD prior to initiation of therapy. Infliximab acts more rapidly than the other available agents, and produces responses in a higher percentage of patients; however, the risks of serious side effects from this agent and the potential for production of neutralizing antibodies limit its use.

Percentage of Patients Clearing with Each Drug

Published data allow for various comparisons between biologic agents, but as trials are designed by the manufacturer to demonstrate the efficacy of the agent, the endpoints of some trials differ. In controlled trials of infliximab, the percentage of patients reaching at least 75% improvement from baseline in the psoriasis area and severity index (PASI

75) at week 10 is about 70% with infliximab 3 mg/kg and 90% with 5 mg/kg, as compared to 6% with placebo. About 35% of patients receiving etanercept 25 mg subcutaneously twice a week achieve PASI 75 at 12 weeks and 45% at 24 weeks. With the 50-mg induction dose administered twice a week, about 46% of patients achieve PASI 75 at 12 weeks and 50% at 24 weeks. In studies of efalizumab, 12 weekly injections of 1.0 mg/kg resulted in PASI 75 in about 27% of patients, and about 44% achieve PASI 75 by 24 weeks. About 14% of patients receiving 12 weekly intramuscular or intravenous injections of alefacept will achieve PASI 75, and about 38% PASI 50. After two 12-injection courses, about 26% of patients reach PASI 75 and 55% PASI 50. The onset of action is somewhat slower than with other agents, but ultimate clearing can be excellent. The data available suggests that about 53% of patients taking 40 mg of adalimumab every other week achieve PASI 75 by week 12, and about 80% of those taking 40 mg a week achieve PASI 75.

Rapidity of Clearing and Relapse

The effects of infliximab are rapid and similar to those achieved with cyclosporin. In contrast to cyclosporin, clinical improvement after three intravenous infusions of infliximab is maintained for as long as 6 months in approximately half the patients. Adalimumab is also rapid in onset, with many patients demonstrating a response within the first week of treatment. Efalizumab is fairly rapid in onset, and produces significant improvements as early as 4 weeks. After discontinuation of efalizumab at week 24, an improvement of 50% or more in PASI score is maintained in approximately 30% of patients during 12 weeks of follow-up. However, relapse is usually seen within 70 days after discontinuation of therapy, and rebound to worse than baseline occurs in about 5% to 15% of patients. About 15% of patients treated with alefacept will maintain benefits for more than 6 months.

Risks

The biologic agents all suppress the normal immune response. Infliximab has been associated with reactivation of tuberculosis, demyelinating disease, and serious systemic opportunistic infection. It may also lose its effect because of neutralizing antibodies. Methotrexate or azathioprine may be needed as concomitant therapy to reduce the incidence of neutralizing antibodies and infusion reactions. Even though adalimumab is a fully human antibody, it may also induce an antibody response. Serious infections have been reported in patients with rheumatoid arthritis treated with this agent. Etanercept has been associated with infection, onset or exacerbation of multiple sclerosis, vasculitis, and lupus erythematosus-like manifestations. All these manifestations are rare, and may not be statistically increased from the general population. A single 12-week course of alefacept does not appear to impair primary or secondary antibody responses to a neoantigen or memory responses to a recall antigen, but roughly 10% of patients have to interrupt therapy because CD4 counts fall below 250/mm^3, and CD4 counts must be monitored with this agent. Efalizumab has been associated with thrombocytopenia, hemolytic anemia and lymphoma, and may have a slightly lower initial response rate than some other agents. Many of the reported complications, such as lymphoma, demyelinating disease, and infection, are not unique to any one biologic agent. Future trials will further define the risks and benefits of each agent.

Combination Therapy In more severe forms of psoriasis a combination of treatment modalities may be employed. In treating patients with methotrexate, for example, concomitant topical agents may be used to minimize the dose. Methotrexate has been combined with infliximab to reduce the incidence of neutralizing antibodies, and has been used with acitretin in managing patients with severe, generalized pustular psoriasis. The use of PUVA and retinoids is called *Re-PUVA* and has been studied extensively. Combination systemic therapy has the potential to reduce overall toxicity if the toxicities of each agent are different. However, new regimens should be used with caution because the potential for cumulative toxicity or drug interaction exists.

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REACTIVE ARTHRITIS WITH CONJUNCTIVITIS/ URETHRITIS/DIARRHEA (REITER SYNDROME)

The syndrome is a characteristic clinical triad of urethritis, conjunctivitis, and arthritis. The disease occurs chiefly in young men of HLA-B27 genotype, generally following a bout of urethritis or diarrheal illness. Systemic involvement can include the gastrointestinal tract, kidneys, central nervous system, and cardiovascular system. As few patients present with the classic triad, the American College of Rheumatology recognizes criteria for limited manifestations of the syndrome, including peripheral arthritis of more than 1 month's duration in association with urethritis, cervicitis or bilateral conjunctivitis.

Hans Reiter was a Nazi war criminal, involved with or knowledgeable of involuntary sterilization, as well as a study of an experimental typhus vaccine that resulted in hundreds of deaths of concentration camp internees. Several authors have suggested that he no longer be afforded the recognition of using his name to designate the syndrome.

Clinical Features

Any part of the triad may occur first, often accompanied by fever, weakness, and weight loss. Although the inciting urethritis may be bacterial, later manifestations include a nonbacterial urethritis with painful urination and pyuria. Cystitis, prostatitis, and seminal vesiculitis may be accompaniments. Vulvar ulceration has been reported. About a third of patients develop conjunctivitis, which may be bulbar, tarsal, or angular. Keratitis is usually superficial and extremely painful. Iritis is common, especially in recurrent cases. Infrequently optic neuritis may occur. An asymmetric arthritis affects peripheral joints, especially those that are weight-bearing. Its onset is usually sudden. Pain in one or both heels is a frequent symptom. Sacroiliitis may develop in up to two-thirds of patients, most of whom are of HLA-B27 type.

The skin involvement commonly begins with small guttate, hyperkeratotic, crusted or pustular lesions of the genitals, palms or soles. Involvement of the glans penis (*balanitis circinata*) occurs in 25% of patients. Lesions on the soles and trunk often become thickly crusted or hyperkeratotic (Fig. 10-12). The eruption on the soles is known as *keratoderma blenorrhagicum* (Fig. 10-13), and occurs in10% of patients. The buccal, palatal, and lingual mucosa may show painless, shallow, red erosions. The nails become thick and brittle, with heavy subungual keratosis. Children are much more likely to have the post-dysenteric form, often with conjunctivitis and arthritis as the most prominent complaints.

The syndrome generally follows an infectious urethritis or diarrheal illness. Implicated organisms include Chlamydia, Shigella, Salmonella, Yersinia, Campylobacter, Ureaplasma, Borrelia , Cryptosporidia, gonococci, and *Bacillus Calmette-Guérin* (BCG). *Chlamydia trachomatis* and *Ureaplasma urealyticum* have been isolated from the synovial fluid of affected joints, and some patients respond to antibiotic therapy. Reiter syndrome has also been observed in HIV disease, but may not be directly related to the virus, as it frequently occurs under treatment as the immune response improves.

The syndrome involves both infection and the resulting immunologically mediated tissue injury in a genetically predisposed patient. HLA-B27 is present in about 80% of cases. A positive family history is often noted.

Peripheral leukocytosis of 10,000 to 20,000/mm^3 and elevated sedimentation rate are the most consistent findings. There is no specific test for Reiter syndrome.

The differential diagnosis includes rheumatoid arthritis, ankylosing spondylitis, gout, psoriatic arthritis, gonococcal arthritis, acute rheumatic fever, chronic mucocutaneous candidiasis, and serum sickness. The presence of associated

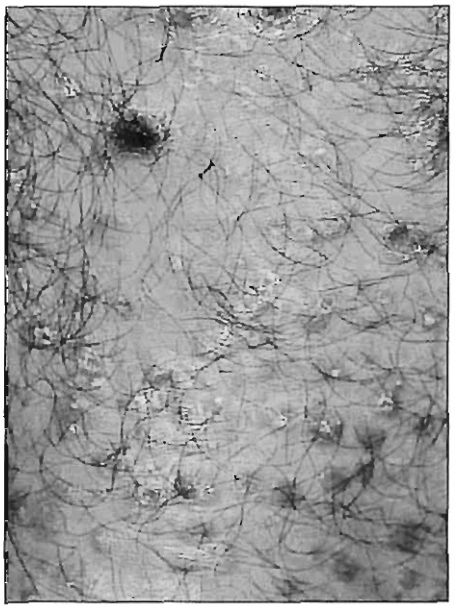

Fig. 10-12
Hyperkeratotic lesions of the reactive arthritis syndrome.

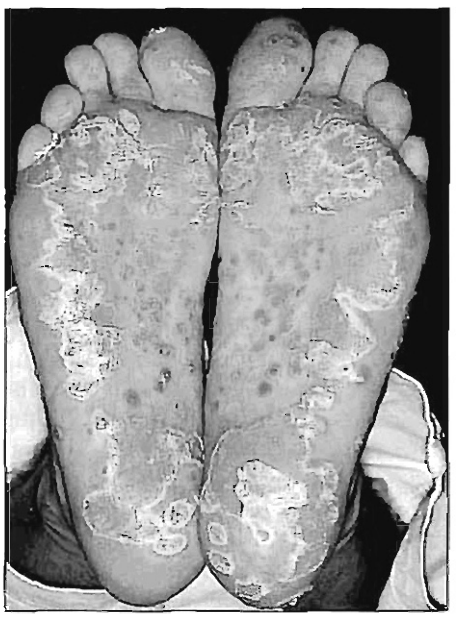

Fig. 10-13
Keratoderma blenorrhagicum.

mucocutaneous lesions establishes the diagnosis. Some cases of Lyme disease overlap with the syndrome. Individual skin lesions may be indistinguishable from those in psoriasis. Hyperkeratotic lesions generally have a thicker scale crust than most psoriatic plaques, but are otherwise identical.

Mucocutaneous lesions are generally self limited and clear with topical steroids. Joint disease is managed with rest and NSAIDs. Antibiotics, such as doxycycline, have been effective in some cases. Immunosuppressive agents, such as methotrexate, are commonly employed for refractory joint disease. Infliximab has been successful in treating severe disease. Refractory skin lesions are treated like refractory psoriasis, and severely affected patients have responded to acitretin or cyclosporine.

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SUBCORNEAL PUSTULAR DERMATOSIS (SNEDDON–WILKINSON DISEASE)

In 1956, Sneddon and Wilkinson described a chronic pustular disease, which occurred chiefly in middle-aged women. The pustules are superficial and arranged in annular and serpiginous patterns, especially on the abdomen, axillae, and groins. Cultures from the pustules are sterile. Oral lesions are rare. Some cases are associated with a monoclonal gammopathy (usually IgA). The condition is chronic with remissions of variable duration.

Histologically, the pustules form below the stratum corneum, as in impetigo. Acantholysis is absent, but spongiform pustules may be noted in the upper epidermis. The histologic differential diagnosis includes pustular psoriasis, and superficial fungal and bacterial infections. Some cases will show upper epidermal intercellular IgA staining.

IgA pemphigus shows significant overlap with subcorneal pustular dermatosis. Presentations of IgA pemphigus include subcorneal pustular dermatosis and intraepidermal neutrophilic IgA dermatosis types. Using immunoblotting techniques, Hashimoto et al have shown that human desmocollin 1 is an autoantigen for the subcorneal pustular dermatosis type of IgA pemphigus.

Localized cases may respond well to topical corticosteroids. Dapsone, 50 to 200 mg/day (for an adult), is effective for most of the remaining cases. Some patients have responded better to sulfapyridine therapy. Acitretin, narrowband UVB phototherapy, colchicine, azithromycin, biologicals, and tetracycline with niacinamide may also be effective.

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EOSINOPHILIC PUSTULAR FOLLICULITIS

Eosinophilic pustular folliculitis (EPF) was first described in 1970 by Ofuji but is also referred to as *sterile eosinophilic pustulosis*. It occurs more commonly in males, and is mostly

reported in Asia. The mean age of onset is 35. It is characterized by pruritic, follicular papulopustules that measure 1 to 2 mm. The lesions tend to be grouped and plaques commonly form. New lesions may form at the edges of the plaques, leading to peripheral extension, while central clearing takes place. The most frequent site is the face, particularly over the cheeks. The trunk and upper extremities are commonly affected, and 20% have palmoplantar pustules. The distribution is commonly asymmetrical, and the typical course is one of spontaneous remissions and exacerbations lasting several years. The condition must be distinguished from HIV-associated eosinophilic folliculitis, which is discussed in Chapter 19.

Histologically, there is spongiosis and vesiculation of the follicular infundibulum and heavy infiltration with eosinophils. Follicular mucinosis may be present. There is a peripheral eosinophilia in half the cases. The cause is unknown; but numerous studies have implicated chemotactic substances, ICAM-1, and cyclooxygenase-generated metabolites. Tryptase-positive and chymase-negative mast cells have also been implicated.

Indomethacin is effective in the vast majority of patients. Topical and intralesional corticosteroids, clofazimine, minocycline, isotretinoin, UVB therapy, dapsone, clochicine, cyclosporin, and cetirizine have also been reported as effective.

Childhood cases have been described. This subset differs from the typical cases in Asian males. Pediatric patients develop sterile pustules and papules preferentially over the scalp, although scattered clusters of pustules may occur over the trunk and extremities. Leukocytosis and eosinophilia are often present. Recurrent exacerbations and remissions usually occur with eventual spontaneous resolution. High-potency topical steroids are the treatment of choice in pediatric patients.

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RECALCITRANT PALMOPLANTAR ERUPTIONS

Dermatitis Repens

Dermatitis repens, also known as *acrodermatitis continua* and *acrodermatitis perstans*, is a chronic inflammatory disease of the hands and feet. It usually remains stable on the extremities, but in rare cases generalized pustular flares may occur. The disease usually begins distally on a digit, either as a pustule in the nailbed or as a paronychia. Extension takes place by eruption of fresh pustules with subsequent hyperkertosis and crusting. The disease is usually unilateral in its beginning and asymmetrical throughout its entire course. As the disease progresses, one or more of the nails may become dystrophic or float away on lakes of pus. Anonychia is common in chronic cases.

Involvement of the mucous membranes may occur even when the eruption of the skin is localized. Painful, circular, white plaques surrounded by inflammatory areolae are found on the tongue and may form a fibrinous membrane. Fissured or geographic tongue may occur.

Histologically, intraepithelial spongiform pustules identical to those of psoriasis are seen in the acute stage. Later stages show hyperkeratosis with parakeratosis or atrophy.

Numerous treatment options have been used, including topical corticosteroids, calipotriene, dapsone, sulfapyridine, methotrexate, PUVA, acitretin, cyclosporin, and topical mechlorethamine. The decision regarding which agent to use should take into consideration the severity of disease, and the patient's age and functional impairment.

Palmoplantar Pustulosis (Pustular Psoriasis of the Extremities)

Chronic palmoplantar pustulosis is essentially a bilateral and symmetrical dermatosis (Fig. 10-14). The favorite locations are the thenar or hypothenar eminences or the central portion of the palms and soles. The patches begin as erythematous areas in which minute intraepidermal pustules form. At the beginning these are pinhead-sized; then they may enlarge and coalesce to form small lakes of pus. As the lesions resolve, denuded areas, crusts or hyperkeratosis may persist. Palmoplantar pustulosis is strongly associated with thyroid disorders and cigarette smoking. Medications, such as lithium, which aggravate psoriasis, have also been reported to induce palmoplantar pustular psoriasis.

In 1968, Kato described the first case of bilateral clavicular osteomyelitis with palmar and plantar pustulosis. In 1974, Sonozaki described persistent palmoplantar pustulosis and sternoclavicular hyperostosis. These conditions belong to the spectrum of skin and joint involvement designated by Kahn as the SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis). Common features include palmoplantar pustulosis, acneiform eruption, and pain and swelling of a sternoclavicular joint, sternomanubrial or costochondral junctions. There is shoulder, neck, and back pain, and limitation of motion of the shoulders and neck is common. Brachial plexus neuropathy and subclavian vein occlusion may occur. The lumbar spine and sacroiliac joints are usually spared. Chronic multifocal osteomyelitis in children may be

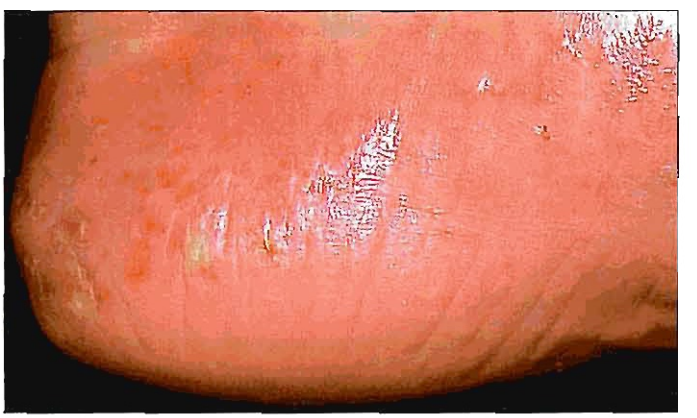

Fig. 10-14 Plantar pustulosis.

a pediatric variant. Others have described an association between palmoplantar pustulosis and arthritis or osteitis. The knees, spine, and ankles may be involved. There is no identifiable HLA antigen pattern.

The disease is commonly resistant to treatment. Topical steroids, retinoids, calcipotriene or macrolactams are of some benefit. Acitretin is generally extremely effective at a dose of 1 mg/kg/day, although rebound occurs more quickly than with etretinate. Low-dose cyclosporin in doses ranging from 1.25 to 5 mg/kg/day has also been very effective, but it is not suitable for long-term treatment. Dapsone, colchicines, and mycophenolate mofetil are occasionally effective. Oral 8-methoxypsoralen and high-intensity UVA irradiation or soak PUVA can both be helpful, and Grenz ray therapy can induce prolonged remissions in some patients.

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Pustular Bacterid

Pustular bacterid was first described by George Andrews. It is characterized by a symmetric, grouped, vesicular or pustular eruption on the palms and soles marked by exacerbations and remissions over long periods. Andrews regarded the discovery of a remote focus of infection, and cure on its elimination, as crucial to the diagnosis.

The primary lesions are pustules. Tiny hemorrhagic puncta intermingled with the pustules are frequently seen. When lesions are so numerous as to coalesce, they form a honeycomb-like structure in the epidermis. The disease usually begins on the mid-portions of the palms or soles, from which it spreads outwardly until it may eventually cover the entire flexor aspects of the hands and feet. There is no involvement of the webs of the fingers or toes, as in tinea pedis.

When the eruption is fully developed, both palms and soles are completely covered, and the symmetry is pronounced. During fresh outbreaks, the white blood count may show a leukocytosis that ranges from 12,000 to 19,000/mm^3 with 65% to 80% neutrophils. As a rule scaling is present in fully evolved lesions, and the scales are adherent, tough, and dry. During exacerbations, crops of pustules or vesicles make their appearance, and there is often severe itching of the areas. Tenderness may be present. Many regard this condition as a variant of psoriasis, triggered by infection.

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Infantile Acropustulosis

Infantile acropustulosis is an intensely itchy vesicopustular eruption of the hands and feet. Most cases begin by 10 months of age. Lesions often predominate at the edges of the palms and soles. Individual crops of lesions clear in a few weeks, but recurrences may continue for months or years. Scabies, tinea, and herpetic infection can produce similar lesions, and must be excluded.

Histologically, a subcorneal pustule with neutrophils is noted. Eosinophils may be numerous. As the lesions are easily punctured to produce smears of the inflammatory cells, biopsies are seldom employed.

Lesions often respond to topical corticosteroids. Refractory lesions may respond to dapsone at doses of 1 to 2 mg/kg/day.

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CHAPTER 11

Pityriasis Rosea, Pityriasis Rubra Pilaris, and Other Papulosquamous and Hyperkeratotic Diseases

SMALL PLAQUE PARAPSORIASIS

Small plaque parapsoriasis is characterized by hyperpigmented, or yellowish-red scaling patches, round to oval in configuration with sharply defined, regular borders. Most lesions occur on the trunk, and all are between 1 and 5 cm in diameter. In the digitate variant, yellowish-tan elongated fingerprint-like lesions are oriented along the cleavage lines predominately on the flank (Fig. 11-1). These lesions may at times be longer than 5 cm. There is an absence of the induration, erythema to purplish-red, large lesions, and poikiloderma that characterize small patches of cutaneous T-cell lymphoma in its early stages. The eruption may be mildly itchy or asymptomatic and has a definite male preponderance.

The histologic findings of small plaque parapsoriasis are characterized by an infiltrate in the superficial dermis composed predominantly of lymphocytes. The overlying epidermis demonstrates mild acanthosis, spongiosis, and focal overlying parakeratosis. Small plaque parapsoriasis is considered a type of chronic, spongiotic dermatitis.

Small plaque parapsoriasis may be refractory to topical steroids alone, but usually responds to phototherapy. Treatment with ultraviolet (UV)B, narrow-band UVB, or natural sunlight, alone or in combination with a low strength topical steroid or simple lubricant, will usually clear small plaque parapsoriasis. Without treatment the patches of small plaque parapsoriasis may persist for years to decades and rarely, if ever, progresses to lymphoma.

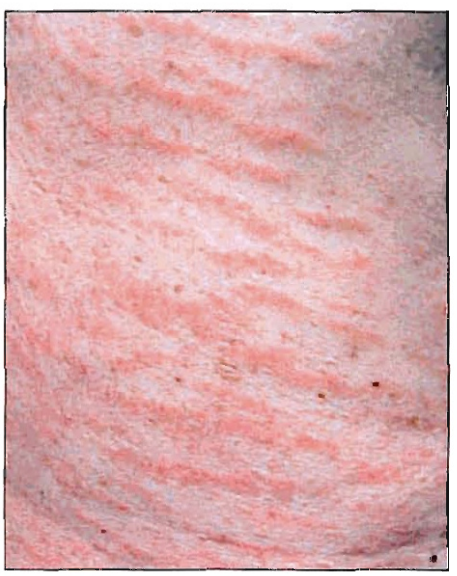

Fig. 11-1 Digitate parapsoriasis. (Courtesy of Thomas Nicotri, MD)

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CONFLUENT AND RETICULATED PAPILLOMATOSIS (GOUGEROT AND CARTEAUD)

This eruption typically begins on the intermammary and upper lateral trunk as slightly scaly macules that over time spread to involve the remainder of the trunk (Fig. 11-2). In white patients the lesions vary from skin-colored or faintly erythematous to hyperpigmented, and in pigmented persons, lesions usually show hyperpigmentation. There may be severe itching or the lesions may be entirely asymptomatic. Histologically, hyperkeratosis, acanthosis, and papillomatosis are generally seen. Familial cases have been reported.

A variety of antibiotics have been successful in treating the disorder, suggesting that bacteria may play a role. Minocycline 100 mg twice a day for 6 weeks is used most commonly. Successful treatment has also been reported with

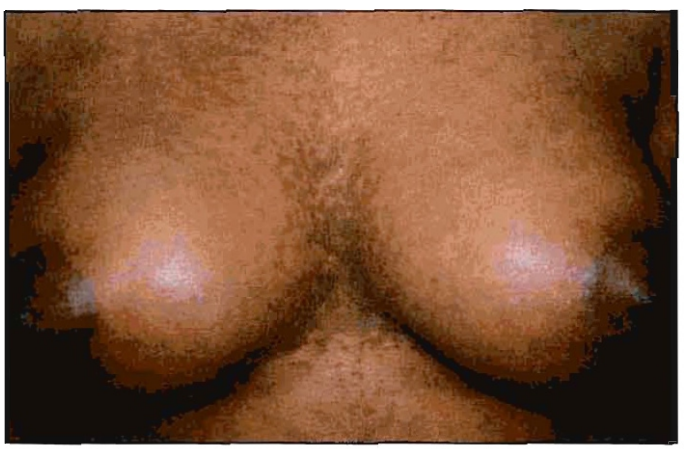

Fig. 11-2 Confluent and reticulated papillomatosis.

oral fusidic acid, clarithromycin, erythromycin, and azithromycin. Topical and oral retinoids have also been used successfully, either alone or in combination with topical lactic acid or urea.

Pseudo-atrophoderma colli may be a related condition that occurs on the neck. Lesions appear as papillomatous, pigmented, and atrophic glossy lesions with delicate wrinkling. The lesions tend to have a vertical orientation and may respond to minocycline.

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PITYRIASIS ROSEA

Clinical Features

Pityriasis rosea is a mild inflammatory exanthem characterized by salmon-colored papular and macular lesions that are at first discrete but may become confluent (Fig. 11-3). The individual patches are oval or circinate, and are covered with finely crinkled, dry epidermis, which often desquamates, leaving a collarette of scaling. When stretched across the long axis, the scales tend to fold across the lines of stretch, the so-called "hanging curtain" sign. The disease most frequently begins with a single herald or mother patch (Fig. 11-4), usually larger than succeeding lesions, which may persist a week or longer before others appear. By the time involution of the herald patch has begun, the efflorescence of new lesions spreads rapidly (Fig. 11-5), and after 3 to 8 weeks they usually disappear spontaneously. Relapses and recurrences are observed infrequently.

The incidence is highest between the ages of 15 and 40, and the disease is most prevalent in the spring and autumn. Women are more frequently affected than men.

The fully developed eruption has a striking appearance because of the distribution and definite characteristics of the individual lesions. These are arranged so that the long axis of the macules runs parallel to the lines of cleavage. The eruption is usually generalized, affecting chiefly the trunk and sparing sun-exposed surfaces. At times it is localized to a certain area, such as the neck, thighs, groins, or axillae. In these regions confluent circinate patches with gyrate borders may be formed; these may strongly resemble tinea corporis. Rarely, the eyelids, palms and soles, scalp, or penis may be involved. Oral lesions are relatively uncommon. They are asymptomatic, erythematous macules with raised borders and clearing centers or aphthous ulcer-like lesions. They involute simultaneously with the skin lesions.

Moderate pruritus may be present, particularly during the outbreak, and there may be mild constitutional symptoms before the onset. Variations in the mode of onset, course, and clinical manifestations are extremely common. An unusual form, common in children under age 5, is papular pityriasis rosea, occurring in the typical sites and running a course similar to that of the common form of pityriasis rosea. Black

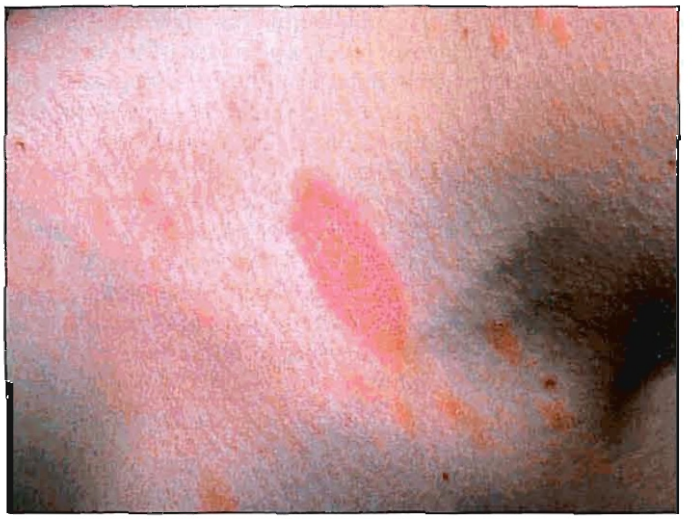

Fig. 11-4 Herald patch of pityriasis rosea.

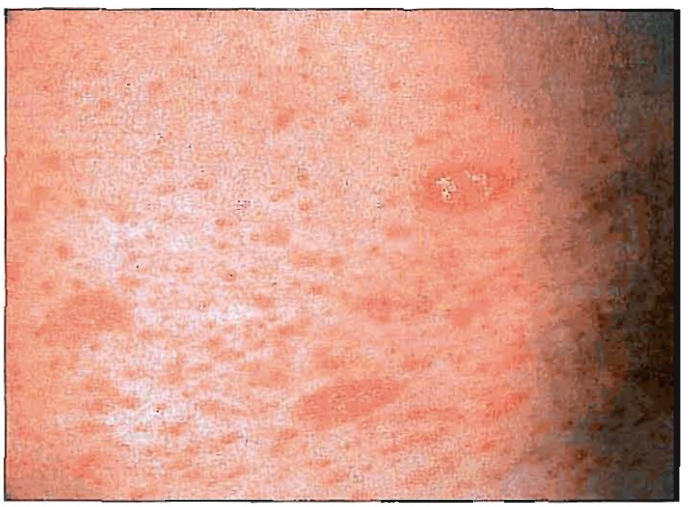

Fig. 11-3 Pityriasis rosea.

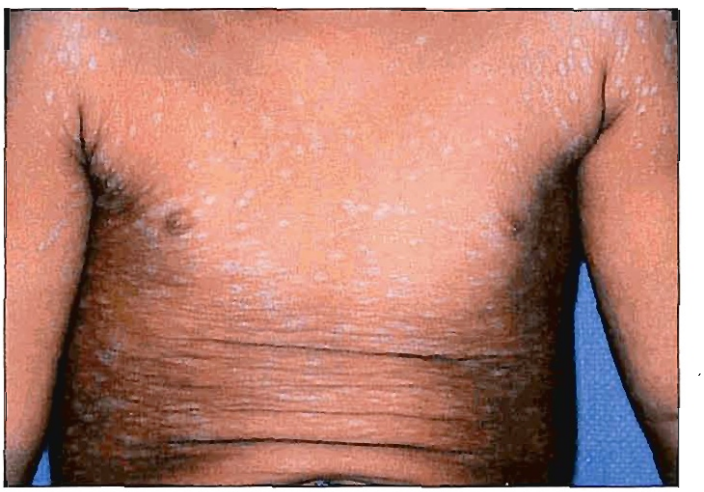

Fig. 11-5 Pityriasis rosea.

children are particularly predisposed to this papular variant. An inverse distribution, sparing covered areas, is unusual but not rare. It is common in papular cases. Purpuric pityriasis rosea may manifest with petechiae and ecchymoses along Langer lines of the neck, trunk, and proximal extremities.

Etiology

Watanabe et al have provided evidence for the long-held belief that pityriasis roseas is a viral exanthem. They demonstrated active replication of human herpes virus (HHV)-6 and -7 in mononuclear cells of lesional skin, as well as identifying the viruses in serum samples of patients. Whereas these viruses are nearly universally acquired in early childhood and remain in a latent phase as mononuclear cells, the eruption is likely secondary to reactivation leading to viremia.

A pityriasis rosea-like eruption may occur as a reaction to captopril, imatinib mesylate, interferon, ketotifen, arsenicals, gold, bismuth, clonidine, methoxypromazine, tripelennamine hydrochloride, ergotamine, lisinopril, or barbiturates.

Histology

The histologic features of pityriasis rosea include mild acanthosis, focal parakeratosis, and extravasation of erythrocytes into the epidermis. Spongiosis may be present in acute cases. A mild perivascular infiltrate of lymphocytes is found in the dermis. Histologic evaluation is especially helpful in excluding the conditions with which pityriasis rosea may be confused.

Differential Diagnosis

Pityriasis rosea may closely mimic seborrheic dermatitis, tinea corporis, macular syphilid, drug eruption, other viral exanthema, and psoriasis. In seborrheic dermatitis, the scalp and eyebrows are usually scaly and there is a predilection for the sternal and interscapular regions, and the flexor surfaces of the articulations, where the patches are covered with greasy scales. Tinea corporis is rarely so widespread. Tinea versicolor may also closely simulate pityriasis rosea. A positive KOH examination serves well to differentiate these last two. In the macular syphilid the lesions are of a uniform size and soon assume a brownish tint. Scaling and itching are absent or slight, and there are generalized adenopathy, mucous membrane lesions, palmoplantar lesions, positive nontreponemal and treponemal tests, and often the remains of a chancre. Scabies and lichen planus may be confused with the papular type.

Treatment

Most patients require no therapy as they are asymptomatic; however, the duration of the eruption may be notably reduced by several interventions. These were found to be useful prior to the realization that the eruption was a viral exanthem, and remain practical treatments for the itchy patient.

UVB in erythema exposures may be used to expedite the involution of the lesions after the acute inflammatory stage has passed. The erythema produced by UV treatment is succeeded by superficial exfoliation. In a comparison study by Leenutaphong et al using a "placebo" of 1 J UVA on the untreated side compared with the UVB-treated side, there was significant improvement in the severity of the disease on the treated side. However, there was no difference in itchiness or the course of the disease.

Pruritus may uncommonly be intense and lead to eczematization and secondary infection as a result of scratching. Corticosteroid lotions or creams give immediate relief. Antihistamines by mouth are also beneficial. One study found erythromycin, 250 mg four times a day for adults and 25 to 40 mg/kg in four divided doses a day for children, over a 2-week period resulted in complete clearance of all lesions. This response in 33 of 45 patients contrasted with none of the 45 placebo patients having the same response. For dryness and irritation, simple emollients are advised.

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PITYRIASIS RUBRA PILARIS

Clinical Features

Pityriasis rubra pilaris (PRP) is a chronic skin disease characterized by small follicular papules, disseminated yellowish-pink scaling patches, and, often, solid confluent palmoplantar hyperkeratosis. The papules are the most important diagnostic feature, being more or less acuminate, reddish-brown, about pinhead size, and topped by a central horny plug (Fig. 11-6). A hair, or part of one, is usually embedded in the horny center. The highest incidence of onset is during the first 5 years of life or between the ages of 51 and 55. The classic disease generally manifests first by

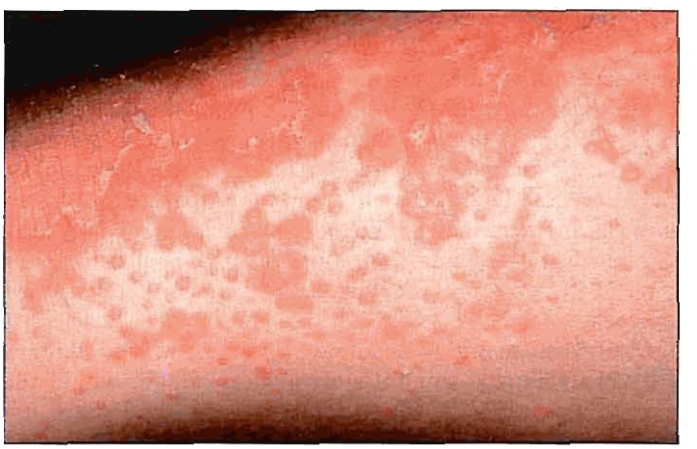

Fig. 11-6 Pityriasis rubra pilaris. (Courtesy of James Fitzpatrick, MD)

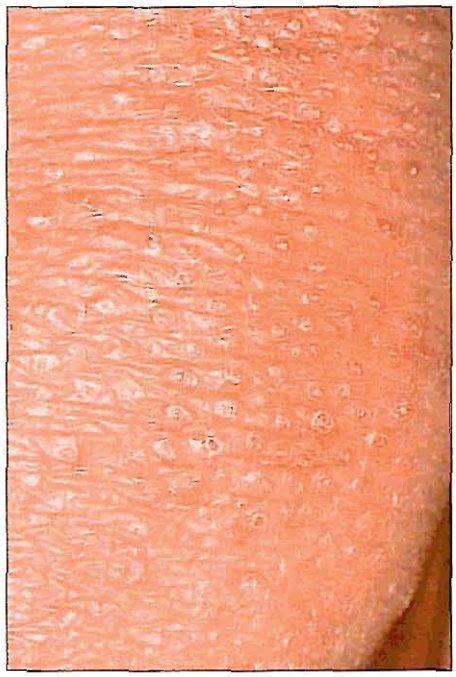

Fig. 11-7 Pityriasis rubra pilaris.

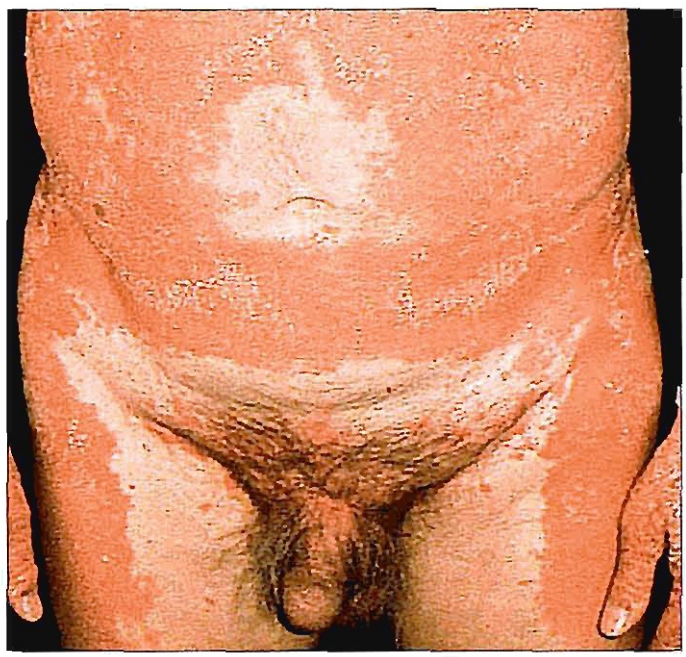

Fig. 11-8 Islands of sparing in pityriasis rubra pilaris.

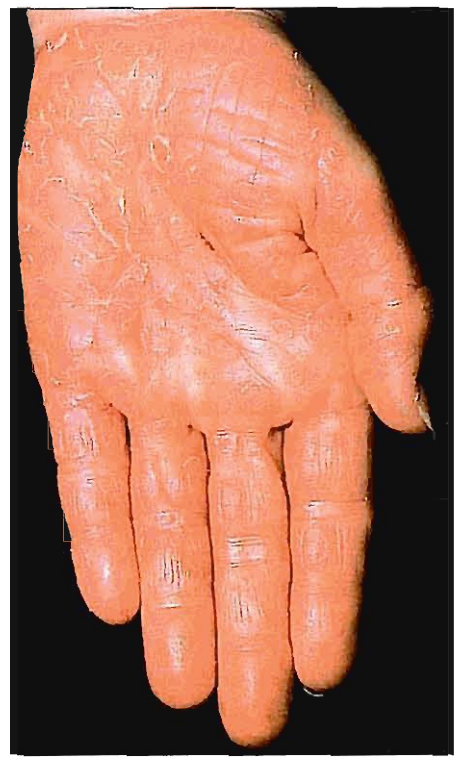

Fig. 11-9 Palmar hyperkeratosis in pityriasis rubra pilaris.

scaliness and erythema of the scalp. The eruption is limited in the beginning, having a predilection for the sides of the neck and trunk, and the extensor surfaces of the extremities, especially the backs of the first and second phalanges. Then, as new lesions occur, extensive areas are converted into sharply marginated patches of various sizes, which look like exaggerated goose-flesh and feel like a nutmeg grater (Fig. 11-7). Any part or the entire skin surface may be affected.

The involvement is generally symmetrical and diffuse, with characteristic small islands of normal skin within the affected areas (Fig. 11-8). There is a hyperkeratosis of the palms (Fig. 11-9) and soles, with a tendency to fissures. On the soles especially, the hyperkeratosis typically extends up the sides, the so-called "sandal." The nails may be dull, rough, thickened, brittle, and striated, and are apt to crack and break. They are rarely, if ever, pitted. The exfoliation may become generalized and the follicular lesions less noticeable, finally disappearing and leaving a widespread dry, scaly erythroderma. The skin becomes dull red, glazed, and atrophic, sensitive to slight changes in temperature, and, over the bony prominences, subject to ulcerations.

There are no subjective symptoms except itching in some cases. Koebner's phenomenon may be present. The general health in most patients is not affected, although occasionally arthritis may accompany the eruption. A number of cases of associated malignancy have recently been reported. It remains to be established whether these are true associations or chance findings.

PRP may be classified in respect to familial or acquired types and to the onset of the disease in childhood or in adulthood. Griffith's classification is useful in this regard. Type I, the classic adult type, is seen most commonly and carries a good prognosis, with 80% involuting over a 3-year period. Likewise, most patients with the classic juvenile type (type III) have clearing of the disease in 1 year. The atypical adult and juvenile variants and the circumscribed juvenile-onset form account for up to 35% of cases, and carry a poorer prognosis for spontaneous recovery. Human immunodeficiency virus (HIV) patients may develop pityriasis rubra pilaris and have associated acne conglobata, hidradenitis suppurative or lichen spinulosus.

Etiology

The etiology is unknown. Familial cases are uncommon. Either sex may be affected, with equal frequency. Both clinically and histologically, the disease has many features that suggest it is a vitamin-deficiency disorder, particularly of vitamin A. Some reports of patients with low serum levels

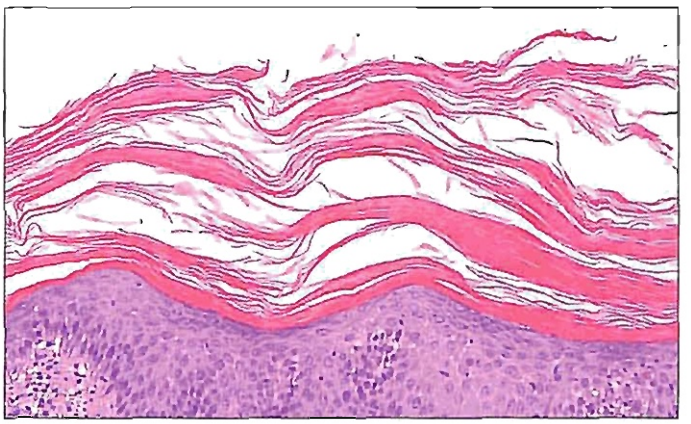

Fig. 11-10 Checkerboard pattern of parakeratosis in pityriasis rubra pilaris.

of retinol-binding protein have appeared, but this is not a reproducible finding.

Histology

There is hyperkeratosis, follicular plugging, and focal parakeratosis at the follicular orifice. Parakeratosis may alternate both vertically and horizontally, producing a checkerboard pattern (Fig. 11-10). Acantholysis is an uncommon finding, but may be present. The inflammatory infiltrate in the dermis is composed of mononuclear cells and is generally mild. Specimens should be obtained from skin sites where hair follicles are numerous. Although there may be difficulty in making an unequivocal histologic diagnosis of PRP, the findings of psoriasis, which is the most common clinical entity in the differential diagnosis, are not present.

Diagnosis

The diagnosis of fully developed PRP is rarely difficult because of its distinctive features, such as the peculiar orange or salmon–yellow color of the follicular papules, containing a horny center, on the backs of the fingers, sides of the neck, and extensor surfaces of the limbs; the thickened, rough, and slightly or moderately scaly, harsh skin; the sandal-like palmoplantar hyperkeratosis; and the islands of normal skin in the midst of the eruption. It is distinguished from psoriasis by the scales, which in the latter are silvery, light, and overlap like shingles, and by the papules, which extend peripherally to form patches. Phrynoderma caused by vitamin A deficiency gives a somewhat similar appearance to the skin, as may also eczematous eruptions caused by vitamin B deficiency. Rheumatologic disorders such as subacute cutaneous lupus erythematosus and dermatomyositis may present with similar cutaneous findings.

Treatment

The management of PRP is generally with systemic retinoids. Isotretinoin in doses of 0.5 to 1 mg/kg/day may induce prolonged remissions or cures. It may take 6 to 9 months for full involution to occur and tapering of the drug may prevent recurrence. Acitretin in doses of 10 to 75 mg is also effective over a course of several months.

Methotrexate has been used with good results in doses of 2.5 to 30 mg either alone or in combination with oral retinoids. UV light may flare some patients, but in others PUVA, UVA1, or narrow-band UVB, alone or in combination with retinoids, may be effective. Phototesting prior to instituting light treatment is recommended. Extracorporeal photochemotherapy, cyclosporin, infliximab and azathioprine have been reported to be effective in resistant and severe cases.

Topical applications of lactic acid or urea containing preparations may helpful. Responses to topical corticosteroids as a rule are not very effective. Systemic steroids are beneficial only for acute short-term management, but are not recommended for chronic use. In HIV-related disease, multiagent antiviral therapy may be useful alone or in combination with retinoids.

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PALMOPLANTAR KERATODERMA

Keratoderma is frequently used synonymously with *keratosis palmaris et plantaris (KPP)* and *tylosis*. This group of conditions is characterized by excessive formation of keratin on the palms and soles. Some varieties exist as part of a syndrome.

Acquired types include keratoderma climactericum, arsenical keratoses, corns, calluses, porokeratosis plantaris discreta, porokeratotic eccrine ostial and dermal duct nevus, glucan-induced keratoderma in acquired immunodeficiency syndrome (AIDS), keratosis punctata of the palmar creases, and many skin disorders that are associated with palmoplantar keratoderma, such as psoriasis, paraneoplastic syndromes, PRP, lichen planus, and syphilis.

The hereditary types include hereditary palmoplantar keratoderma (Unna-Thost), punctate palmoplantar keratosis, Papillon-Lefèvre syndrome, mal de Meleda, familial keratoderma with carcinoma of the esophagus (Howell-Evans), autosomal-dominant hereditary punctate keratoderma associated with malignancy (Buschke-Fisher-Brauer), KPP of Sybert (palmoplantar hyperkeratosis with transgrediens, autosomal-dominant inheritance, and lacking associated

systemic features), acrokeratoelastoidosis, focal acral hyperkeratosis, and several inherited disorders that have palmoplantar keratoderma as an associated finding, such as pachyonychia congenita, tyrosinemia II (Richner-Hanhart), Darier's disease, Naxos syndrome (keratoderma, wooly hair, and cardiomyopathy), and dyskeratosis congenita. Many disorders that have palmoplantar keratoderma as a feature will be discussed in other chapters.

A number of mutations in keratin genes have been found. American patients with nonepidermolytic palmoplantar keratoderma associated with malignancy are linked to abnormalities of 17q24 distal to the keratin cluster. Pachyonychia congenita is associated with mutations in the helical initiation peptide of K6a, K16, or K17. Epidermolytic palmoplantar keratoderma (EPPK) is an autosomal-dominant disease caused by mutations of the keratin 9 gene. The mutations localize to sequences encoding the highly conserved 1 A rod domain.

Keratolysis Exfoliativa (Lamellar Dyshidrosis, Recurrent Palmar Peeling)

Keratolysis exfoliativa is a superficial exfoliative dermatosis of the palms and sometimes soles. Clinically, there is little to no inflammation, but white spots appear and gradually extend peripherally. The lesions rupture to produce an annular adherent collarette (Fig. 11-11), but remain largely asymptomatic. The eruption is often exacerbated by environmental factors. Many patients have an atopic background and some have lesions of dyshidrotic eczema. Although some authors have suggested it is a disorder of cohesion of the stratum corneum, it is more likely that the condition represents subclinical eczema. The condition must be differentiated from dermatophytosis, and a KOH examination is recommended.

Because the condition is generally asymptomatic, no treatment may be necessary. In some patients, spontaneous involution occurs in a few weeks. For patients who require treatment, emollients, corticosteroid preparations, tar, urea and lactic acid or ammonium lactate may be effective.

Keratosis Punctata of the Palmar Creases

Keratosis punctata of the palmar creases has also been referred to as *keratotic pits of the palmar creases*, *punctate keratosis of the palmar creases*, *keratosis punctata*, *keratodermia punctata*, *hyperkeratosis penetrans*, *lenticular atrophia of the palmar creases*, and *hyperkeratosis punctata of the palmar creases*. This common disorder occurs most often in black patients. The primary lesion is a 1- to 5-mm depression filled with a comedo-like keratinous plug. The lesions localize to the creases of the palms or fingers (Fig. 11-12). The soles may be involved. An autosomal-dominant inheritance pattern has been suggested, but onset is often delayed until adulthood.

Keratosis punctata of the palmar creases has been reported to be associated with atopic dermatitis, Dupuytren contractures, pterygium inversum unguis, dermatitis herpetiformis, knuckle pads, striate keratoderma, and psoriasis. Keratolytic agents and topical retinoids have provided temporary relief. Very painful lesions respond to punch excision.

Punctate Keratoses of the Palms and Soles

Punctate keratoses of the palms and soles has also been referred to as *punctate keratoderma*, *keratodermia punctata*, *keratosis punctata palmaris et plantaris*, *keratoma hereditarium dissipatum palmare et plantare*, *keratoderma disseminatum palmaris et plantaris*, *palmar keratoses*, and *palmar and plantar seed dermatoses* (Fig. 11-13). The spiny keratoderma of the palms and soles, known as "music box spines," is a distinct variant (Fig. 11-14).

There may be from one to over 40 papules, with an average in one series of 8.3. The main symptom is pruritus.

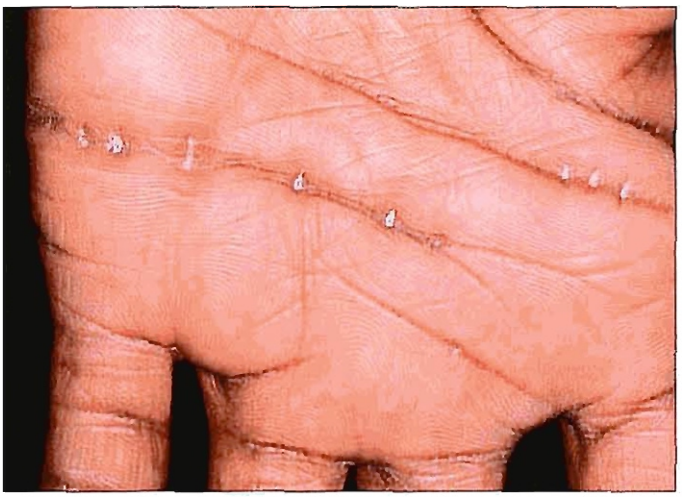

Fig. 11-12 Keratosis punctata of the palmar creases.

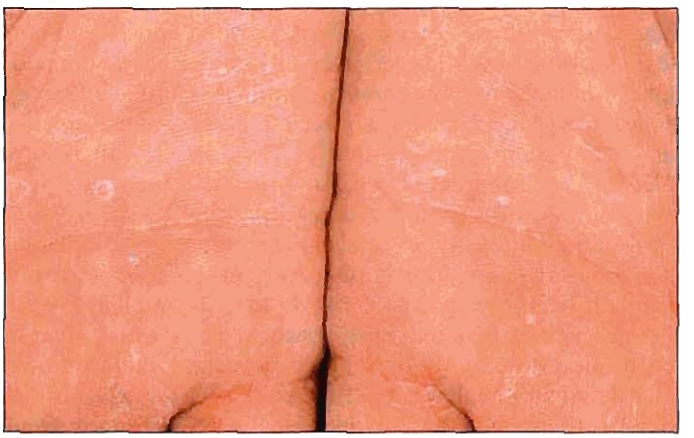

Fig. 11-11 Keratolysis exfoliativa.

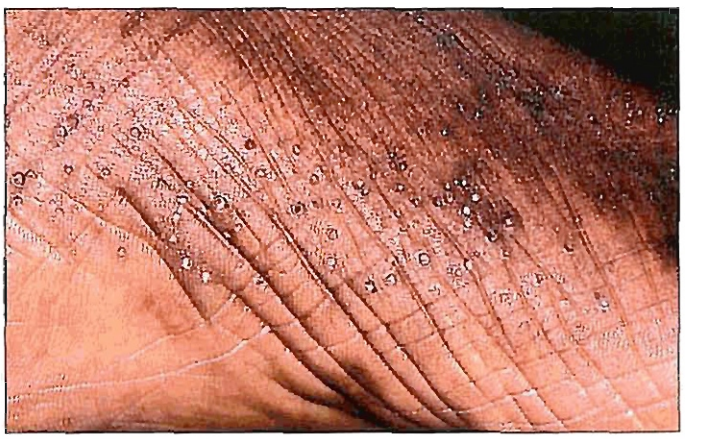

Fig. 11-13 Plantar seedlike keratoderma.

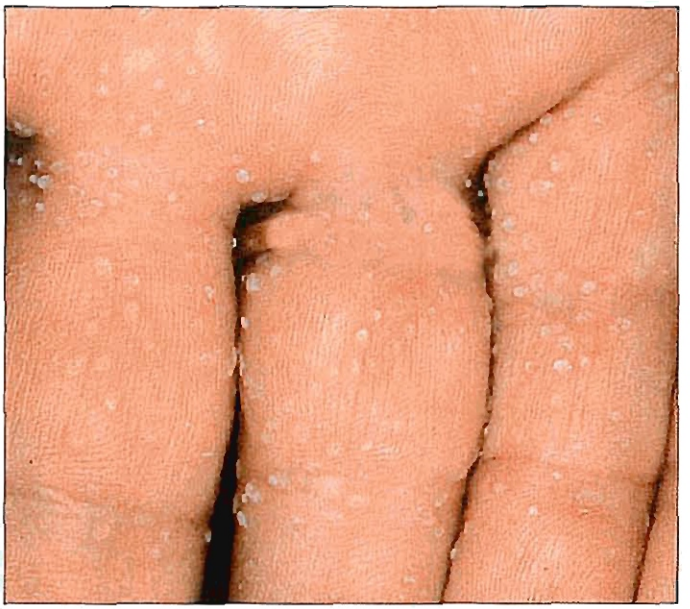

Fig. 11-14 "Music box" spine keratoderma.

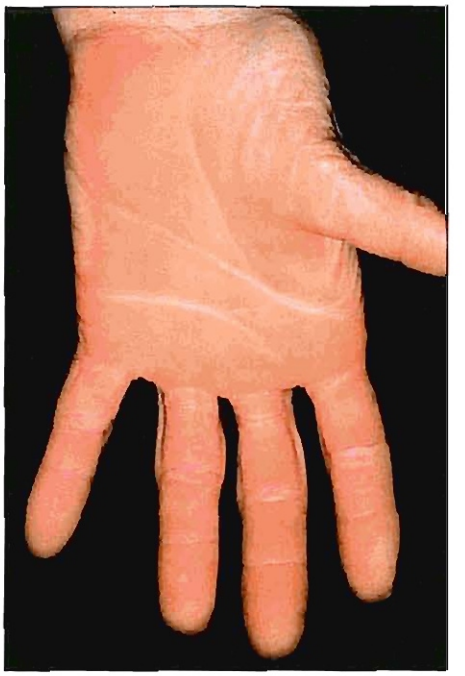

Fig. 11-15 Unna-Thost keratoderma.

The onset is between ages 15 and 68. Black individuals predominate, and it most frequently afflicts men. There have been reports of autosomal-dominant inheritance. The histology demonstrates hyperkeratosis and parakeratosis, pyknotic, vacuolated epithelium, basal layer spongiosis and dilated, occluded sweat ducts, blood vessels, and lymph vessels. Only mechanical debridement and excision have achieved any permanent results.

Porokeratosis Plantaris Discreta

Porokeratosis plantaris discreta occurs in adults, with a 4:1 female preponderance. It is characterized by a sharply marginated, rubbery, wide-based papule that on blunt dissection reveals an opaque plug without bleeding on removal. Lesions are multiple, painful, and usually 7 to 10 mm in diameter. They are usually confined to the weight-bearing area of the sole, beneath the metatarsal heads. Treatment may begin with fitted foot pads to redistribute the weight. Surgical excision, blunt dissection, and cryotherapy have been successful.

Keratoderma Climactericum

Keratoderma climactericum is characterized by hyperkeratosis of the palms and soles (especially the heels) beginning at about the time of the menopause. The discrete, thickened, hyperkeratotic patches are most pronounced at sites of pressure such as around the rim of the sole. Fissuring of the thickened patches may be present. There is a striking resemblance to plantar psoriasis, and indeed, keratoderma climacterium may represent a form of psoriasis. Therapy consists of keratolytics such as 10% salicylic acid ointment, lactic acid creams, or 20% to 30% urea mixtures. The response to topical corticosteroids is often disappointing. Acitretin is more effective than isotretinoin.

Hereditary Palmoplantar Keratoderma

Hereditary palmoplantar keratoderma (Unna-Thost) is characterized by a dominantly inherited, marked, congenital thickening of the epidermal horny layer of the palms and soles, usually symmetrically and affecting all parts equally (Fig. 11-15). At times the thickening extends to the lateral or dorsal surfaces, especially over the knuckles. The arches of the feet are generally spared. The epidermis is thick, yellowish, and horny. The uniform thickening forms a rigid plate, which ends with characteristic abruptness at the periphery of the palm. Hyperhidrosis may cause a sodden appearance.

The condition is poorly responsive to therapy. Five percent salicylic acid, 12% ammonium lactate, and 40% urea have been used. Systemic retinoid therapy is impractical because of bone toxicity, and topical retinoids are generally not effective.

Palmoplantar Keratodermas and Malignancy

Howell-Evans reported a diffuse, waxy keratoderma of the palms and soles occurring as an autosomal-dominant trait associated with esophageal carcinoma. Other related features are oral leukoplakia, esophageal strictures, squamous cell carcinoma of tylotic skin, and carcinoma of the larynx and stomach. The tylosis esophageal cancer gene has been localized to chromosome 17q25. Acquired forms of palmoplantar keratodermas have also been associated with cancers of the esophagus, lung, breast, urinary bladder, and stomach.

Mutilating Keratoderma of Vohwinkel

Vohwinkel described honeycomb palmoplantar hyperkeratosis, associated with starfish-like keratoses on the backs of the hands and feet, linear keratoses of the elbows and knees, and annular constriction (pseudo-ainhum) of the digits (Fig. 11-16), which may progress to autoamputation.

Inheritance is mostly autosomal dominant, although a recessive type exists. The disease is more frequent in women and in whites, with onset in infancy or early childhood. Reported associations include deafness, deaf–mutism, high-tone acoustic impairment, congenital alopecia universalis, pseudopelade-type alopecia, acanthosis nigricans, ichthyosiform dermatoses, spastic paraplegia, myopathy, nail changes, mental retardation, and bullous lesions on the soles.

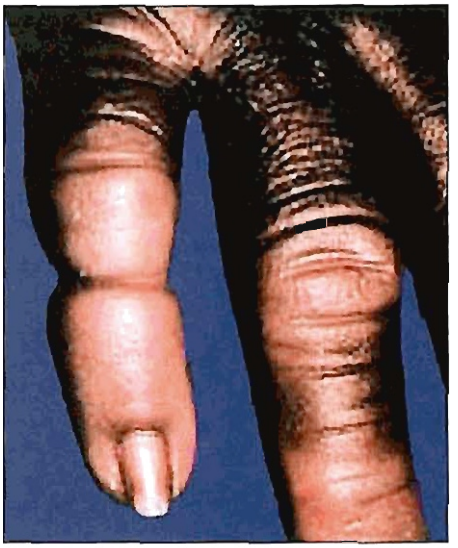

Fig. 11-16 Vohwinkel keratoderma.

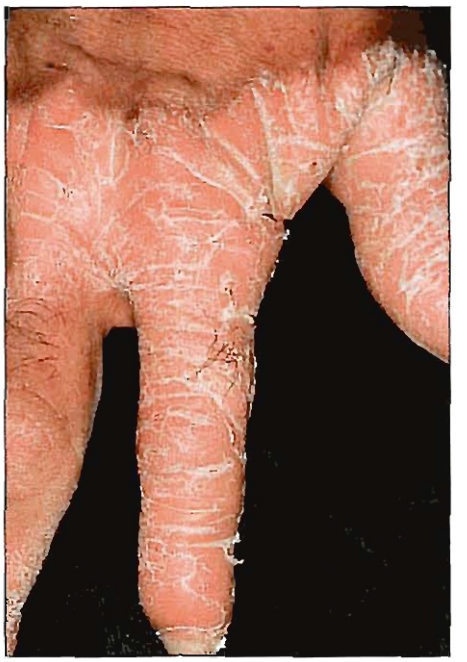

Fig. 11-17 Mutilating keratoderma.

Vohwinkel keratoderma maps to chromosome 1q21 and represents a mutation of loricrin. There have been some reports of a response to acitretin (or etretinate) therapy. Mutations in connexin 26 produce a similar phenotype.

Other forms of mutilating keratoderma also occur. They lack the constricting bands, honeycomb palmoplantar hyperkeratosis, and starfish-like keratoses of Vohwinkel syndrome. The affected digits are often shortened, narrow, rigid, and tapered (*Fig. 11-17*).

Olmstead Syndrome

Olmstead syndrome is characterized by mutilating palmoplantar keratoderma and periorificial keratotic plaques. The distinctive features of this syndrome include a congenital, sharply marginated palmoplantar keratoderma; constriction of the digits; linear keratotic streaks on the flexural aspects of the wrists; onychodystrophy; and periorificial keratoses. Constriction of digits may result in spontaneous amputations. Most cases of Olmsted syndrome are sporadic. Associated abnormalities have included hyperhidrosis of the palms and soles and congenital deafness. Histologically, there is acanthosis, papillomatosis, and orthokeratotic hyperkeratosis. The finding of Ki-67 staining of suprabasal keratinocytes suggests that Olmsted syndrome is a hyperproliferative disorder of the epidermis.

Acrokeratoelastoidosis of Costa

This autosomal-dominantly inherited condition is more common in women. Small, round, firm papules occur over the dorsal hands, knuckles, and lateral margins of the palms and soles. The lesions appear in early childhood and progress slowly. They are most often asymptomatic. The characteristic histologic feature is dermal elastorrhexis.

Papillon-Lefèvre Syndrome

The Papillon-Lefèvre syndrome is inherited in an autosomal-recessive fashion and presents with palmoplantar keratoderma and destructive periodontitis usually beginning in young childhood. Well-demarcated, erythematous, hyperkeratotic lesions on the palms and soles may extend to the dorsal hands and feet. Hyperkeratosis may also be present on the elbows, knees, and Achilles tendon areas. Transverse grooves of the fingernails may occur. Severe gingival inflammation with loss of alveolar bone is typical. Histology reveals a psoriasiform pattern. Mutations in the cathepsin C gene have been detected. The condition usually has an early age of onset, but a late-onset variant has been reported. Some patients with late-onset disease have not shown mutations in the cathepsin C gene.

The early onset of periodontal disease has been attributed to alterations in polymorphonuclear leukocyte function caused by *Actinomyces actinomycetemcomitans*, although a variety of other bacteria have also been implicated. Acroosteolysis and pyogenic liver abscesses may occur. There are asymptomatic ectopic calcifications in the choroid plexus and tentorium. Some patients have responded to acitretin, etretinate or isotretinoin.

The stocking-glove distribution of the hyperkeratosis is similar to that seen in mal de Meleda. Haim-Muuk syndrome is autosomal recessive with periodental disease, keratoderma and onychogryposis, linked to cathepsin C mutations.

Mal de Meleda

Mal de Meleda is a rare, autosomal-recessive form of palmoplantar keratoderma seen in individuals from the island of Meleda. The hyperkeratosis does not remain confined to the palms, and the extensor surfaces of the arms are frequently affected. The disease has been mapped to chromosome 8qter, and mutations in the ARS (component B) gene have been identified in families with this disorder. Mutations in the gene encoding secreted lymphocyte antigen-6/urokinase-type plasminogen activator receptor-related protein-1 (*SLURP-1*) have been found.

Striate Keratodermas

The striate keratodermas are a group of autosomal-dominant palmoplantar keratodermas with streaking hyperkeratosis involving the fingers and extending onto the palm of the hand. In some patients, a heterozygous C-to-A transversion involving the desmoglein 1 gene has been found. Mutations in the desmoplakin gene have also been described. Ultra-

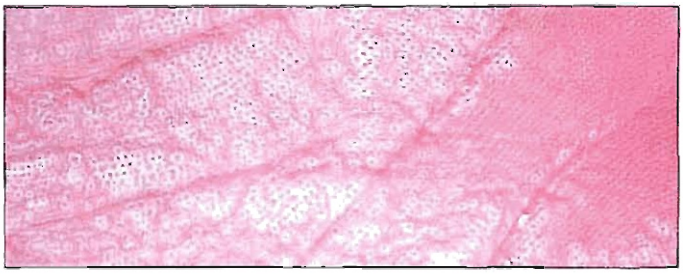

Fig. 11-18 Acquired aquagenic syringeal acrokeratoderma.

structurally, desmosome numbers are normal, but their inner plaques are attenuated.

Aquagenic Wrinkling of the Palms (Acquired Aquagenic Syringeal Acrokeratoderma)

Patients with this disorder also called papulotranslucent acrokeratoderma develop white papules on the palms after water exposure. The lesions are sharply demarcated from the surrounding skin and appear white. There may be a central prominent pore within each white lesion (Fig. 11-18). The lesions appear 3 to 5 min after exposure to water and resolve within a short time after drying. Sometimes the white skin can be peeled off. The cause is unknown, but autosomal-dominant inheritance has been suggested. It may be a marker for cystic fibrosis.

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EXFOLIATIVE DERMATITIS (ERYTHRODERMA)

Exfoliative dermatitis is also known as dermatitis exfoliativa, pityriasis rubra (Hebra), and erythroderma (Wilson–Brocq). Patients present with extensive erythema and scaling. Ultimately the entire body surface is dull scarlet and covered by small, laminated scales that exfoliate profusely. Vesiculation and pustulation are usually absent. An extensive telogen effluvium is often noted. In both PRP and mycosis fungoides distinctly spared islands of skin are frequently noted. Patients with PRP also commonly have thickened, orange palms and "nutmeg grater" follicular papules on the dorsa of the fingers (see above).

Itching of the erythrodermic skin may be severe and the onset is often accompanied by symptoms of general toxicity including fever and chills. Secondary infections by pyogenic organisms often complicate the course of the disease in the absence of treatment. Severe complications include sepsis, high output cardiac failure, adult respiratory distress syndrome, and capillary leak syndrome. The mortality rate attributable to the erythroderma approaches 7% in some series.

Etiology

Erythroderma is frequently the result of generalization of a preexisting chronic dermatosis such as psoriasis or atopic dermatitis. Many other cases are related to a medication, and some occur as a manifestation of an internal malignancy, erythrodermic mycosis fungoides, or the Sézary syndrome. In children immune disorders must be considered. Internal malignancies, pemphigus foliaceus, generalized dermatophytosis, and even Norwegian scabies may show the picture of generalized exfoliative dermatitis. There have been reports of inadequate intake of branched-chain amino acids in infants with maple syrup urine disease producing exfoliative erythroderma. However, in a significant number of patients the cause remains idiopathic, even after extensive evaluation.

In several reported series the largest group of patients had preexisting dermatoses, including atopic dermatitis, chronic actinic dermatitis, psoriasis, seborrheic dermatitis, pityriasis rubra pilaris, and allergic contact dermatitis. Drug eruptions

are generally the next most common group, followed by idiopathic cases, cutaneous T-cell lymphoma, paraneoplastic erythroderma, and leukemia cutis. Common implicated drugs include allopurinol, sulfa drugs, gold, phenytoin, phenobarbital, isoniazid, carbamazepine, cisplatin, dapsone, mefloquine, tobramycin, minocycline, nifedipine, and iodine.

In a study of erythrodermic patients managed in the community, exacerbation of preexisting dermatoses accounted for 61% as compared to 51% of those evaluated at a university medical; idiopathic cases for 14% and 31%, respectively; and cutaneous T-cell lymphoma for 1% and 6%, respectively.

In a study of 51 children with erythroderma, immunodeficiency was diagnosed in 30%, ichthyosis in 24%, Netherton syndrome in 18%, and eczematous or papulosquamous dermatitis in 20%. Five of the 51 patients remained idiopathic. A biopsy established the diagnosis in only 19 (45%) of 42 cases. The mortality rate was 16%, usually related to an immunodeficiency disorder.

In a comparison of patients with and without HIV infection, erythroderma in the HIV-positive group was most commonly related to drug reactions (40.6%), with ethambutol accounting for 30.8%. In the non-HIV group, drug reactions accounted for only 22.5%. HIV-positive patients did not have an overall increase in the number of episodes of erythroderma.

Mycosis fungoides can be erythrodermic without meeting the criteria for the Sézary syndrome. Sézary syndrome consists of generalized exfoliative dermatitis with intense pruritus, leonine facies, alopecia, palmoplantar hyperkeratosis, and onychodystrophy. The criteria for a diagnosis of Sézary syndrome include an absolute Sézary cell count of at least 1000 cells/mm^3; a CD4/CD8 ratio of 10 or higher by flow cytometry caused by an increase in circulating T-cells or loss of expression of pan-T-cell markers; increased lymphocyte counts with evidence of a T-cell clone by Southern blot or polymerase chain reaction; or a chromosomally abnormal T-cell clone. Prognosis is poor and similar to that of patients with nodal involvement.

Hodgkin's disease may show generalized exfoliative dermatitis. Fever, lymphadenopathy, splenomegaly, and hepatomegaly are frequently present. The erythrocyte sedimentation rate is elevated in most of these patients.

Histopathology

Exfoliative dermatitis may retain the histologic features of the original disease process. This is particularly true in psoriasis and mycosis fungoides. Often, however, the histology is nonspecific, with hyperkeratosis, mild acanthosis, and focal parakeratosis.

Treatment

In drug-induced erythroderma, the offending drug must be stopped. Application of a mid-strength corticosteroid after soaking, and occlusion under a sauna suit are often helpful, regardless of the cause of the erythroderma. Wet pajamas can be added under the sauna suit. Acitretin, cyclosporin, and methotrexate are useful in psoriatic erythroderma. Isotretinoin, acetretin, and methotrexate are useful in erythroderma caused by PRP. Immunosuppressive agents such as azathioprine and methotrexate may occasionally be necessary in idiopathic erythroderma not responding to therapy.

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CHAPTER

12 Lichen Planus and Related Conditions

LICHEN PLANUS

Lichen planus is a common, pruritic, inflammatory disease of the skin, mucous membranes, and hair follicles. It occurs throughout the world, in all races. It may be familial in 1% to 2% of cases. It appears in men at a constant rate from the early 20s through the 60s, whereas in women the rate of new cases continues to increase with increasing age, reaching a peak in the 60s. The primary lesions of lichen planus are characteristic, almost pathognomonic, small, violaceous, flat-topped, polygonal papules (Fig. 12-1). The color of the lesions initially is erythematous, but well developed lesions are violaceous. Older and resolving lesions are often hyperpigmented (Fig. 12-2). The surface is glistening, dry, with scant, adherent scales. On the surface, gray or white puncta or streaks (Wickham striae) cross the lesions. Dermoscopy may enhance the visualization of this critical diagnostic element of lichen planus lesions. Lesions begin as pinpoint papules and expand to 0.5- to 1.0-cm plaques. Infrequently, larger lesions are seen. There is a predilection for the flexor wrists, trunk, medial thighs, shins, dorsal hands, and glans penis (Fig. 12-3). The face is only rarely involved, and when it is, lesions are usually confined to the eyelids and/or lips. The palms and soles may be affected with small papules or hyperkeratotic plaques. Certain morphologic patterns favour certain locations, e.g. annular lesions favoring the penis, and keratotic lesions favoring the anterior shins (Fig. 12-4). Koebner's phenomenon occurs in lichen planus.

Pruritus is often prominent in lichen planus. The pruritus may precede the appearance of the skin lesions, and, as with scabies, the intensity of the itch may seem out of proportion to the amount of skin disease. It may be almost intolerable in acute cases. Most patients react to the itching of lichen planus by rubbing rather than scratching and consequently scratch marks are usually not present.

The natural history of lichen planus is highly variable and dependent on the site of involvement and the clinical pattern. Two-thirds of patients with skin lesions will have lichen planus for less than 1 year and many patients spontaneously clear in the second year. Mucous membrane disease is much more chronic. Recurrences are common.

Children represent only 4% of cases of lichen planus, and the lesions are often atypical. Linear or segmental patterning, prominent follicular involvement, significant nail changes with deformities, and a long course are common in children.

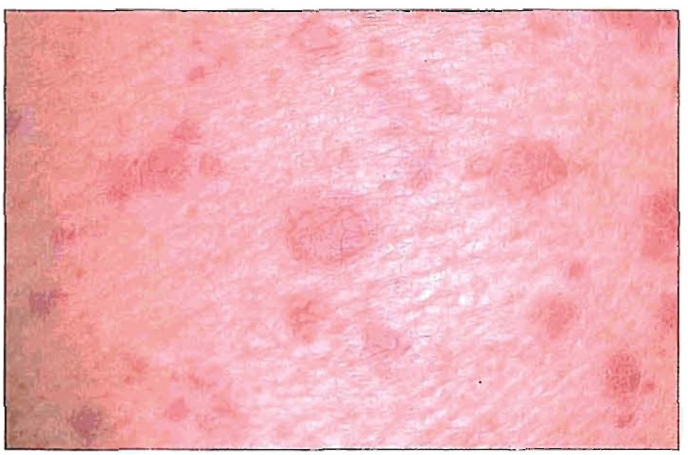

Fig. 12-1 Lichen planus, violaceous, flat-topped papules with minimal scale.

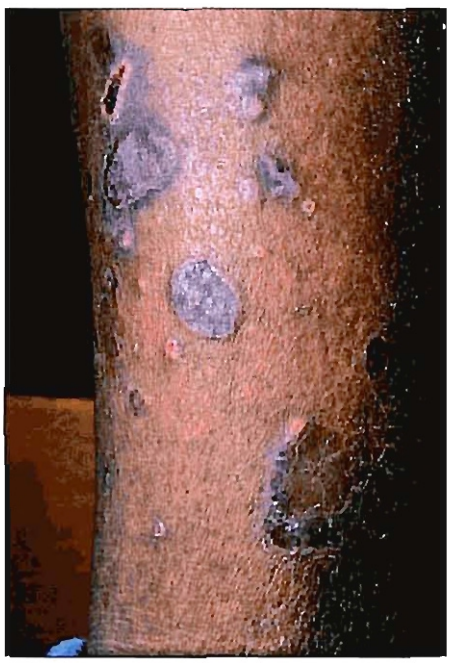

Fig. 12-2 Lichen planus, hyperpigmented lesions in a person of color.

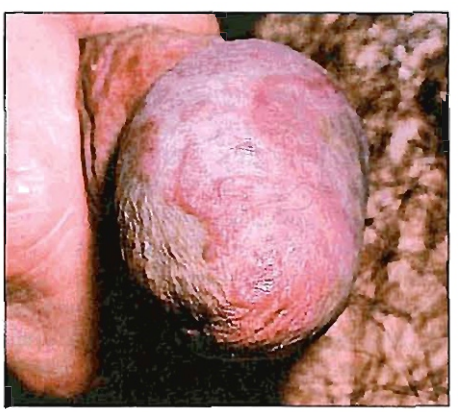

Fig. 12-3 Lichen planus, penile plaques.

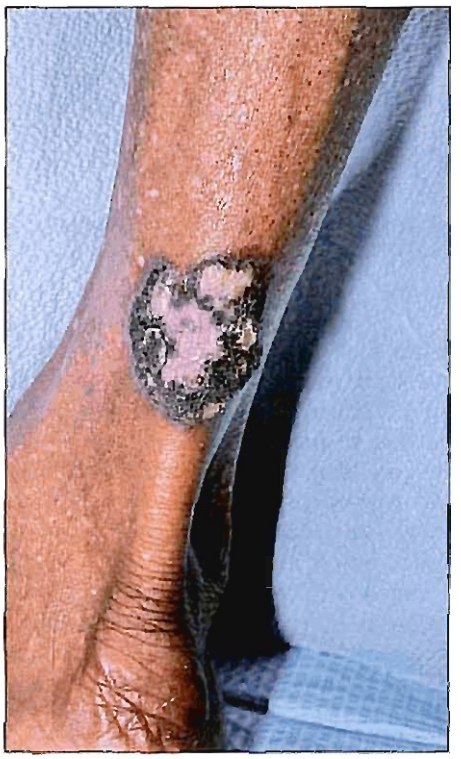

Fig. 12-4 Lichen planus, hypertrophic type.

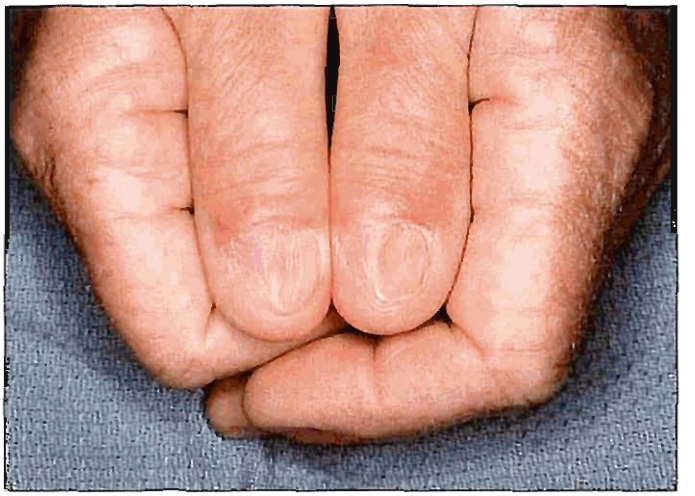

Fig. 12-5 Lichen planus, nail involvement with pterygium.

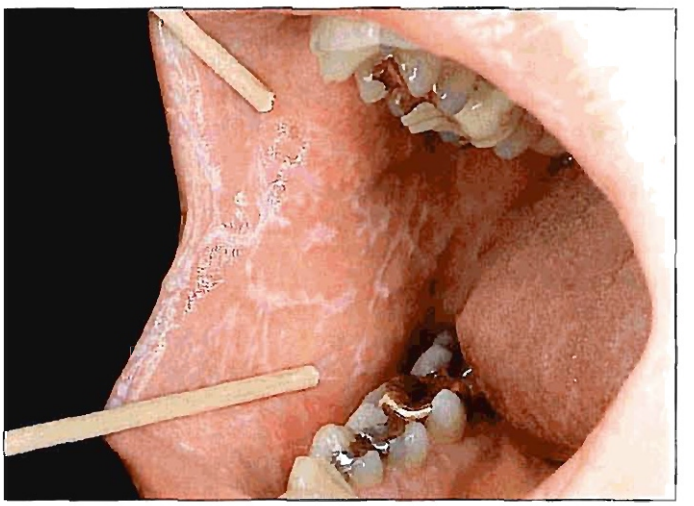

Fig. 12-6 Lichen planus, reticulate white lesions of the buccal mucosa.

Classic lesions are uncommon. Children with lichen planus often have affected family members. Children from the Indian subcontinent appear to have lichen planus more frequently.

Nail changes are present in approximately 5% to 10% of patients, and are proportionately more common in children with lichen planus. Especially in children, involvement of the nail apparatus only by lichen planus is typical. Longitudinal ridging and splitting are most common. Onycholysis may be present and the lunula may be red. Involvement of the entire matrix may lead to obliteration of the whole nail plate (idiopathic atrophy of the nail). Yellow nail syndrome may be simulated by lichen planus of the nails. Pterygium formation is very characteristic of lichen planus of the nails (Fig. 12-5). The nail matrix is destroyed by the inflammation and replaced by fibrosis. The proximal nailfold fuses with the proximal portion of the nailbed. Lichen planus may be a cause of some cases of twenty-nail dystrophy of childhood, a pattern of nail lichen planus that usually spontaneously resolves.

The mucous membranes, especially the oral mucosa, are frequently affected. Fifteen percent of patients with oral lichen planus will also have skin lesions. Women represent 75% of patients with oral lichen planus. Oral lichen planus in women begins 10 years later than in men (57 years vs 47 years). Oral lesions may be reticulate (reticular) (Fig. 12-6), erythematous (atrophic), or ulcerative (erosive). Patients may simultaneously have several patterns, so patients are characterized by the primary form they exhibit. The most common pattern in oral lichen planus is the ulcerative form (40% of patients). Usually reticulate and erythematous lesions are found adjacent to the ulcerative areas. The erythematous pattern is the predominant pattern in 37% of patients, but reticulate lesions are almost always also seen in these patients. In oral lichen planus the "classic" reticulate lesions are most prominent in 23% of patients. Symptoms are least common in patients with reticulate lesions; 23% are symptomatic and only when the tongue is involved. All patients with erosive lesions are symptomatic. Oral lichen planus may involve any portion of the mouth. The buccal mucosa is involved in 90% of cases, and the gingiva in more than 50%. Gingival involvement is particularly hard to diagnose, and often requires biopsy for both histology and direct immunofluorescense to confirm the diagnosis. Gingival involvement is associated with accelerated gingival recession and aggressive management of oral hygiene, and control of candidial overgrowth is critical in the management of oral lichen planus patients. Mechanical injury from dental procedures and poor fitting appliances, as well as increased plaque from an inability to clean teeth due to pain, may trigger or exacerbate gingival lichen planus, probably via the Koebner's phenomenon. On the tongue and palate lesions are often mistaken for leukoplakia. The lower lip is involved in 15% of oral lichen planus patients, but the upper lip in only 2%. Oral lichen planus is stable but chronic, with less than 3% of patients having a spontaneous remission in an average 5-year follow-up.

Mercury, gold, and palladium sensitivity may be found in patients with oral lichenoid reactions. Patch testing may not

identify all patients whose oral lichenoid lesions improve with removal of the oral metal. This has made the role of metals in the induction of oral lichenoid lesions and oral lichen planus very controversial. Rarely, patients with metal sensitivity will also have skin and nail lesions that improve with removal of the oral metal. Metal sensitivity as a cause of an oral lichenoid reaction should be considered especially in those patients whose oral involvement is directly adjacent to fillings.

Involvement of the genitalia, with or without lesions at other sites, is common. On the glans penis the lesions consist of flat, polygonal papules, or these may be annular. On the labia and anus similar lesions are observed; they are generally whitish, owing to maceration. In the vulvovaginal areas, erosive or ulcerative disease is common and may coexist with typical reticulate lesions. Twenty-five percent of women with oral lichen planus have vulvovaginal involvement. Vulvovaginal lichen planus must be distinguished from lichen sclerosus.

Conjunctival involvement is a very rare complication of lichen planus. It occurs in patients with oral and gingival involvement. Cicatrization and subepithelial scarring can occur as well as keratitis. It may closely simulate mucous membrane pemphigoid. Routine histology and direct immunofluorescence (DIF) may be required to confirm the diagnosis.

There are many clinical variants of lichen planus. Whether these represent separate diseases or part of the lichen planus spectrum is unknown. They all demonstrate typical lichen planus histologically. They are described separately, since their clinical features are distinct from classic lichen planus. Some patients with these clinical variants may have typical skin lesions of classic lichen planus as well. The more common or well-known variants are described below.

Linear Lichen Planus

Small linear lesions caused by Koebner's phenomenon often occur in classic lichen planus. Limitation of lichen planus to one band or streak has also been described in less than 1% of patients, except in Japan, where up to 10% of reported cases are linear. Although originally described as following dermatomes (zosteriform), the lesions actually follow lines of Blaschko. It is more common in children, but also occurs in adults. Papules with varying degrees of overlying hyperkeratosis, or simple hyperpigmentation may be the presenting manifestations. There are often skip areas of normal skin between the individual lesions.

Annular Lichen Planus

Men represent 90% of patients with annular lichen planus. Lesions with this configuration favour the axilla, penis/scrotum, and groin. Lichen planus lesions of the mucosae, scalp, and nails are rare in patients with annular lichen planus. Patients usually have fewer than 10 lesions. Most patients with annular lichen planus are asymptomatic. The ringed lesions are composed of small papules and measure about 1 cm in diameter. Central hyperpigmentation may be the dominant feature. They may coalesce to form polycyclic figures. Annular lesions may also result from central involution of flat papules or plaques, forming lesions with violaceous, elevated borders and central hyperpigmented macules.

Hypertrophic Lichen Planus (Lichen Planus Verrucosus)

Hypertrophic lichen planus occurs most commonly on the shins, although it may be situated anywhere. The typical lesions are verrucous plaques with variable amounts of scale. At the edges of the plaques, small, flat-topped, polygonal papules may at times be discovered. Superficial inspection of the lesion often suggests psoriasis or a keratinocytic neoplasm rather than lichen planus. The lesions are of variable size, but frequently several centimetres in diameter and larger than the lesions of classic lichen planus. Clinical diagnosis may be difficult and biopsy is often required. Histologically, the pseudoepitheliomatous keratinocyte hyperplasia may be marked, leading to the erroneous diagnosis of squamous cell carcinoma. In addition, keratoacanthoma-like proliferations may occur in lesions of hypertrophic lichen planus. Hypertrophic lichen planus is chronic and often refractory to topical therapy. Hypertrophic lupus erythematosus resembles hypertrophic lichen planus both clinically and histologically. Hypertrophic lupus tends to affect the distal extremities, face, and scalp. The finding of continuous granular immunoglobulin on DIF strongly suggests a diagnosis of hypertrophic lupus erythematosus rather than lichen planus.

Ulcerative Lichen Planus

Ulcerative lichen planus is rare on the skin but common on the mucous membranes. Typical skin lesions of lichen planus rarely ulcerate. A rare ulcerative variant of cutaneous lichen planus affects the feet and toes, causing bullae, ulcerations, and permanent loss of the toenails. These chronic ulcerations on the feet are painful and disabling. Cicatricial alopecia may be present on the scalp and the buccal mucosa may also be affected. Skin grafting of the soles has produced successful results.

Although erosion or ulceration is rare in cutaneous lichen planus, in the oral mucosa this is the most common form, and it is usually chronic. Lesions appear on any portion of the mouth, and multisite involvement is common. The buccal mucosa is involved in 90%, the gingiva in more than half, and the tongue in about 40%. On the gingiva, lichen planus may produce desquamative gingivitis. Erosive lichen planus universally causes discomfort or pain.

Involvement of the vulva and vagina with lichen planus, along with gingivitis, has been described as the vulvovaginal–gingival syndrome. Although all three of these mucous membranes may be involved, the disease may begin on one and later appear on another. This characteristic has resulted in expansion of the spectrum of lichen planus and demonstrates that erosive disease of the female genitalia is more frequently present than previously appreciated. These women have vulvar pain or burning; however, many women with lichen planus will not volunteer their vulvovaginal complaints unless specifically asked. The vulva has lesions very similar to oral lichen planus, with erythema, leukokeratosis, and erosion. Surrounding the red or eroded lesions is a narrow rim of white reticulation. This rim is the most fruitful area to biopsy to confirm the diagnosis. The vaginal mucosa is involved in two-thirds of patients. Scarring of the vagina and vulva with adhesions, vestibular bands, and atrophy of the labia minora or prepuce occurs, making the morphology similar to vulvar lichen sclerosus. In one-third,

typical reticulate buccal lichen planus is seen, and 10% have cutaneous lichen planus.

Cancer Risk and Lichen Planus

Rare cases of squamous cell carcinoma of the skin occurring on the lower leg in lesions of hypertrophic lichen planus have been reported. These patients had also received agents known to be carcinogenic (arsenic and radiation therapy). There is no statistical increase in cutaneous or visceral carcinoma in patients with cutaneous lichen planus, and cutaneous lichen planus alone is not considered a condition with increased cancer risk. Oral and vulvovaginal lichen planus does appear, however, to increase the risk of developing squamous cell carcinoma. Between 0.4% and 5% (on average about 1%) of patients with oral lichen planus will develop oral squamous cell carcinoma. Squamous cell carcinoma only occurs in patients with erythematous or ulcerative lichen planus, not in patients with only the reticulate pattern. Clinicians should have a low threshold to biopsy fixed erosive or leukokeratotic lesions in patients with mucosal lichen planus.

Hepatitis-Associated Lichen Planus

Three liver conditions have been associated with lichen planus: hepatitis C virus (HCV), HBV immunization, and primary biliary cirrhosis. HCV infection is found in proportionately more patients with lichen planus than in controls. Depending on the background rate of HCV infection in the region, between 4% and 60% of patients with lichen planus may have coexistent HCV infection. In northern Japan, where the seroprevalence of HCV infection is 8%, 60% of patients with oral lichen planus had HCV infection. This association has been questioned by other investigators, however. In a large series of patients with oral lichen planus from the US, none of the 195 patients was infected with HCV; while 29% of patients with oral LP from Italy had HCV. Twenty percent of patients infected with HCV in Scotland had oral lichen planus, as compared to 1% of seronegative patients. Although the data are conflicting, screening for HCV appears appropriate in persons from a geographic region or population in which HCV infection is common. The clinical features of lichen planus in patients with hepatitis C infection are identical to classic lichen planus, but lichen planus patients with HCV infection are reported more likely to have erosive mucous membrane disease. The existence of underlying hepatitis cannot be predicted by clinical pattern or the results of liver function tests. Treatment of hepatitis C with interferon-α may be associated with the initial appearance of lichen planus or exacerbation of preexisting lichen planus. Lichen planus may occur at the sites of interferon injections, and skin testing may reproduce lichen planus-like lesions. Lichen planus may improve or not change with interferon and ribavirin treatment for hepatitis C. Improvement is usually seen towards the end of the treatment course. Most patients do not completely clear their lichen planus. The HCV genome is not found in lesions of lichen planus associated with HCV infection.

HBV immunization may be associated with the appearance of lichen planus in both children and adults. More than 30 cases have been reported. Lesions are typical of lichen planus and the oral mucosa may be affected. Most typically the first lesions of lichen planus appear about 1 month after the second dose of vaccine. Lesions typically resolve after some time.

Primary biliary cirrhosis and lichen planus may coexist. Patients with this liver abnormality, in addition, have a marked propensity to develop a lichenoid eruption while on D-penicillamine therapy. Xanthomas in patients with primary biliary cirrhosis may appear initially in lesions of lichen planus, and the infiltrate, while lichenoid, may contain xanthomatous cells. Primary sclerosing cholangitis has been associated with oral lichen planus in at least five patients.

Lichen Planus–Lichen Sclerosus Overlap

Very rarely patients with skin lesions of lichen planus and lichen sclerosus have been reported. In most of these cases the lichen sclerosus lesions were actually overlying morphea, and are actually cases of coexistent lichen planus and morphea. One patient with lichen planus and lichen sclerosus had HCV infection.

Bullous Lichen Planus

Two forms of lichen planus may be accompanied by bullae. In classic lichen planus, usually on the lower extremities, individual lesions will vesiculate centrally. This represents macroscopic exaggeration of the subepidermal space formed by the lichenoid interface reaction destroying the basal keratinocytes. These lesions often spontaneously resolve.

Lichen planus pemphigoides describes a rare subset of patients who usually have typical lichen planus, then develop blistering on their lichen planus lesions and on normal skin. Less commonly the blistering antedates the lichen planus. They clinically appear to be a combination of lichen planus and bullous pemphigoid. Oral disease may occur and resemble either lichen planus or pemphigoid. Lichen planus pemphigoides has been triggered by medications and PUVA. Pruritus may be severe and lesions may evolve to resemble pemphigoid nodularis. Histologically, the lichen planus lesions show lichen planus and the bullous lesions show the features of bullous pemphigoid. DIF is positive in a linear pattern with IgG and C3 along the basement membrane zone, at the roof of saline split skin. The antigen targeted by the autoantibody in lichen planus pemphigoides is located in the same region as the bullous pemphigoid antigen (at the basal hemidesmosome). Antibodies from patients with lichen planus pemphigoides bind the 180-kD bullous pemphigoid antigen, but in a different region from bullous pemphigoid sera. Lichen planus pemphigoides tends to follow a benign and chronic course, even when compared to bullous pemphigoid. Treatment is similar to bullous pemphigoid, with potent topical steroids, systemic steroids, tetracycline and nicotinamide, intravenous immunoglobulin, and immunosuppressives all being variably effective.

Pathogenesis and Histology

Lichen planus is characterized by an immunologic reaction mediated by T-cells. These cells induce keratinocytes to undergo apoptosis by an unknown mechanism. Lichen planus pemphigoides is hypothesized to result from exposure to the immune system of epitopes in the BP180 antigen as keratinocytes are destroyed by the lichenoid inflammation. Epitope spreading can occur, and lichen planus pemphigoides patients may also have autoantibodies to the same

epitopes as bullous pemphigoid patients. A rarer phenomenon is the development of antibodies to desmoplakin I and II in a patient with primary ulcerative mucocutaneous lichenoid eruption.

The histologic features of lichen planus are distinctive and vary with the stage of the lesion. In early lesions there is an interface dermatitis along the dermoepidermal junction. As the lesion evolves, the epidermis takes on a characteristic appearance. There is destruction of the basal layer with a "saw-tooth" pattern of epidermal hyperplasia, orthokeratosis, and beaded hypergranulosis. The basal cells are lost, so the basal layer is described as "squamatized." In the superficial dermis there is a dense, bandlike infiltrate composed of lymphocytes, and melanophages. "Civatte bodies" (cytoid bodies, colloid bodies) represent necrotic keratinocytes in the superficial dermis. Hypertrophic lichen planus shows marked epidermal hyperplasia (pseudoepitheliomatous hyperplasia). Old lesions of lichen planus show effacement of the rete ridge pattern, melanophages in the upper dermis, and occasional Civatte bodies. Lichen planus rarely demonstrates parakeratosis or eosinophils. The presence of either of these suggests a different cause of lichenoid tissue reaction, such as lichenoid drug eruption.

Lichen planopilaris, frontal fibrosing alopecia, and Graham Little-Piccardi-Lassueur syndrome show the findings of lichen planus, centered on the superficial follicular epithelium. On DIF, clumps of IgM and less frequently IgA, IgG, and C3 are commonly present subepidermally, corresponding to the colloid bodies. Dense shaggy staining for fibrinogen along the basement membrane zone is characteristic of lichen planus. A lichenoid drug eruption may be difficult to differentiate from lichen planus. The presence of eosinophils or parakeratosis supports the diagnosis of lichenoid drug eruption. Although lichen planus virtually never has eosinophils or parakeratosis, they are not universally present in other lichenoid eruptions such as lichenoid drug eruption. Graft-versus-host disease tends to have as sparser infiltrate and bowenoid atypia within the epidermis. Hypertrophic lupus may be histologically identical to lichen planus, and the diagnosis is best made by clinical correlation and DIF. In most other forms of lupus erythematosus, there is a greater tendency for epidermal atrophy with parakeratosis, dermal mucin is found, and follicular plugging is more prominent. The infiltrate in lupus tends to surround and involve deep portions of the appendageal structures, such as the follicular isthmus and eccrine coil. Deep nodular perivascular lymphoplasmacytic infiltrates and necrosis of the fat lobule with fibrin or hyalin rings are also findings characteristic of lupus erythematosus.

Differential Diagnosis

Classic lichen planus displays lesions that are so characteristic that clinical examination is often adequate to suspect the diagnosis. Lichenoid drug eruptions may be difficult to distinguish. A lichenoid drug reaction should be suspected if the eruption is photodistributed, scaly but not hypertrophic, confluent or widespread—clinical features that are unusual for idiopathic lichen planus. The presence of oral mucosa involvement may prompt suspicion of lichen planus, but oral lesions may occasionally occur in lichenoid drug eruptions as well. Pityriasis rosea, guttate psoriasis, the small papular or lichenoid syphilid, and pityriasis lichenoides et varioliformis acuta are dermatoses that may resemble generalized lichen planus. Mucous membrane lesions may be confused with leukoplakia, lupus erythematosus, mucous patches of syphilis, candidiasis, cancer, and the oral lesions of autoimmune bullous diseases, such as pemphigus or cicatricial pemphigoid. On the scalp the atrophic lesions may be mistaken for other cicatricial alopecias such as lupus erythematosus, folliculitis decalvans, and pseudopelade of Brocq. Hypertrophic lichen planus type may simulate psoriasis, and squamous cell carcinoma in situ. Isolated patches of lichen planus may resemble lichen simplex chronicus or, if heavily pigmented, may suggest a fixed drug eruption.

Treatment

Limited lesions may be treated with superpotent topical steroids or intralesional steroid injections. In patients with widespread disease, these treatments are usually unsatisfactory. Widespread lesions respond well to systemic corticosteroids but tend to relapse as the dose is reduced. However, by treating with prednisone at a dose of 1 mg/kg/day (average 60 mg) for 7 days, 40 mg for 7 days, and 20 mg for 7 days, and then slowly tapering at a rate of 2.5 mg/week, relapses may be less common. Phototherapy may be effective for cutaneous lichen planus, including narrow-band UVB, UVA1, and PUVA. Topical cream PUVA has been used effectively in genital lichen planus. Isotretinoin and acetretin in doses similar to or slightly lower than used for psoriasis may also be useful and avoid the long-term complications of systemic steroids. They are especially useful in cases of hypertrophic lichen planus. Retinoid therapy may be combined with phototherapy in refractory cases. Photodynamic therapy with topical 5-aminolevulinic acid can be effective in penile lichen planus. Low molecular weight heparin (enoxaparin), 3 mg injected subcutaneously once a week led to remission of cutaneous and reticulate oral lichen planus in 61% of patients, and improvement in 11%. Erosive oral lichen planus responded variably and lichenplanopilaris not at all. Oral immunosuppressive agents may be effective for cutaneous lichen planus, but their potential toxicity limits use to the most severe cases. Cyclosporin in typical psoriasis doses is very beneficial. Similarly mycophenolate mofetil can induce remission in severe cases of cutaneous and oral lichen planus.

For oral lesions, superpotent steroids in orabase or gel form are useful. Vinyl dental trays may be used to apply steroid ointments to the gingiva. Begin with 30-min applications three times a day and reduce to maintenance of 20 min every evening. Addition of nystatin to clobetasol in Orabase may be especially effective. Intralesional injections may be used for focal unresponsive lesions. Topical tacrolimus 0.1% ointment has become standard treatment in erosive lichen planus of the oral and genital mucosa. While burning may occur initially, this can be reduced by concomitant use of topical steroids or initial use of a lower strength. Higher concentrations, up to 0.3%, may be used. Most patients have a partial but significant response, with increased ability to eat with much less pain. Blood levels can be detected, independent of area of involvement, but tend to decrease over time as the oral erosions heal. Sustained remissions are rare, and chronic use is usually required to maintain remission. PUVA and 308-nm excimer laser have been effective in oral lichen planus. Hydroxychloroquine,

200 to 400 mg/day for 6 months, was reported to produce an excellent response in 9 of 10 patients with oral lichen planus. Thalidomide has also proven effective in doses of 150 mg/day. The systemic agents recommended above to treat cutaneous lichen planus may also improve oral disease. For *vulvovaginal–gingival syndrome*, *corticosteroids topically* and systemically are beneficial. Topical therapy with corticosteroids may be enhanced by mixing the steroid in vaginal bioadhesive moisturizer (Replens). Iontophoresis may improve delivery. Mycophenolate mofetil and cyclosporin are usually effective in the most refractory cases.

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Follicular Lichen Planus (Lichen Planopilaris)

Lichen planopilaris is lichen planus involving the follicular apparatus. Most cases involve the scalp and it is an important cause of cicatricial alopecia (see Chapter 33). Seventy to 80% of affected patients are women, usually around the age of 50. The oral mucosa is involved with reticulate lichen planus in 7% to 27% of patients, and between 20% and 40% of patients have cutaneous involvement. Graham Little-Piccardi-Lassueur syndrome describes patients with lichen planopilaris of the scalp with coexistent keratosis pilaris-like lichen planopilaris lesions with alopecia of the eyebrows, axillae, and pubic area.

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"TROPICAL" DYSCHROMIC LICHENOID DISORDERS

This section discusses a disease group that is very common in tropical countries, Latin America, and Japan. They are all lichenoid dermatoses, but the predominant clinical feature is marked dyschromia, usually hyperpigmentation. Numerous names have been applied to these diseases. In Central America these cases are diagnosed as either lichen planus pigmentosus or erythema dyschromicum perstans. In the Middle East, Japan, and Indian subcontinent, lichen planus actinicus and lichen planus pigmentosus are the terms used to describe these conditions. Idiopathic eruptive macular pigmentation may also represent a disease from this category. Whether these represent variations of one disease, variants of lichen planus, or several different diseases is unknown. In all the descriptions young persons are affected most frequently (younger than 40); macular hyperpigmentation is prominent with few or no antecedent inflammatory lesions; the upper half of the body is primarily affected; and biopsies may show various stages of lichenoid dermatitis. Mucosal involvement is very uncommon. No pathogenic cause has been identified.

Lichen Planus Actinicus

Lichen planus actinicus has been variously named *lichen planus actinicus*, *actinic lichen planus*, *lichenoid melanodermatitis*, and *summertime actinic lichenoid eruption*. It is a disorder seen most frequently in Africa, the Middle East, and Indian subcontinent. Cases are diagnosed clinically and are regionally reasonably uniform. There seems to be a genetic predilection, since Europeans who move into areas of endemicity are not affected by this disorder but regularly develop typical lichen planus. Most cases occur in childhood through young adulthood. It represents a substantial proportion of cases diagnosed as lichen planus in endemic regions.

The disease presents in the spring or summer and is frequently quiescent during the winter. The third decade of life is the primary age of appearance. Lesions favor the sun-exposed parts of the body, especially the face, which is almost always most severely affected. Most lesions occur on the forehead, cheeks, and lips. Outside the face, the V area of the chest, the neck, the backs of the hands, and the lower extensor forearms are involved. Associated pruritus, the hallmark of lichen planus, is usually described as mild or nonexistent. Lesions are usually annular but may be reticulate or diffuse. Individual lesions are often macular but may be plaques with peripheral violaceous papules.

Characteristically, lesions are hyperpigmented, sometimes with the blue–gray tinge of dermal melanin. Lesions may resemble melasma.

Actinic lichen planus is hypothesized to be elicited by long exposure to sun, particularly in adolescents and young adults who work all day in the fields. Phototesting with UVB has not uniformly reproduced the lesions. In cases seen in the US, blacks have been preferentially affected. Intense sun exposure may be required to elicit the lesions. In one case, six times the minimal erythema dose (MED) was applied to reproduce the lesions. Typical lichenoid papules, eczematous-appearing plaques with a lichenoid histology, or lesions with the clinical and histologic features of lichen nitidus (lichen nitidus actinicus) appearing on the dorsal hands may be seen. Rarely, lichen planus may appear in ports of radiation therapy.

Histologically, there are variable degrees of effacement of the rete ridge pattern and vacuolar alteration along the basal cell layer. Cytoid bodies are sometimes seen. An inflammatory infiltrate is found if an infiltrated papule or plaque is biopsied. It will show an inflammatory infiltrate composed of lymphocytes and macrophages along the dermoepidermal junction or around the superficial blood vessels. In all cases, incontinence of pigment is prominent, correlating with the prominent dyspigmentation observed clinically.

In summary, sun-induced lichenoid eruptions seem to be common in tropical countries and are not related to medication ingestion. They affect primarily young males and result in annular or diffuse hyperpigmented lesions of the face. Rare cases with a similar clinical appearance, but spongiotic dermatitis histologically, may represent a subtype of polymorphous light eruption.

Lichen Planus Pigmentosus

Lichen planus pigmentosus is seen in Central America, the Indian subcontinent, and Japan. These patients are young (between 20 and 45 in most cases), and men and women are equally represented. Men present a decade earlier (mean age 26 vs 34). The face and neck are primarily involved. The condition is usually mild (<10% body surface area) and patients may have associated pruritus. Sometimes classic lichen planus papules occur at other sites or at the periphery of the lesions. Facial involvement is common and dyspigmentation marked. This appears to represent lichen planus, which resolves with marked hyperpigmentation, probably related to the racial background of the affected patients. In the US, persons of color may demonstrate this pattern of lichen planus.

Erythema Dyschromicum Perstans

Erythema dyschromicum perstans is also known as *ashy dermatosis* or *dermatosis cinecienta*. The age of onset is virtually always before 40, but since it is a chronic disease, patients of all ages are seen. Lesions are usually symmetrical and generalized, involving the face, neck, trunk, and proximal extremities. Lesions are of various sizes and shapes, ashy-gray, and macular. Sometimes a characteristic, very fine (several millimeters), erythematous, palpable, nonscaling border is seen at the periphery of the lesions. This is described as feeling like a small cord. Pruritus is not reported, and typical lichenoid papules are said not to occur. Nail and mucosal involvement is not found.

At the active border the characteristic histologic features are those of a lichenoid dermatitis. In the centers of the lesions, the histologic changes are those of postinflammatory pigmentation: the characteristic gray–blue skin hue reflects the presence of melanin-laden macrophages in the dermis. Immunofluorescence microscopy reveals cytoid bodies. Therapeutic agents used for lichen planus may benefit the acute inflammatory stage, but have limited effect on the pigmented lesions. Clofazimine at 100 mg/day for patients over 40 kg and every other day for patients under 40 kg has been reported to induce clearing in approximately 50%, but clofazimine pigment may complicate prolonged treatment.

Idiopathic Eruptive Macular Pigmentation

Although rarely reported, this condition is not rare. Young persons (mean age 11 years) in one study presented with asymptomatic widespread brown to gray macules of up to several centimeters in diameter on the neck, trunk, and proximal extremities. Lesions are not confluent and there is no history of preceding inflammation. Lesions may spontaneously involute.

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KERATOSIS LICHENOIDES CHRONICA

This very rare dermatosis is characterized by its chronicity. It may begin in childhood or even near birth. The typical lesions are violaceous papulonodular, hyperkeratotic lesions covered with gray scales. These lesions favor the extremities and buttocks. Although initially discrete, the lesions frequently coalesce to form linear and reticulate arrays of warty lichenoid lesions. Keratotic plugs and prominent telangiectasia may be present. The palms and soles may be diffusely thickened or have discrete hyperkeratotic papules. There is an associated sharply marginated erythema, scaling, and telangiectasia of the face superficially resembling

seborrheic dermatitis or rosacea. Nail changes, including thickening of the nail plate, yellowing, longitudinal ridging, onycholysis, hyperkeratosis of the nailbed, paronychia, and warty lesions of the periungual areas, have been described. In addition, painful oral aphthae-like lesions often occur. Other findings include hoarseness due to vocal cord edema, and involvement of the eyelids (one-third of patients), conjunctiva, iris or anterior chamber. Topical calcipotriol, PUVA, re-PUVA, and oral retinoids (isotretinoin and acitretin) may all prove beneficial. Keratosis lichenoides chronica rarely responds to topical or systemic steroids.

Histologically, there is irregular acanthosis, a lichenoid infiltrate consisting of lymphocytes, histiocytes, and plasma cells with vacuolar alteration at the basal cell layer.

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LICHEN NITIDUS

Clinical Features

Lichen nitidus is a chronic inflammatory disease characterized by minute, shiny, flat-topped, pale, exquisitely discrete, uniform papules, rarely larger than the head of a pin. Pruritus is usually minimal or absent, but may be more prominent in more generalized cases. Linear arrays of papules (Koebner's phenomenon) are common, especially on the forearms and dorsal hands. Initially, lesions are localized and often remain limited to a few areas, chiefly the penis and lower abdomen, the inner surfaces of the thighs, and the flexor aspects of the wrists and forearms (Figs 12-7 to 12-9).

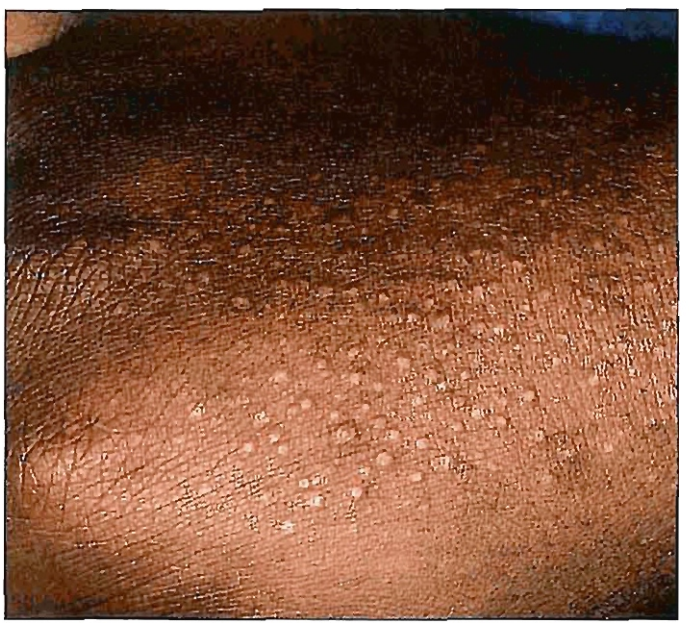

Fig. 12-7 Lichen nitidus, small, pinhead-sized hypopigmented papules.

In other cases the disease assumes a more widespread distribution, and the papules fuse into erythematous, finely scaly plaques. The reddish color varies with tints of yellow, brown, or violet.

Palm and sole involvement by lichen nitidus may occur, and the disease may be restricted to these areas. It presents with multiple, tiny, hyperkeratotic papules. The papules may coalesce to form diffuse hyperkeratotic plaques that fissure. The differentiation of lichen nititdus from hyperkeratotic hand eczema and lichen planus of the palms is aided by the presence of a keratotic plug in the center of lesions of palmoplantar lichen nitidus. Nail involvement with pitting; beaded, longitudinal ridging; and nailfold inflammation has been reported. Oral involvement with gray–yellow papules or petechiae of the hard palate is rare.

A variant of lichen nitidus, termed *actinic lichen nitidus*, has been reported in black patients from the Middle East and Indian subcontinent. These patients are identical to some patients reported as having summer actinic lichenoid eruption. They have lesions clinically and histologically

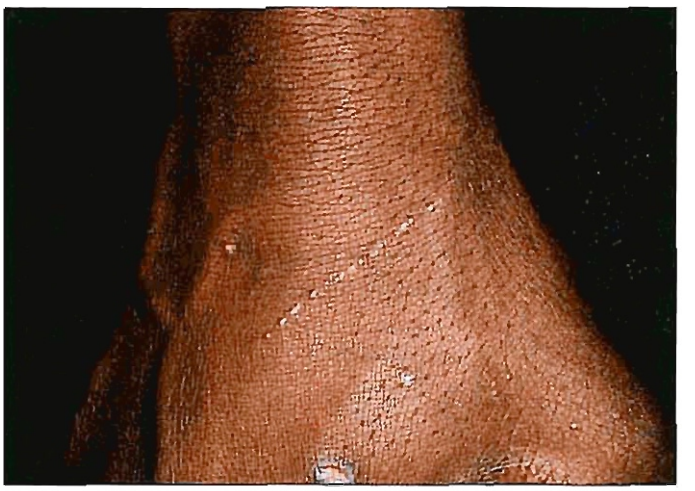

Fig. 12-8 Lichen nitidus, linear lesion from trauma.

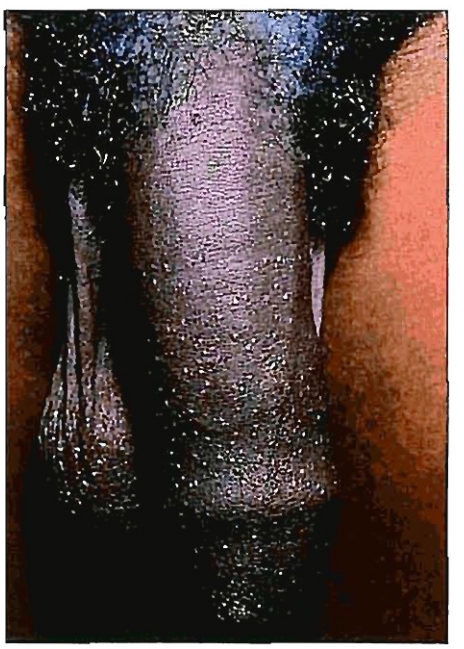

Fig. 12-9 Lichen nitidus, characteristic lesions of the penile shaft.

identical to lichen nitidus that are limited to the sun-exposed areas of the dorsal hands, brachioradial area, and posterior neck. They usually respond to sun protection with or without topical steroids.

The course of lichen nitidus is slowly progressive, with a tendency for remission. The lesions may remain stationary for years but sometimes disappear spontaneously and entirely. The cause of lichen nitidus is unknown. Rare familial cases do occur. It is clinically and histologically distinct from lichen planus. Immunohistochemical studies also suggest they are distinct disorders. However, patients have been reported who have had both disorders, suggesting some pathogenic relationship. Lichen nitidus has a characteristic histologic appearance. Dermal papillae are widened and contain a dense infiltrate composed of lymphocytes, histiocytes, and melanophages. Multinucleate giant cells are often present, imparting a granulomatous appearance to the infiltrate. The epidermal rete ridges on either side of the papilla form a clawlike collarette. The overlying epidermis is attenuated, and there is usually vacuolar alteration of its basal layer.

Because lichen nitidus is usually asymptomatic, treatment is often not necessary. Topical application of high or superpotent topical corticosteroids is helpful to suppress pruritus and may lead to resolution of skin lesions. PUVA, systemic steroids with UVA/UVB phototherapy, and retinoids (etretinate and acitretin) have been effective. Second-generation antihistamines (astemizole and cetirizine) have led to rapid resolution in a few cases.

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LICHEN STRIATUS

Lichen striatus is a fairly common self-limited eruption that is seen primarily in children. Most frequently it appears before age 6, but young adults, and more uncommonly, older adults may also be affected. Lesions begin as small papules that are erythematous and slightly scaly. In more darkly pigmented persons, hypopigmentation is prominent. The 1- to 3-mm papules coalesce to form a band 1- to 3-cm wide, either continuous or interrupted, that over a few weeks progresses down the extremity or around the trunk, following lines of Blaschko (Fig. 12-10). An extremity is more commonly involved, but trunk lesions, or lesions extending from the trunk onto an extremity, can also occur. Ten percent or fewer of cases occur on the face. Multiple bands can rarely occur. Lesions are usually asymptomatic.

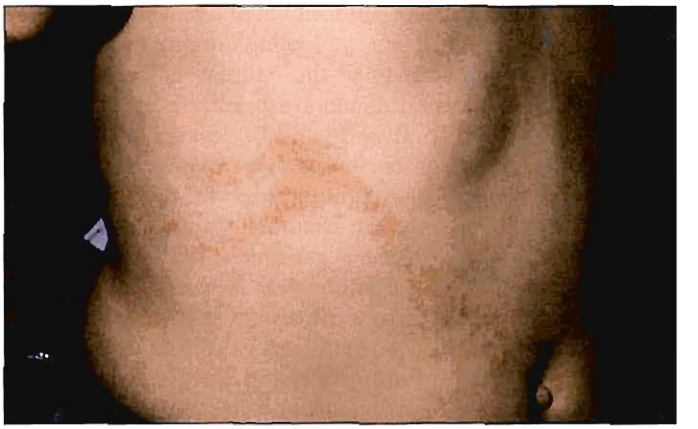

Fig. 12-10 Lichen striatus, lesion following lines of Blaschko.

Nail involvement can occur if the process extends down the digit to the nail. Most commonly the lichen striatus appears first on the skin, or the skin and nail abnormality appear simultaneously. Uncommonly, only the nail may be involved for months, with later appearance of the band on the skin, or the nail may remain the sole area of involvement throughout the course of the disease. Nail-plate thinning, longitudinal ridging, splitting, and nailbed hyperkeratosis may be seen. Often only a part of the nail is involved. The histology of involved nails is identical to the skin lesions.

The active lesions of lichen striatus last for an average of 1 year, but may persist for up to 4 years. Eventually all the lesions, including dystrophic nails, spontaneously resolve without scarring. Hypopigmentation may persist for several years.

The histologic features of lichen striatus vary, partly reflecting the stage of evolution of the lesion. There may be a spongiotic dermatitis, but most frequently a lichenoid component is present. There is a bandlike infiltrate with necrotic keratinocytes at the dermoepidermal junction. Granulomatous inflammation may occasionally be present. Typically there is a dense lymphoid infiltrate around the eccrine sweat glands and ducts. This helps to distinguish lichen striatus from lichen planus.

Multiple reports exist of simultaneous cases in siblings. There is also a seasonal variation, with most cases occurring in the spring and summer. Epidemic outbreaks have been reported.

Usually the diagnosis is straightforward in the setting of a young child, with the sudden onset of an eruption following the lines of Blaschko. The differential diagnosis could include linear lichen planus, linear psoriasis, inflammatory linear verrucous epidermal nevus, epidermal nevus, linear cutaneous lupus erythematosus, and verruca plana. Histologic evaluation will usually distinguish these entities, but is rarely required.

Treatment is usually not necessary. Parents may be reassured of the uniformly excellent prognosis. Topical steroids and topical tacrolimus ointment 0.1% may accelerate the resolution of lesions. In children with an acquired nail dystrophy of one or two digits, this diagnosis must be considered, and watchful waiting might be considered before

biopsying the nail. In one series, hydroxychloroquine led to rapid resolution of fixed nasal lesions of many years duration.

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LICHEN SCLEROSUS (LICHEN SCLEROSUS ET ATROPHICUS)

Lichen sclerosus is a chronic disease of the skin and mucosa. The terms lichen sclerosus et atrophicus, kraurosis vulvae, and balanitis xerotica obliterans are synonymous and replaced by the single term lichen sclerosus. It can present from childhood to old age. Although lichen sclerosus occurs in all races, whites appear to be preferentially affected. Both sexes are affected both before and after puberty, with females predominating at all ages. Autoimmune diseases (thyroid disease, vitiligo, alopecia areata, and pernicious anemia) occur in between one-fifth and one-third of women with lichen sclerosus, but are much less common in men.

In females, there is a bimodal age distribution—prepubertal and postmenopausal. The initial lesions of lichen sclerosus are white, polygonal, and flat-topped papules, plaques, or atrophic patches (Fig. 12-11). Follicular, black, horny plugs resembling comedos are often evenly spaced within the lesions. Lesions may be surrounded by an erythematous to violaceous halo. In atrophic lesions, the skin is smooth, slightly wrinkled, soft, and white (Fig. 12-12). Bullae, often hemorrhagic, may occur on the patches. Itching is frequently severe, especially in the anogenital area. In the genital area, fissuring and erosion may occur. This may result

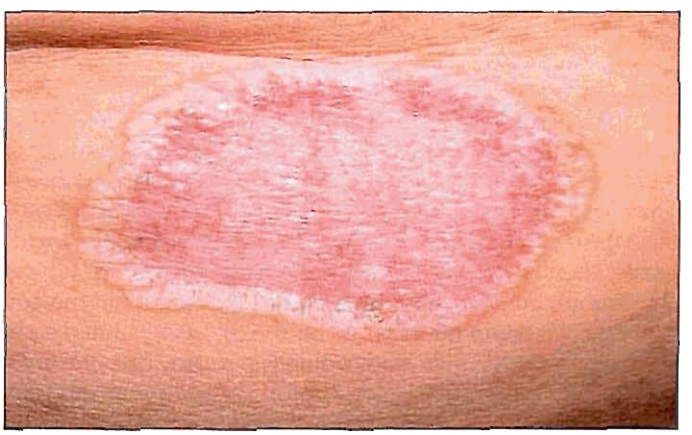

Fig. 12-11 Lichen sclerosus of the glabrous skin.

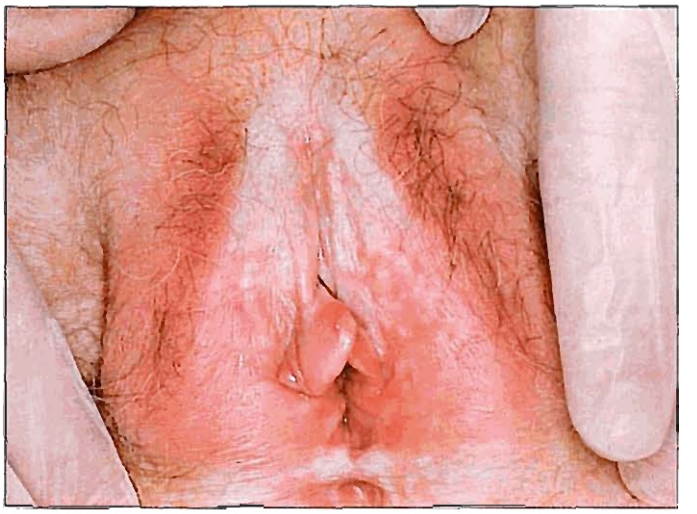

Fig. 12-12 Lichen sclerosus, white atrophic lesions with loss of normal tissue markings.

in dysuria, urethral and vaginal discharge, dyspareunia, and burning pain. Normal anatomic structures may be obliterated with loss of the labia minora, clitoral hood, and urethral meatus. In women, this perineal involvement typically involves the vulvar and perianal areas, giving a "figure-eight" or "hourglass" appearance. Introital stenosis or fusion may occur. The vaginal and cervical mucosa are not involved by lichen sclerosus (in contrast to lichen planus). Prepubertal girls may also be affected and usually have vulvar and perianal lesions. Vulvar disease is associated with similar skin changes as in adult women, and pruritus may be a prominent symptom. Perianal involvement may produce significant symptomatology of constipation, stool holding, and rectorrhagia due to rectal fissures. Infantile perineal protusion refers to a pyramidal soft tissue swelling covered by red or rose colored skin along the median perineal raphe (the skin between the posterior forchette and the anus). This occurs only in girls and appears to be a manifestation of lichen sclerosus in prepubertal girls. Two-thirds of girls with lichen sclerosus have been evaluated for sexual abuse, largely due to the ecchymoses that accompany the lesions. If risk of sexual abuse is suspected, appropriate investigations must be performed. About 9% of women with lichen sclerosus are asymptomatic and the changes are identified on routine gynecologic examination.

In males, lesions are atrophic and may be markedly hypopigmented or depigmented, resembling vitiligo (Figs 12-13 and 12.14). Lesions usually involve only the glans penis, but may extend onto the penile shaft and scrotum. If the glans is involved, hemorrhage is common, and shallow erosions may occur. Lichen sclerosus of the glans does not usually lead to nonhealing erosions of the glans, but rather simply skin fragility. Phimosis and paraphimosis is a common complication of lichen sclerosus in men. Up to 60% of acquired phimosis in boys and at least 10% in adult men is associated with lichen sclerosus. Most men with lichen sclerosus are uncircumcised. However, circumcision does not universally "cure" lichen sclerosus in boys or men, with at least 50% of men so treated continuing to have lesions of lichen sclerosus. Urethral meatal stenosis may occur and requires surgical correction. Perianal involvement by lichen sclerosus is much less common in men and boys.

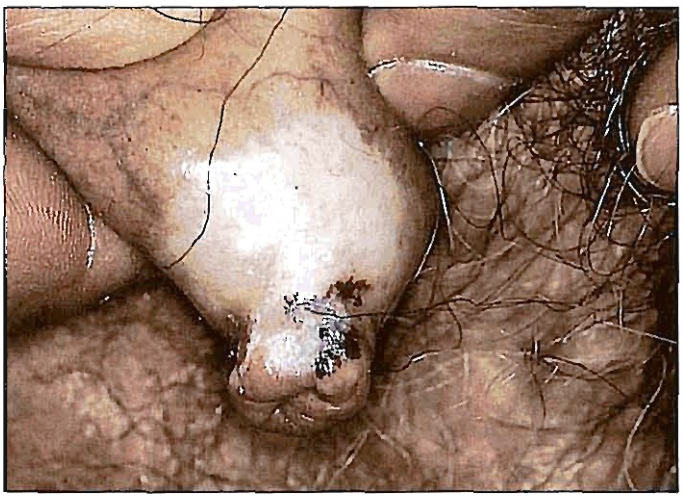

Fig. 12-13 Lichen sclerosus, paraphimosis due to lichen sclerosus; note the hemorrhagic macule.

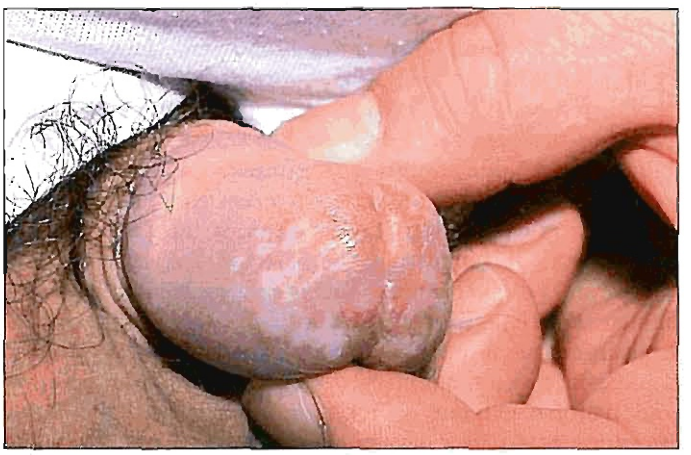

Fig. 12-14 Lichen sclerosus, early lesion of the glans penis.

Extragenital lesions are most frequent on the upper back, chest, and breasts, and are usually asymptomatic. The tongue and oral mucosa may also be involved, either alone or with lesions elsewhere. Peristomal involvement around colostomy sites may occur. Patients with only extragenital lesions with histologic features of both lichen sclerosus and morphea have been reported. They may simultaneously have other cutaneous lesions of morphea or atrophoderma of Pasini and Perini. These patients are best viewed as having morphea with overlying lichen sclerosus-like changes, rather than a form of lichen sclerosus. Rarely in Europe, *Borrelia afzelii* has been reported to cause extragenital lichen sclerosus, and treatment with antibiotics has arrested the progression of the lesions.

Lichen Sclerosus and Cancer

Although not as high as was proposed early in this century, lichen sclerosus of the genitalia is a condition with increased risk for genital squamous cell carcinoma (SCC) in both women and men. The lifetime risk for women who are carefully followed appears to be 5% or less, but is clearly higher than for the general population. In one study 14 of 23 anogential SCCs in women were associated with lichen sclerosus. Human papilloma virus (HPV) appears to be associated with only about 15% of SCCs arising in women with lichen sclerosus. In men with lichen sclerosus the risk for genital SCC is less than in women with lichen sclerosus. However, between 44% and 55% of cases of penile SCC are associated with lichen sclerosus. Oncogenic HPV types do not appear to be associated with lichen sclerosus-associated penile cancer. The use of potent topical steroids is associated with activation of latent HPV infection and is of theoretical concern.

Histopathology

Early lesions are characterized by an interface dermatitis with vacuolar alteration of keratinocytes. With evolution the epidermis is thinned and the rete ridges are effaced. Compact orthokeratosis and follicular and eccrine plugging are present. The upper dermis is edematous, with the upper dermal collagen homogenized. Immediately beneath the altered papillary dermis there is a sparse bandlike and perivascular lymphoid infiltrate. In pruritic lesions, coexistent changes of lichen simplex chronicus may be seen, with acanthosis rather than atrophy of the epidermis.

Differential Diagnosis

Extragenital lichen sclerosus must be differentiated from guttate morphea and lichen planus, especially of the atrophic type. Anogenital lichen sclerosus must be distinguished from genital lichen planus, lichen simplex chronicus, vulvar intraepithelial neoplasia (SCC in situ), and extramammary Paget's disease. The white color and atrophic surface are characteristic, and such areas are most fruitful for biopsy to confirm the diagnosis.

Treatment

The use of superpotent topical steroids has dramatically changed the management of anogenital lichen sclerosus. They are universally accepted as the treatment of choice for all forms of genital lichen sclerosus. Most patients will respond to application once a day of these agents and can subsequently be tapered to less frequent applications (once or twice a week) or to lower-strength steroids. In general, weekend application of an ultrapotent steroid is more effective than daily application of a mild steroid. Generally, the untreated lesions are atrophic, and pulsed weekend applications of a potent topical steroid treatment is associated with clinical and histologic reversal of the epidermal atrophy as the inflammatory process is controlled. Coexistent candidiasis may be present or appears with this treatment, and can be managed with topical or oral agents. Penile, vulvar, and prepubertal lichen sclerosus in girls have all been documented to respond to this form of treatment.

Topical tacrolimus 0.1% ointment has also been demonstrated to be effective in genital lichen sclerosus in women, girls, and men. It is an attractive alternative since it does not cause atrophy. However, since superpotent steroids have proven so effective in genital lichen sclerosus, tacrolimus should be reserved for patients in whom topical steroids are ineffective or not tolerated. Oral retinoid therapy and topical tretinoin may be useful in anogenital lichen sclerosus in both men and women in cases only partially responsive to topical steroids. Topical calcipotriene may also be of benefit. Topical testosterone is no more effective than emollient and in one trial was worse than emollients as

maintenance therapy after the clearing of lichen sclerosus with topical steroids. Its use is no longer recommended. Photodynamic therapy has led to significant improvement of vulvar lichen sclerosus in an open study. If superpotent topical steroids are ineffective, extragenital lichen sclerosus may be treated with potassium *p*-aminobenzoic acid, PUVA, UVA1, or antimalarials. Reports supporting their use are limited.

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CHAPTER

13 Acne

ACNE VULGARIS

Clinical Features

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous follicles, characterized by comedones, papules, pustules, nodules, and often scars. The comedo is the primary lesion of acne. It may be seen as a flat or slightly elevated papule with a dilated central opening filled with blackened keratin (open comedo or blackhead) (Fig. 13-1). Closed comedones (whiteheads) are usually 1-mm yellowish papules that may require stretching of the skin to visualize. Macrocomedones, which are uncommon, may reach 3 to 4 mm in size. The papules and pustules are 1 to 5 mm in size, and are caused by inflammation, so there is erythema and edema (Fig. 13-2). They may enlarge, become more nodular, and coalesce into plaques of several centimeters that are indurated or fluctuant, contain sinus tracts, and discharge serosanguinous or yellowish pus (Fig. 13-3).

Patients will typically have a variety of lesions in various states of formation and resolution. In light-skinned patients, lesions often resolve with a reddish-purple macule that is short lived. In dark-skinned individuals, macular hyperpigmentation results and this may last several months (Fig. 13-4). Acne scars are heterogeneous in appearance. Morphologies include deep, narrow ice-pick scars seen most commonly on the temples and cheeks, canyon-type atrophic lesions on the face (Fig. 13-5), whitish-yellow papular scars on the trunk and chin, anetoderma-type scars on the trunk, and hypertrophic and keloidal elevated scars on the neck and trunk.

Acne affects primarily the face, neck, upper trunk (Fig. 13-6), and upper arms. On the face it occurs most frequently on the cheeks, and to a lesser degree on the nose, forehead, and chin. The ears may be involved, with large comedones in the concha, cysts in the lobes, and sometimes pre- and retro-auricular comedones and cysts. On the

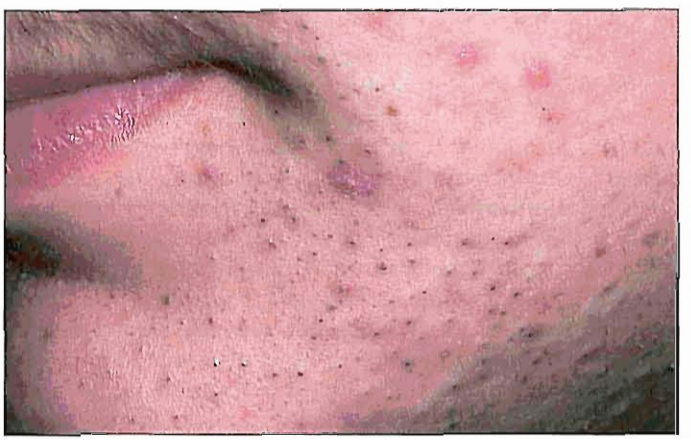

Fig. 13-1 Acne vulgaris, with comedones, on the chin.

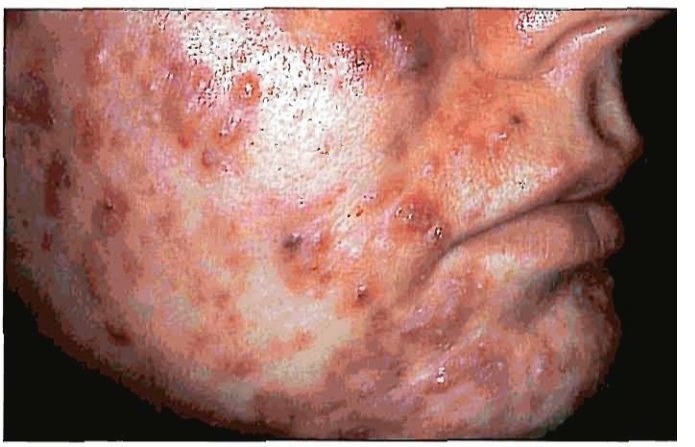

Fig. 13-3 Inflammatory acne with papules and nodules.

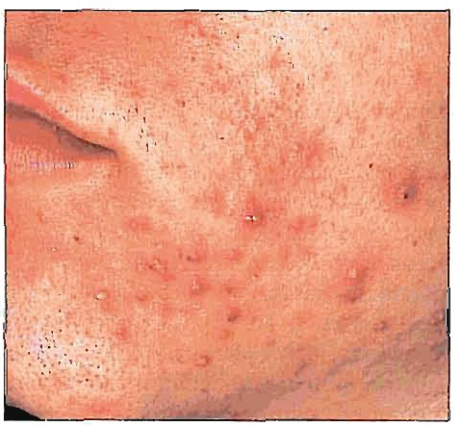

Fig. 13-2 Acne vulgaris, with papules and pustules, on the cheek.

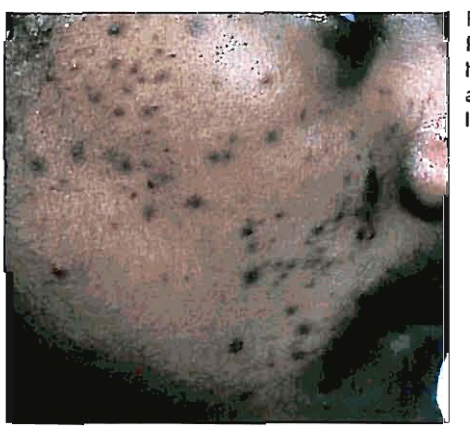

Fig. 13-4 Postinflammatory hyperpigmentation at sites of acne lesions.

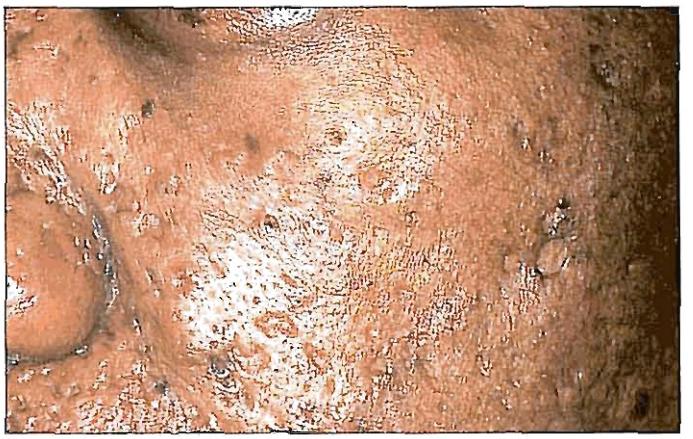

Fig. 13-5 Acne scarring on the cheek.

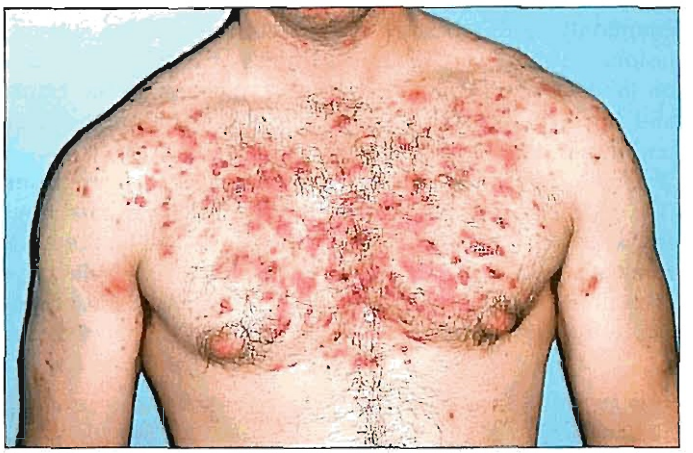

Fig. 13-6 Upper chest involvement with acne.

neck, especially in the nuchal area, large cystic lesions may predominate.

Acne typically begins at puberty and is often the first sign of increased sex hormone production. When acne begins at the age of 8 to 12 years, it is frequently comedonal in character, affecting primarily the forehead and cheeks. It may remain mild in its expression with only an occasional inflammatory papule. However, as hormone levels rise into the middle teenage years, more severe inflammatory pustules and nodules occur, with spread to other sites. Young men tend to have an oilier complexion and more severe widespread disease than young women. Women may experience a flare of their papulopustular lesions a week or so before menstruation. Acne may also begin in 20- to 35-year-old women who have not experienced teenage acne. This acne frequently manifests as papules, pustules, and deep painful persistent nodules on the jawline, chin, and upper neck.

Acne is primarily a disease of the adolescent, with 85% of all teenagers being affected to some degree. It occurs with greatest frequency between the ages of 15 and 18 in both sexes. Generally, involution of the disease occurs before age 25; however, great variability in age at onset and of resolution occurs. Twelve percent of women and 3% of men will continue to have clinical acne until 44 years of age. A few will have inflammatory papules and nodules into late adulthood.

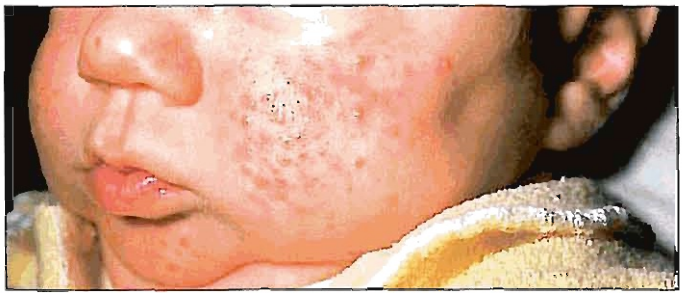

Fig. 13-7 Infantile acne.

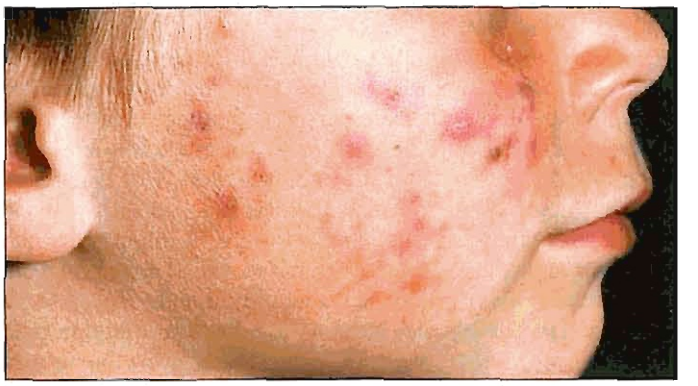

Fig. 13-8 Childhood acne.

Neonatal acne is a common condition that develops a few days after birth, has a male sex preponderance, and is characterized by transient facial papules or pustules which usually clear spontaneously in a few days or weeks (Fig. 13-7). Infantile acne includes those cases that persist beyond the neonatal period or have an onset after the first 4 weeks of life. The acne process can extend into childhood, puberty, or adult life. In prolonged cases, topical benzoyl peroxide, erythromycin or the retinoids may be effective. With more inflammatory disease, oral erythromycin 125 mg twice a day or trimethoprim 100 mg twice a day may be added to topical medications. Oral isotretinoin has been utilized in the infantile period and is effective. Childhood acne may evolve from persistent infantile acne or begin after age 2. It is uncommon and has a male predominance. Grouped comedones, papules, pustules, and nodules can occur alone or in any combination, usually limited to the face (Fig. 13-8). The duration is variable, from a few weeks to several years, and occasionally extends into more severe pubertal acne. Often there is a strong family history of moderately severe acne.

Pathogenesis

Acne vulgaris is exclusively a follicular disease, with the principle abnormality being comedo formation. It is produced by the impaction and distension of the follicles with a keratinous plug in the lower infundibulum. The keratinous plug is caused by hyperproliferation and abnormal differentiation of keratinocytes of unknown causes. Androgens, alterations in lipid composition, and an abnormal response to local cytokines are all hypothesized to be important. Androgen stimulation of the sebaceous glands is also critical. Acne begins after sebum secretion increases and women with hyperandrogenic states often manifest acne, along with

hirsutism and menstrual abnormalities. Treatment directed at reducing sebaceous secretion, such as isotretinoin, estrogens or antiandrogens, is effective in clearing acne.

As the retained cells block the follicular opening, the lower portion of the follicle is dilated by entrapped sebum. Disruption of the follicular epithelium permits discharge of the follicular contents into the dermis. The combination of keratin, sebum, and microorganisms, particularly *Propionibacterium acnes*, leads to the release of proinflammatory mediators and the accumulation of T-helper lymphocytes, neutrophils, and foreign body giant cells. This, in turn, causes the formation of inflammatory papules, pustules, and nodulocystic lesions.

Additional factors may exacerbate acne or, in a predisposed patient, cause the onset of acne. Comedogenic greasy or occlusive products may induce closed comedones and at times inflammatory lesions. Other types of cosmetics may initiate or worsen acne, but acne cosmetica is uncommon as most cosmetics are tested for comedogenicity.

Many types of mechanical or frictional forces can aggravate existing acne. A common problem is the overexuberant washing some patients feel may help rid them of their blackheads or oiliness. A key feature of mechanical or frictional acne is an unusual distribution of the acne lesions. Provocative factors include chin straps, violins, hats, collars, surgical tape, orthopedic casts, chairs, and seats. One acne patient who had laser hair removal repeatedly developed flares of inflammatory lesions localized to the acne-prone sites and not the legs or abdomen. All the above factors likely irritate the follicular epithelium and exacerbate the changes that lead to comedogenesis and follicular rupture. Prophylactic measures against various mechanical forces are beneficial.

In all women or children with acne the possibility of a hyperandrogenic state should be considered. In the former, the presence of irregular menses and hirsutism increases the likelihood of finding clinically significant hyperandrogenism. Additionally, gynecologic endocrine evaluation may be indicated in women who have acne resistant to conventional therapy, who relapse quickly after a course of isotretinoin, or in whom there is a sudden onset of severe acne. Screening tests to exclude a virilizing tumor include serum dehydroepiandrosterone sulfate (DHEAS) and testosterone, obtained 2 weeks before the onset of menses. DHEAS levels may be very high in adrenal tumors (>8000 ng/mL) or less dramatic in congenital adrenal hyperplasia (4000–8000 mg/mL). Ovarian tumor is suggested by testosterone levels above 200 ng/dL. Many patients with late-onset congenital adrenal hyperplasia will have normal levels of DHEAS. Although 17-hydroxyprogesterone and adrenocorticotropic hormone (ACTH) stimulation tests have been used in this setting, the baseline 17-hydroxyprogesterone may be normal in some women with adult 21-hydroxylase deficiency, and ACTH-stimulation may result in overdiagnosis of the syndrome. It is not clear that screening for adult-onset 21-hydroxylase deficiency improves patient outcome. Patients with polycystic ovarian syndrome (PCOS) may have a high serum testosterone level (150–200 ng/dL) or an increase in the luteinizing hormone (LH)/follicle stimulating hormone (FSH) ratio (>2–3), but recent American College of Obstetricians and Gynecologists (ACOG) guidelines suggest that laboratory and imaging studies are best used to exclude a virilizing tumor. The diagnosis of PCOS is made clinically by the presence of anovulation (fewer than nine periods per year or periods >40 days apart) and signs of hyperandrogenism.

Acne neonatorum is explained by circulating maternal hormones, whereas acne extending or developing after the neonatal period may be a form of acne cosmetica, acne venenata, drug-induced acne, or part of an endocrinologic disorder. In the absence of any of these etiologies, qualitative or quantitative alterations of cutaneous androgen, metabolism or increased end-organ sensitivity could be postulated as pathogenetic mechanisms for preadolescent acne.

Pathology

Comedones reveal a thinned epithelium and a dilated follicular canal filled with lamellar lipid-impregnated keratinous material. In pustular cases there are folliculocentric abscesses surrounded by a dense inflammatory exudate of lymphocytes and polymorphonuclear leukocytes. In addition to these findings, indolent nodular lesions frequently show plasma cells, foreign body giant cells, and proliferation of fibroblasts. Epithelial-lined sinus tracts may form.

Treatment

General Principles

It is important to take a complete historical record of prior therapies, including all over-the-counter products. The dose, timing, combinations, side effects, and response to interventions should be obtained. Corticosteroids, anabolic steroids, neuroleptics, lithium, and cyclosporin may worsen acne. A family history of acne and, if present, its tendency to scarring should be noted. Women should be queried regularly about menstrual irregularities, hair growth in a male pattern, as well as use of cosmetics.

Failure of treatment may be because of drug interactions, coexisting conditions, or antibiotic resistance; however, the most common and important cause is lack of compliance. Utilizing medications that are well tolerated, have convenient dosing regimens, and are cosmetically acceptable will help, but thorough patient education is essential for excellent compliance. Explaining how lesions form, and the expected response to, and duration and possible side effects of treatment, and giving clear unambiguous instructions is key. Patients should be aware of the difference between active inflammatory lesions and the purplish-red or hyperpigmented macules of inactive resolved lesions. Topical application to the entire affected area rather than to specific lesions should be emphasized and the fact discussed that oral and topical medications should be used daily as the treatment is preventative in nature.

Finally, some misconceptions should be addressed. Avoidance of specific foods is not necessary. Scrubbing of the face will not only increase irritation but may worsen acne due to friction. Utilization of only the prescribed medications and avoidance of potential drying over-the-counter products, such as astringent, harsh cleansers or antibacterial soaps, should be emphasized. Non-comedogenic cosmetics are recommended and pressed powders and oil-based products should be avoided.

Medical Therapy

Systemic and topical retinoids, systemic and topical antimicrobials, and systemic hormonal therapy are the main therapeutic classes of treatment available (Boxes 13-1 and

Box 13-1 Topical acne medications

1. Retinoids
   - Adapalene—cream, gel, solution and pledgets (0.1%)
   - Tretinoin—cream (0.025%, 0.05%, 0.1%); gel (0.01%, 0.025%); liquid (0.05%); microsphere (0.1% and 0.04% gel); polymerized (0.025% cream, 0.025% gel)
   - Tazarotene—cream or gel (0.05%, 0.1%)
2. Antimicrobials
   - Clindamycin gel, solution, lotion, pledget (1%)
   - Erythromycin solution, gel, ointment (1.5 to 2%)
   - Benzoyl peroxide gel, lotion, cream, wash, bar (2.5 to 10%)
   - Combination: benzoyl peroxide plus clindamycin; *benzoyl peroxide plus erythromycin*; benzoyl peroxide plus zinc
3. Azelaic acid 20% cream
4. Sodium sulfacetamide–sulfur combinations, gel, lotion, wash
5. Salacylic acid gel, cream, lotion, foam, solution (1–2%)

Box 13-2 Oral acne medications

1. *Antibiotics*
   - Tetracycline, 250–500 mg one to four times a day
   - Doxycycline, 50–100 mg once or twice a day
   - Minocycline, 50–100 mg once or twice a day
   - Trimethoprim–sulfamethoxizole, one double strength dose once or twice a day
   - Trimethoprim, 300 mg twice a day
   - Erythromycin, 250–500 mg two to four times a day
2. Isotretinoin, 0.5–1.0 mg/kg/day divided doses
3. Hormonal agents
   - Spironolactone, 50–200 mg in divided doses
   - Prednisone, 2.5–5 mg once at night
   - Birth control pills

Box 13-3 Surgical/physical agents

Comedo extraction Electrocautery Chemical peels	Treatment of comedones
Intralesional corticosteroids (2.5 mg/ml)	Treatment of inflammatory nodules
Photodynamic Blue light 1450-nm laser	Treatment of inflammatory lesions
Chemical peels Dermabrasion Excisions Laser resurfacing Filler substances	All treatment of scarring

Box 13-4 Acne treatment

Mild

1. Comedonal
   - Topical retinoid ± physical extraction (first line)
   - Alternate retinoid, salicylic acid, azelaic acid (second line)
2. Papular/pustular
   - Topical antimicrobial combination + topical retinoid, benzoyl peroxide wash if mild trunkal lesions (first line)
   - Alternate antimicrobials + alternate topical retinoids, azelaic acid, sodium sulfacetamide–sulfur, salacylic *acid (second line)*

Moderate

1. Papular/pustular
   - Oral antibiotic + topical retinoid + benzoyl peroxide *(first line)*
   - Alternate antibiotic, alternate topical retinoid, alternate benzoyl peroxide (second line)
   - In women, spironolactone + oral birth control pill + topical retinoids ± topical antibiotic and/or benzoyl peroxide
   - Isotretinoin if relapses quickly off oral antibiotics, does not clear or scars

Severe

1. Nodular/conglobate
   - Isotretinoin
   - Oral antibiotic + topical retinoid + benzoyl peroxide
   - In women, spironolactone + oral birth control pill + topical retinoid, ± topical or oral antibiotics and/or benzoyl peroxide

13-2). Procedural interventions, some of which are under active investigation or are used for the treatment of complications, are listed in Box 13-3. Treatment guidelines are outlined in Box 13-4.

Topical Treatment

As all topical treatments are preventative, use for 6 to 8 weeks is required to judge their efficacy. The entire acne-affected area is treated, not just the lesions, and long-term usage is the rule. In many patients, topical therapy may be effective as maintenance therapy after initial control is achieved with a combination of oral and topical treatment.

Topical Retinoids. It has long been appreciated that these agents are especially effective in promoting normal desquamation of the follicular epithelium; thus, they reduce comedones and inhibit the development of new lesions. Additionally, they have a marked anti-inflammatory effect, inhibiting the activity of leukocytes, the release of pro-inflammatory cytokines and other mediators, and the expression of transcription factors and toll-like receptors involved in immunomodulation. They also help penetration of other active agents. Thus, they should be utilized in nearly every patient with acne and are the preferred agents in maintenance therapy.

Tretinoin was the first of this group of agents to be used for acne. Popular forms of tretinoin are 0.025% and 0.05% in a cream base because these are less irritating than the gels and liquids. Its incorporation into microspheres and a polyoyl-prepolymer also help to limit irritation and make the product more stable in the presence of light and oxidizers. Tretinoin treatment may take 8 to 12 weeks before improvement occurs. When patients are tolerating the medication and are slow to respond, retinoic acid gel or solution may be utilized. Tretinoin should be applied at night and is in pregnancy category C.

Adapalene is a well-tolerated retinoid-like compound, which has efficacy equivalent to the lower concentrations of tretinoin. As it is light stable, it may be applied either in the morning or evening. It is in pregnancy category C.

Tazarotene is comparatively strong in its action, but also relatively irritating. It should be applied once at night or every other night, and as it is in pregnancy category X, contraceptive counseling should be provided.

Initially utilizing retinoids on an every-other-night basis, or using a moisturizer with them, may lessen their irritancy. They are also particularly useful in patients with skin of color as they may lighten postinflammatory hyperpigmentation.

Benzoyl Peroxide. Benzoyl peroxide has a potent antibacterial effect. *P. acnes* resistance does not develop during use. Its concomitant use during treatment with antibiotics will limit the development of resistance, even if only given for short 2- to 7-day pulses. While it is most effective in inflammatory acne, some studies have shown it to be comedolytic also. The wash formulations may be utilized for mild trunkal acne when systemic therapies are not required.

Treatment is usually once or twice a day. Benzoyl peroxide may irritate the skin and produce peeling. Water-based formulations of lowest strength are least irritating. Application lessened to once a day or every other day will also help limit this. Allergic contact dermatitis will rarely develop, suggested by the complaint of itch rather than stinging or burning. It is in pregnancy category C.

Topical Antibacterials. Topical clindamycin and erythromycin are available in a number of formulations. In general, they are well tolerated and are effective in mild-to-moderate inflammatory acne. These topical products are in pregnancy category B. Use of topical antibiotics alone, however, is not recommended because of increasing antibiotic resistance. As mentioned above, concurrent therapy with benzoyl peroxide, available as combination products, will limit this problem. Concomitant use with a topical retinoid will hasten the response and allow for more rapid discontinuance of the antibiotic.

Sulfur, Sodium Sulfacetamide, Resorcin, and Salicyclic Acid. Although benzoyl peroxide, retinoids, and topical antibiotics have largely supplanted these older medications, sulfur, resorcin, and salicylic acid preparations are still useful and moderately helpful if the newer medications are not tolerated. They are frequently found in over-the-counter preparations. Sulfacetamide–sulfur combination products are mildly effective in both acne and rosacea. The latter should be avoided in patients with known hypersensitivity to sulfonamides.

Azeleic Acid. This dicarboxylic acid is remarkably free from adverse actions and has mild efficacy in both inflammatory and comedonal acne. It may help to lighten postinflammatory hyperpigmentation and is in pregnancy category B.

Oral Antibiotics

These agents are indicated for moderate-to-severe acne, in patients with inflammatory disease in whom topical combinations have failed or are not tolerated, for the treatment of chest, back or shoulder acne, or in patients in whom absolute control is deemed essential, such as those who scar with each lesion or develop inflammatory hyperpigmentation. It generally takes 6 to 8 weeks to judge efficacy. Starting at a high dose and reducing it after control is preferred. Working to eventually maintain control with topical retinoids or retinoid–benzoyl peroxide combination therapy is ideal; however, keeping patients free of disease for 1 to 2 months before each decrease in dosage is best to prevent flaring. Most courses of oral therapy are of at least 3 to 6 months duration.

There is concern that tetracyclines may reduce the effectiveness of oral birth control pills. It is appropriate for this as yet unproved association to be discussed with patients and a second form of birth control offered. To reduce the incidence of esophagitis, tetracyclines should not be taken at bedtime.

Tetracycline. Tetracycline is the safest and cheapest choice, and will give a positive response in approximately 70% of patents. Tetracycline is given usually at an initial dose of 250 to 500 mg one to four times a day, with gradual reduction of the dose, depending on clinical response. It is best taken on an empty stomach, at least 30 min before meals and 2 h afterwards, which often limits dosage to twice a day. Calcium or iron in food supplements combine with tetracycline, reducing absorption by as much as half.

Vaginitis or perianal itching may result from tetracycline therapy in about 5% of patients, with *Candida albicans* usually present in the involved site. The only other common side effects are gastrointestinal symptoms such as nausea. Staining of growing teeth occurs, precluding its use in pregnant women and in children under the age of 9 or 10. Tetracycline should also be avoided when renal function is impaired.

Doxycycline. The usual dose is 50 to 100 mg once or twice a day depending on the disease severity. Photosensitivity reactions are common with this form of tetracycline and can be dramatic. Subantimicrobial dose doxycycline, doxycycline hyclate 20 mg, is being evaluated. The advantage of this is that the anti-inflammatory activity is being utilized but no antibiotic resistance results because of the low dose. It appears to be of low efficacy, however.

Minocycline. Minocycline is the most effective oral antibiotic in treating acne vulgaris. In patients whose *P. acnes* develops tetracycline resistance, minocycline is an alternative. The usual dose is 50 to 100 mg once or twice a day depending on the severity of disease. Its absorption is less affected by milk and food than is that of tetracycline. Vertigo may occur and beginning therapy with a single dose in the evening may be prudent. Pigmentation in areas of inflammation, of oral tissues, in postacne osteoma or scars, in a photodistributed pattern, on the shins, in the sclera, nailbed, ear cartilage, teeth, or in a generalized pattern may also be seen (Figs 13-9 and 13-10). Additionally, lupus-like syndromes, a hypersensitivity syndrome (consisting of fever, hepatitis, and eosinophilia), serum sickness, pneumonitis, and hepatitis are uncommon but potentially serious adverse effects of minocycline.

Erythromycin. For those who cannot take tetracyclines because of side effects or in pregnant women requiring oral antibiotic therapy, erythromycin may be considered. The efficacy is low. Side effects are mostly gastrointestinal upset; vaginal itching is a rare occurrence. The initial dose is 250 to 500 mg two to four times a day, reduced gradually after control is achieved. Erythromycin may increase blood levels of other drugs metabolized by the cytochrome P450 system.

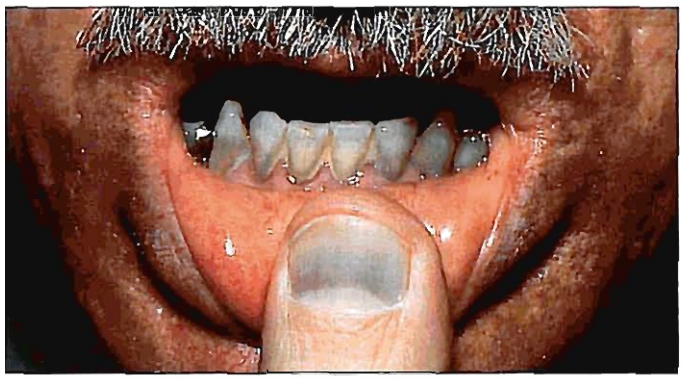

Fig. 13-9 Minocycline-induced blue pigmentation of the teeth and nails.

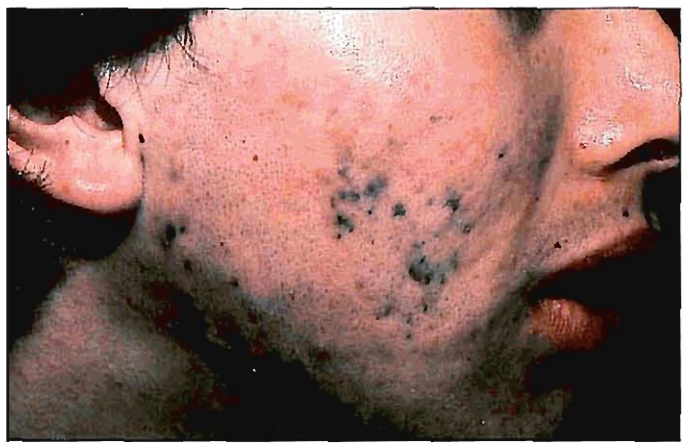

Fig. 13-10 Minocycline-induced pigmentation at sites of inflammation in a patient with acne.

Clindamycin. Past experience has shown clindamycin to give an excellent response in the treatment of acne; however, the potential for the development of pseudomembranous colitis and the availability of retinoids has limited its use. The initial dose is 150 mg three times a day, reduced gradually as control is achieved.

Other Antibiotics. Sulfonamides are occasionally prescribed; however, the potential for severe drug eruptions limits their use. Trimethoprim–sulfamethoxazole (Bactrim, Septra) in double-strength doses twice a day initially is effective in many cases unresponsive to other antibiotics. Trimethoprim alone, 300 mg twice a day, is also effective. Dapsone has been used in severe acne conglobata, but is rarely used today. Isotretinoin is favored.

Bacterial Resistance. *P. acnes* antimicrobial resistance has become a clinically relevant problem. Erythromycin and clindamycin resistance is widespread and usually present simultaneously. Once *P. acnes* becomes resistant to tetracycline it is also resistant to doxycycline, so if lack of efficacy due to prolonged oral therapy with one of them is suspected, a switch to minocycline is necessary. While concomitant use of benzoyl peroxide will help limit cutaneous drug resistance problem, it is now appreciated that *Staphylococcus aureus* in the nares, streptococci in the oral cavity, and enterobacteria in the gut may also become resistant, and close contacts, including treating dermatologists, may harbor such drug-resistant bacteria. Strategies to prevent antibiotic resistance include limiting the duration of treatment, stressing the importance of good compliance, restricting the use of antibiotics to inflammatory acne, encouraging retreatment with the same antibiotic unless it has lost its efficacy, avoiding the use of dissimilar oral and topical antibiotics at the same time, and using isotretinoin if unable to maintain clearance without oral antibacterial treatment.

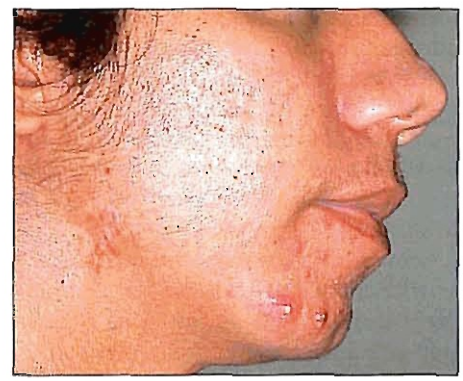

Fig. 13-11 Typical jawline lesions in an adult woman.

Hormonal Therapy

Hormonal interventions in women may be beneficial in the absence of abnormal laboratory tests. The work-up for the woman with signs of hyperandrogenism, such as menstrual irregularities, hirsutism, or androgenetic alopecia is presented above. Women with normal laboratory values often respond to hormonal therapy. Results take longer to be seen with these agents, with first evidence of improvement often not apparent for 3 months and continued improved response seen for at least 6 months. Particularly good candidates for hormonal treatment include women with PCOS, late-onset adrenal hyperplasia, or another identifiable endocrinologic condition; and women with late-onset acne, severe acne, acne that has not responded to other oral and topical therapies, or acne that has relapsed quickly after isotretinoin treatment. Women with acne primarily located on the lower face and neck, and deep-seated nodules that are painful and long lasting, are often most responsive to hormonal intervention (Fig. 13-11).

Oral Contraceptives. These agents block both adrenal and ovarian androgens. Ortho Tri-Cyclin, Estrostep, Alesse, and Yasmin are examples of birth control pills that have beneficial effects on acne. Both the physician and patient should be familiar with the adverse reactions associated with oral contraceptives, such as nausea, vomiting, abnormal menses, melasma, weight gain, breast tenderness, and rarely thrombophlebitis, pulmonary embolism, and hypertension.

Spironolactone. As pregnancy while on antiandrogen treatment will result in feminization of a male fetus, spironolactone is usually prescribed in combination with oral contraceptives. It may be effective in doses from 25 to 200 mg/day. Most women will tolerate a starting dose of 50 mg/day to 100 mg/day. Side effects are dose dependent and include breast tenderness, headache, dizziness, lightheadedness, fatigue, irregular menstrual periods, and diuresis. In a study by Shaw in patients treated with 50–100 mg/day, hyperkalemia was measurable, but in the absence of renal or cardiac disease was clinically insignificant. In his series, a third of patients cleared, a third had marked improvement, a quarter showed partial improvement, and 7% had no response. It is often used with other topical or oral acne

therapy. Several months of treatment are usually required to see benefit.

Dexamethasone. Marynick et al found dexamethasone in doses from 0.125 to 0.5 mg given once at night reduced androgen excess and alleviated cystic acne. Corticosteroids are effective in the treatment of adult-onset adrenal hyperplasia, but antiandrogens are also used increasingly in this setting.

Prednisone. Although steroids may produce steroid acne, they are also effective anti-inflammatory agents in severe and intractable acne vulgaris. In severe acne cystica and acne conglobata, corticosteroid treatment is effective; however, side effects restrict its use. It is generally only given to patients with severe inflammatory acne during the first few weeks of treatment with isotretinoin, for initial reduction of inflammation, and to reduce isotretinoin-induced flares.

Other Hormonal Agents. Finasteride, flutamide, gonadotropin-releasing agonists, estrogen, and metformin (by decreasing testosterone levels) have all been shown to have a beneficial effect on acne but due to side effects, expense or other considerations are not commonly used.

Oral Retinoid Therapy

Isotretinoin. This drug is approved only for severe cystic acne: however, it is useful in less severe forms of acne so as to prevent the need for continuous treatment and the repeated office visits that many patients require. It was a consensus of experts that oral isotretinoin treatment is warranted for severe acne, poorly responsive acne that improves by less than 50% after 6 months of therapy with combined oral and topical antibiotics, acne that relapses off oral treatment, scars, or acne that induces psychological distress. Additionally, other agreed indications were gram-negative folliculitis, inflammatory rosacea, pyoderma faciale, acne fulminans, and hidradenitis suppurativa.

This retinoid is a reliable remedy in nearly all acne patients (Fig. 13-12). The dose is 0.5 to 1 mg/kg/day in one or two doses. For severe truncal acne in patients who tolerate higher doses treatment may be given in doses up to 2 mg/kg/day. In practice, most patients are started at a 20- to 40-mg dose so as to avoid an early flare, and then increased to 40 to 80 mg/day so as to limit side effects, which generally are dose related. Doses as low as 0.1 mg/kg/day are very nearly as effective as the higher doses in clearing acne; the disadvantage is that they are less likely to produce a prolonged remission even after 20 weeks of treatment. To obtain the greatest chance of a prolonged remission, patients should receive 120 to 150 mg/kg over the treatment course. An easy way to calculate the total dose needed is to multiply the weight in kilograms by 3. The product is the total number of 40-mg capsules needed to reach the low end of the dosage spectrum.

The major advantage of isotretinoin is that it is the only acne therapy that is not open ended (i.e. that leads to a remission, which may last many months or years). Approximately 40% of patients remain acne free after a single course of isotretinoin. White et al's experience is that 39% remain clear without treatment 3 years after stopping isotretinoin, 17% will need additional topical medication, 25% will need additional oral antibiotics, and 19% will need additional isotretinoin.

Some subsets of patients tend to relapse more often. In patients under 16, 40% need a second course of isotretinoin within 1 year and 73% within 2 years. Adult women and patients with mild acne tend to relapse more often and more quickly than severely affected 17- to 22-year olds. While patients' tolerance and response to repeated courses is similar to their experience with the first course, adult women who relapse may be better managed with hormonal therapies, and mild acne treated with standard therapy.

In adult acne patients, who frequently tolerate the side effects of isotretinoin less well, lower doses and/or intermittent therapy is possible. Goulden et al studied 80 adult acne patients whom they treated with 0.5 mg/kg/day for 1 week in every 4 over a period of 6 months. Acne resolved in 88% and 39% relapsed after 1 year. Seukeran and Cunliffe treated nine patients aged 56 to 75 years with 0.25 mg/kg/day for 6 months. All patients cleared and all but one remained clear 36 months later.

Patient education is critical in isotretinoin therapy. Its most serious adverse effect is the risk of severe damage to the fetus if it is given during pregnancy. Retinoid embryopathy is a well-defined syndrome characterized by craniofacial, cardiovascular, central nervous system, and thymus

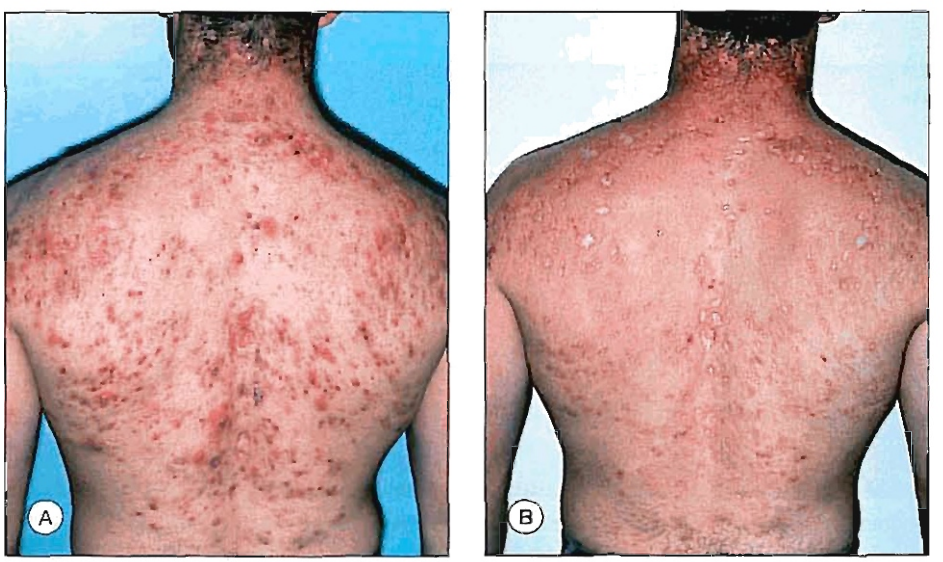

Fig. 13-12 *A*, Severe back acne before isotretinoin. *B*, Response to treatment.

abnormalities. It is of the utmost importance that a woman of child-bearing potential follows closely the recommendations clearly outlined in extensive material provided by the manufacturer. The use of consent forms, contraception education, and unequivocal documentation of the absence of pregnancy through monthly laboratory testing are important components of an FDA-mandated verification program designed to prevent pregnancy during treatment. Women should not become pregnant until off medication for at least 1 month. The drug is not mutagenic and there is no risk to a fetus conceived while the male partner is taking the drug.

Another major area of educational emphasis is the psychological effects of the medication. Reports of depression, psychosis, suicidal ideation, suicide and attempted suicide have prompted numerous studies of the mental health of patients taking isotretinoin. While the usual outcome is an improvement of mood because of the clearance of the disease, and no large-scale population-based data has found evidence of increased depression, risk for suicide or other psychological problems, there are a small number of patients who have developed depression and have positive dechallenge and rechallenge tests. Close monitoring for depression, fully educating the patient, and enlisting the help of a roommate or family member to look for changes in mood are all methods used to assess the psychological status of the patient on isotretinoin.

Other side effects of isotretinoin are dose dependent and generally not serious. Dry lips, skin, eyes, and oral and nasal mucosa occur in up to 90% of patients. These can be treated with moisturization. Dryness of the nasal mucosa leads to colonization by *S. aureus* in 80% to 90% of treated subjects. Skin abscesses, staphylococcal conjunctivitis, impetigo, facial cellulitis, and folliculitis may result (Fig. 13-13). Such colonization may be avoided by the use of bacitracin ointment applied to the anterior nares twice a day during isotretinoin therapy. Arthralgias may occur, but like other side effects, do not require interruption of therapy unless severe. Monitoring of serum lipids is done as some patients will develop hypertriglyceridemia. This may be controlled by avoidance of smoking and alcohol, and by following a diet that is low in fat. It should be realized that patients who develop this complication, and their families, are at risk for the development of the metabolic syndrome.

Liver function tests should be checked at regular intervals depending on patient risk factors and the dose utilized.

Intralesional Corticosteroids

Intralesional corticosteroids are especially effective in reducing inflammatory nodules. Kenalog-10 (triamcinolone acetonide 10 mg/mL) is best diluted with sterile normal saline solution to 2.5 mg/mL. Injecting less than 0.1 mL directly into the center of the nodule will help safeguard against atrophy and hypopigmentation.

Physical Modalities

Local surgical treatment is helpful in bringing about quick resolution of the comedones, although many clinicians wait until after 2 or more months of topical retinoids to extract those that remain. The edge of the follicle is nicked with a No 11 scalpel blade and the contents of the comedo are expressed with a comedo extractor. Scarring is not produced by this procedure. Light electrode desiccation is an alternative. In isotretinoin-treated patients, macrocomedones present at week 10 to 15 may be expressed, since they tend to persist throughout therapy.

The use of photodynamic therapy and various forms of light or laser energy are under investigation. It is clear that there is an ability to destroy sebaceous glands or kill *P. acnes* with such interventions; however, the methods to deliver such treatments in an efficient and practical manner are evolving.

Complications

Even with the excellent treatment options available, scarring may occur. This may be quite prominent and often results from the cystic type of acne, although smaller lesions may produce scarring in some individuals. Pitted scars, and wide-mouthed depressions and keloids, primarily seen along the jawline and chest, are common types of scarring (Fig. 13-14). These may improve spontaneously over the course of a year or more. Many treatment options are available. Chemical peeling, ultrapulsed laser resurfacing, dermabrasion, scar excision, punch grafts alone or followed by dermabrasion, imiquimod, and the use of filler substances are among the procedures effective in improving the appearance.

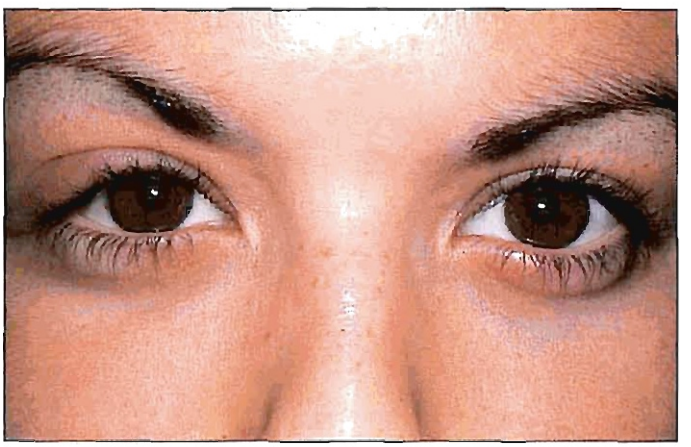

Fig. 13-13 Staphylococcal infection while on accutane. (Courtesy of Curt Samlaska, MD)

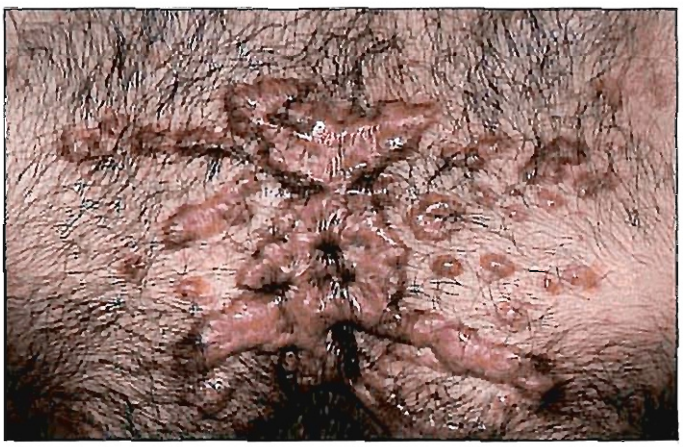

Fig. 13-14 Keloid of the chest secondary to acne.

Other complications from acne are prominent residual hyperpigmentation, especially in darker-skinned patients; pyogenic granuloma formation, which is more common in acne fulminans and in patients treated with high-dose isotretinoin; osteoma cutis, which are small, firm papules resulting from long-standing acne vulgaris; and solid facial edema. The latter is a persistent, firm facial swelling that is an uncommon, though distressing, result of acne vulgaris or acne rosacea. Both corticosteroids and isotretinoin have been reported to be effective treatments.

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ACNE CONGLOBATA

Cystic acne is the mildest form of acne conglobata (*conglobate* means shaped in a rounded mass or ball), an unusually severe form of acne. This form is characterized by numerous comedones (many of which are double or triple) and large abscesses with interconnecting sinuses, cysts, and

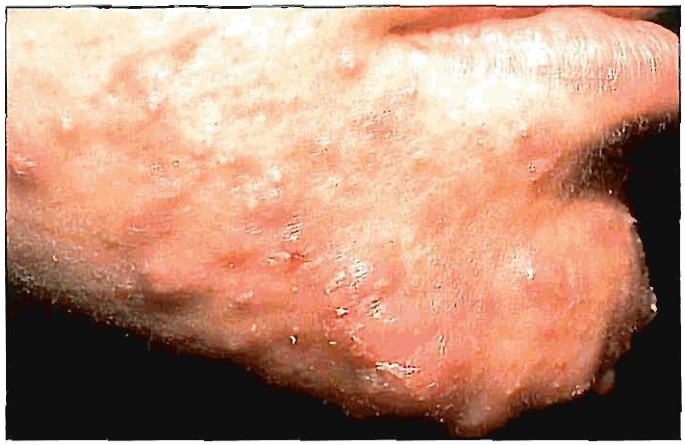

Fig. 13-15 Acne conglobata.

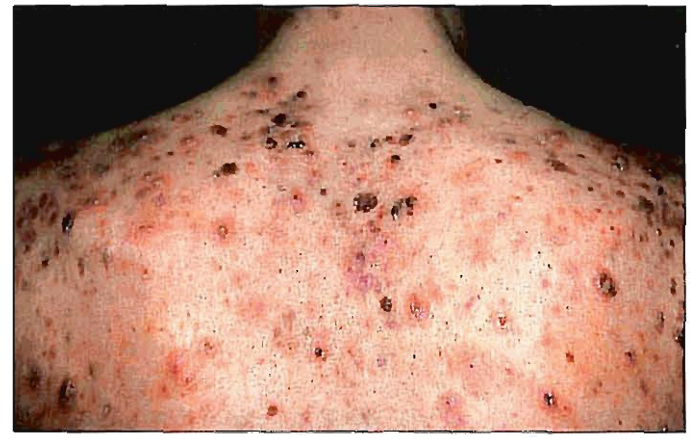

Fig. 13-17 Acne conglobata of the back.

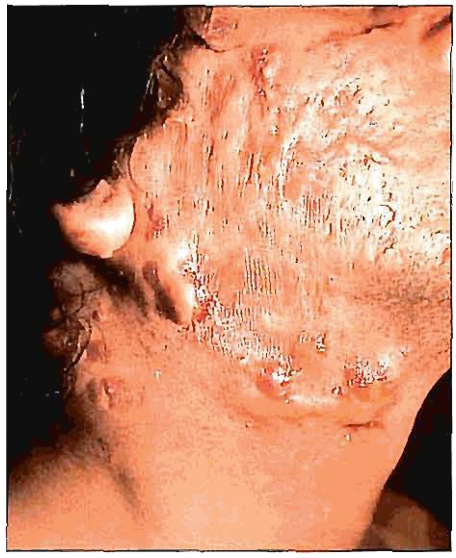

Fig. 13-16 Acne conglobata with fistula formation.

grouped inflammatory nodules (Figs 13-15 and 13-16). Suppuration is characteristic of acne conglobata. Pronounced scars remain after healing.

The cysts occur on the back, buttocks, chest, forehead, cheeks, anterior neck, and shoulders (Fig. 13-17). They contain a thick, yellowish, viscid, stringy, blood-tinged fluid. After incision and drainage of the cyst there is frequently a prompt refilling with the same type of material. These cysts are suggestive of the type found in hidradenitis suppurative. Hidradenitis suppurativa and dissecting cellulitis of the scalp may be seen with acne conglobata, an association known as the follicular occlusion triad.

This severe and painful disease occurs most frequently in young men aged around 16; it may extend and persist into adulthood and even into the fifth decade of life, especially on the posterior neck and back. Women are less frequently affected.

The therapy of choice in all but the earliest lesions is isotretinoin, 0.5–1 mg/kg/day for 5 months, with a second course if resolution does not occur after a rest period of 2 months. Pretreatment with prednisone and low initial doses of isotretinoin as described for acne fulminans are recommended to avoid flaring of disease.

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ACNE FULMINANS

This rare form of extremely severe cystic acne occurs primarily in teenage boys. It is characterized by highly inflammatory nodules and plaques that undergo swift suppurative degeneration, leaving ragged ulcerations, mostly on the chest and back. The face is usually less severely involved. Fever and leukocytosis are common. Polyarthralgia and polymyalgia, destructive arthritis, and myopathy have been reported in association with it. Focal lytic bone lesions may be seen.

Prednisone 40 to 60 mg is necessary during the initial 4 to 6 weeks to calm the dramatic inflammatory response. Ten to 20 mg of isotretinoin is added after 4 weeks. This should be slowly increased to standard doses and continued for a full 120 to 150 mg/kg cumulative course. Large cysts may be opened and the contents expressed. Intralesional corticosteroids will aid their resolution. Infliximab may also be useful.

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SAPHO SYNDROME

SAPHO syndrome is characterized by synovitis, acne, pustulosis, hyperostosis, and osteomyelitis. Skin findings include acne fulminans, acne conglobata, pustular psoriasis, and palmoplantar pustulosis. The chest wall and mandible are the most common sites for musculoskeletal complaints. Others report similar findings as the acquired hyperostosis syndrome (AHYS) and in a familial setting of a dominantly inherited disorder of pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA syndrome). The latter is due to mutations in the CD2-binding protein on chromosome

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OTHER ACNE VARIANTS

Tropical Acne

Tropical acne is unusually severe acne occurring in the tropics during the seasons when the weather is hot and humid. Nodular, cystic, and pustular lesions occur chiefly on the back, buttocks, and thighs (Fig. 13-18). Characteristically, the face is spared. Conglobate abscesses occur often, especially on the back. Comedones are sparse. Acne tropicalis usually occurs in young adults who may have had acne vulgaris at an earlier age. This is especially true of those in the armed forces stationed in the tropics and carrying backpacks. Treatment is that for cystic acne, but acne tropicalis may persist until the patient moves to a cooler and less humid climate.

Acne Aestivalis

Also known as *Mallorca acne*, this rare form of acne starts in the spring, progresses during the summer, and resolves completely in the fall. It affects almost exclusively women between the ages of 25 and 40. Dull red, dome-shaped, hard, small papules, usually not larger than 3 to 4 mm, develop on the cheeks and commonly extend onto the sides of the neck, chest, shoulders, and characteristically the upper arms. Comedones and pustules are notably absent or sparse. Acne aestivalis does not respond to antibiotics but benefits from application of retinoic acid.

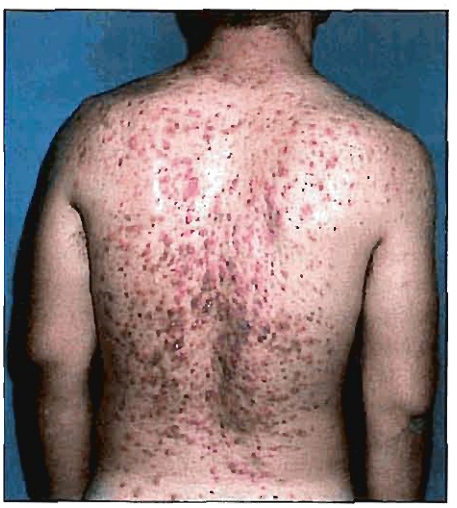

Fig. 13-18 Tropical acne.

Excoriated Acne

Also known as *picker's acne* and *acne excoriée des jeunes filles*, excoriated acne is seen primarily in young women with a superficial type of acne in which the primary lesions are trivial or even nonexistent, but in which the compulsive neurotic habit of picking the face and squeezing minute comedones produces secondary lesions that crust and may leave scars. Often the lesion that is excoriated is minute, seen only in a magnifying mirror.

This condition may be a sign of depression or anxiety. It is an obsessive-compulsive symptom. If the patient admits to picking but being unable to stop this habit, improvement may follow support and aggressive acne therapy. However, most patients will require interventions with selective serotonin reuptake inhibitors, such as fluoxetine, paroxetine, or sertraline, behavior modification or psychotherapy. Other pharmacologic treatments that have been successful in case reports include doxepin, clomipramine, naltrexone, pimozide, and olanzapine.

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ACNEIFORM ERUPTIONS

Acneiform eruptions are follicular eruptions characterized by papules and pustules resembling acne. Breaks in the epithelium and spillage of follicular contents into the dermis lead to the lesions. They are not necessarily confined to the usual sites of acne vulgaris, often have a sudden onset, are monomorphous, and usually appear in a patient well past adolescence. If secondary to a drug, it begins within days of initiation of the medication, may be accompanied by fever and malaise, and resolves when the drug is stopped.

Acneiform eruptions may originate from skin exposure to various industrial chemicals, such as fumes generated in the manufacture of chlorine and its byproducts. These chlorinated hydrocarbons may cause chloracne, consisting of cysts, pustules, folliculitis, and comedones. The most potent acneiform-inducing agents are the polyhalogenated hydrocarbons, notably dioxin (2,3,7,8-tetrachlorobenzodioxin). Cutting and lubricating oils, crude coal tar applied to the skin for medicinal purposes, heavy tar distillates, coal tar pitch, and asbestos are known to cause acneiform eruptions.

Acneiform eruptions are induced by medications such as iodides from radiopaque contrast media or potassium iodide, bromides in drugs such as propantheline bromide (Pro-Banthine), testosterone, cyclosporin, antiepileptic medications, lithium, epidermal growth factor inhibitors including monoclonal antibodies and tyrosine kinase inhibitors used in cancer therapy, and systemic corticosteroids. When

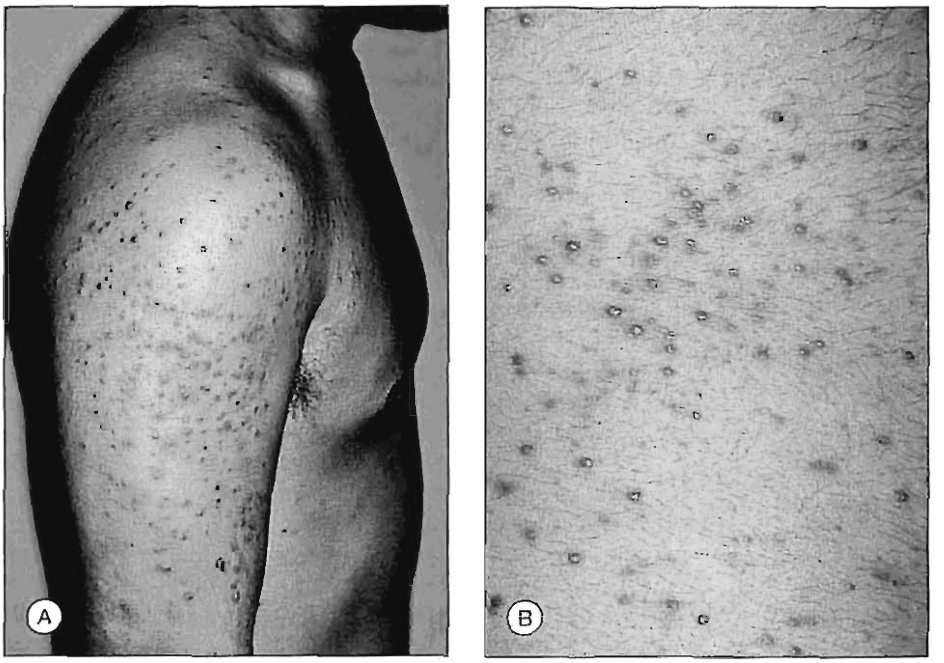

Fig. 13-19 *A* and *B*, Steroid acne. (Courtesy of Curt Samlaska, MD)

medium or high doses of corticosteroids are taken for as short a time as 3 to 5 days, a distinctive eruption may occur, known as *steroid acne*. It is a sudden outcropping of inflamed papules, most numerous on the upper trunk and arms (Fig. 13-19), but also seen on the face. The lesions typically present as papules rather than comedones; however, Hurwitz's histologic study clearly showed them to be follicular with microcomedone formation. Tretinoin (Retin-A), 0.05% cream applied once or twice a day, may clear the lesions within 1 to 3 months despite the continuation of high doses of corticosteroid. Oral antibiotics and other typical acne medications are also effective. Topical steroids, especially the fluorinated types, or when applied under occlusion, may also induce an acneiform eruption. Finally, radiation therapy for malignancy can induce acne in the radiation port.

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GRAM-NEGATIVE FOLLICULITIS

Gram-negative folliculitis occurs in patients who have had moderately inflammatory acne for long periods and have been treated with long-term antibiotics, mainly tetracyclines. While on antibiotic treatment, patients develop either superficial pustules 3 to 6 mm in diameter flaring out from the anterior nares, or fluctuant, deep-seated nodules (Fig. 13-20). Culture of these lesions usually reveals a species of *Klebsiella*, *Escherichia coli*, *Enterobacter*, or, from the deep cystic lesions, *Proteus*.

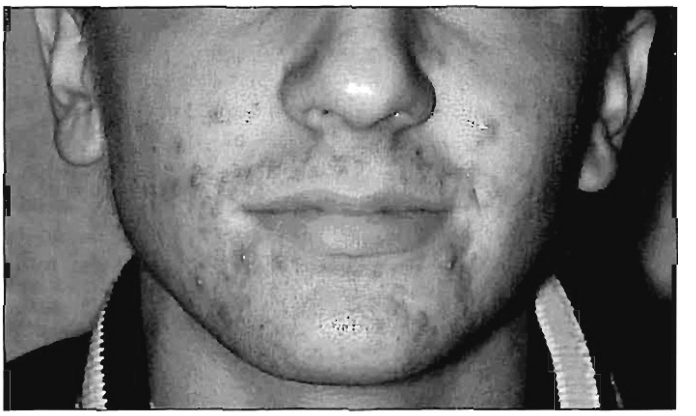

Fig. 13-20 Gram-negative folliculitis.

With long-term, broad-spectrum antibiotic therapy the anterior nares may become colonized with these Gram-negative organisms. As the use of long-term antibiotic therapy declines this disease has become less common.

Isotretinoin is very effective and is the treatment of choice in this disease. James and Leyden have shown that this treatment not only clears the acne component of the disease but also eliminates the colonization of the anterior nares with gram-negative organisms. If isotretinoin cannot be tolerated or is contraindicated, amoxicillin or trimethoprim–sulfamethoxazole may be effective in suppressing the disease.

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ACNE KELOIDALIS

Acne keloidalis is most frequently encountered in young adult black, Hispanic or Asian men who otherwise are in

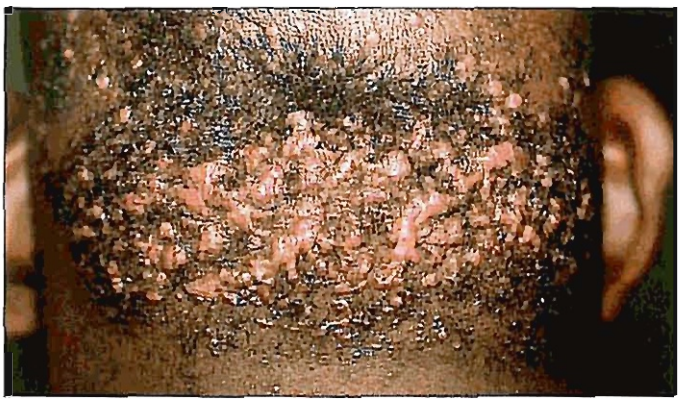

Fig. 13-21 Acne keloidalis nuchae.

excellent health. It is not associated with acne vulgaris and is a primary cicatricial alopecia variant. It is a persistent folliculitis and perifolliculitis of the back of the neck that presents as inflammatory papules and pustules. Over time fibrosis ensues with coalescence of firm papules into keloidal plaques (Fig. 13-21). At times sinus tract formation results.

Histologically, acne keloidalis is characterized by perifollicular, chronic (lymphocytic and plasmacytic) inflammation, most intense at the level of the isthmus and lower infundibulum. There is lamellar fibroplasia, most marked at the level of the isthmus and, eventually, in the keloidal masses, the connective tissue becomes sclerotic, forming hypertrophic scars or keloids. Persistent free hairs in the dermis may be responsible for the prolonged inflammation and eventual scarring.

Topical therapy with potent steroid ointments alone, or following tretinoin gel, twice a day is useful for the follicular papules. Oral antibiotics of the tetracycline group may be added and are helpful in suppressing the inflammatory response. Triamcinolone acetonide by intralesional injection, using Kenalog-10, into the inflammatory follicular lesions, and Kenalog-40 into the hypertrophic scars and keloids, is useful in reducing inflammation and fibrosis. Smaller lesions may be excised to a level below the hair follicle and closed. This is followed by either topical imiquimod daily or every other day as tolerated for 6 weeks or Kenalog-40 every 3 weeks. For larger lesions deep excision or CO_2 laser ablation left to heal by primary intention may be necessary.

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HIDRADENITIS SUPPURATIVA (ACNE INVERSA)

Clinical Features

Hidradenitis suppurativa is a chronic disease characterized by recurrent abscess formation, primarily within the folded areas of skin that contain both terminal hairs and apocrine glands. The axillae and inguinal and perineal areas are favored (Figs 13-22 and 13-23), but buttock and submammary involvement is not uncommon. It is a post-pubertal process that affects women approximately four times as often as men. Affected patients are often overweight.

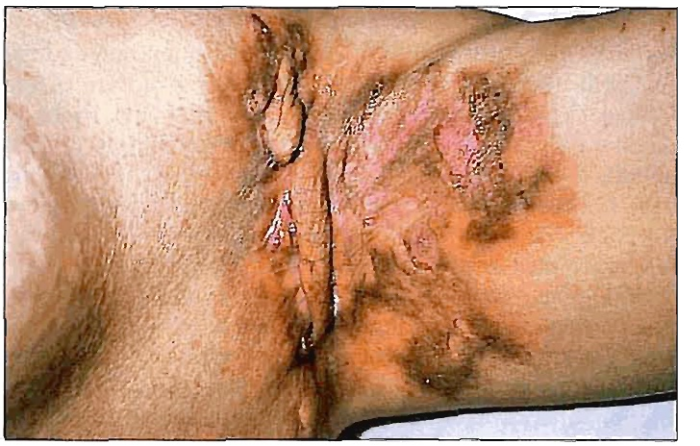

Fig. 13-22 Acne inverse of the axilla.

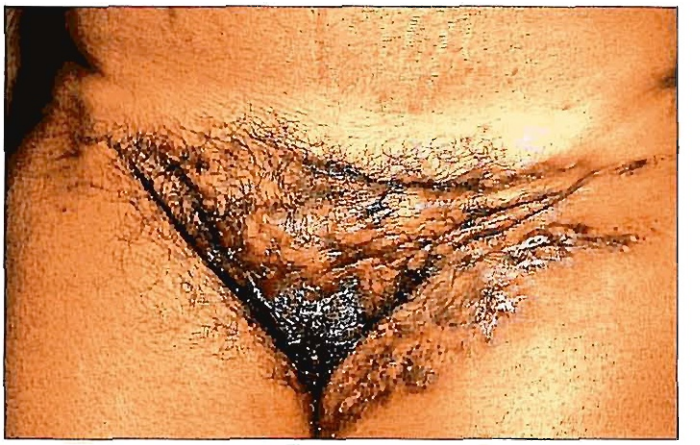

Fig. 13-23 Acne inverse of the groin. (Courtesy of James Fitzpatrick, MD)

The disease is characterized by the development of tender, red nodules, which at first are firm but soon become fluctuant and painful. Rupture of the lesion, suppuration, formation of sinus tracts, and extensive scarring are distinctive. As one area heals, recurrent lesions form, so that the course of the disease is protracted. An average of five painful abscesses appear per month. It may eventually lead to the formation of honeycombed, fistulous tracts with chronic infection. The individual lesions contain a thick, viscous, mucoid, suppurative material. When a probe is used to explore the suppurating nodule, a burrowing sinus tract is usually detected that may extend for many centimeters, running horizontally just underneath the skin surface.

Hidradenitis suppurativa occurs most frequently in the axillae of young women. Men also are affected, but more frequently the groin and perianal area are the sites of involvement. In its severest form, hidradenitis suppurativa is associated with acne conglobata, pilonidal sinus, and dissecting cellulitis of the scalp. Squamous cell carcinoma (after an average of 19 years of active disease), interstitial keratitis, spondyloarthropathy, urethral vesical and rectal fistulas, anemia, hypoproteinemia, and amyloidosis have been reported to complicate hidradenitis suppurativa, but are extremely rare.

Etiology

Detailed histologic studies of hidradenitis suppurative reveal that follicular hyperkeratosis is followed by rupture of the follicular epithelium, and release of keratin, sebum, bacteria, and hairs into the dermis. The resulting inflammatory process engulfs the apocrine gland, leads to rupture of the overlying skin, fibrosis, and sinus tract formation. Secondary bacterial infection with *S. aureus*, *Streptococcus pyogenes*, and various Gram-negative organisms may occur. The initiating event is unknown. Hyperandrogenism, other endocrinopathies, immunologic dysfunction, obesity, various irritants, and smoking have all be implicated in the past but have since been shown not to be primary pathogenic events. Mechanical friction, often worsened by obesity, is certainly an exacerbating factor, as is bacterial infection. There is an autosomal dominantly inherited form of this disease.

Differential Diagnosis

Hidradenitis is to be differentiated from common furuncles, which are typically unilateral and not associated with comedones as hidradenitis is. Hidradenitis must also be differentiated from Bartholin abscess, scrofuloderma, actinomycosis, granuloma inguinale, and lymphogranuloma venerum.

Treatment

Despite the numerous forms of treatment available, a permanent cure is uncommon. The earliest lesions often heal quickly with intralesional steroid therapy, and this should be tried initially in combination with topical cleocin or oral tetracycline or minocycline. Topical daily cleansing with an antibacterial soap and application of topical clindamycin is an important preventative measure. Reduction of friction by wearing loose-fitting clothing and weight loss if needed, and avoidance of excessive sweating through the use of topical aluminum chloride and heat avoidance may help. In cases with draining sinuses, culture of the pus may reveal *S. aureus* or Gram-negative organisms. The latter are usually cultured in chronic cases. Antibiotics should be selected based on sensitivities of the cultured organism. Incision and drainage is strongly discouraged.

Isotretinoin is effective in some cases, but a remission seldom follows its use. In the largest study to date, Boer et al treated 68 patients with a mean dose of 0.56 mg/kg of isotretinoin for 4 to 6 months. Clearing was obtained in 23.5% and long-term remission was seen in 16.2%. Secondary infection with *S. aureus* often occurs. Infliximab and finasteride have produced improvement.

Medical therapy has limitations and the chances for permanent cure are best when excision of the affected areas is done. Wide surgical excision, using intraoperative color-marking of sinus tracts, is most effective at limiting recurrence; however, it has moderate morbidity, especially in the groin and perianal areas. The recurrence rate is low in the axillary and perianal areas; however, the inguinal folds and especially the submammary sites more often recur so that excision of the latter site is uncommonly recommended. Because the effect on the quality of life with this chronic, painful, odiferious condition is tremendous, some recommend early excision. However, patients often need to live with the condition for years before making this dramatic decision.

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PERIFOLLICULITIS CAPITIS ABSCEDENS ET SUFFODIENS

Also known as *dissecting cellulitis of the scalp*, perifolliculitis capitis abscedens et suffodiens is an uncommon chronic suppurative disease of the scalp characterized by numerous follicular and perifollicular inflammatory nodules. These nodules suppurate and undermine to form intercommunicating sinuses as long as 5 cm (Fig. 13-24). Scarring and alopecia ensue, although seropurulent drainage may last indefinitely.

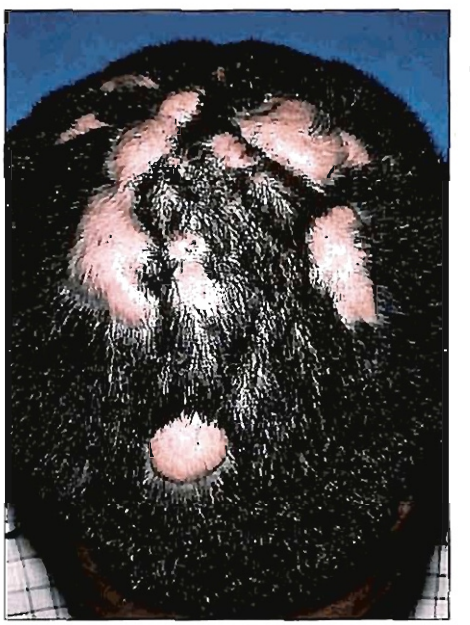

Fig. 13-24
Dissecting folliculitis. (Courtesy of Curt Samlaska, MD)

Adult black men are most commonly affected and the vertex and occiput of the scalp are the sites of predilection.

The primary lesions are follicular and perifollicular erythematous papules which progress to abscesses. This disease is likely a variant of acne vulgaris; it closely resembles acne conglobata and hidradenitis suppurativa. Coagulase-positive *S. aureus* may be found in the lesions.

Histologically, the disease is an occluded folliculitis with keratinous debris and a perifolliculitis. The inflammatory reaction is similar to that of acne keloidalis.

Treatment is generally unsuccessful unless the most vigorous procedures are followed. The combination of intralesional steroid injections and isotretinoin at a dose of 0.5 to 1.5 mg/kg/day for 6 to 12 months may be successful. The length of remission with isotretinoin is variable, but treatment may be repeated with similar results expected. Oral antibiotics as given in acne vulgaris and oral zinc have occasionally produced good results. If *S. aureus* is cultured, the combination of oral rifampin and clindamycin has produced excellent results.

A surgical approach is at times necessary. Marsupialization or excision of sinus tracks may help limit inflammation. Various lasers designed to remove hair have led to involution of the disease.

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ACNE MILIARIS NECROTICA (ACNE VARIOLIFORMIS)

Acne miliaris necrotica consists of follicular vesicopustules, sometimes occurring as solitary lesions that are usually very itchy. They appear anywhere in the scalp or adjacent areas, rupture early, and dry up after a few days. In some patients, especially those who manipulate the lesions, *S. aureus* may be cultured. If they leave large scars the term *acne varioliformis* is used; they are probably not separate diseases.

Treatment is with culture-directed antibiotics, or if the culture is negative, oral tetracycline or minocycline. Doxepin is helpful if patients manipulate their lesions.

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ROSACEA

Clinical Features

Rosacea is characterized by a persistent erythema of the convex surfaces of the face, with the cheeks and nose most frequently affected, followed by involvement of the brow and chin (Fig. 13-25). There is a tendency to spare the periocular skin. Rosacea occurs most often in light-skinned

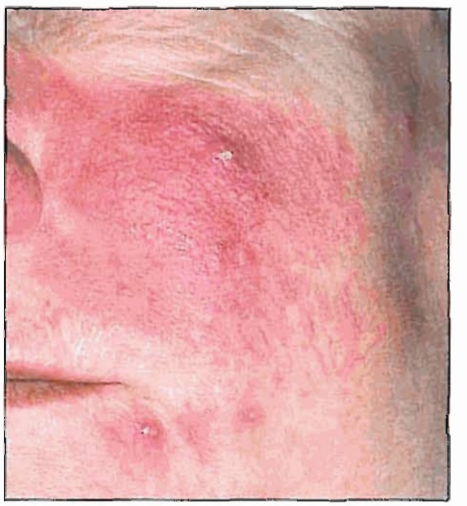

Fig 13-25 Rosacea.

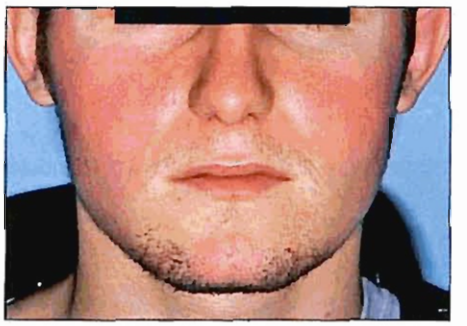

Fig 13-26 Erythrotelangiectatic rosacea.

women between the ages of 30 and 50; however, the severe phymatous changes occur in men. Additional features commonly manifested include telangiectasia, flushing, erythematous papules and pustules. These tend to cluster in patterns, allowing for the identification of several subsets of patients, the importance of their recognition being that the therapeutic implications differ.

The *erthemaotelangiectatic* type (Fig. 13-26) is characterized by a prominent history of a prolonged (over 10 min) flushing reaction to various stimuli, such as emotional stress, hot drinks, alcohol, spicy foods, exercise, cold or hot weather, or hot baths and showers. Often a burning or stinging sensation accompanies the flush, but sweating, light headedness, or palpitations do not. The skin is of fine texture, may have a roughness and scaling of the affected central facial sites, and is easily irritated. Over time a purplish suffusion and prominent telangiectasia may result.

The *papulopustular* subset of patients manifests a strikingly red central face accompanied by erythematous papules often surmounted by a pinpoint pustule (Fig. 13-27). The history of flushing is also present in most patients, but usually symptoms of irritancy are not prominent. The skin is of normal or at times slightly sebaceous quality and edema of the affected sites may be present.

In *glandular* rosacea, men with thick sebaceous skin predominate. The papules are edematous, the pustules are often 0.5 to 1.0 cm in size, and nodulocystic lesions may be present (Fig. 13-28). They tend to cluster in the central face, but in affected women the chin is favored. There is frequently a history of adolescent acne and typical scars may be seen.

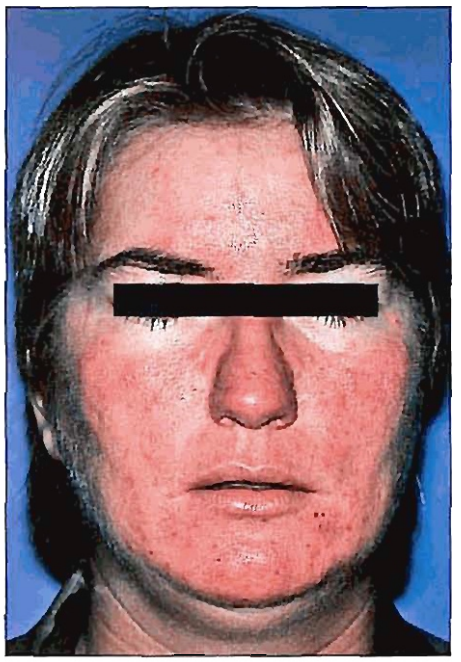

Fig. 13-27 Papulopustular rosacea. (Courtesy of Curt Samlaska, MD)

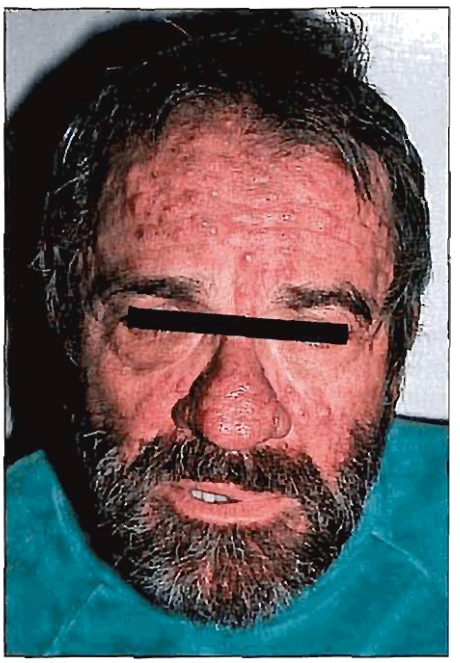

Fig. 13-28 Glandular rosacea.

Flushing is less common, as is telangiectasia but persistent edema may be problematic.

It is in this subtype that rhinophyma (Fig. 13-29) most commonly occurs. Hypertrophic, hyperemic, large nodular masses are centered over the distal half of the nose. Rarely, such soft tissue overgrowth can affect the chin, ears or forehead. Hugely dilated follicles contain long vermicular plugs of sebum and keratin. The histologic features are pilosebaceous gland hyperplasia with fibrosis, inflammation, and telangiectasia.

Etiology

The cause of rosacea remains unknown. Most patients have an abnormal vasomotor response to thermal and other stimuli as described above. Additionally, chronic solar damage is an important contributor in producing damage to the dermal matrix and ground substance. Chronic vasodilatation, edema, and compromise of lymphatic drainage occur and lead to telangiectasia and fibrosis. Pilosebaceous unit abnormalities are not commonly felt to be part of the pathogenesis of this condition; however, some evidence points to abnormalities being present, especially in the glandular type of patient. It is to be expected that the pathogenic factors will vary among the subsets of patients. *Demodex* and *Helicobacter pylori* have been extensively investigated and do not appear to be central to the etiology of rosacea.

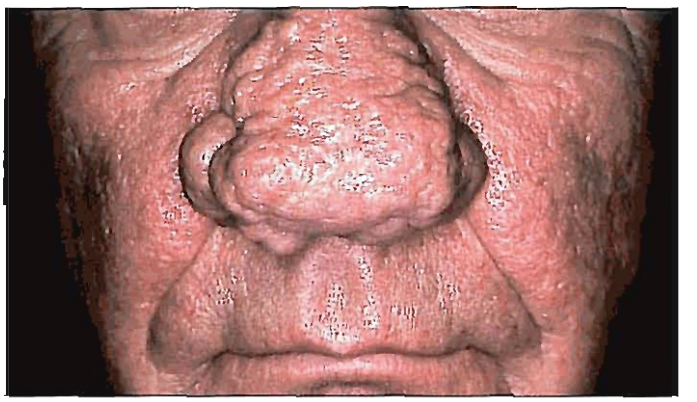

Fig. 13-29 Rhinophyma.

Other Clinical Considerations

Ocular Findings Blepharitis, recurrent chalazion, and conjunctivitis may be seen in all subsets of rosacea (Fig. 13-30). The eye itself may be affected, with keratitis, iritis, and episcleritis. An abnormal Schirmer test occurs in 40% of rosacea patients. Complaints are often of a gritty, stinging, itchy or burning sensation in the eye. Light sensitivity and a foreign body sensation are also present at times. Ocular rosacea occurs equally in men and women. Such eye findings may occur before the skin disease. Since these findings have therapeutic implications and patients will not always complain of them to their dermatologist, these signs and symptoms should be actively sought when evaluating rosacea patients.

Extrafacial Lesions Flushing may involve the ears, lateral facial contours, neck, upper chest, and scalp. Papules and pustules may be present in persistent erythema of the scalp or the earlobes.

Topical Steroid Use Long-term use of topical steroids on the face may result in persistent erythema, papules, and pustules. The sites involved correspond to the areas of application and are not necessarily limited to the central convexities (Fig. 13-31). Treatment is discontinuance of the offending drug and institution of topical tacrolimus in combination with short-term minocycline.

Perioral Dermatitis While this condition has been classified within the umbrella of rosacea variants, its distribution, signs, and symptoms vary such that it is included separately in this chapter.

Granulomatous Lesions Some patients with persistent facial erythema of the convexities will have on biopsy of

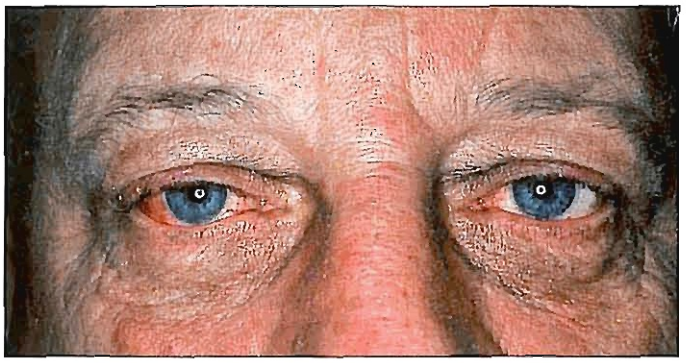

Fig. 13-30 Ocular rosacea.

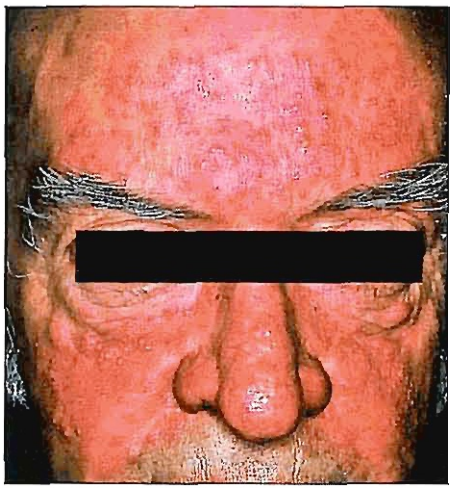

Fig. 13-31 Steroid rosacea.

an erythematous papule a granulomatous response closely resembling sarcoidosis or a necrotizing granuloma. Many experienced clinicians will accurately predict such findings from a clinical examination. Here the most important consideration is the response to treatment may be slower. When involvement of granulomatous facial papules includes the eyelids and upper lip, and is not associated with vascular manifestations, such as flushing, erythema or telangiectasia, the term *granulomatous facial dermatitis* is preferred. This condition is discussed separately.

Differential Diagnosis

The persistent erythema of the central face should be differentiated from that seen in polycythemia vera, carcinoid, mastocytosis, and connective tissue disease (lupus erythematosus, dermatomyositis, and mixed connective tissue disease). These conditions do not have associated papules and pustules, will manifest a variety of systemic symptoms and extrafacial signs, and specific laboratory markers are available to confirm clinical suspicions. Haber syndrome is a genodermatosis characterized by a rosacea-like facial dermatosis and multiple verrucous lesions on non-sun-exposed skin. Onset of the facial lesions is in the first two decades of life, in contrast to the later onset of rosacea. While rosacea may occur in human immunodeficiency virus (HIV) disease, a papulonodular eruption of the face that may simulate acne rosacea also occurs in patients with acquired immunodeficiency syndrome (AIDS). On expressing the contents of hair follicles with a comedo extractor, numerous *Demodex* mites are seen. In such cases success with permethrin cream and lindane have been reported and also lotions containing 5% benzoyl peroxide and 5% precipitated sulfur (Sulfoxyl) are helpful.

Box 13-5 Treatments for rosacea

1. Control of inflammation
   - Topical products
     1. Metronidazole
     2. Sodium sulfacetamide–sulfur
     3. Azelaic acid
     4. Benzoyl peroxide
     5. Erythromycin/clindamycin
     6. Tacrolimus
     7. Tretinoin
   - Oral medications
     1. Tetracyclines
     2. Macrolides
     3. Metronidazole
     4. Isotretinoin
2. Repair of structural damage
   - Laser
   - Intense pulsed light
   - Surgical techniques (rhinophyma)
   - Tretinoin
3. Prevention of further damage
   - Sunscreens
   - Cosmetics
   - Avoidance of trigger factors (flushing)
   - Massage (Soybe)

Treatment

Numerous therapeutic agents are available (Box 13-5). These treatments are directed at specific findings manifested by rosacea patients. Since telangiectasias, papules and pustules, and skin sensitivity are variably present in the three subsets of disease, the specific approach utilized will differ according to the factors present. Other treatments are useful in all patients. The general therapeutic recommendations are presented in Box 13-6.

Sunscreens are an important component of therapy for all patients. They should be applied each morning. Those containing physical blockers are in general better tolerated, especially by the erythrotelangiectatic patients, than those with chemical agents. Cosmetic coverage of the erythema and telangiectases is best with a light green-tinted foundation set with powder. If flushing is induced by specific trigger factors, their avoidance as far as possible is best. Lasers such as the standard pulsed dye laser, long-pulsed dye lasers, potassium-titanyl-phosphate (KTP) laser, and diode-pumped frequency-doubled laser are all useful for treating the erythema and telangiectases, but the cost is not covered by insurance and this limits their availability. Some vascular lasers may also help in dermal collagen remodeling and nonablative rejuvenation, such that the dermal matrix may be strengthened. Soybe hypothesized that the central face is predisposed to rosacea as the edema and lack of movement of tissues with muscular movement may lead to lymphedema and inflammation. Circular massage for several minutes a day led to impressive improvement. This benign intervention may be considered and ought to be studied.

Box 13-6 Treatment of rosacea by subset

1. All subsets
   - Daily sunscreen
   - Sun avoidance strategies
   - Cosmetic coverage
   - Avoidance of specific factors that trigger flushing
   - Laser and intense pulsed light
   - If ocular involvement, oral tetracyclines
2. Erythrotelangiectatic subset
   - Morning: sodium sulfacetamide–sulfur cleanser followed by a moisturizing sunscreen and/or camouflaging cosmetic with sunscreen
   - Night: leave on metronidazole, azelaic acid or sodium sulfacetamide–sulfur product
3. Papulopustular subset
   - Morning: Topical metronidazole, azelaic acid, sodium sulfacetamide–sulfur or benzoyl peroxide–antibiotic combination + suncreens
   - Nightly: sodium sulfacetamide–sulfur cleanser + different one of the above topical products for AM usage
   - Oral antibiotics or isotretinoin depending on severity
4. Glandular subset
   - Benzoyl peroxide–antibiotic combination most effective, other topicals less so
   - *Oral antibiotics or isotretinoin depending on severity*
   - Surgical intervention as needed for phymatous changes

Of the topical products, metronidazole, sodium sulfacetamide, sulfur cleansers and creams, and azelaic acid are approved for use in rosacea. They are the most commonly prescribed medications and are especially useful for the papulopustular patients and some patients with the erythrotelangiectatic type. Pimecrolimus may also improve such patients. Benzoyl peroxide and topical clindamycin, alone or in combination, are often quite beneficial and well tolerated by the glandular subset of patients. Topical tacrolimus helps the scaly, irritated erythrotelangictatic skin. It calms inflammation and abates symptoms in these patients, but requires brief (no longer than 1 week) pretreatment with a potent topical steroid to be tolerated initially. The role of topical retinoids requires study. Many rosacea patients may tolerate a night-time application of tretinoin if cetaphil lotion is placed on the skin immediately prior to use. Retinoids may help repair sun-damaged skin and normalize some of the abnormalities present.

Oral antibiotics, particularly tetracycline 250 to 500 mg each morning or minocycline 100 mg once or twice a day, control more aggressive papular and pustular lesion, and aid in the treatment of ocular lesions. Isotretinoin given in lower doses than in acne vulgaris, and at times as a long-term suppressant, may be necessary for management of more resistant disease. It produces dramatic improvement even in cases resistant to other forms of therapy, but relapse often occurs in a few weeks or months. The authors rarely use oral metronidazole (side effects) or the macrolides (lack of efficacy) despite their reported utility in this condition.

Surgical approaches to the reshaping of rhinophyma have included the use of a heated scalpel, electrocautery, dermabrasion, laser ablation, tangential excision combined with scissor sculpting, and radiofrequency electrosurgery. Often a combination of these approaches is used to obtain the best esthetic result.

An advocacy group that supports research and education in roseacea, the National Rosacea Society, is an excellent resource for patients.

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PYODERMA FACIALE

This uncommon eruptive facial disorder consists of an intense reddish or cyanotic erythema, combined with superficial and deep abscesses, cystic lesions (Fig. 13-32), and sometimes sinus tracts. The lesions often contain greenish or yellowish purulent material. Older cysts contain an oily substance. The condition occurs mostly in postadolescent women and is distinguished from acne by the absence of comedones, rapid onset, fulminating course, and absence of acne on the back and chest.

A Mayo Clinic series of 29 patients, all women, ranged in age from 19 to 59 years old; only 2 were older than 40. Late-onset acne preceded pyoderma faciale by 7–20 years. None had Gram-negative organisms; only two had *S. aureus*. Plewig et al reported 20 women with a mean age of 25. All were flushers and blushers. They consider it a variant of severe rosacea and suggest the name *rosacea fulminans*.

Treatment is similar to that of acne fulminans. Oral steroids are given for several weeks followed by the addition of isotretinoin, 10 or 20 mg, increasing to 0.5 to 1 mg/kg only after the acute inflammatory component is well under control. Steroids may usually be discontinued after 2 weeks of isotretinoin, but the latter should be given for a full

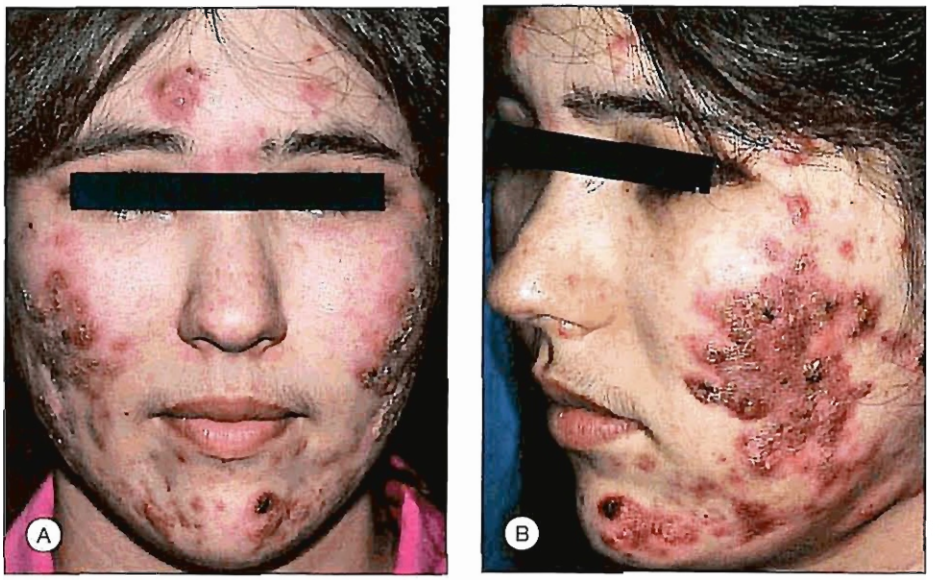

Fig 13-32 *A* and *B*, Pyoderma faciale. (Courtesy of Curt Samlaska, MD)

120 to 150 mg/kg total dose. As patients are predominately women of child-bearing age, pregnancy issues require full discussion. Indeed, four of Plewig et al's patients were pregnant and thus could only use erythromycin.

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PERIORAL DERMATITIS

This common perioral eruption consists of discrete papules and pustules on an erythematous and at times scaling base. It is a distinctive dermatitis confined symmetrically around the mouth, with a clear zone of some 5 mm between the vermilion border and the affected skin (Fig. 13-33). There is no itching; however, an uncomfortable burning sensation may be present. It occurs almost exclusively in women between the ages of 20 and 35.

The use of fluorinated topical steroids is the most frequently identified cause. Exposure may be in the form of creams, ointments, or inhalers.

Treatment includes discontinuing topical steroids or protecting the skin from the inhaled product. Additionally, tetracycline, 250 to 500 mg once a day or minocycline 100 mg once or twice a day will lead to control. Tacrolimus ointment 0.1% will prevent flaring after stopping steroid use. In those patients without steroid exposure, oral or topical antibiotics, and topical adapalene, azelaic acid, and metronidazole have been successful in clearing the eruption.

Periorbital Dermatitis

Periorbital (periocular) dermatitis is a variant of perioral dermatitis occurring on the lower eyelids and skin adjacent to the upper and lower eyelids. Fluorinated topical steroids have been implicated as the cause. If intranasal inhaled steroids are used, a perinasal distribution may be seen. Prompt response to the same treatment employed in the perioral site is expected.

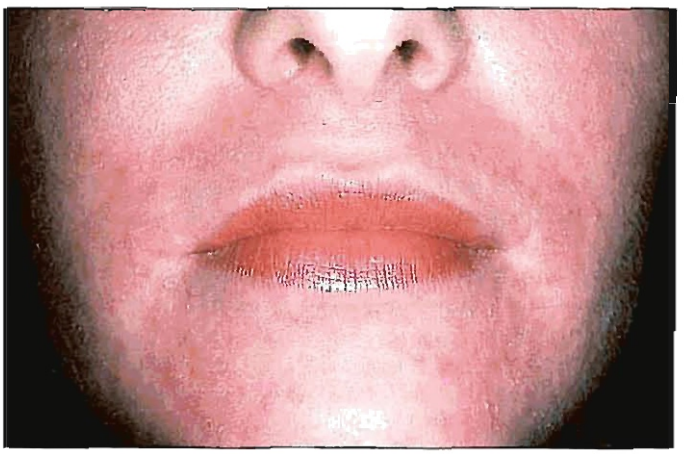

Fig. 13-33 Perioral dermatitis.

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GRANULOMATOUS FACIAL DERMATITIS

Several dermatoses of the face characterized by granulomas are included in this caterory. Patients with persistent facial erythema involving one or more convex surfaces of the face will have lesions that show a granulomatous reaction histologically, and are included within rosacea. Some patients have no other stigmata of rosacea and their nosology is unclear. These other entities which meet no other criteria for rosacea other than having pink papules on the face are included here. Skowron et al have proposed the term FIGURE (facial idiopathic granulomas with regressive evolution).

Lupus Miliaris Disseminatus Faciei

Firm yellowish-brown or red 1- to 3-mm monomorphous smooth-surfaced papules are present not only on the butterfly areas but also on the lateral areas, below the mandible,

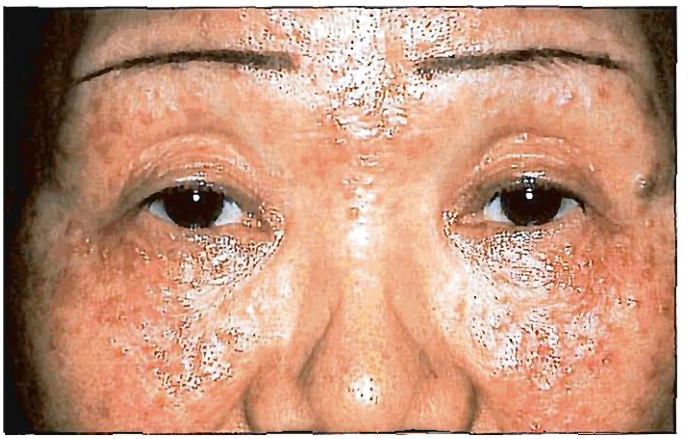

Fig. 13-34 Granulomatous facial dermatitis in an adult.

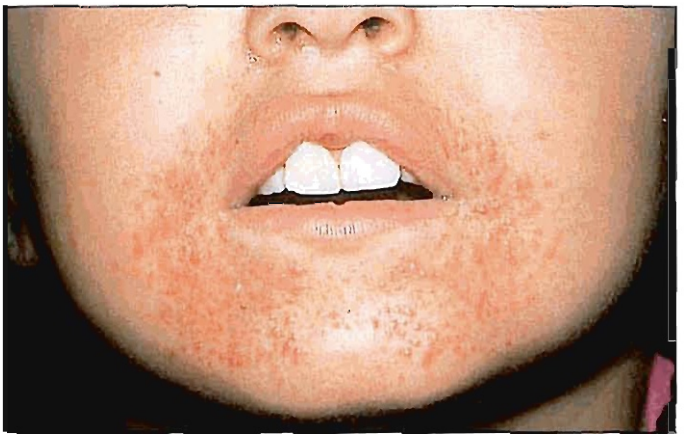

Fig. 13-35 Childhood granulomatous facial dermatitis.

and periorificially (Fig. 13-34). The eyelid skin is characteristically involved. The discrete papules appear as yellowish-brown lesions on diascopy and as caseating epithelioid cell granulomas histologically. Patients usually lack a history of flushing, do not have persistent erythema or telangiectasia, have involvement of the eyelids, and heal with scarring as opposed to rosacea patients. Long-term therapy with minocycline or clofazimine is necessary or isotretinoin may be used, often with gratifying results. Eventually self-involution is expected but may take several years to do so.

Granulomatous Perioral Dermatitis in Children

In otherwise healthy prepubertal children a profusion of grouped papules may develop on the perioral, periocular, and perinasal areas (Fig. 13-35). Eight of the initial 59 reported cases have also had generalized lesions. Besides extremity and trunkal lesions, several of the girls have had dramatic lesion of the labia majora. Both sexes are affected equally. Patients with skin of color (Afro-Caribbean, African American, and Asian) children dominate the reports but white patients are also susceptible. Because the histologic appearance is granulomatous, sarcoidosis is often considered. Topical steroids, however, may worsen the condition and systemic involvement is not present. Topical metronidazole, erythromycin, sulfacetamide–sulfur combinations, and oral macrolide and tetracycline are usually effective.

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CHAPTER

14 Bacterial Infections

Bacterial infections in the skin often have distinct morphologic characteristics that should alert the clinician that a potentially treatable and reversible condition exists. These cutaneous signs may be an indication of a generalized systemic process or simply an isolated superficial event.

Immunodeficiencies with low immunoglobulins, neutropenia, reduced neutrophil migration or killing, and disease caused by the human immunodeficiency virus (HIV) may be associated with severe or refractory pyogenic infections. Atopic dermatitis and syndromes with atopic-like dermatitis are also predisposed to bacterial infections.

The categorization of these infections will be first those diseases caused by Gram-positive bacteria, then those caused by Gram-negative bacteria, and finally several miscellaneous diseases caused by the rickettsiae, mycoplasmas, chlamydiae, and spirochetes.

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INFECTIONS CAUSED BY GRAM-POSITIVE ORGANISMS

STAPHYLOCOCCAL INFECTIONS

The skin lesions induced by this Gram-positive coccus appear usually as pustules, furuncles, or erosions with honey-colored crusts; however, bullae, widespread erythema and desquamation, or vegetating pyodermas may also be indicators of *Staphylococcus aureus* infection. Purulent purpura may indicate bacteremia or endocarditis caused by *S. aureus*, or, in immunocompromised patients, *Staphylococcus epidermidis*. Two distinctive cutaneous lesions that occur with endocarditis are the Osler node and Janeway lesion or spot. The former is a painful, erythematous nodule with a pale center located on the fingertips. The latter is a nontender, angular hemorrhagic lesion of the palms (Fig. 14-1) and soles. These lesions are likely due to septic emboli.

S. aureus is a normal inhabitant of the anterior nares in 20% to 40% of adults, and also resides on the hands and perineum in smaller numbers of individuals. Nasal carriers are particularly prone to infections with this bacterium because of its continuous presence on the skin and nasal mucosa. Spread of infection in the hospital setting is frequently traced to the hands of a healthcare worker. Proper handwashing technique is essential in limiting this nosocomial complication. HIV-infected patients are at least twice as commonly nasal carriers, and they tend to harbor *S. aureus* in higher frequency and density at other sites of the body, thus predisposing them to skin and systemic infection.

Antibiotic resistance is becoming a clinically important consideration in many infections, but methicillin-resistant *S.*

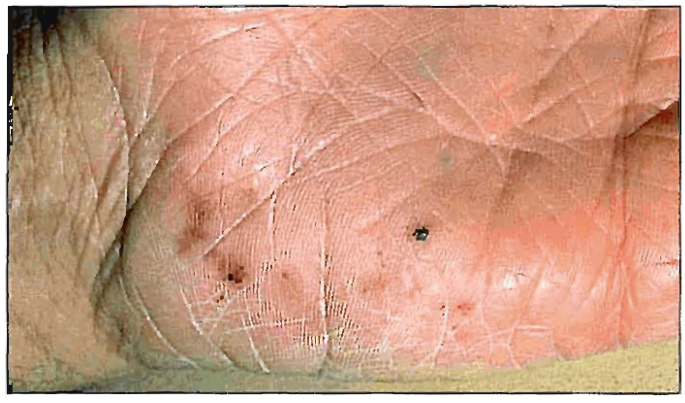

Fig. 14-1 Janeway lesion in subacute bacterial endocarditis. (Courtesy of James Fitzpatrick, MD)

aureus (MRSA), which has been a nosocomial problem for years, in some areas is now a common community-acquired skin infection. MRSA infection may be suspected from a knowledge of local patterns of resistance, lack of response to initial methicillin-sensitive *S. aureus* (MSSA)-directed therapy, such as cephalexin, and factors predisposing to colonization and infection with this organism. Predisposing factors include age (older than 65), exposure to others with MRSA infection, prior antibiotic therapy, and recent hospitalization or chronic illness. In patients with risk factors, multiple drug resistance is likely and treatment with intravenous vancomycin or linezolid may be necessary. In community-acquired infection in patients without risk factors, clindamycin, trimethoprim–sulfamethoxazole (alone or combined with rifampin), minocycline, or oral linezolid will often be effective. In patients with colonization of the anterior nares with MRSA or with localized impetigo, mupirocin may be effective. Definitive antibiotic therapy may be tailored to the antibiotic susceptibility of the cultured organism.

Superficial Pustular Folliculitis (Impetigo of Bockhart)

Bockhart impetigo is a superficial folliculitis with thin-walled pustules at the follicle orifices. Favorite locations are the extremities and scalp, although it is also seen on the face, especially periorally. These fragile, yellowish-white, domed pustules develop in crops and heal in a few days. *S. aureus* is the most frequent cause. The infection may secondarily arise in scratches, insect bites, or other skin injuries.

Sycosis Vulgaris (Sycosis Barbae)

Sycosis vulgaris, formerly known as barber's itch, is a perifollicular, chronic, pustular staphylococcal infection of the bearded region (Fig. 14-2), characterized by the presence of inflammatory papules and pustules, and a tendency to recurrence. The disease begins with erythema and burning or itching, usually on the upper lip near the nose. In a day or two one or more pinhead-sized pustules, pierced by hairs, develop. These rupture after shaving or washing and leave an erythematous spot, which is later the site of a fresh crop of pustules. In this manner the infection persists and gradually spreads. At times the infection may extend deep into the follicles. A hairless, atrophic scar bordered by pustules and crusts may result. Marginal blepharitis with conjunctivitis usually is present in severe cases of sycosis.

Sycosis vulgaris is to be distinguished from tinea, acne vulgaris, pseudofolliculitis barbae, and herpetic sycosis. Tinea barbae rarely affects the upper lip, which is a common location for sycosis. In tinea barbae the involvement usually is in the submaxillary region or on the chin, and spores and hyphae are found in the hairs. Pseudofolliculitis barbae manifests torpid papules at the sites of ingrowing beard hairs in black men. In herpes simplex the duration is usually only a few days and even in persistent cases there are vesicles, which help to differentiate the disease from sycosis vulgaris.

Folliculitis

Staphylococcal folliculitis may affect other areas, such as the eyelashes, axillae, pubis, and thighs (Fig. 14-3). On the pubis it may be transmitted among sexual partners, and mini-epidemics of folliculitis and furunculosis of the genital and gluteal areas may be considered a sexually-transmitted disease (STD). Staphylococcal folliculitis has also been reported frequently among patients with acquired immunodeficiency syndrome (AIDS) and may be a cause of pruritus. An atypical, plaque-like form has been reported.

Treatment

A thorough cleansing of the affected areas with antibacterial soap and water three times a day is recommended. Deep lesions of folliculitis represent small follicular abscesses and must be drained. Superficial pustules will rupture and drain spontaneously. Many patients will heal with drainage and topical therapy. Bactroban (mupirocin) ointment and topical cleocin are effective topical agents. Skin surface staphylococcal carriage in abrasions and eczematous areas may be addressed with topical mupirocin, topical clindamycin or topical chlorhexidine. If drainage and topical therapy fail or if there is accompanying soft-tissue infection, a first-generation cephalosporin, or a penicillinase-resistant penicillin such as dicloxacillin, is indicated, unless MRSA is suspected (see above). When the inflammation is acute, hot, wet soaks with Burow solution diluted 1:20 (Domeboro) are beneficial. An anhydrous formulation of aluminum chloride (Drysol, Xerac-AC) is effective when used once a night for chronic folliculitis, especially of the buttocks. Antibiotic ophthalmic ointments are used for blepharitis.

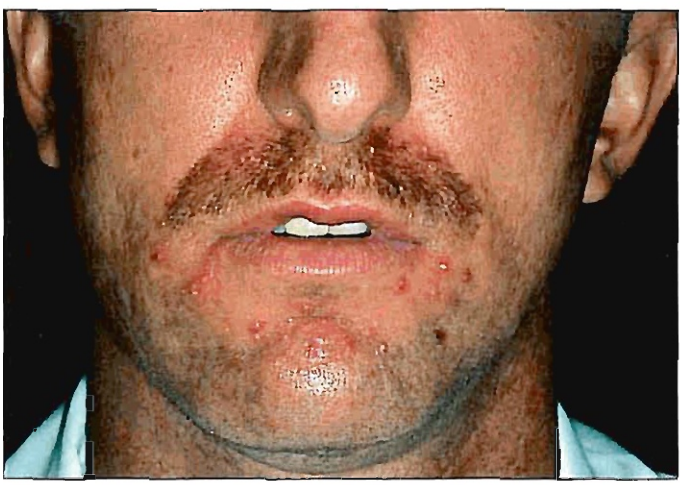

Fig. 14-2 Sycosis barbae.

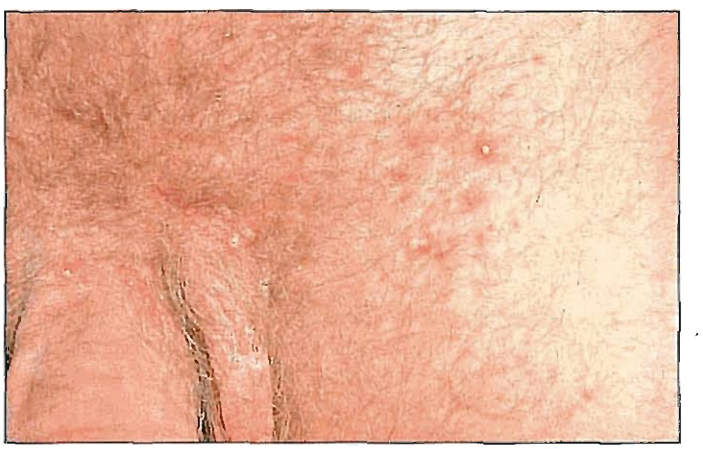

Fig. 14-3 Staphylococcal folliculitis.

Furunculosis

A furuncle, or boil, is an acute, round, tender, circumscribed, perifollicular staphylococcal abscess that generally ends in central suppuration (Fig. 14-4). A carbuncle is merely two or more confluent furuncles, with separate heads.

The lesions begin in hair follicles, and often continue for a prolonged period by autoinoculation. Some lesions disappear before rupture, but most undergo central necrosis and rupture through the skin, discharging purulent, necrotic debris. Sites of predilection are the nape, axillae, and buttocks, but boils may occur anywhere (Fig. 14-5).

The integrity of the skin surface may be impaired by irritation, pressure, friction, hyperhidrosis, dermatitis, dermatophytosis, or shaving, among other factors. Local barrier compromise predisposes to infection by providing a portal of entry for the ubiquitous *S. aureus*. The proximate cause is either contagion or autoinoculation from a carrier focus, usually in the nose or groin.

Certain systemic disorders may predispose to furunculosis: alcoholism; malnutrition; blood dyscrasias; disorders of neutrophil function; iatrogenic or other immunosuppression, including AIDS; and diabetes (Fig. 14-6). Patients with several of these diseases, as well as those receiving renal dialysis or under treatment with isotretinoin or etretinate, are often nasal carriers of *S. aureus*. Additionally, atopic dermatitis also predisposes to the *S. aureus* carrier state. This fact helps explain the observed increases in the incidence of infections in these diseases.

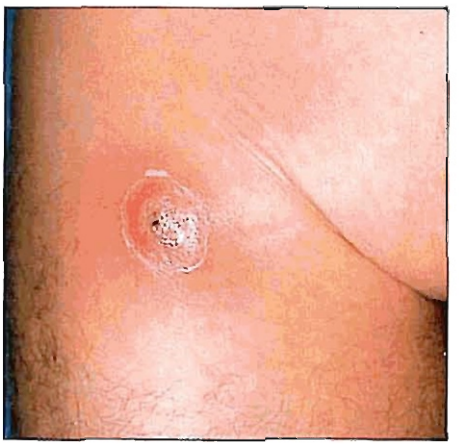

Fig. 14-4 Staphylococcal abscess.

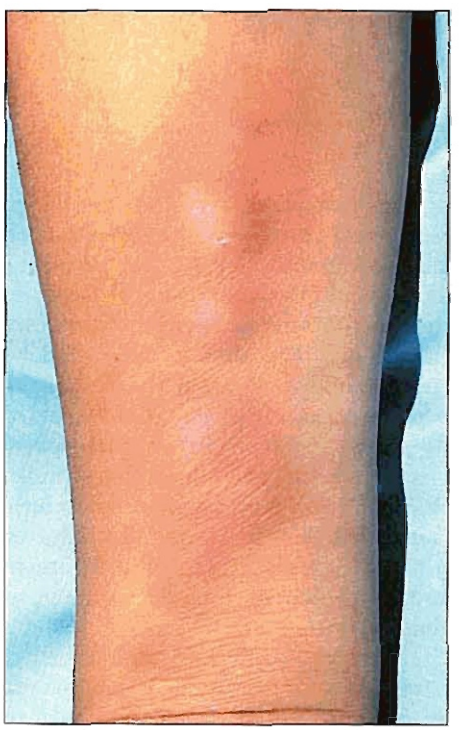

Fig. 14-5 Sporotricoid staphylococcal abscesses. (Courtesy of James Fitzpatrick, MD)

Hospital Furunculosis Epidemics of staphylococcal infections occur in hospitals. Marked resistance to antibacterial agents in these cases is commonplace. Attempts to control these outbreaks center on meticulous handwashing. In nurseries, a fall in neonatal colonization and infections with *S. aureus* and non-group A streptococci may be achieved by using a 4% solution of chlorhexidine for skin and umbilical cord care.

The histopathologic appearance is of a deep abscess with both lymphocytes and neutrophils, and in long-standing cases, plasma cells and foreign-body giant cells.

Treatment

Warm compresses and antibiotics taken internally may arrest early furuncles. A penicillinase-resistant penicillin or a first-generation cephalosporin should be given orally in a dose of 1 to 2 g/day according to the severity of the case. Some newer extended-spectrum cephalosporins also provide excellent staphylococcal coverage. Methicillin-resistant and even vancomycin-resistant strains occur as described above. In cases of staphylococcal infections that are unresponsive to these usual measures, antibiotic-resistant strains should be suspected and sensitivities checked. Bactroban applied to the anterior nares daily for 5 days may help prevent recurrence.

When the lesions are incipient and acutely inflamed, incision should be strictly avoided and moist heat employed. When the furuncle has become localized and shows definite fluctuation, incision with drainage is indicated. The cavity should be packed with iodoform or vaseline gauze. In boils of the external auditory canal, upper lip, and nose, incision and drainage is generally only performed if antibiotic therapy fails. In these latter circumstances, antibiotic ointment (Bactroban) should be applied, and antibiotics given internally. Warm saline-solution compresses should be applied liberally.

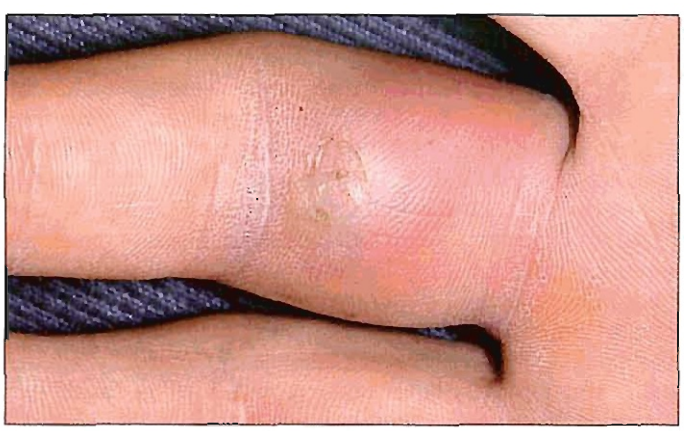

Fig. 14-6 Staphylococcal abscess in a diabetic patient.

Chronic Furunculosis Despite treatment, recurrences of some boils may be anticipated. Usually no underlying disease is present to predispose to this; rather, autoinoculation and intrafamilial spread among colonized individuals is responsible.

One of the most important factors in prevention is to avoid autoinoculation. It is important to emphasize that the nasal carrier state predisposes to chronic furunculosis. The skin surface in the region of the furuncles may be a source of colonization, especially if there are cuts, excoriation or eczematous changes. In addition, the hazard of contamination from the perianal and intertriginous areas is to be considered. Routine precautions to be taken in attempting to break the cycle of recurrent furunculosis should be the daily use of a chlorhexidine wash, with special attention to the axillae, groin, and perianal area; laundering of bedding and clothing daily initially; and frequent handwashing. Additionally, the application of Bactroban ointment twice a day to the nares of patients and family members every fourth week has been found to be effective. Rifampin, 600 mg/day, combined with dicloxacillin for MSSA or trimethoprim–sulfamethoxazole for MRSA, for 10 days, or low-dose (150 mg/day) clindamycin for 3 months are other options that are effective in eradicating the nasal carriage state. The use of bacitracin ointment inside the nares twice a day throughout the course of isotretinoin therapy eliminates, or markedly reduces, the risk of inducing nasal carriage of *S. aureus*, and hence staphylococcal infections.

Pyogenic Paronychia

Paronychia is an inflammatory reaction involving the folds of the skin surrounding the fingernail. It is characterized by acute or chronic purulent, tender, and painful swellings of the tissues around the nail, caused by an abscess in the nailfold. When the infection becomes chronic, horizontal ridges appear at the base of the nail. With recurrent bouts new ridges appear.

The primary predisposing factor that is identifiable is separation of the eponychium from the nail plate. The separation is usually caused by trauma as a result of moisture-induced maceration of the nailfolds from frequent wetting of the hands. The relationship is close enough to justify treating chronic paronychia as work-related in bartenders, food servers, nurses, and others who often wet their hands. The moist grooves of the nail and nailfold become secondarily invaded by pyogenic cocci and yeasts. The causative bacteria are usually *S. aureus*, *Streptococcus pyogenes*, *Pseudomonas* species, *Proteus* species, or anaerobes. The pathogenic yeast is most frequently *Candida albicans*.

The bacteria usually cause acute abscess formation (*Staphylococcus*) (Fig. 14-7) or erythema and swelling (*Streptococcus*) (Fig. 14-8), and *C. albicans* most frequently causes a chronic swelling. If an abscess is suspected, applying light pressure with the index finger against the distal volar aspect of the affected digit will better demonstrate the extent of the collected pus by inducing a well-demarcated blanching. Smears of purulent material will help confirm the clinical impression. Myremecial warts may at times mimic paronychia. Subungual black macules followed by edema, pain, and swelling have been reported to be a sign of osteomyelitis caused by *S. aureus* or *Streptococcus viridans*, in children with atopic dermatitis.

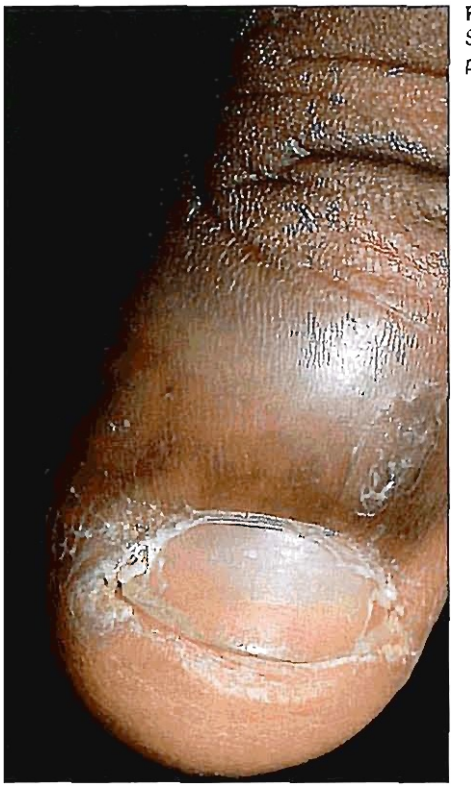

Fig. 14-7 Staphylococcal *paronychia.*

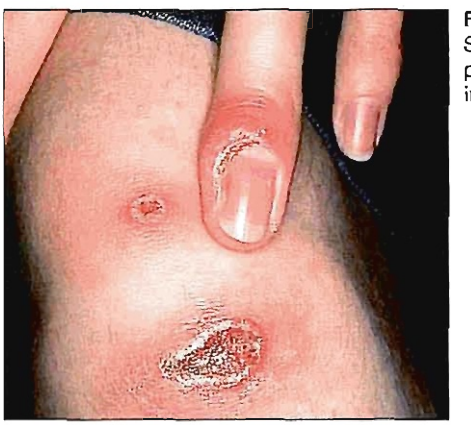

Fig. 14-8 Streptococcal paronychia and impetigo.

Treatment of pyogenic paronychia consists mostly of protection against trauma and concentrated efforts to keep the affected fingernails meticulously dry. Rubber or plastic gloves over cotton gloves should be used whenever the hand must be placed in water. Acutely inflamed pyogenic abscesses should be incised and drained. The abscess may often be opened by pushing the nailfold away from the nail plate. In acute suppurative paronychia, especially if stains show pyogenic cocci, a semisynthetic penicillin or a cephalosporin with excellent staphylococcal activity should be given orally. If these are ineffective, MRSA or a mixed anaerobic bacteria infection should be suspected. Augmentin for the latter or treatment dictated by the sensitivities of the cultured organism will improve cure rates. Rarely, long-term antibiotic therapy may be required.

While *Candida* is the most frequently recovered organism in chronic paronychia, topical or oral antifungals lead to cure in only about 50% of cases. If topical steroids are used to

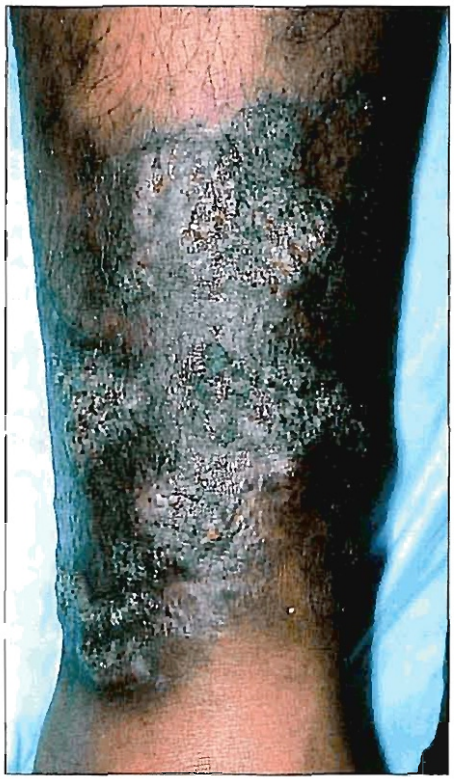

Fig 14-9
Botryomycosis.

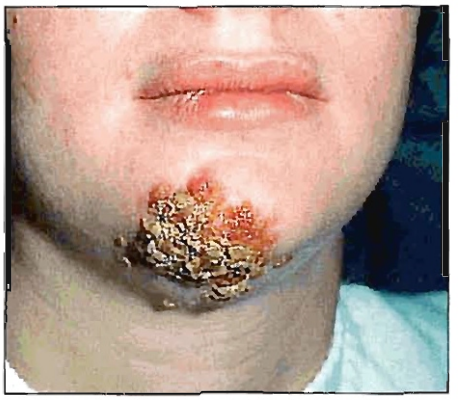

Fig. 14-10 Impetigo.

decrease inflammation and allow for tissue repair, cure results more reliably (nearly 80% in one study). Often an antifungal liquid such as miconazole is combined with a topical corticosteroid cream or ointment.

Botryomycosis

Botryomycosis is an uncommon, chronic, indolent disorder characterized by nodular, crusted, purulent lesions (Fig. 14-9). Sinuses that discharge sulfur granules are present. These heal with atrophic scars. The granules yield most commonly *S. aureus* on culture, although cases caused by *Pseudomonas aeruginosa, Escherichia coli, Proteus, Bacteroides*, and *Streptococcus* have been reported. It occurs frequently in patients with altered immune function, such as patients with neutrophilic defects. Other predisposing factors include diabetes, HIV infection, alcoholism, and Job syndrome. Appropriate antibiotics, surgical drainage, and surgical excision are methods used to treat botryomycosis.

Blastomycosis-Like Pyoderma

Large verrucous plaques with elevated borders and multiple pustules occur. Most patients have some underlying systemic or local host compromise. Bacteria such as *S. aureus, P. aeruginosa, Proteus, E. coli*, or streptococci may be isolated. Antibiotics appropriate for the organism isolated are curative; however, response may be delayed and prolonged therapy required. Acetretin may also be useful.

Pyomyositis

S. aureus abscess formation within the deep, large, striated muscles usually presents with fever and muscle pain. It is more common in the tropics, where it may affect adults but most commonly occurs in children. In temperate climates it occurs in children and patients with AIDS. The most frequent site in tropical disease is the thigh, while in HIV-infected patients the deltoid muscle is most often involved, followed closely by the quadriceps. Swelling and, occasionally, erythema or yellow or purplish discoloration are visible signs of pyomyositis, but these are late findings. Magnetic resonance imaging (MRI) with gadolinium injection will help delineate the extent of disease. Drainage of the abscess and appropriate systemic antibiotics are the recommended treatment.

Impetigo Contagiosa

Impetigo contagiosa is staphylococcal, streptococcal, or combined infection characterized by discrete, thin-walled vesicles that rapidly become pustular and then rupture. Impetigo occurs most frequently on the exposed parts of the body: the face (Fig. 14-10), hands, neck, and extremities. Impetigo on the scalp is a frequent complication of pediculosis capitis.

The disease begins with 2-mm erythematous macules, which may shortly develop into vesicles or bullae. As soon as these lesions rupture, a thin, straw-colored, seropurulent discharge is noted. The exudate dries to form loosely stratified golden-yellow crusts, which accumulate layer upon layer until they are thick and friable.

The crusts can usually be removed readily, leaving a smooth, red, moist surface that soon collects droplets of fresh exudate again; these are spread to other parts of the body by fingers or towels. As the lesions spread peripherally and the skin clears centrally, large circles are formed by fusion of the spreading lesions to produce gyrate patterns. In streptococcal-induced impetigo, regional lymphadenopathy is common, but not serious.

Although in the past streptococci caused the majority of cases of impetigo, by the end of the 1970s it became apparent that the predominant pathogen was *S. aureus*. Most studies now find 50% to 70% of cases are due to *S. aureus*, with the remainder either being due to *S. pyogenes* or a combination of these two organisms. Streptococci may represent an early pathogen in the pathogenesis of impetigo with staphylococci replacing streptococci as the lesion matures. Group B streptococci are associated with newborn impetigo and groups C and G are rarely isolated from impetigo, as opposed to the usual group A.

Impetigo occurs most frequently in early childhood (Fig. 14-11), although all ages may be affected. It occurs in the temperate zone, mostly during the summer in hot, humid weather. Common sources of infection for children are pets, dirty fingernails, and other children in schools, daycare

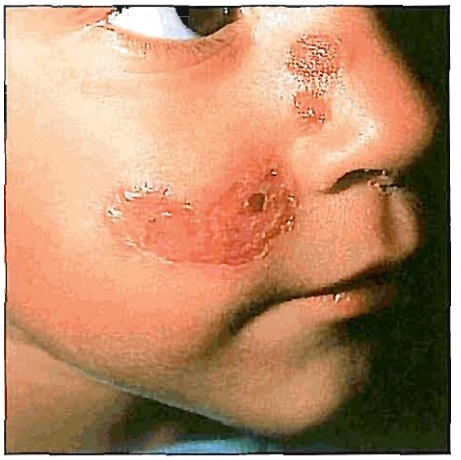

Fig. 14-11 Impetigo.

centers, or crowded housing areas; for adults, common sources include infected children and self-inoculation from nasal or perineal carriage. Impetigo often complicates pediculosis capitis, scabies, herpes simplex, insect bites, poison ivy, eczema, and other exudative, pustular or itching skin diseases.

Group A beta-hemolytic streptococcal skin infections are sometimes followed by acute glomerulonephritis (AGN). Nephritogenic streptococci are generally associated with impetigo rather than with upper respiratory infections. There is no evidence that AGN occurs with staphylococcal impetigo. The important factor predisposing to AGN is the serotype of the streptococcus producing the impetigo. Type 49, 55, 57, and 60 strains and strain M-type 2 are related to nephritis.

The incidence of AGN with impetigo varies from about 2% to 5% (10–15% with nephritogenic strains of streptococcus) and occurs most frequently in childhood, generally under the age of 6. The prognosis in children is mostly excellent; however, in adults the prognosis is not as good. Treatment, however early and however appropriate, is not believed to reduce the risk of occurrence of AGN.

The histopathology is that of an extremely superficial inflammation about the funnel-shaped upper portion of the pilosebaceous follicles. A subcorneal vesicopustule is formed, containing a few scattered cocci, together with debris of polymorphonuclear leukocytes and epidermal cells. In the dermis there is a mild inflammatory reaction—vascular dilation, edema, and infiltration of polymorphonuclear leukocytes.

Impetigo may simulate several diseases. The circinate patches are frequently mistaken for ringworm, but clinically are quite different. Impetigo is characterized by superficial, very weepy lesions covered by thick, bright yellow or orange crusts with loose edges, which do not resemble the scaling patches with peripheral erythema seen in tinea. Impetigo may be mistaken for *Toxicodendron* dermatitis, but it is more crusted and pustular, and more liable to involve the nostrils, corners of the mouth, and ears; it is not associated with the puffing of the eyelids, the linear lesions or the itchiness that are so often present in dermatitis caused by poison ivy or oak. In varicella the lesions are small, widely distributed, discrete, umbilicated vesicles that are usually also present in the mouth, a site not involved by impetigo. In ecthyma the lesions are crusted ulcers, not erosions.

Treatment

Systemic antibiotics combined with topical therapy are advised. Because most cases are caused by *Staphylococcus*, a semisynthetic penicillin or a first-generation cephalosporin is recommended, unless MRSA is suspected, as detailed above. All treatment should be given for 7 days. It is necessary to soak off the crusts frequently, after which bacitracin or mupirocin ointment should be applied. If the lesions are localized, especially if facial, and are present in an otherwise healthy child, topical therapy may be effective as the sole treatment.

Applying antibiotic ointment as a prophylactic to sites of skin trauma will prevent impetigo in high-risk children attending daycare centers. In one study infections were reduced by 47% with antibiotic ointment compared with 15% with a placebo. Additionally, if recurrent staphylococcal impetigo develops, a culture of the anterior nares may yield this organism. Such carrier states may be treated by application of mupirocin ointment to the anterior nares twice a day or a 10-day course of rifampin, 600 mg/day combined with dicloxacillin (for MSSA) or trimethoprim–sulfamethoxazole (for MRSA).

Bullous Impetigo

This variety of impetigo occurs characteristically in newborn infants, though it may occur at any age. The neonatal type is highly contagious and is a threat in nurseries. In most cases the disease begins between the fourth and tenth days of life with the appearance of bullae, which may appear on any part of the body. Common early sites are the face and hands. Constitutional symptoms are at first absent, but later weakness and fever or a subnormal temperature may be present. Diarrhea with green stools frequently occurs. Bacteremia, pneumonia, or meningitis may develop rapidly, with fatal termination.

In warm climates particularly, adults may have bullous impetigo (Fig. 14-12), most often in the axillae or groins, or on the hands. Usually no scalp lesions are present. The lesions are strikingly large, fragile bullae, suggestive of pemphigus. When these rupture they leave circinate, weepy, or crusted lesions, and in this stage it may be called *impetigo circinata*. Children with bullous impetigo may give a history of an insect bite at the site of onset of lesions. The majority are caused by phage types 71 or 55 coagulase-positive *S. aureus* or a related group 2 phage type. Bullous impetigo may be an early manifestation of HIV infection.

Staphylococcal Scalded Skin Syndrome

Staphylococcal scalded skin syndrome (SSSS) is a generalized, confluent, superficially exfoliative disease, occurring most commonly in neonates and young children. It was known in the past as Ritter's disease or dermatitis exfoliativa neonatorum. It has been reported to occur rarely in adults. When it does occur in an adult, usually either renal compromise or immunosuppression is a predisposing factor.

SSSS is a febrile, rapidly evolving, generalized, desquamative infectious disease, in which the skin exfoliates in sheets. It does not separate at the dermoepidermal junction, as in toxic (drug-induced) epidermal necrolysis (TEN), but within the granular layer. The lesions are thus much more superficial and less severe than in TEN, and healing is much more rapid. They also extend far beyond areas of actual staphylococcal

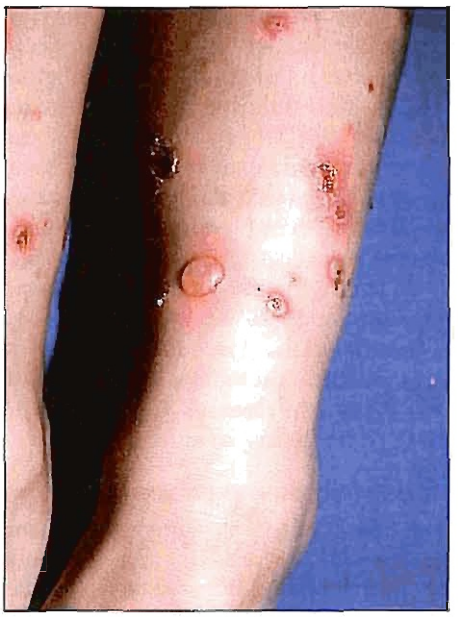

Fig. 14-12 Bullous impetigo.

infection, by action of the exfoliative exotoxins types A and B elaborated by the staphylococcus in remote sites. Usually the staphylococci are present at a distant focus, such as the pharynx, nose, ear, or conjunctiva. Septicemia or a cutaneous infection may also be the causative focus.

Its clinical manifestations begin abruptly with fever, skin tenderness, and erythema involving the neck, groins, and axillae (Fig. 14-13A). There is sparing of the palms, soles, and mucous membranes. Nikolsky sign is positive. Generalized exfoliation follows within the next hours to days, with large sheets of epidermis separating (Fig. 14-13B).

Group 2 *S. aureus*, most commonly phage types 71 or 55, is the causative agent in most cases. If cultures are taken, they should be obtained from the mucous membranes because the skin erythema and desquamation is due to the distant effects of the exfoliative toxins, unlike the situation in bullous impetigo, where *S. aureus* is present in the lesions.

Rapid diagnosis can be made by examining frozen sections of a blister roof and observing that the full thickness of the epidermis is not necrotic as in TEN but rather is cleaved below the granular layer. The exfoliative toxins A, B, and D specifically cleave desmoglein 1, the antigenic target of autoantibodies in pemphigus foliaceus, thus accounting for the clinical and histologic similarity to pemphigus observed in SSSS and bullous impetigo. Treatment of choice is a penicillinase-resistant penicillin such as dicloxacillin combined with fluid therapy and general supportive measures. If MRSA is cultured, and response is sluggish, antibiotics directed according to the susceptibilities of the recovered organism is needed. The prognosis is good in children, however the mortality rate in adults can reach 60%.

Toxic Shock Syndrome

Toxic shock syndrome (TSS), an acute, febrile, multisystem illness, has as one of its major diagnostic criteria a widespread macular erythematous eruption. It is usually caused by toxin-producing strains of *S. aureus*, most of which were initially isolated from the cervical mucosa in menstruating young women. Recent cases are most often due to infections in wounds, catheters, contraceptive diaphragms, or nasal packing. The mortality of these nonmenstrual cases is higher (12%) compared with menstrual-related cases (5%), probably as a result of delayed diagnoses. Additionally, a very similar syndrome in which the cause is group A, or rarely group B, streptococci has been defined. This latter multiorgan disease has systemic components similar to classic staphylococcal TSS; however, the infection is usually a rapidly progressive, destructive soft-tissue infection such as necrotizing fasciitis. It has a case fatality rate of 30%. The streptococci are usually of M-types 1 and 3, with 80% of the isolates producing pyrogenic exotoxin A.

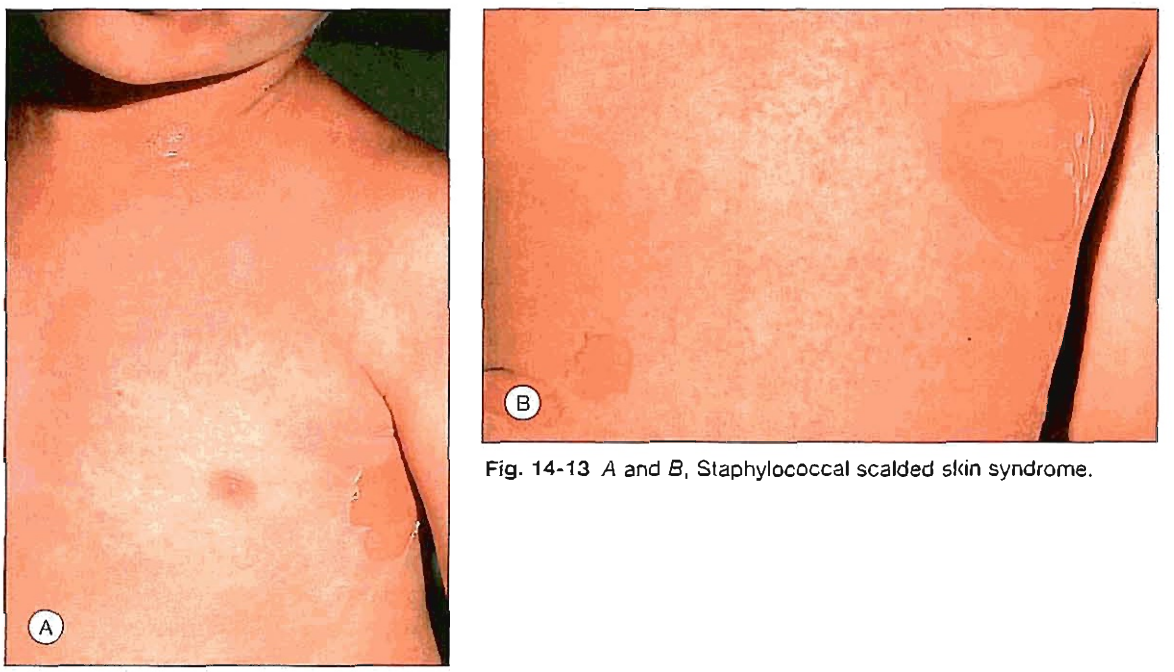

Fig. 14-13 *A* and *B*, Staphylococcal scalded skin syndrome.

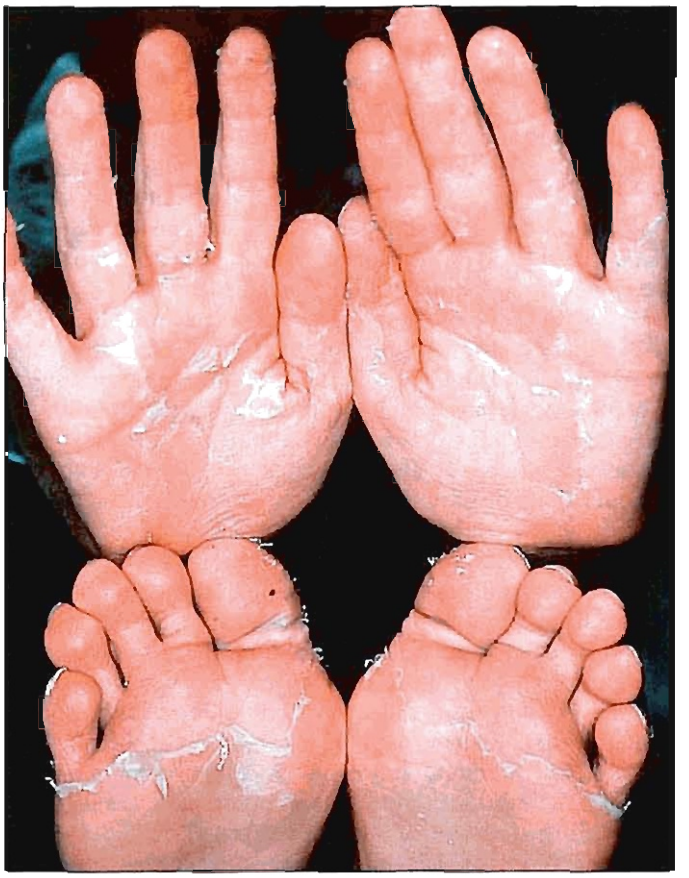

Fig. 14-14 Desquamation of the palms and soles.

The Center for Communicable Diseases (CDC) case definition of TSS includes the following: a temperature of 38.9° C or higher, an erythematous eruption, desquamation of the palms and soles 1 to 2 weeks after onset (Fig. 14-14), hypotension, and involvement of three or more other systems—gastrointestinal (vomiting, diarrhea), muscular (myalgias, increased creatinine phosphokinase level), mucous membrane (hyperemia), renal (pyuria without infection or raised creatinine or blood urea nitrogen levels), hepatic (increased bilirubin, SGOT, or SGPT), hematologic (platelets <100,000/mm^3), or central nervous system (CNS) (disorientation). In addition, serologic tests for Rocky Mountain spotted fever, leptospirosis, and rubeola, and cultures of blood, urine, and cerebrospinal fluid should be negative. Bulbar conjunctival hyperemia and palmar edema are two additional clinical clues.

Ninety percent of the early cases occurred in young women between the first and sixth days of a menstrual period. During the initial outbreak, between 1979 and 1982, the majority were using a superabsorbent tampon. Cases have been reported in women using contraceptive sponges, in patients with nasal packing after rhinoplasty, and in patients with staphylococcal infections of bone, lung, or soft tissue. The offending *S. aureus* strain produces one or more exotoxins.

Histologic findings are spongiosis, neutrophils scattered throughout the epidermis, individual necrotic keratinocytes, perivascular and interstitial infiltrates composed of lymphocytes and neutrophils, and edema of the papillary dermis. TSS must be differentiated from other diseases that can closely mimic its cutaneous presentation, such as viral exanthems, Kawasaki's disease, scarlet fever, drug eruptions, Rocky Mountain spotted fever, systemic lupus erythematosus, TEN, and SSSS. In Kawasaki's disease, TSS-toxin-producing staphylococcus has been recovered and streptococci that produce pyrogenic exotoxin B and C may be isolated; thus, some feel Kawasaki's disease is caused by toxin-secreting bacteria. Manders et al reported two patients with recurrent perineal erysipelas-like erythema that resolved with desquamation, a staphylococcal or streptococcal pharyngitis, and a marked tendency to recurrence. They termed this *recurrent toxin-mediated perianal erythema*.

Treatment consists of systemic antibiotics such as nafcillin, 1 to 1.5 g intravenously every 4 h, vigorous fluid therapy to treat shock, and drainage of the *S. aureus*-infected site.

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STREPTOCOCCAL SKIN INFECTIONS

Ecthyma

Ecthyma is an ulcerative staphylococcal or streptococcal pyoderma, nearly always of the shins or dorsal feet. The disease begins with a vesicle or vesicopustule, which enlarges and in a few days becomes thickly crusted. When the crust is removed there is a superficial saucer-shaped ulcer with a raw base and elevated edges (Fig. 14-15). In urban areas these lesions are due to *S. aureus* and are seen in intravenous drug users and HIV-infected patients.

The lesions tend to heal after a few weeks, leaving scars, but rarely may proceed to gangrene when resistance is low. In fact, a debilitated condition and a focus of pyogenic infection precede the onset of ecthyma in many cases. Local adenopathy may be present. Uncleanliness, malnutrition, and trauma are predisposing causes.

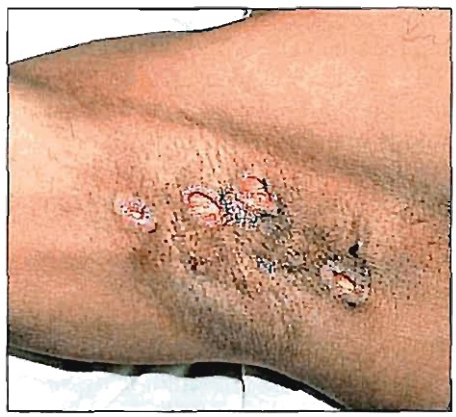

Fig. 14-15 Ecthyma.

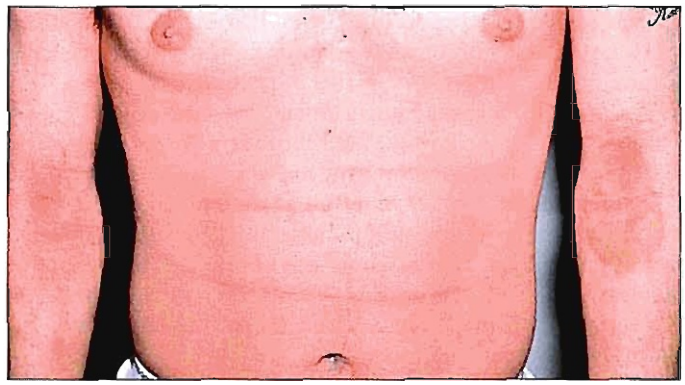

Fig. 14-16 Scarlet fever.

Treatment is cleansing with soap and water, followed by the application of mupirocin or bacitracin ointment, twice a day. Oral dicloxacillin or a first-generation cephalosporin is also indicated, with adjustments made according to the cultured organism's susceptibilities.

Scarlet Fever

Scarlet fever is a diffuse erythematous exanthem that occurs during the course of streptococcal pharyngitis. It affects primarily children, who develop the eruption 24 to 48 h after the onset of pharyngeal symptoms. The tonsils are red, edematous, and covered with exudate. The tongue has a white coating through which reddened, hypertrophied papillae project, giving the so-called white strawberry tongue appearance. By the fourth or fifth day the coating disappears, the tongue is bright red, and the red strawberry tongue remains.

The cutaneous eruption begins on the neck, spreads to the trunk (Fig. 4-16), and finally the extremities. Within the widespread erythema are 1- to 2-mm papules, which give the skin a rough sandpaper quality. There is accentuation over the skinfolds, and a linear petechial eruption, called *Pastia lines*, is often present in the antecubital and axillary folds. There is facial flushing and circumoral pallor. A branny desquamation occurs as the eruption fades, with peeling of the palms and soles taking place about 2 weeks after the acute illness. The latter may be the only evidence that the disease has occurred.

The eruption is produced by erythrogenic exotoxin-producing group A streptococci. Cultures of the pharynx, or rarely a surgical wound or burn, will recover this organism. An elevated antistreptolysin O titer may provide evidence of recent infection if cultures are not taken early. A condition known as *staphylococcal scarlatina* has been described that mimics scarlet fever; however, the strawberry tongue is not seen.

Penicillin, erythromycin, or dicloxacillin treatment is curative, and the prognosis is excellent.

Erysipelas

Also once known as *St Anthony's fire* and *ignis sacer*, erysipelas is an acute beta-hemolytic group A streptococcal infection of the skin involving the superficial dermal lymphatics. Occasional cases caused by streptococci of group C or G are reported in adults. Group B streptococcus is often responsible in the newborn and may be the cause of abdominal or perineal erysipelas in postpartum women. It is characterized by local redness, heat, swelling, and a highly characteristic raised, indurated border (Fig. 14-17A). The onset is often preceded by prodromal symptoms of malaise for several hours, which may be accompanied by a severe constitutional reaction with chills, high fever, headache, vomiting, and joint pains. There is commonly a polymorphonuclear leukocytosis of 20,000/mm^3 or more. However, many cases present solely as an erythematous lesion without associated systemic complaints.

The skin lesions may vary from transient hyperemia followed by slight desquamation to intense inflammation with vesicles or bullae (Fig. 14-17B). The eruption begins at any one point as an erythematous patch and spreads by peripheral extension. In the early stages the affected skin is scarlet, hot to the touch, brawny, and swollen. A distinctive feature of the inflammation is the advancing edge of the patch. This is raised and sharply demarcated, and feels like a wall to the palpating finger. In some cases vesicles or bullae that contain seropurulent fluid occur and may result in local gangrene.

The legs and face are the most frequent sites affected. When on the face the inflammation generally begins on the cheek near the nose or in front of the lobe of the ear and spreads upward to the scalp, the hairline acting in some instances as a barrier against further extension. When on the legs, edema and bullous lesions are prominent features in many cases (Fig. 14-17C). Septicemia, deep cellulitis, or necrotizing faciitis may occur as complications.

Predisposing causes are operative wounds, fissures (in the nares, in the auditory meatus, under the lobes of the ears, on the anus or penis, and between or under the toes, usually the little toe), abrasions or scratches, unclean tying of the umbilical cord, venous insufficiency, obesity, lymphedema, and chronic leg ulcers.

Recognition of the disease generally is not difficult. It may be confused with contact dermatitis from plants, drugs or dyes, and with angioneurotic edema; however, with each of these, fever, pain, and tenderness are absent and itching is severe. In scarlet fever, there is a widespread punctate erythema, which is never localized and edematous as in erysipelas. A butterfly pattern on the face may mimic lupus erythematosus and ear involvement may suggest relapsing polychondritis.

Systemic penicillin is rapidly effective. Improvement in the general condition occurs in 24 to 48 h, but resolution of the cutaneous lesion may require several days. Vigorous treatment with antibiotics should be continued for at least 10 days. Erythromycin is also efficacious, although some macrolide-resistant streptococci are encountered. Locally, ice bags and cold compresses may be used. Leg involvement, especially when bullae are present, will more likely require hospitalization with intravenous antibiotics. The elderly, those with underlying immunocompromise, a longer dura-

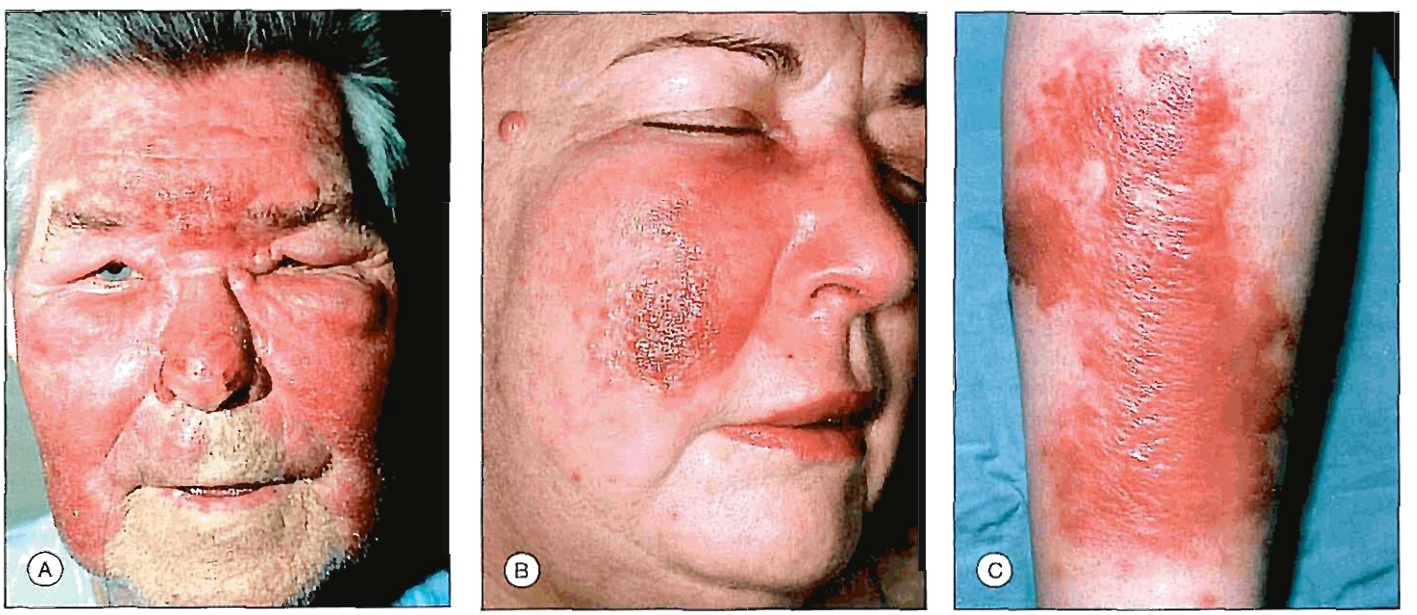

Fig. 14-17 *A–C*, Erysipelas.

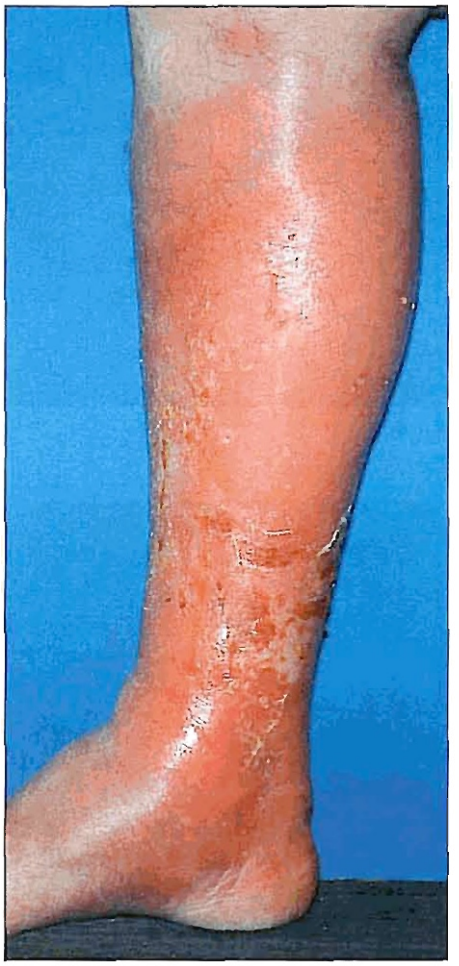

Fig. 14-18 Cellulitis.

tion of illness prior to presentation, and patients with leg ulcers will require longer inpatient stays.

Cellulitis

Cellulitis is a suppurative inflammation involving particularly the subcutaneous tissue, caused most frequently by *S. pyogenes* or *S. aureus*. Usually, but not always, this follows some discernible wound. On the leg tinea pedis is the most common portal of entry. Mild local erythema and tenderness, malaise, and chilly sensations, or a sudden chill and fever may be present at the onset. The erythema rapidly becomes intense and spreads (Fig. 14-18). The area becomes infiltrated and pits on pressure. Sometimes the central part becomes nodular and surmounted by a vesicle that ruptures and discharges pus and necrotic material. Streaks of lymphangitis may spread from the area to the neighboring lymph glands (Fig. 14-19). Gangrene, metastatic abscesses, and grave sepsis may follow. These complications are unusual in immunocompetent adults, but children and compromised adults are at higher risk.

Hook evaluated 50 patients with cellulitis prospectively by culture of the primary site of infection (when one was present), and also by aspiration of the advancing edge, by skin biopsy, and by blood culture. In 24 patients the primary site was identified and in 17 beta-hemolytic streptococci were isolated, with *S. aureus* being present in 13. Kielhofner et al also evaluated needle aspirates in cellulitis. Of 87 patients, 33 were culture positive. Of significance is that 26

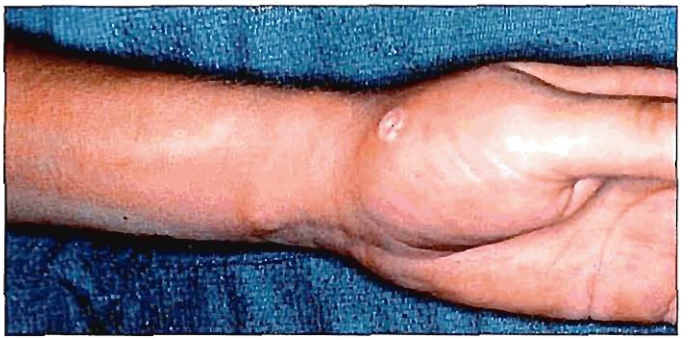

Fig. 14-19 Lymphangitis.

of 46 patients (57%) were positive if there was coexistent underlying disease, such as hematologic malignancy, diabetes mellitus, intravenous drug abuse, or cardiovascular disorders. *S. aureus* was present in 33% and group A streptococci in 27%. Other cultures were seldom positive and yielded no additional information.

Initial empiric therapy should cover both staphylococci and streptococci. Intravenous penicillinase-resistant penicillins or a first-generation cephalosporin are usually effective. If there is a lack of response, MRSA should be considered and treatment strategies chosen depending on whether the infection was hospital or community acquired, as outlined above.

Chronic Recurrent Erysipelas, Chronic Lymphangitis

Erysipelas or cellulitis may be recurrent. Predisposing factors include alcoholism, diabetes, immunodeficiency, tinea pedis, venous stasis, lymphedema with or without lymphangiectasias, prosthetic surgery of the knee, a history of saphenous phlebectomy, lymphadenectomy, or irradiation. Chronic lymphedema is the end result of recurrent bouts of bacterial lymphangitis and obstruction of the major lymphatic channels of the skin. The final result is a permanent hypertrophic fibrosis to which the term *elephantiasis nostras* has been given. It must be differentiated from lymphangioma, acquired lymphangiectasia, and other causes such as neoplasms, syphilis, filariasis, and tuberculous lymphangitis.

During periods of active lymphangitis, antibiotics in large doses are beneficial and their use must be continued intermittently in smaller maintenance doses for long periods to achieve their full benefits. Compression therapy to decrease lymphedema will aid in the prevention of recurrence.

Necrotizing Fasciitis

Necrotizing fasciitis is an acute necrotizing infection involving the fascia. It may follow surgery or perforating trauma or may occur de novo. Within 24 to 48 h redness, pain, and edema quickly progress to central patches of dusky blue discoloration, with or without serosanguineous blisters (Fig. 14-20). Anesthesia of the involved skin is very characteristic. By the fourth or fifth day, these purple areas become gangrenous. Many forms of virulent bacteria have been cultured from necrotizing fasciitis, including microaerophilic beta-hemolytic streptococci, hemolytic staphylococcus, coliforms, enterococci, *Pseudomonas*, and *Bacteroides*. Both aerobic and anaerobic cultures should always be taken.

Early surgical debridement is an essential component of successful therapy. Signs and tests that can aid in delineating

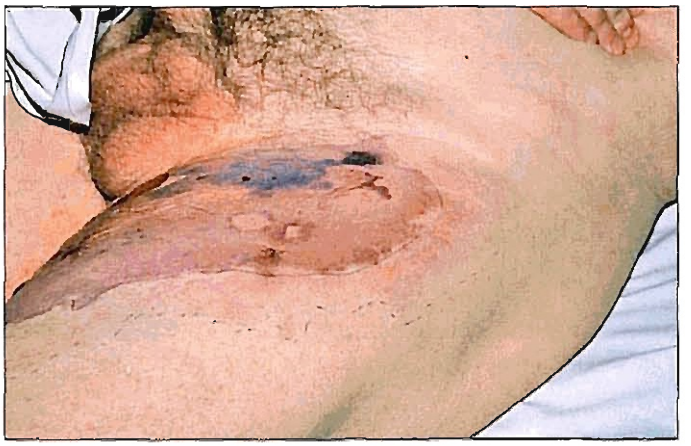

Fig. 14-20 Necrotizing fasciitis.

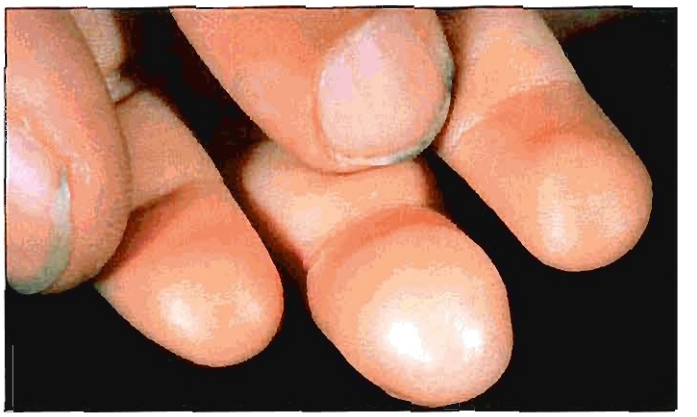

Fig. 14-21 Blistering dactylitis.

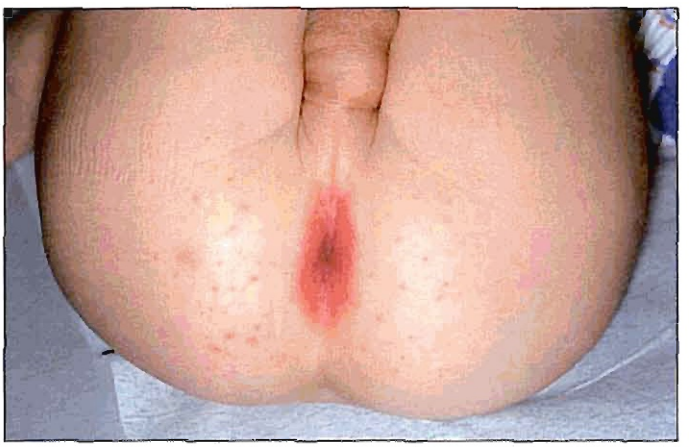

Fig. 14-22 Perianal dermatitis.

the extent of deep involvement include the presence of hypotension, an admission white blood cell count greater than 15.4, serum sodium less than 135 mmol/L, and an MRI. It may be necessary to infiltrate the site with anesthetic, make a 2-cm incision down to the fascia, and probe with the finger. Lack of bleeding, a murky discharge, and lack of resistance to the probing finger are ominous signs. Treatment should include early surgical debridement, intravenously administered appropriate antibiotics, and supportive care. There may be a 20% mortality even in the best of circumstances. Poor prognostic factors are age over 50, underlying diabetes or atherosclerosis, delay of more than 7 days in diagnosis and surgical intervention, and infection on or near the trunk rather than the more commonly involved extremities. Neonatal necrotizing fasciitis most commonly occurs on the abdominal wall and has a higher mortality rate than in adults.

Blistering Distal Dactylitis

Blistering distal dactylitis is characterized by tense superficial blisters occurring on a tender erythematous base over the volar fat pad of the phalanx of a finger or thumb or occasionally a toe (Fig. 14-21). The typical patient is aged between 2 and 16. Group A beta-hemolytic streptococcus or *S. aureus* are the most common causes. They may be cultured from blister fluid and occasionally from clinically unapparent infections of the nasopharynx or conjunctiva.

Perineal Dermatitis

Clinically, this entity presents most commonly as a superficial perianal, well-demarcated rim of erythema; sometimes fissuring may also be seen. Pain or tenderness, especially prominent on defecation, may lead to fecal retention in affected patients, who are usually between ages 1 and 8. It may not resemble a cellulitis, but rather a dermatitis. It may also affect the vulvar and penile tissues. Group A streptococci are most often the cause; however *S. aureus* may be recovered rarely (Fig. 14-22). As the vast majority of infections are due to streptococci, a systemic penicillin or erythromycin combined with a topical antiseptic or antibiotic is the treatment of choice. The duration should be 14 to 21 days depending on clinical response. Post-treatment swabs and urine analysis to monitor for post-streptococcal glomerulonephritis are recommended.

Streptococcal Intertrigo

Infants and young children may develop a fiery-red erythema and maceration in the neck, axillae or inguinal folds. There are no satellite lesions. It may be painful and have a foul odor. Group A beta-hemolytic streptococci are the cause, and topical and oral penicillin combined with a low potency topical steroid is curative.

Erythema Marginatum

Delayed nonsuppurative sequelae of streptococcal infections include erythema nodosum, post-streptococcal glomerulonephritis, and rheumatic fever. While the latter only follows pharyngitis or tonsillitis, two skin signs are among the diagnostic criteria of rheumatic fever—erythema marginatum and subcutaneous nodules. The remaining major signs making up the revised Jones criteria are carditis, polyarthritis and chorea. Erythema marginatum appears as a spreading patchy erythema that migrates peripherally and often forms polycyclic configurations (Fig. 14-23). It is evanescent, appearing for a few hours or days on the trunk or proximal extremities. Heat may make it more visible and successive crops may appear over several weeks. It is usually part of the early phase of the disease, coexisting with carditis but usually preceding the arthritis. Children younger than 5 are more likely to manifest the eruption than older patients. A skin biopsy will show a perivascular and interstitial polymorphonuclear leukocyte predominance. In contrast, the subcutaneous nodules occur over bony prominences and appear as a

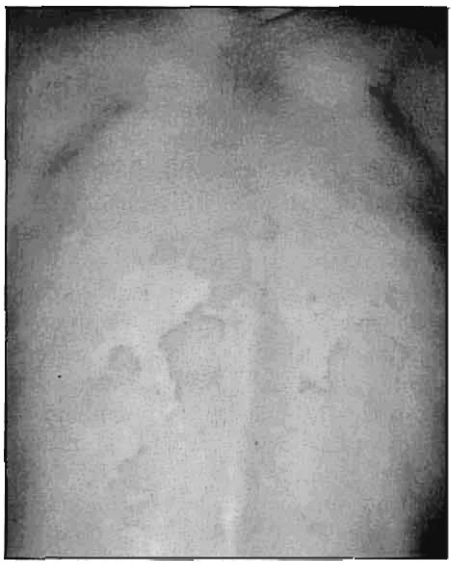

Fig. 14-23 Erythema marginatum.

late manifestation. The lesions usually are asymptomatic and resolve spontaneously.

Group B Streptococcal Infection

Streptococcus agalactiae is the major cause of bacterial sepsis and meningitis in neonates. It may cause orbital cellulitis or facial erysipelas in these patients. Up to 25% of healthy adults harbor group B streptococcus in their genital or gastrointestinal tract. It has been reported to cause balanitis, toxic shock-like syndrome, cellulitis, perianal dermatitis, recurrent erysipelas, or blistering dactylitis in adults. Diabetes mellitus, neurologic impairment, cirrhosis, and peripheral vascular disease predispose patients to infection with this organism. In the postpartum period, abdominal or perineal erysipelas may be due to this organism. Both Farley et al and Schwartz et al document that invasive disease caused by this organism is becoming more common.

Streptococcus Iniae Infections

Cellulitis of the hands may be caused by this fish pathogen. In Asian cuisine tilapia (also known as St Peter's fish or Hawaiian sunfish) is often purchased live from aquariums in retail stores. In cleaning the freshly killed fish before cooking, puncture wounds of the skin may be sustained from the dorsal fin, a fish bone, or a knife. Within 24 h fever, lymphangitis, and cellulitis without skin necrosis or bulla formation occur. Treatment with penicillin is curative.

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MISCELLANEOUS GRAM-POSITIVE SKIN INFECTIONS

Erysipeloid of Rosenbach

The most frequent form of erysipeloid is a purplish marginated swelling on the hands. The first symptom is pain at the site of inoculation; this is followed by swelling and erythema. The most distinctive feature is the sharply marginated and often polygonal patches of bluish erythema (Fig. 14-24). The erythema slowly spreads to produce a sharply defined, slightly elevated zone that extends peripherally as the central portion fades away. If the finger is

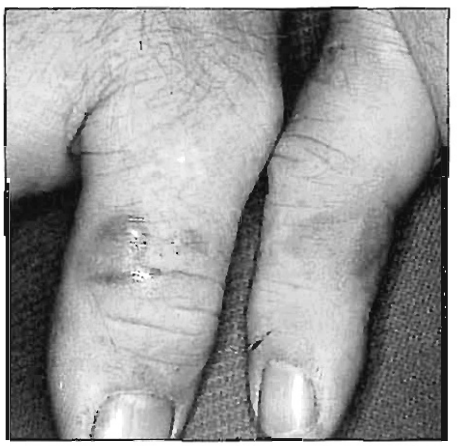

Fig. 14-24
Erysepiloid.

involved the swelling and tenseness make movement difficult. Vesicles frequently occur.

Another characteristic of the disease is its migratory nature; new purplish red patches appear at nearby areas. If the infection originally involved one finger, eventually all of the fingers and the dorsum of the hand, palm, or both may become infected, the erythema appearing and disappearing; or extension may take place by continuity. The disease involutes without desquamation or suppuration.

A diffuse or generalized eruption in regions remote from the site of inoculation may occur, with fever and arthritic symptoms. Rarely, septicemia may eventuate in endocarditis, with prolonged fever and constitutional symptoms.

The infection is caused by *Erysipelothrix rhusiopathiae*. *E. rhusiopathiae* is present on dead matter of animal origin. Swine are more frequently infected than any other animal. A large percentage of healthy swine are carriers of the organism. Turkeys are also often infected and the disease may arise from handling contaminated dressed turkeys. It is also present in the slime of saltwater fish, on crabs, and on other shellfish.

The disease is widespread along the entire Atlantic seacoast among commercial fishermen who handle live fish, crabs, and shellfish. The infection also occurs among veterinarians and in the meat-packing industry, principally from handling pork products.

E. rhusiopathiae is a rod-shaped, nonmotile, Gram-positive organism that tends to form long-branching filaments. The organism is cultured best on media fortified with serum, at room temperature.

Treatment

The majority of the mild cases of erysipeloid run a self-limited course of about 3 weeks. In some patients, after a short period of apparent cure, the eruption reappears either in the same area or, more likely, in an adjacent previously uninvolved area. Penicillin, 1 g/day for 5 to 10 days, is the best treatment for localized disease. If penicillin cannot be used, ciprofloxacin, clindamycin, or imipenem may be used. For systemic forms 12 to 20 MU/day of intravenous penicillin for up to 6 weeks may be necessary.

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Pneumococcal Cellulitis

Cellulitis may be caused by *Streptococcus pneumoniae*. Children present with facial or periorbital cellulitis, which may manifest a violaceous hue or bullae. Most patients under 36 month of age are previously healthy. Fever, leukocytosis, and septicemia are nearly universal. Response to treatment with penicillin, or in resistant cases, vancomycin is excellent. As most reported disease was caused by those strains included in the pneumococcal vaccine, this condition will likely become rare, as has occurred with *Haemophilus influenzae* cellulites. Chronically ill or immunosuppressed adults also may develop pneumococcal cellulitis. In patients with diabetes or substance abuse extremity involvement is the rule, while in those with systemic lupus erythematosus, nephritic syndrome, hematologic disorders or HIV disease, the head, neck and upper torso are typically affected. Septicemia, tissue necrosis, and suppurative complications are frequent so aggressive management with surgical drainage and intravenous antibiotics directed at the susceptibility of the cultured organism is vital.

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Anthrax

Cutaneous anthrax is an uncommon event in much of the world as human infection generally results from infected animals or the handling of hides or other animal products from stock that has died from splenic fever. Cattlemen, woolsorters, tanners, butchers, and workers in the goat-hair industry are most liable to infection. Human-to-human transmission has occurred from contact with dressings from lesions. The threat of bioterrorism and delivery of *Bacillus anthracis* spores through the mail which resulted in outbreaks of disease in the US has led to renewed interest in this condition.

Anthrax is an acute infectious disease characterized by a rapidly necrosing, painless eschar with suppurative regional adenitis. Three forms of the disease occur in humans: cutaneous, accounting for 95% of cases worldwide but nearly all US cases; inhalation, known as *woolsorter's disease*; and gastrointestinal, not yet reported in the US. The first clinical manifestation of the cutaneous form is an inflammatory papule, which begins about 3 to 5 days after inoculation, usually on an exposed site. The inflammation develops rapidly so that there is a bulla surrounded by intense edema and infiltration within another 24 to 36 h. It then ruptures spontaneously and a dark brown or black eschar is then visible surrounded by vesicles situated on a red, hot, swollen, and indurated area. The lesion is neither tender nor painful. This is of diagnostic importance. Pustules are almost never present. The regional lymph glands become tender, enlarged and frequently suppurate.

In severe cases the inflammatory signs increase; there is extensive edematous swelling and other bullae and necrotic lesions develop, accompanied by a high temperature and

prostration, terminating in death in a few days or weeks. This may occur in up to 20% of untreated cases. In mild cases the constitutional symptoms are sometimes slight; the gangrenous skin sloughs and the resulting ulcer heals.

Internally, inhalation anthrax is manifested as a necrotizing, hemorrhagic mediastinal infection. Anthrax spores involve the alveoli, then the hilar and tracheobronchial nodes. Bacteremia followed by hemorrhagic meningitis is the usual sequence of events, almost always ending in death. Gastrointestinal anthrax results when spores are ingested and multiply in the intestinal submucosa. A necrotic ulcerative lesion in the terminal ileum or cecum may lead to hemorrhage.

The disease is produced by *Bacillus anthracis*, a large, square-ended, rod-shaped, Gram-positive organism, which occurs singly or in pairs in smears from the blood or in material from the local lesion, or in long chains on artificial media, where it tends to form spores. The bacillus possesses three virulence factors: a polyglutamate acid capsule inhibits phagocytosis; an edema toxin composed of edema factor and a transport protein termed *protective antigen*; and lethal toxin, composed of lethal factor plus protective antigen.

A biopsy should be obtained as this allows for immunohistochemical and polymerase chain reaction (PCR) studies, as well as routine histology and tissue Gram stain. Microscopically, there is loss of the epidermis at the site of the ulcer, with surrounding spongiosis and intraepidermal vesicles. Leukocytes are abundant in the epidermis. The dermis is edematous and infiltrated with abundant erythrocytes and neutrophils. Vasodilation is marked. The causative organisms are numerous and are easily seen, especially with Gram stain.

The diagnosis is made by the demonstration of the causative agent in smears and cultures of the local material. Because aerobic nonpathogenic bacilli may be confused with *B. anthracis*, a specific γ-bacteriophage may be used to identify the organism. All virulent strains are pathogenic to mice. A four-fold rise in the enzyme-linked immunosorbent assay (ELISA) titer in paired serum specimens for antibodies against protective antigen or capsular antigens confirms the diagnosis. The characteristic gangrenous lesion, surrounded by vesiculation, intense swelling, and redness, lack of pain, and the occupation of the victim are accessory factors. Staphylococcal carbuncle is the most easily confused entity, but here tenderness is prominent.

Early diagnosis and prompt treatment with ciprofloxacin, 500 mg, or doxycycline, 100 mg, both given twice a day for 60 days, is curative in the cutaneous form when there are no systemic symptoms, lesions are not on the head or neck and are without significant edema, and the patient is not a child under 2. In these latter conditions, more aggressive intravenous therapy is required, as outlined in the CDC management guidelines available at the CDC website. Asymptomatic exposed individuals should be given prophylactic treatment with a 6-week course of doxycycline or ciprofloxacin. A vaccine is approved and alternate vaccines are being developed.

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Listeriosis

Listeria monocytogenes is a Gram-positive bacillus with rounded ends that may be isolated from soil, water, animals, and asymptomatic individuals. Human infection probably occurs via the gastrointestinal tract; however, in the majority of patients the portal of entry is unknown. Infections in man usually produce meningitis or encephalitis with monocytosis. Risk factors include alcoholism, advanced age, pregnancy, and immunosuppression.

Cutaneous listeriosis is a rare disease. Owens reported a veterinarian who contracted cutaneous listeriosis from an aborting cow. The organism in the skin lesions was identical to that isolated from the fetus. The eruption consisted of erythematous tender papules and pustules scattered over the hands and arms. There were axillary lymphadenopathy, fever, malaise, and headache. Treatment with sulfonamides caused the disease to disappear within a few days.

Neonates are also at risk. Smith et al reported a newborn of an HIV-infected mother who died with a diffuse papular, petechial, and pustular eruption secondary to disseminated listeriosis. *Listeria* may cause a granulomatous disease of infants (granulomatosis infanta peptica). The endocarditis, meningitis, and encephalitis caused by listeria may be accompanied by petechiae and papules in the skin.

Cases of listeriosis may easily be missed on bacteriologic examination, because the organism produces few colonies on original culture and may be dismissed as a streptococcus or as a contaminant diphtheroid because of the similarity in Gram-stained specimens. Serologic tests help to make the diagnosis.

L. monocytogenes is sensitive to most antibiotics. Ampicillin is the recommended antibiotic of choice, trimethoprim–sulfamethoxazole an effective alternate agent.

Owens CR, et al: Case of primary listeriosis. N Engl J Med 1960;262:1026.

Posfay-Barbe K, et al: Listeriosis. Pediatr Rev 2004;25:151.

Smith KJ, et al: Diffuse petechial pustular lesions in a newborn. Arch Dermatol 1994;130:243.

Cutaneous Diphtheria

The skin may become infected by the Klebs-Loeffler bacillus, *Corynebacterium diphtheriae*, in the form of ulcerations. The ulcer is punched-out and has hard, rolled, elevated edges with a pale blue tinge (Fig. 14-25). Often the lesion is covered with a leathery, grayish membrane. Regional lymph nodes may be affected. Another type of skin involvement is that occurring in eczematous, impetiginous, vesicular, or pustular scratches, from which *C. diphtheriae* may be

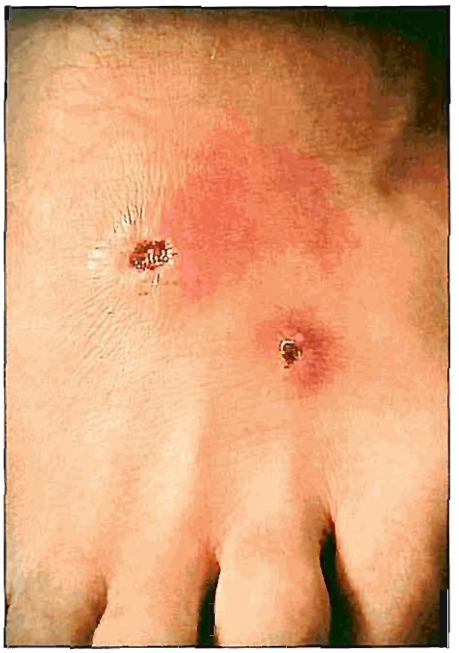

Fig. 14-25 Cutaneous diphtheria.

recovered. Post-diphtherial paralysis and potentially fatal cardiac complications may occur. These are mediated by a potent exotoxin, which stops protein production at the ribosome level.

Cutaneous diphtheria is common in tropical areas. Most of the cases occurring in the US are in nonimmunized migrant farm worker families and in elderly alcoholics. Travelers to third world countries may also import disease.

Treatment consists of intramuscular injections of diphtheria antitoxin, 20,000 to 40,000 U, after a conjunctival test has been performed to rule out hypersensitivity to horse serum. One drop of antitoxin diluted 1:10 is placed in one eye and a drop of saline in the other eye. If after 30 min there is no reaction 20,000 to 40,000 U of antitoxin is given. Erythromycin, 2 g/day, is the drug of choice, unless large proportions of resistant organism are known in the area. In severe cases intravenous penicillin G, 600,000 U/day for 14 days is indicated. Rifampin, 600 mg/day for 7 days, will eliminate the carrier state.

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Group JK *Corynebacterium* Sepsis

Group JK *Corynebacterium (C. jeikeium)* colonize the skin of healthy individuals, with highest concentration being in the axillary and perineal areas. Hospitalized patients are more heavily colonized. Patients with granulocytopenia, indwelling catheters, prosthetic devices, exposure to multiple antibiotics, and valvular defects are at highest risk for the development of sepsis or endocarditis. A papular eruption, cellulitis, subcutaneous abscesses, tissue necrosis, and palpable purpura may be seen on the skin. Vancomycin is the drug of choice. Mortality is over 30% in those with leukopenia, but only 5% if the marrow recovers. Hematopoetic growth factors should then be considered adjunctive therapy in these patients.

Jucgla A, et al: Papular eruption secondary to infection with *Corynebacterium jeikeium*, with histopathological features mimicking botryomycosis. Br J Dermatol 1995;133:801.

van der Lelie H, et al: Corynebacterium CDC group JK (*Corynebacterium jeikeium*) sepsis in haematological patients. Scand J Infect Dis 1995;27:581.

Desert Sore

Also known as *veldt sore*, *septic sore*, *diphtheric desert sore*, and *Barcoo rot*, desert sore is an ulcerative disease that is endemic among bushmen and soldiers in Australia and Burma. The disease is characterized by the occurrence of grouped vesicles on the extremities, chiefly on the shins, knees, and backs of the hands. These rupture and form superficial indolent ulcers. The ulcers enlarge and may attain a diameter of 2 cm. The floor of the ulcer may be covered by a diphtheritic membrane. The original lesions may start as insect bites. Cultures show staphylococci, streptococci, and *Corynebacterium diphtheriae*. Treatment of the desert sore is with diphtheria antitoxin if *C. diphtheriae* is present. Antibiotic ointments are used topically, and oral penicillin or erythromycin is the treatment of choice.

Bailey H: Ulcers of the leg and their differential diagnosis. Dermatol Trop 1962;1:45.

Tropical Ulcer

Tropical ulcer is also known as *tropical phagedena*, Aden ulcer, Malabar ulcer, and jungle rot, as well as various native terms. It occurs on exposed parts of the body, chiefly the legs and arms, frequently on preexisting abrasions or sores, sometimes beginning from a mere scratch. As a rule, only one extremity is affected and usually there is a single lesion, although it is not uncommon to find multiple ulcers on both legs. Satellite lesions ordinarily occur as a result of autoinoculation.

The lesions begin with inflammatory papules that progress into vesicles and rupture with the formation of an ulcer. The ulcers vary in diameter and may, through coalescence, form extensive lesions. The lesions of some varieties are elevated or deeply depressed and generally the edges are undermined and either smooth or ragged. At times the ulcers are covered by thick, dirty crusts or by whitish pseudomembranes. The edges are flat, without thickening, and around them there is a zone of inflammation characterized by redness, swelling, and some tenderness. Other than a slight itching, there is usually no distress.

The disease is most common in native laborers and in schoolchildren during the rainy season; it is probably caused in many instances by the bites of insects, filth, and pyogenic infection. Malnutrition appears to be a predisposing factor.

Tropical ulcer is a descriptive term used when more specific etiologic classification is not documented. If investigated microbiologically anaerobic bacteria together with aerobes, some of them facultative anaerobes, are present in early lesions. The differential diagnosis includes a wide variety of conditions. The septic desert ulcer is superficial and shows

C. diphtheriae. The gummatous ulcer is punched out, with a sinking floor. Other signs of syphilis are present, and the serologic test for syphilis is positive. The tuberculous ulcer is undermined and usually not found on the leg. The mycobacterium can be isolated from the lesion. The mycotic ulcer is noduloulcerative, with demonstrable fungi both by direct microscopic examination and by culture. The frambesia ulcer grows rapidly and yields *Treponema pertenue*. The Buruli ulcer shows abundant *Mycobacterium ulcerans* in biopsies. The leishmanial ulcer contains *Leishmania tropica*; it is not usually found on the leg. Carcinoma must be considered in any leg ulcer of long duration. A biopsy is indicated.

The arteriosclerotic ulcer is seen in older people at sites of frequent trauma; it is deep and penetrates through the deep fascia to expose tendons. The hypertensive ischemic ulcer is caused by thrombosis of the cutaneous arterioles. These painful ulcers are extremely shallow, usually bilateral, and seen most frequently on the mid and lower parts of the leg. Varicosities are usually absent. The varicose or venous ulcer is shallow and has irregularly shaped edges. It is located typically on the lower half of the shins, mostly above and anterior to the medial malleolus along the course of the long saphenous vein.

The ulcers of blood dyscrasias are frequent in sickle cell anemia, in hereditary spherocytosis, Mediterranean anemia, and Felty syndrome. The diagnosis is aided by the fact that there is hypersplenism in each of these diseases. The ulcer of rheumatoid arthritis occurs frequently in patients who have abundant concomitant subcutaneous nodules. The ulcer of Kaposi sarcoma frequently occurs on the lower extremities and is accompanied by a purpuric discoloration of the skin and by other violaceous nodules that may occur anywhere on the body. In the tropics it is endemic among the South African Bantus.

Prevention of the disease is aided by protection from insect bites and from predisposing causes, such as debility, malnutrition, and filth. Topical and systemic antibiotic treatment is indicated in most patients.

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Aribi M, et al: Tropical phagendenic ulcer. Eur J Dermatol 1999; 9:321.
MacDonald P. Tropical ulcers. J Wound Care 2003;12:85.

Erythrasma

Erythrasma is characterized by sharply delineated, dry, brown, slightly scaling patches occurring in the intertriginous areas, especially the axillae, the genitocrural crease (Fig. 14-26), and the webs between the fourth and fifth toes and, less commonly, between the third and fourth toes. There may also be patches in the intergluteal cleft, perianal skin, and inframammary area. Rarely, widespread eruptions with lamellated plaques occur.

The lesions are asymptomatic except in the groins, where there may be some itching and burning. Patients with extensive erythrasma have been found to have diabetes mellitus or other debilitating diseases.

Erythrasma is caused by the diphtheroid *Corynebacterium minutissimum*. This Gram-positive non–spore-forming rod-shaped organism may occasionally cause cutaneous granulomas or bacteremia in immunocompromised patients. Two other diseases caused by a corynebacterium, pitted keratolysis and trichomycosis axillaris, may occur as a triad. In the differential diagnosis, tinea cruris caused by fungi, intertrigo, seborrheic dermatitis, inverse psoriasis, candidiasis, and lichen simplex chronicus must be considered

The Wood's light is the diagnostic medium for erythrasma. The affected areas show a coral red fluorescence, which results from the presence of a porphyrin. Washing of the affected area before examination may eliminate the fluorescence. Topical erythromycin solution or topical clindamycin is easily applied and rapidly effective. Oral erythromycin, 250 mg four times a day for 1 week, or tolnaftate solution applied twice a day for 2 to 3 weeks or topical miconazole is equally effective.

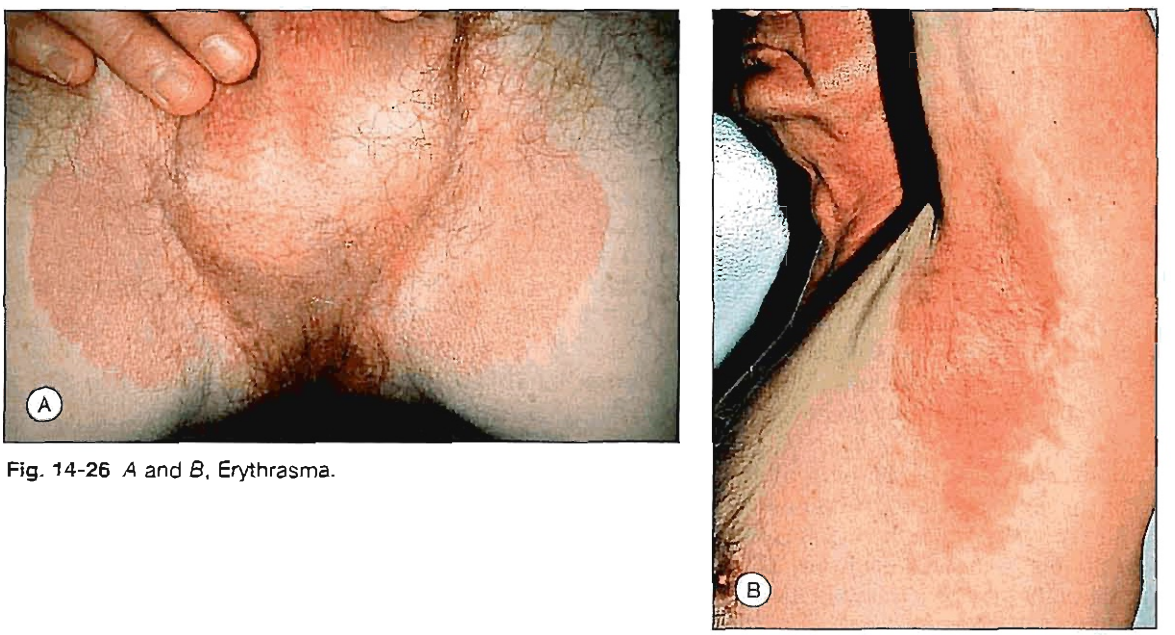

Fig. 14-26 *A* and *B*, Erythrasma.

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Arcanobacterium Haemolyticum Infection

This pleomorphic, nonmotile, non-spore-forming, beta-hemolytic, Gram-positive bacillus causes pharyngitis and an exanthem in young adults. Acute pharyngitis in the 10- to 30-year-old age group is only due to group A streptococci 10% to 25% of the time. A proportion of the remainder will be caused by *Arcanobacterium haemolyticum*.

The exanthem is an erythematous morbilliform or scarlatiniform eruption involving the trunk and extremities. Although it usually spares the face, palms, and soles, atypical acral involvement has been reported. The general clinical presentation may include mild pharyngitis, severe diphtheria-like illness, or even septicemia.

Cultures for this organism should be done on 5% blood agar plates and observed for 48 h. The diagnostic features are enhanced by a 5% to 8% CO_2 atmosphere during incubation at 37° C. Routine pharyngeal specimens are done on sheep blood agar and will miss the growth of this organism because of its slow hemolytic rate and growth of normal throat flora. Treatment of choice is erythromycin, or in the case of severe infection, high-dose penicillin G.

Gaston DA, Zurowski SM: *Arcanobacterium haemolyticum* pharyngitis and exanthem. Arch Dermatol 1996;132:61.

Mehta CL: *Arcanobacterium haemolyticum*. J Am Acad Dermatol 2003;48:298.

Intertrigo

Intertrigo is a superficial inflammatory dermatitis occurring where two skin surfaces are in apposition. It is discussed here because of its clinical association with several diseases in this chapter. As a result of friction (skin rubbing skin), heat, and moisture, the affected fold becomes erythematous, macerated, and secondarily infected. There may be erosions, fissures, and exudation, with symptoms of burning and itching. Intertrigo is most frequently seen during hot and humid weather, chiefly in obese persons. Children and the elderly are also predisposed. This type of dermatitis may involve the retroauricular areas; the folds of the upper eyelids; the creases of the neck, axillae, antecubital areas; finger webs; inframammary area; umbilicus; inguinal, perineal, and intergluteal areas; popliteal spaces; and toe webs.

As a result of the maceration, a secondary infection by bacteria (or fungi) is induced. The inframammary area in obese women is most frequently the site of intertriginous candidiasis. The groins are also frequently affected by fungal (yeast or dermatophyte) infection. Bacterial infection may be caused by streptococci, staphylococci, pseudomonas, or corynebacteria.

In the differential diagnosis, seborrheic dermatitis typically involves the skinfolds. Intertriginous psoriasis and erythrasma are frequently overlooked, especially when the inguinal and intergluteal areas or fourth toe webs are involved, as in erythrasma. Fissured groin lesions may be a manifestation of Langerhans cell histiocytosis.

Treatment is directed toward the elimination of the maceration. Appropriate antibiotics or fungicides are applied locally. The apposing skin surfaces may be separated with gauze or other appropriate dressings. Castellani paint is also useful, as is Polysporin ointment. Low potency topical corticosteroids and topical tocrolimus are helpful to reduce inflammation, but should always be used in conjunction with a topical antifungal or antimicrobial agent.

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Honig PJ, et al: Streptococcal intertrigo. Pediatrics 2003; 112:1427.

Laube S, et al: Bacterial skin infections in the elderly. Drugs Aging 2002;19:331.

Pitted Keratolysis

This bacterial infection of the plantar stratum corneum was first named keratoma plantare sulcatum by Castellani in 1910, but was given its present name, *pitted keratolysis*, by Taplin and Zaias in 1967. The thick, weight-bearing portions of the soles become gradually covered with shallow asymptomatic discrete round pits 1 to 3 mm in diameter, some of which become confluent, forming furrows (Fig. 14-27). Men with very sweaty feet during hot, humid weather are most susceptible. Rarely, palmar lesions may occur. No discomfort is produced, though the lesions are often malodorous.

The causative organism is still debated; however, *Kytococcus sedentarius* has been implicated as the primary pathogen and produces two serine proteases which can degrade keratin. Clinical diagnosis is not difficult, based on its unique appearance. Histologic examination generally demonstrates keratin pits lined by small cocci as well as filamentous bacteria.

Topical erythromycin or clindamycin, are curative. Miconazole or clotrimazole cream and Whitfield ointment are effective alternatives. Both 5% benzoyl peroxide gel and a 10% to 20% solution of aluminum chloride may be used. Botulinum toxin helps if there is associated hyperhidrosis.

Shah AS, et al: Painful, plaque-like, pitted keratolysis occurring in childhood. Pediatr Dermatol 1992;9:251.

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Clostridial Infections and Gangrene of the Skin (Dermatitis Gangrenosa)

Gangrene of the skin results from loss of the blood supply of a particular area and, in some instances, from bacterial invasion that promotes necrosis and sloughing of the skin. The various forms of bacterial infections causing gangrene will be discussed here. The infectious causes are often severe and acute in nature. These may involve deep tissues and MRI may delineate the depth of involvement. Vascular gangrene,

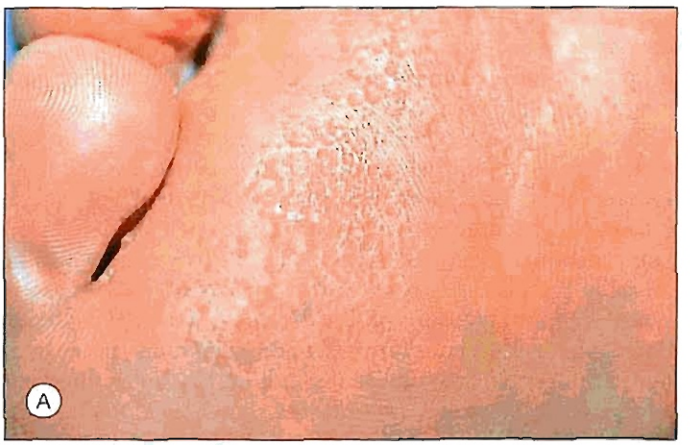
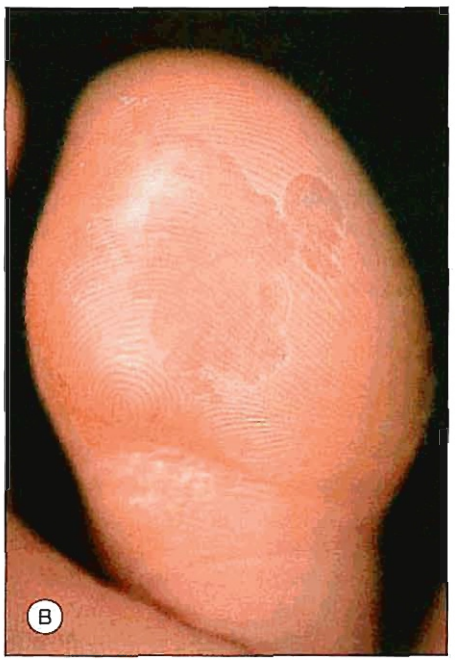


Fig. 14-27 *A* and *B*, Pitted keratolysis.



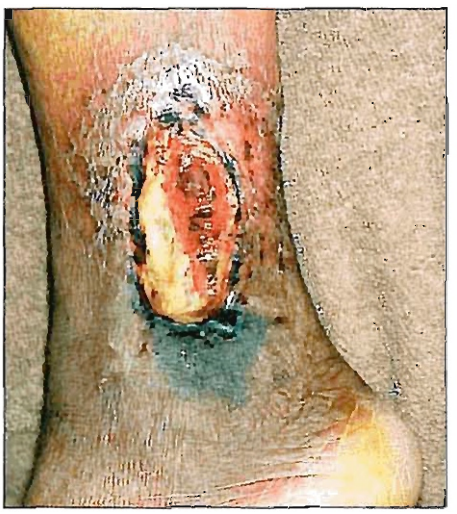


Fig. 14-28 Clostridial gas gangrene.

purpura fulminans, and diabetic gangrene are covered in Chapter 35; vaccinia gangrenosa in Chapter 19; and necrotizing fasciitis in earlier in this chapter.

Gas Gangrene (Clostridial Myonecrosis) Gas gangrene is the most severe form of infectious gangrene; it develops in deep lacerated wounds of muscle tissue (Fig. 14-28). The incubation period is only a few hours. Onset is usually sudden and is characterized by a chill, a rise in temperature, marked prostration, and severe local pain. Gas bubbles (chiefly hydrogen) produced by the infection cause crepitation when the area is palpated. A mousy odor is characteristic. Gas gangrene is caused by a variety of species of the genus *Clostridium*, most frequently *Clostridium perfringens*, *Clostridium oedematiens*, *Clostridium septicum*, *Clostridium difficile*, and *Clostridium haemolyticum*. These are thick, Gram-positive rods.

A subacute variety occurs, which may be due to an anaerobic streptococcus (peptostreptococcus), Bacteroides, or Prevotella. This nonclostridial myositis may be clinically similar, but with delayed onset (several days). The purulent exudate has a foul odor, and Gram-positive cocci in chains are present. It is important to distinguish these two entities, since involved muscle may recover in nonclostridial myositis, and debridement may safely be limited to removal of grossly necrotic muscle. Infections with both clostridial and nonclostridial organisms such as *Streptococcus faecalis*, *Streptococcus anginosus*, *Proteus*, *E. coli*, *Bacteroides*, and *Klebsiella* species may also cause crepitant cellulitis, when the infection is limited to the subcutaneous tissue. Treatment of all clostridial infections is wide surgical debridement and intensive antibiotic therapy with intravenous penicillin G. Clindamycin is added as up to half of the infections are polymicrobial. Hyperbaric oxygen therapy may be of value if immediately available. Infections in patients with cirrhosis and diabetes have a poorer prognosis.

Chronic Undermining Burrowing Ulcers (Meleney Gangrene) This entity was first described by Meleney as postoperative progressive bacterial synergetic gangrene. It usually follows drainage of peritoneal abscess, lung abscess, or chronic empyema. After 1 or 2 weeks the wound markings or retention suture holes assume a carbunculoid appearance, finally differentiating into three skin zones: outer, bright red; middle, dusky purple; and inner, gangrenous with a central area of granulation tissue. The pain is excruciating. In Meleney postoperative progressive gangrene, the essential organism is a microaerophilic, non-hemolytic streptococcus (peptostreptococcus) in the spreading periphery of the lesion, associated with *S. aureus* or *Enterobacteriaceae* in the zone of gangrene. This disease is differentiated from ecthyma gangrenosum, which begins as vesicles rapidly progressing to pustulation and gangrenous ulceration in debilitated subjects, and is due to *P. aeruginosa*. Amebic infection with gangrene usually follows amebic abscess of the liver. The margins of the ulcer are raised and everted, and the granulations have the appearance of raw beef covered with shreds of necrotic material. Glairy pus can be expressed from the margins. Pyoderma gangrenosum occurs in a different setting, lacks the bacterial findings, and does not respond to antibiotic therapy. Fusospirochetal gangrene occurs following a human bite.

Wide excision and grafting are primary therapy. Antimicrobial agents, penicillin, and an aminoglycoside should be given as adjunctive therapy.

Fournier Gangrene of the Penis or Scrotum

Fournier syndrome is a malignant gangrenous infection of the penis, scrotum, or perineum, which may be due to infection with group A streptococci or a mixed infection with enteric bacilli and anaerobes. This is usually considered a form of necrotizing fasciitis, as it spreads along fascial planes. Peak incidence is between 20 and 50 years, but cases have been reported in children. Culture for aerobic and anaerobic organisms should be done, and appropriate antibiotics started; surgical debridement and general support should be instituted.

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Majeski JA, et al: Necrotizing soft tissue infections. South Med J 2003;96:900.

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Schexnayder SM, et al: Images in clinical medicine: gas gangrene. NEJM 2004;350:2603.

Singh G, et al: Necrotising infections of soft tissues—a clinical profile. Eur J Surg 2002;168:366.

Wang C, et al: Hyperbaric oxygen for treating wounds: a systematic review of the literature. Arch Surg 2003;138:272.

Actinomycosis

Actinomycosis is an anaerobic, Gram-positive, filamentous bacteria. Infections are seen most often in the cervicofacial area but also commonly on the abdominal region, thoracic area or pelvis. Middle-aged men are affected most often. The lesions begin as firm nodules or plaques and develop draining sinuses. Grains or sulfur granules may be present in the exudate, just as in fungal mycetomas. In the cervicofacial region, the infection is known as lumpy jaw. The underlying bone may be involved with periostitis or osteomyelitis. Mandibular infection is seen four times as often as maxillary involvement (Fig. 14-29). When the gastrointestinal system is involved, the cecum and appendix are the more commonly affected sites. Extension into the abdomen and then the abdominal wall may produce draining sinuses on the abdominal skin. In the oropharynx, actinomycotic grains are normally found in tonsillar crypts. In the thoracic region, lung infection may spread to the thoracic wall.

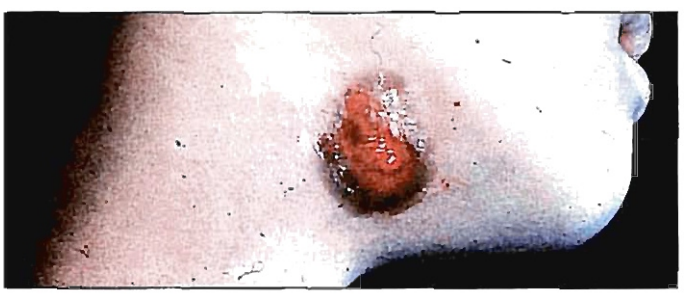

Fig. 14-29 Actinomycosis.

Oropharyngeal actinomycosis is caused by *Actinomyces israelii* and *Actinomyces gerencseriae*. *Actinomyces radingae* is frequently associated with chronic skin and soft tissue infections. *Actinomyces europaeus* is associated with skin and genital involvement. *Actinomyces turicensis* may also be found in the skin.

Sulfur granules consist of fine delicate branching filaments. Eosinophilic clubs composed of immunoglobulin are seen at the periphery of the granule (Splendore-Hoeppli's phenomenon). They resemble rays; hence the name, ray fungus (*Actinomyces*). Gram stain demonstrates long Gram-positive filaments.

The crushed granule is used for inoculating cultures containing brain–heart infusion blood agar, incubated under anaerobic conditions at 37° C. Culture is difficult, therefore direct microscopy is important.

Penicillin G in large doses, 10 to 20 MU/day for 1 month, followed by 4 to 6 g/day of oral penicillin for another 2 months, may produce successful and lasting results. Other effective medications have been ampicillin, erythromycin, tetracyclines, ceftriaxone, and clindamycin. Surgical incision, drainage, and excision of devitalized tissue are important.

Clarridge JE 3rd, et al: Genotypic diversity of clinical Actinomyces species: phenotype, source, and disease correlation among genospecies. J Clin Microbiol 2002;40:3442.

Kargi E, et al: Primary extremity actinomycosis causing osteomyelitis of the hand. Plast Reconstr Surg 2003;112:1495.

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Xia T, et al: Occurrence of Actinomyces in infections of endodontic origin. J Endod 2003;29:549.

Nocardiosis

Nocardiosis usually begins as a pulmonary infection from which dissemination occurs. Disseminated disease occurs most commonly in association with debilitating disease, such as Hodgkin's disease, periarteritis nodosa, leukemia, AIDS, organ transplants, or systemic lupus erythematosus. Skin involvement is seen in 10% of disseminated cases in the form of abscesses or veiculopusutal lesions (Fig. 14-30). Primary cutaneous disease also occurs in healthy individuals in the form of actinomycetoma or lymphangitic nodules following a cutaneous injury.

Nocardia asteroides is usually responsible for this disseminated form of nocardiosis. *Nocardia brasiliensis* is the most common cause of primary cutaneous disease. A prick by a thorn or briar, other penetrating injury, or an insect bite or sting may be the inciting event.

Nocardia are Gram-positive, partially acid-fast, aerobic, filamentous bacteria. Some are branched, but filaments tend to be shorter and more fragmentary than those of *Actinomyces*. The surrounding red layer of immunoglobulin tends to be smooth rather than club shaped. On Sabouraud dextrose agar, without antibacterial additives, there are creamy or moist, white colonies, which later become chalky and orange-colored.

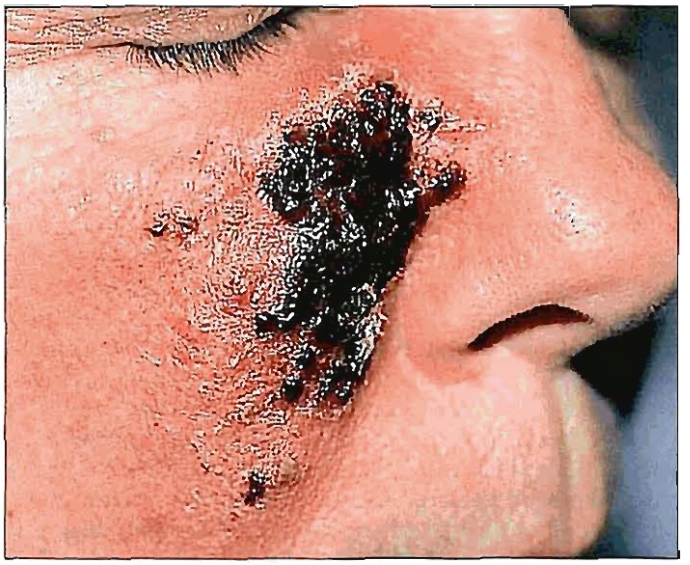

Fig. 14-30 Nocardiosis.

Trimethoprim–sulfamethoxazole (Bactrim, Septra), four tablets twice a day for 6 to 12 weeks, is the drug of first choice. Minocycline for *N. asteroides* and Augmentin for *N. brasiliensis* are alternatives. Amikacin has been used in combination with a variety of other antibiotics. Synergism has been observed with amikacin in combination with cefotaxime, imipenem or sparfloxacin.

Corti ME, et al: Nocardiosis: a review. Int J Infect Dis 2003;7:243.
Kanemitsu K, et al: Efficacy of amikacin combinations for nocardiosis. Tohoku J Exp Med 2003;201:157.
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Smego RA Jr, et al: Lymphocutaneous syndrome. A review of non-sporothrix causes. Medicine (Baltimore) 1999;78:38.
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INFECTIONS CAUSED BY GRAM-NEGATIVE ORGANISMS

PSEUDOMONAS INFECTIONS

Ecthyma Gangrenosum

In the gravely ill patient opalescent, tense vesicles or pustules are surrounded by narrow pink to violaceous halos. These lesions quickly become hemorrhagic and violaceous, and rupture to become round ulcers with necrotic black centers (Fig. 14-31). They are usually on the buttocks and extremities and are often grouped closely together.

Ecthyma gangrenosum occurs in debilitated persons who may be suffering from leukemia, in the severely burned patient, in pancytopenia or neutropenia, in patients with a functional neutrophilic defect, terminal carcinoma, or other severe chronic disease. Healthy infants may develop lesions in the perineal area after antibiotic therapy in conjunction with maceration of the diaper area.

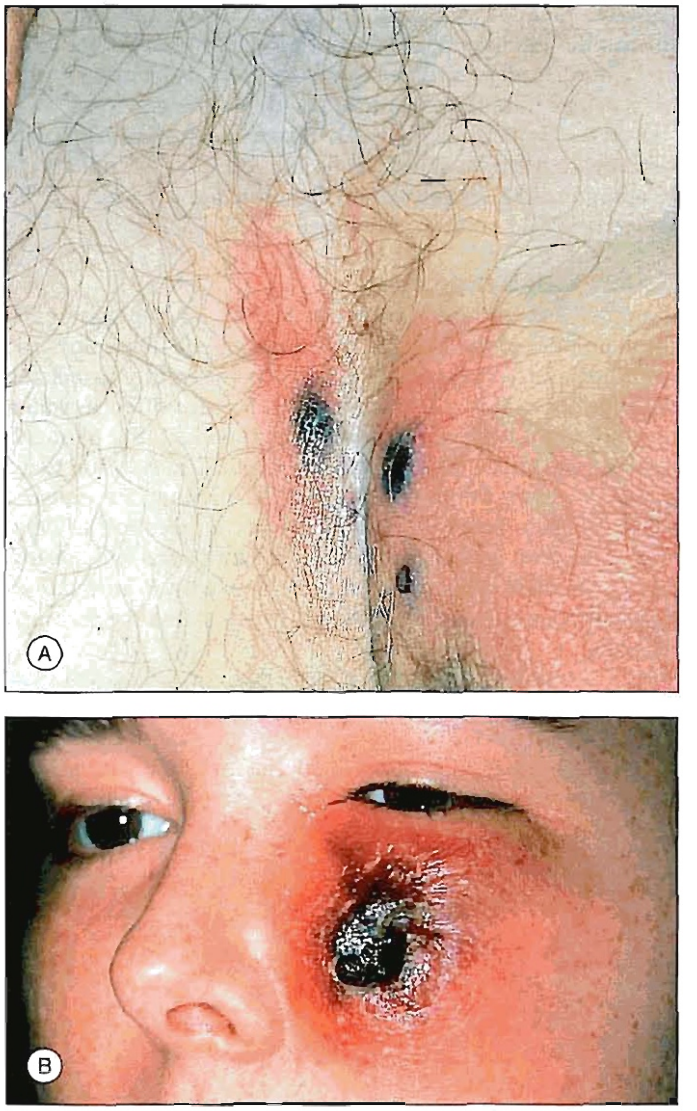

Fig. 14-31 *A* and *B*, Ecthyma gangrenosum.

The classic vesicle suggests the diagnosis. The contents of the vesicles or hemorrhagic pustules will show Gram-negative bacilli on Gram stain and cultures will be positive for *P. aeruginosa*. As this is usually a manifestation of sepsis, the blood culture will show *P. aeruginosa*. However, in healthy infants with diaper-area lesions, in patients with HIV infection, and in other occasional cases, early lesions may occur at the portal of entry, allowing for diagnosis and treatment before evolution into sepsis occurs.

Treatment is the immediate institution of intravenous antipseudomonal medications. An aminoglycoside in combination with an antipseudomonal penicillin is recommended. The addition of granulocyte–macrophage colony-stimulating factor to stimulate both proliferation and differentiation of myeloid precursors is an adjunct in a patient with myelodysplasia or treatment-induced neutropenia. Patients have a poorer prognosis if there are multiple lesions, if there is a delay in diagnosis and institution of appropriate therapy, and if neutropenia does not resolve by the end of a course of antibiotics. Instrumentation or catheterization increases the risk of this infection.

Other lesions are also seen with *Pseudomonas* septicemia. These may be sharply demarcated areas of cellulitis, macules,

papules, plaques, and nodules, characteristically found on the trunk. *Pseudomonas mesophilica*, *Citrobacter freundii*, and *Stenotrophomonas maltophilia* may also produce such skin lesions in immunocompromised individuals.

Several patients with AIDS have been reported who developed nodular skin lesions or abscesses secondary to *P. aeruginosa*. Generally, these patients are systemically ill; however, blood cultures are negative.

Green Nail Syndrome

Green nail syndrome is characterized by onycholysis of the distal portion of the nail and a striking greenish discoloration in the separated areas (Fig. 14-32). It is frequently associated with paronychia in persons whose hands are often in water. Overgrowth of *P. aeruginosa* accounts for the pigment. Soaking the affected finger in a 1% acetic acid solution twice a day has been found to be helpful. Trimming the onycholytic nail plate followed by twice a day application of Neosporin solution is also effective. Green foot syndrome results from colonization of rubber sports shoes with *P. aeruginosa*. The organism produces pyoverdin which stains the foot and toenails.

Gram-Negative Toe Web Infection

This type of infection often begins with dermatophytosis. Dermatophytosis may progress with increasing inflammation, maceration, and inflammation to dermatophytosis complex, where many types of Gram-negative organisms may be recovered, but it is harder to culture dermatophytes. Finally, denudation with purulent or serous discharge and marked edema and erythema of the surrounding tissue may be seen (Fig. 14-33). Prolonged immersion may also cause hydration and maceration of the interdigital spaces, with overgrowth of Gram-negative organisms. *P. aeruginosa* is the most prominent among them, but commonly a mixture of other Gram-negative organisms, such as *E. coli* and *Proteus* are present. Patients may suffer from red, painful nodules of the calf that do not drain, spontaneously involute, then reappear 1 to 2 weeks later. Culture of these subcutaneous abscesses will reveal *Pseudomonas* or other Gram-negatives, which likely originate in the macerated toe webs.

Early dermatophytosis, dermatophytosis simplex, may simply be treated with topical antifungals. However, once the scaling and peeling progress to white maceration, soggy scaling, bad odor, edema, and fissuring, treatment must also include topical antibiotics or acetic acid compresses. Full-blown Gram-negative toe web infection with widespread denudation and erythema, purulence, and edema requires systemic antibiotics. A third-generation cephalosporin or a fluoroquinolone is recommended.

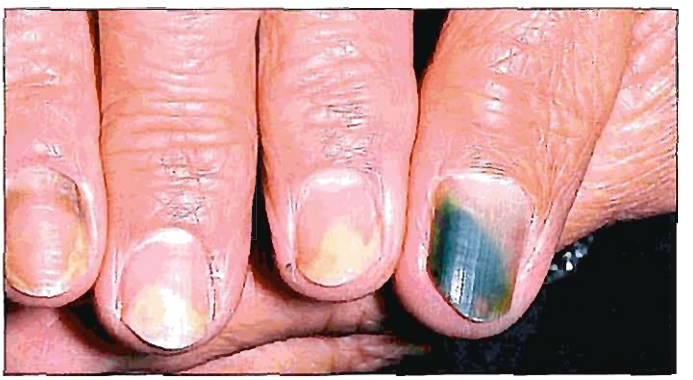

Fig. 14-32 Green nail syndrome complicating onycholysis.

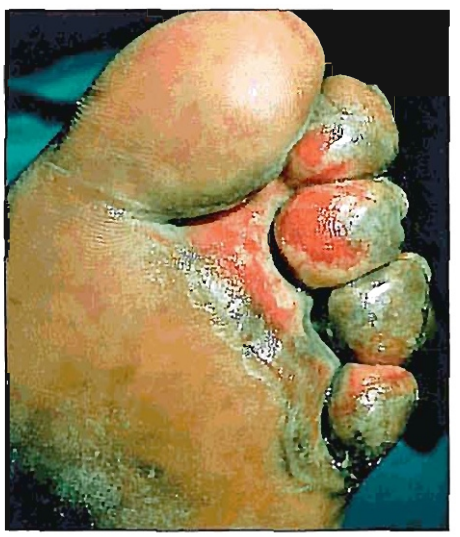

Fig. 14-33 Gram-negative toe web infection.

Blastomycosis-Like Pyoderma

Large verrucous plaques with elevated borders and multiple pustules may occur as a chronic vegetating infection. Most patients have an underlying systemic or local host compromise. Bacteria such as *P. aeruginosa*, *S. aureus*, *Proteus*, *E. coli*, or streptococci may be isolated.

Pseudomonas Aeruginosa Folliculitis (Hot Tub Folliculitis)

Pseudomonas folliculitis is characterized by pruritic follicular, maculopapular, vesicular, or pustular lesions occurring within 1 to 4 days after bathing in a hot tub, whirlpool, or public swimming pool (Fig. 14-34). As the water temperature rises, free chlorine levels fall, even though total chlorine levels appear adequate. This allows the bacteria to proliferate. Diving suits may become colonized and wearing them may result in *P. aeruginosa* folliculitis. Most lesions occur on the sides of the trunk, axillae, buttocks, and proximal extremities. The apocrine areas of the breasts and axilla are

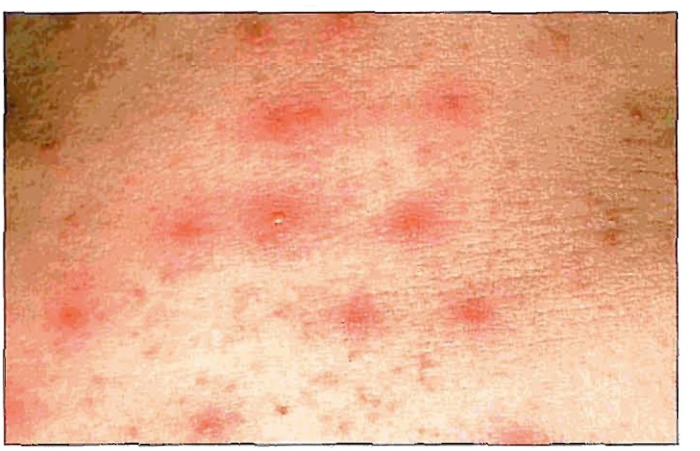

Fig. 14-34 Pseudomonas hot tub folliculitis. (Courtesy of James Fitzpatrick, MD)

often involved. Associated complaints may include earache, sore throat, headache, fever, and malaise. Rarely, systemic infection may result; breast abscess and bacteremia have been reported. Large outbreaks have occurred.

The folliculitis involutes usually within 7 to 14 days without therapy, although on occasion multiple prolonged recurrent episodes have been reported. In patients with fever, constitutional symptoms, or prolonged disease a third-generation oral cephalosporin or a fluoroquinolone such as ciprofloxacin or ofloxacin may be useful. Preventive measures have been water filtration, automatic chlorination to maintain a free chlorine level of 1 ppm, maintenance of water at pH 7.2 to 7.8, and frequent changing of the water. Bromination of the water and ozone ionization are other options.

Pseudomonas hot-foot syndrome was reported in a group of 40 children who developed painful, erythematous plantar nodules or pustules after wading in a community pool whose floor was coated with abrasive grit. One biopsy showed neutrophilic eccrine hidradenitis and one dermal microabsceses. Most were treated symptomatically and resolution occurred within 2 weeks.

External Otitis

Swelling, maceration, and pain may be present. In up to 70% of cases *P. aeruginosa* may be cultured. This is especially common in swimmers. Local applications of antipseudomonal and anti-inflammatory Cortisporin Otic Solution or Suspension, or 2% acetic acid compresses with topical steroids, will help clear this infection. Application of Otic Domeboro solution after swimming will help prevent recurrence. Fungi such as *Candida* and *Aspergillus* are other causes. Antifungal solutions, such as ciclopiroxolamine solution, combined with steroid solutions are effective in otomycosis. There is also a threat of external otitis occurring after ear surgery (Fig 14-35). If the patient is a swimmer or has diabetes, acetic acid compresses for a day or two before surgery may prevent this complication.

External otitis must be distinguished from allergic contact dermatitis due to neomycin in Cortisporin Otic Suspension. Allergic contact dermatitis produces severe pruritus, although tenderness may also be noted. Dermatitis may extend down the side of the cheek in a pattern suggesting drainage of the suspension.

A severe type, referred to as *malignant external otitis*, occurs in elderly patients with diabetes or in those immunocompromised with HIV infection, on chemotherapy, or living with organ transplants. The swelling, pain, and erythema are more pronounced, with purulence and a foul odor. Facial nerve palsy develops in 30% of cases, and cartilage necrosis may occur. This is a life-threatening infection in these older, compromised individuals, and requires swift institution and prolonged administration (4–6 weeks) of oral quinolone antibiotics.

Finally, commercial ear piercing of the upper ear cartilage may lead to infection with *Pseudomonas*, with resulting cosmetic deformity a reported complication.

Gram-Negative Folliculitis

Although this is usually due to *Enterobacteriaceae*, *Klebsiella*, *Escherichia*, *Proteus*, or *Serratia* (Fig. 14-36), occasional cases caused by *Pseudomonas* have been seen. They differ from Gram-negative infection in patients with acne in that the site of colonization of *Pseudomonas* is the external ear, and topical therapy alone to the face and ears was sufficient for cure. Finally, an outbreak of Gram-negative pustular dermatitis on the legs, arms, torso, and buttocks occurred in a group of college students who hosted a mud-wrestling social event.

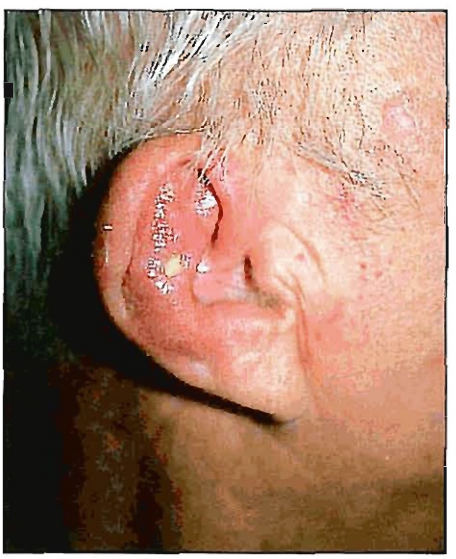

Fig. 14-35 Pseudomonas external otitis after shave biopsy.

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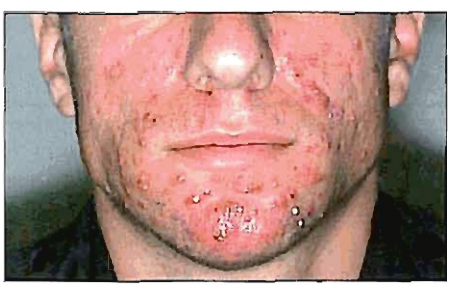

Fig. 14-36 Gram-negative folliculitis.

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MALACOPLAKIA (MALAKOPLAKIA)

This rare granuloma, originally reported only in the genitourinary tract of immunosuppressed renal transplant recipients, may also occur in the skin and subcutaneous tissues of other patients with deficient immune responsiveness such as is present in HIV infection. Patients are unable to resist infections with *S. aureus*, *P. aeruginosa*, and *E. coli*. There is defective intracellular digestion of the bacteria once they have been phagocytized.

The granulomas may arise as yellowish-red papules in the natal cleft, as draining sinuses in the vicinity of the urethra, as perianal ulcers, as a painful draining abscess on the thigh, an inflammatory mass on the neck, or as lesions on the vulva.

Histologically, there are foamy eosinophilic Hansemann macrophages containing calcified, concentrically laminated, intracytoplasmic bodies called *Michaelis-Gutmann bodies*. Scattered immunoblasts, neutrophils, and lymphocytes are found in the dermis.

Successful treatment depends on the isolated organism; a fluoroquinolone such as ciprofloxacin or ofloxacin is usually useful.

Pang C: Malacoplacia manifesting as a chronic inflammatory mass at the site of a nonhealing surgical wound. Ear Nose Throat 2003;82:876.
Schmerber S, et al: Malakoplakia of the neck. Arch Otolaryngol Head Neck Surg 2003;129:1240.
Wittenberg GP, et al: Cutaneous malacoplakia in a patient with AIDS. Arch Dermatol 1998;134:244.

HAEMOPHILUS INFLUENZAE CELLULITIS

Haemophilus influenzae type B causes a distinctive bluish or purplish-red cellulitis of the face accompanied by fever in children younger than age 2. The condition is rarely seen in countries where the vaccination is available. It is given at 2, 4, and 6 months of age. The importance of recognizing the entity is related to the bacteremia that often accompanies the cellulitis. The bacteremia may lead to meningitis, orbital cellulitis, osteomyelitis, or pyarthrosis. Cultures of the blood and needle aspirates of the cellulitis should yield the organism. Cefotaxime or ceftriaxone are effective. In a family with children under the age of 4, the index case, both parents, and children at risk (unvaccinated) should be given rifampin to clear the nasal carriage state and prevent secondary cases.

Barone SR, et al: Periorbital and orbital cellulitis in the *H. influenzae* vaccine era. J Pediatr Ophthalmol Strabismus 1997;34:293.

CHANCROID

Chancroid (soft chancre) is an infectious, ulcerative, STD caused by the Gram-negative bacillus *Haemophilus ducreyi* (the Ducrey bacillus). One or more deep or superficial tender ulcers on the genitalia, and painful inguinal adenitis in 50%, which may suppurate, are characteristic of the disease. Men outnumber women manyfold.

Chancroid begins as an inflammatory macule or pustule 1 to 5 days—or rarely as long as 2 weeks—after intercourse. It generally appears on the distal penis (or perianal area) in men, or on the vulva, cervix, or perianal area in women. However, many cases of extragenital infection on hands, eyelids, lips, or breasts have been reported. Autoinoculation frequently forms kissing lesions on the genitalia, and women are apt to have more numerous lesions.

The pustule ruptures early with the formation of a ragged ulcer that lacks the induration of a chancre, usually being soft with an indefinite inflammatory thickening. The ulcers appear punched-out or have undermined irregular edges surrounded by mild hyperemia (Fig. 14-37). The base is covered with a purulent, dirty exudate. The ulcers bleed easily and are very tender.

A number of clinical variants have been described, including granuloma inguinale-like, giant ulcers, serpiginous ulcers, transient chancroid, and follicular and papular variants.

Only about half the cases of genital chancroid manifest inguinal adenitis. Suppuration of the bubo (inguinal lymph node) may occur despite early antibiotic therapy. The lymphadenitis of chancroid, mostly unilateral, is tender and may rupture spontaneously. Left untreated, the site of perforation of the broken-down bubo may assume the features of a soft chancre (chancrous bubo).

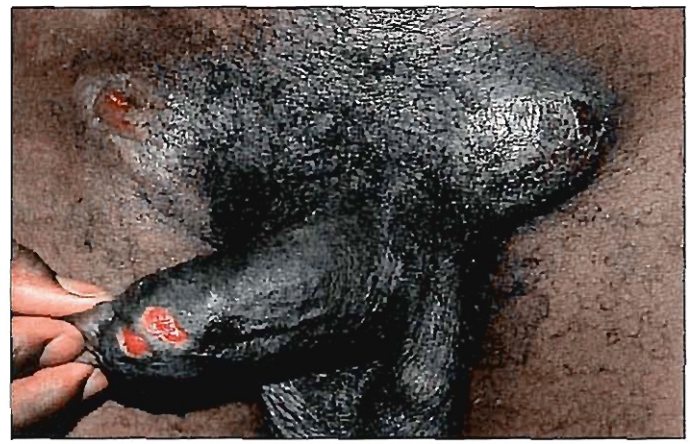

Fig. 14-37 Chancroid.

As a result of mixed infection, phagedenic and gangrenous features may develop. Gangrenous balanitis is a form of phagedena. Clinically, the disease is characterized by chronic, painful, destructive ulcers that begin on the prepuce or glans and spread by direct extension along the shaft of the penis, sometimes attacking the scrotum or pubes. The edges of the ulcer are likely to be elevated, firm, and undermined. The granulating base, which bleeds easily, is covered with a thick, purulent exudate and dirty, necrotic detritus. The neighboring skin may be edematous and dusky red, and the regional lymph glands may be swollen, although this is not necessarily a marked feature. There is severe mutilation as a result of sloughing, without any evidence of spontaneous healing.

This type of phagedena (spreading and sloughing ulceration) is a rare complication of chancre and chancroidal infections together with another secondary bacterial infection. Treatment is by the use of antibiotics locally and internally, directed against secondary bacteria, as well as the primary process, such as chancroid, syphilis, or granuloma inguinale, if present.

Chancroid is caused by the Gram-negative bacillus *H. ducreyi* and is sexually transmitted.

On histologic investigation the ulcer may include a superficial necrotic zone with an infiltrate consisting of neutrophils, lymphocytes, and red blood cells. Deep to this, new vessel formation is present, with vascular proliferation. Deeper still is an infiltrate of lymphocytes and plasma cells. Ducrey bacilli may or may not be seen in the sections.

The definitive diagnosis of chancroid requires identification by culture. Solid-media culture techniques have made definitive diagnosis possible, and permit sensitivity testing; however, culture is unavailable in many settings and recovery is only about 80% successful. Specimens for culture should be taken from the purulent ulcer base and active border without extensive cleaning. They should be inoculated in the clinic, as transport systems have not been evaluated. The selective medium contains vancomycin, and cultures are done in a water-saturated environment with 1% to 5% CO_2, at a temperature of 33° C. Occasional outbreaks are due to vancomycin-sensitive strains. In these cases, culture will only be successful using vancomycin-free media.

Smears are only diagnostic in 50% of cases in the best hands. No FDA-approved PCR test is available. A probable diagnosis is made by a clinically compatible examination and negative testing for those conditions whose presentation may mimic chanchroid. Probably the disease for which chancroid is most frequently mistaken is herpes progenitalis. A history of recurrent grouped vesicles at the same site should help eliminate the chance of a misdiagnosis. Traumatic ulcerations should also be ruled out. These occur mostly along the frenulum or as multiple erosions on the prepuce. Adenopathy is absent and some degree of phimosis is present.

The clinical features that differentiate chancroid from syphilitic chancre are described in Chapter 18. However, the diagnosis of chancroid does not rule out syphilis. Either the lesion may be already a mixed sore or the subsequent development of syphilis should be anticipated, since the incubation period of the chancre is much longer than that of chancroid. Repeated darkfield examinations for *Treponema pallidum* are necessary even in a sore where the diagnosis of chancroid has been established. Serologic tests for syphilis should be obtained initially, and monthly for the next 3 months, and serologic testing for HIV infection should also be done. Chancroidal genital ulcer disease facilitates the transmission of HIV infection.

Treatment

The treatment of choice for chancroid is azithromycin, 1 g orally in a single dose. Erythromycin, 500 mg four times a day for 7 days; ceftriaxone, 250 mg intramuscularly in a single dose; or ciprofloxacin, 500 mg orally twice a day for 3 days, are also recommended treatments. Ciprofloxacin should not be used in pregnant or lactating women, or in children younger than 17 years of age. Partners who have had sexual contact with the patient within the 10 days before the onset of symptoms should be treated with a recommended regimen.

Phimosis that does not subside following irrigation of the preputial cavity may have to be relieved by a dorsal slit. Circumcision should be deferred for at least 2 or 3 months. If frank pus is already present, repeated aspirations (not incisions) may be necessary.

Bong CT, et al: *Haemophilus ducreyi*. Microbes Infect 2002; 4:1141.

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Sehgal VN, et al: Chanchroid. Int J Dermatol 2003;42:182.

STD Guidelines 2002. MMWR 2002;51:1.

GRANULOMA INGUINALE (GRANULOMA VENEREUM, DONOVANOSIS)

Granuloma inguinale is a mildly contagious, chronic, granulomatous, locally destructive disease characterized by progressive, indolent, serpiginous ulcerations of the groins, pubes, genitalia, and anus.

The disease begins as single or multiple subcutaneous nodules, which erode through the skin to produce clean, sharply defined lesions, which are usually painless. More than 80% of cases demonstrate hypertrophic, vegetative granulation tissue, which is soft, has a beefy-red appearance, and bleeds readily (Fig. 14-38A). Approximately 10% of cases have ulcerative lesions with overhanging edges and a dry or moist floor (Fig. 14-38 B and C). A membranous exudate may cover the floor of fine granulations, and the lesions are moderately painful. Occasional cases are misdiagnosed as carcinoma of the penis. The lesions enlarge by autoinoculation and peripheral extension with satellite lesions, and by gradual undermining of tissue at the advancing edge.

The genitalia are involved in 90% of cases, inguinal region in 10%, anal region in 5% to 10%, and distal sites in 1% to 5%. Lesions are limited to the genitalia in approximately 80% of cases and to the inguinal region in less than 5%. In men, the lesions most commonly occur on the prepuce or glans, and in women, lesions on the labia are most common.

The incubation period is unknown; it may vary between 8 and 80 days, with a 2- to 3-week period being most common.

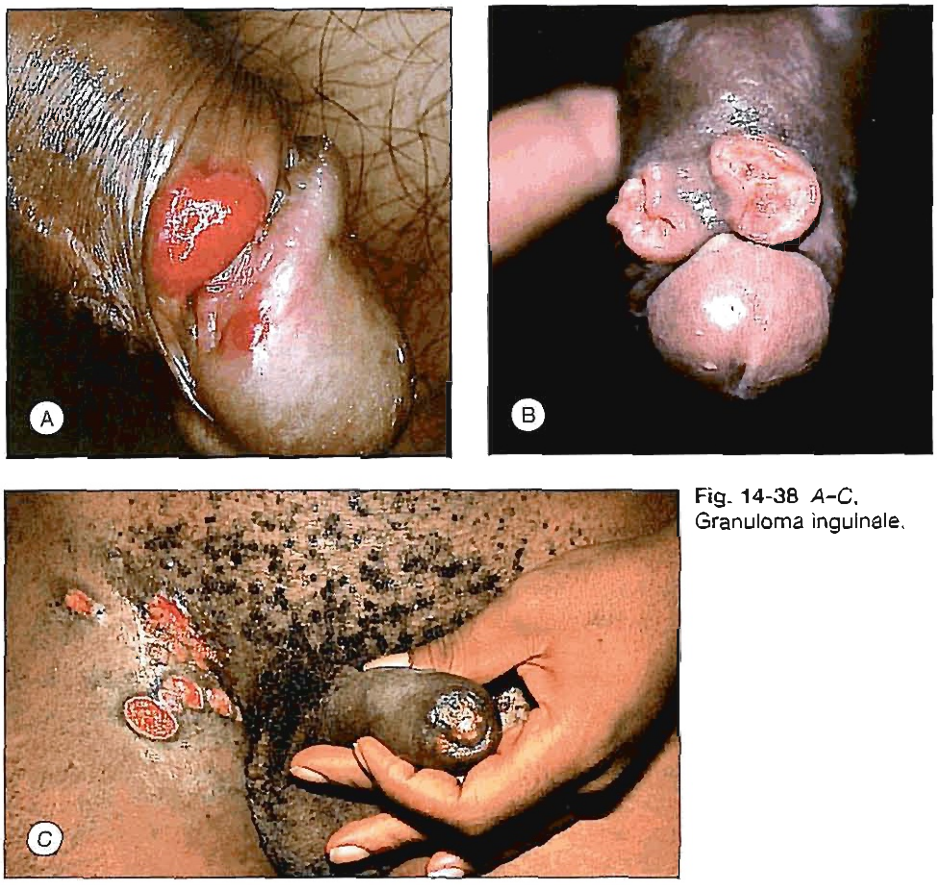

Fig. 14-38 *A–C*, Granuloma inguinale.

Persisting sinuses and hypertrophic scars, devoid of pigment, are fairly characteristic of the disease. The regional lymph nodes are usually not enlarged. In later stages, as a result of cicatrization, the lymph channels are sometimes blocked and pseudoelephantiasis of the genitals (esthiomene) may occur. Mutilation of the genitals and destruction of deeper tissues are observed in some instances.

Dissemination from the inguinal region may be by hematogenous or lymphatic routes. There may be involvement of liver, other organs, eyes, face, lips, larynx, chest, and, rarely, bones. During childbearing the cervical lesions may extend to the internal genital organs. Squamous cell carcinoma may rarely supervene.

Granuloma inguinale is caused by the Gram-negative bacterium *Klebsiella granulomatis*. The exact mode of transmission of infection is undetermined. The role of sexual transmission is controversial, but several factors, including the genital location of the initial lesion in the majority of cases, the relationship of the first lesion to an incubation period following coitus, and the occurrence of conjugal infection in 12% to 52% of marital or steady sexual partners, strongly favor sexual transmission. Also, it has been speculated that *K. granulomatis* is an intestinal inhabitant that leads to granuloma inguinale through autoinoculation, or sexually through vaginal intercourse if the vagina is contaminated by enteric bacteria, or through rectal intercourse, heterosexual or homosexual. *K. granulomatis* probably requires direct inoculation through a break in the skin or mucosa to cause infection. Those affected are generally young adults.

On histologic investigation, in the center of the lesion, the epidermis is replaced by serum, fibrin, and polymorphonuclear leukocytes. At the periphery the epidermis demonstrates pseudoepitheliomatus hyperplasia. In the dermis there is a dense granulomatous infiltration composed chiefly of plasma cells and histiocytes, and scattered throughout are small abscesses containing polymorphonuclear leukocytes.

Characteristic pale-staining macrophages that have intracytoplasmic inclusion bodies are found. The parasitized histiocytes may measure 20 μm or more in diameter. The ovoid Donovan bodies measure 1 to 2 μm and may be visualized by using Giemsa or silver stains. The best method, however, is toludine blue staining of semi-thin, plastic-embedded sections. Crushed smears of fresh biopsy material stained with Wright or Giemsa stain permit the demonstration of Donovan bodies and provide rapid diagnosis.

Granuloma inguinale may be confused with ulcerations of the groin caused by syphilis or carcinoma, but it is differentiated from these diseases by its long duration and slow course, by the absence of lymphatic involvement, and, in the case of syphilis, by a negative test for syphilis and failure to respond to antisyphilitic treatment. It should not be overlooked that other venereal diseases, especially syphilis, often coexist with granuloma inguinale. Additionally, all patients presenting with STDs should be tested for HIV infection and their sexual partners evaluated. Lymphogranuloma venereum at an early stage would most likely be accompanied by inguinal adenitis. In later stages when stasis, excoriations, and enlargement of the outer genitalia are common to granuloma inguinale and lymphogranuloma venereum, the absence of a

positive lymphogranuloma venereum complement-fixation test and the presence of Donovan bodies in the lesions permit the diagnosis of granuloma inguinale.

Treatment

Trimethoprim–sulfamethoxazole, one double-strength tablet orally twice a day for a minimum of 3 weeks, or doxycycline, 100 mg orally twice a day for a minimum of 3 weeks, are the recommended regimens. Therapy should be continued until all lesions have healed completely. Alternative regimens are ciprofloxacin, 750 mg orally twice a day for a minimum of 3 weeks, or erythromycin base, 500 mg orally four times a day for a minimum of 3 weeks. Azithromycin, 1 g orally once a week for at least 3 weeks, has been a successful new therapy. The addition of an aminoglycoside (gentamicin), 1 mg/kg intravenously every 8 h, should be considered if lesions do no respond within the first few days and in HIV-infected patients.

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Czelusta A, et al: An overview of sexually transmitted diseases Part III. J Am Acad Dermatol 2000;43:409.
Hart G: Donovanosis. Clin Infect Dis 1997;25:24.
Manders SM, et al: Granuloma inguinale and HIV. J Am Acad Dermatol 1997;37:494.
O'Farrell N: Donovanosis. Sex Transm Infect 2002;78:452.
STD Guidelines 2002. MMWR 2002;51:1.

GONOCOCCAL DERMATITIS

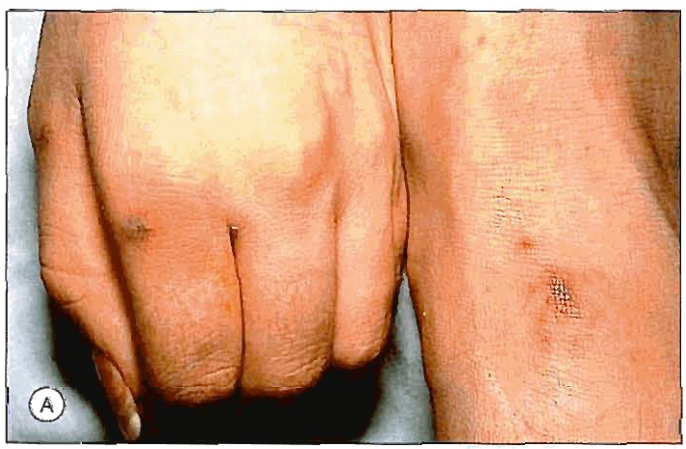
Primary gonococcal dermatitis is a rare infection that occurs after primary inoculation of the skin from an infected focus. It may present as grouped pustules on an erythematous base on the finger, simulating herpetic whitlow, with or without an ascending lymphangitis. Scalp abscesses in infants may occur secondary to direct fetal monitoring in mothers with gonorrhea. It may also cause an inflammation of the median raphae or a lymphangitis of the penis with or without accompanying urethritis. Treatment is the same as that of gonorrheal urethritis. A single oral dose of any of the following is effective, ciprofloxacin 500 mg, cefixime 400 mg, ofloxacin 400 mg or levofloxacin 250 mg. For infections acquired in Asia, the Pacific (including Hawaii) or California the frequency of quinolone-resistant *Neisseria gonorrhoeae* is enough to recommend non-fluoroquinolone treatment be utilized. Ceftriaxone is also effective as a 125 mg single intramuscular dose.

Gonococcemia

Gonococcemia is characterized by a hemorrhagic vesiculopustular eruption, bouts of fever, and arthralgia or actual arthritis of one or several joints.

The skin lesions begin as tiny erythematous macules that evolve into vesicopustules on a deeply erythematous or hemorrhagic base or into purpuric macules that may be as much as 2 cm in diameter (Fig. 14-39). These purpuric lesions occur acrally, mostly on the palms and soles, and over joints. They are accompanied by fever, chills, malaise, migratory polyarthralgia, myalgia, and tenosynovitis. The vesicopustules are usually tender and sparse, and occur principally on the extremities. Involution of the lesions takes place in about 4 days.

Many patients are women with asymptomatic anogenital infections in whom dissemination occurs during pregnancy or menstruation. Liver function abnormalities, myocarditis, pericarditis, endocarditis, and meningitis may complicate



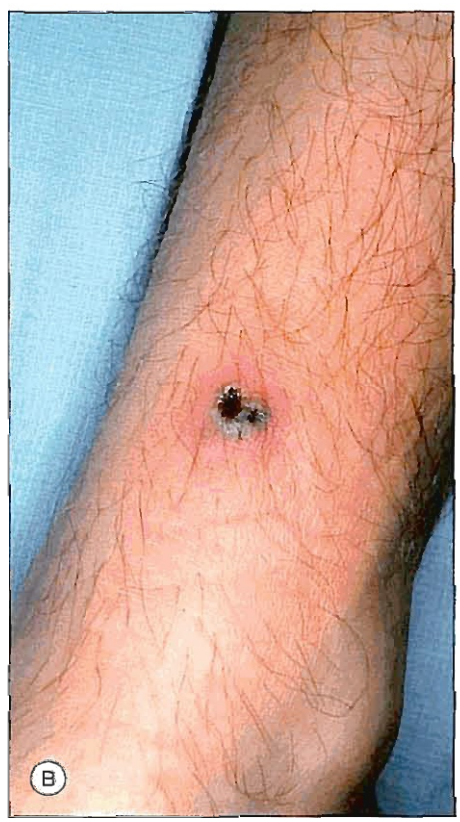


Fig. 14-39 *A* and *B*, Gonococcemia.

this infection. In severe or recurrent cases complement deficiency, especially of the late (C5, C6, C7, or C8) components, should be investigated.

The causative organism is *N. gonorrhoeae*. These organisms can at times be demonstrated in the early skin lesion histologically, by smears, and by cultures. Gonococci may be found in the blood, genitourinary tract, pharynx, joints, and skin.

The skin lesions of gonococcemia may be identical to those seen in meningococcemia, nongonococcal bacterial endocarditis, rheumatoid arthritis, the rickettsial diseases, systemic lupus erythematosus, periarteritis nodosa, Haverhill fever, and typhoid fever. Septic emboli with any Gram-negative organism or *Candida* classically manifest as hemorrhagic pustules.

The treatment of choice for disseminated gonococcal infection is ceftriaxone, 1 g/day intravenously or intramuscularly for 24 to 48 h after improvement begins. Then therapy may be switched to either cefixime, 400 mg orally twice a day, or ciprofloxacin, 500 mg orally twice a day, ofloxacin, 400 mg orally twice a day or levofloxacin 500 mg/day. Treatment with these should continue for a full week. There are many alternate initial intravenous drugs, including cefotaxime 1 g every 8 h, ceftizoxime 1 g every 8 h, or any of the quinolones in intravenous form. Spectinomycin, 2 g intramuscularly every 12 h, may be used for persons allergic to beta-lactam drugs.

Ciprofloxacin is contraindicated for children under the age of 17, and in pregnant and lactating women. If a cephalosporin is used, either doxycycline given 100 mg twice a day for 7 days or azithromycin 1 g as a single dose, should be given to treat coexisting chlamydial infection. Serologic testing for HIV infection should also be done as well as screening for syphilis. Sex partners within 30 days for symptomatic infection and 60 days for asymptomatic infection should be referred for treatment.

Brown TJ, et al: An overview of sexually transmitted diseases Part I. J Am Acad Dermatol 1999;41:511.

Harth W, et al: Dermatological symptoms and sexual abuse. J Eur Acad Dermatol Venereol 2000;14:489.

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STD Guidelines 2002. MMWR 2002;51:1.

MENINGOCOCCEMIA

Acute meningococcemia presents with fever, chills, hypotension, and meningitis. Half to two-thirds of patients develop a petechial eruption, most frequently on the trunk and lower extremities, which may progress to ecchymoses, bullous hemorrhagic lesions, and ischemic necrosis (Fig. 14-40). Often acral petechiae are present, and petechiae may be noted on the eyelids. Angular infarctive lesions with an erythematous rim and gun-metal gray interior are characteristic of meningococcal sepsis. Occasionally a transient, blanchable, morbilliform eruption is the only cutaneous finding. The oral and conjunctival mucous membranes may be affected. Chronic meningococcemia is characterized by acral hemorrhagic pustules identical to those found in gonococcal sepsis.

Meningococcemia primarily affects young children, males more frequently than females. Patients with asplenia, immunoglobulin deficiencies, or inherited or acquired deficiencies of the terminal components of complement or properdin are predisposed to infection.

A rare variant is chronic meningococcemia. There are recurrent episodes of fever, arthralgias, and erythematous macules that may evolve into lesions with central hemorrhage. Patients are generally young adults with fevers lasting 12 h interspersed with 1 to 4 days of well-being.

The disease is caused by the fastidious Gram-negative diplococcus *Neisseria meningitides*. It has a polysaccharide capsule that is important in its virulence and serotyping.

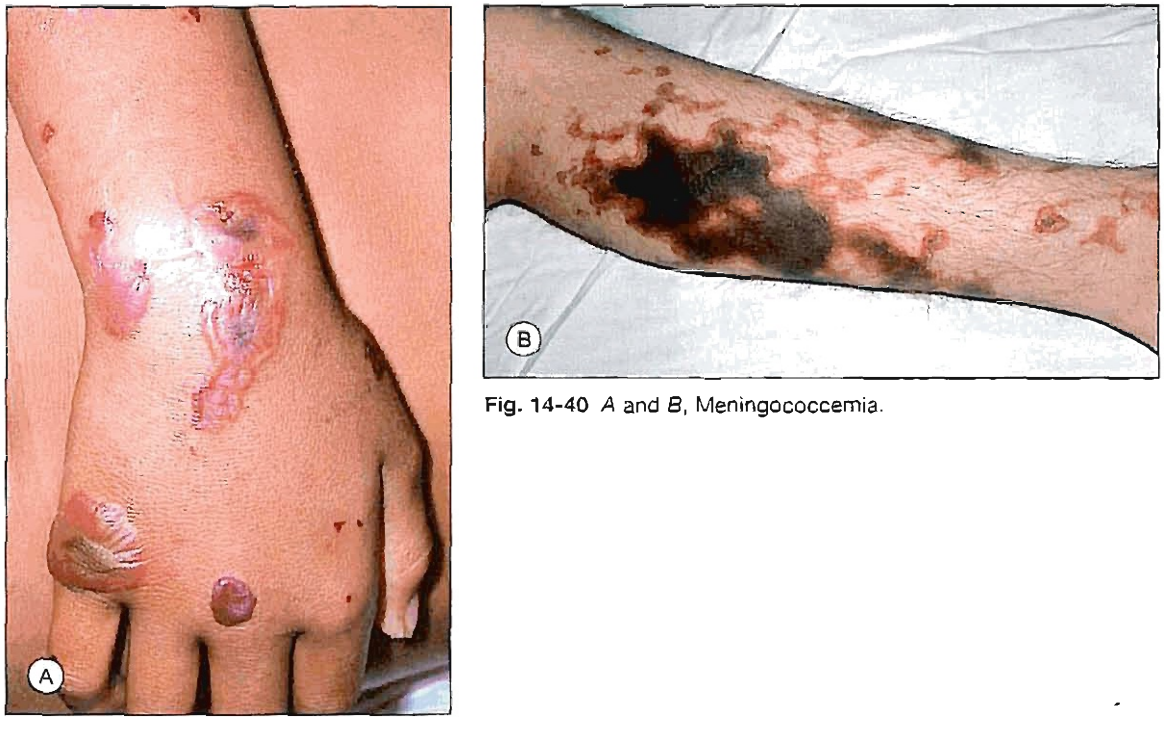

Fig. 14-40 *A* and *B*, Meningococcemia.

The human nasopharynx is the only known reservoir, with carriage rates in the general population estimated to be 5% to 10%.

Treatment is with penicillin G, 300,000 U/kg/day intravenously up to 24 MU/day for 10 to 14 days. Cefotaxime, ceftriaxone, chloramphenicol, and trimethoprim–sulfomethoxazole are alternatives. One dose of ciprofloxacin 500 mg is given after the initial course of antibiotics to clear nasal carriage. Household members and daycare and close school contacts should receive prophylactic therapy. Rifampin, 10 mg/kg every 12 h for 2 days, is an alternate for children. A polyvalent vaccine is effective against groups A, C, Y, and W-135, and is recommended for high-risk groups.

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Ferguson LE, et al: *Neisseria meningitidis*: presentation, treatment and prevention. J Pediatr Health Care 2002;16:119.
Nelson CG, et al: Meningococcemia in a patient coinfected with hepatitis C virus and HIV. Emerg Infect Dis 2000;6:646.
Ploysangam T, et al: Chronic meningococcemia in childhood. Pediatr Dermatol 1996;13:483.

VIBRIO VULNIFICUS INFECTION

Infection with *Vibrio vulnificus*, a Gram-negative rod of the non-cholera group of vibrios, produces a rapidly expanding cellulitis or septicemia in patients who have been exposed to the organism, which occurs mainly along the Atlantic seacoast. It may be acquired via the gastrointestinal tract, where, after being ingested with raw oysters or other seafood, the bacterium enters the bloodstream at the level of the duodenum. Pulmonary infection by the aspiration of seawater has been reported. Localized skin infection may result after exposure of an open wound to seawater.

Skin lesions characteristically begin within 24 to 48 h of exposure, with localized tenderness followed by erythema, edema, and indurated plaques. They occur in nearly 90% of patients and are most common on the lower extremities. A purplish discoloration develops centrally and then undergoes necrosis, forming hemorrhagic bullae or ulcers (Fig. 14-41). Other reported lesions include hemorrhagic bullae, pustules, petechiae, generalized macules or papules, and gangrene.

If the skin is invaded primarily, septicemia may not develop, but the lesions may be progressive and at times limb amputation may be necessary. With septicemia, cellulitic lesions are the result of seeding of the subcutaneous tissue during bacteremia. Patients with advanced liver disease are at particular risk for developing septicemia. Other predisposing disorders are immunosuppression, alcoholism, diabetes, renal failure, male sex, and iron-overload states. The virulence of the bacterium is related to the production of exotoxin and various other factors. The mortality in patients with septicemia is greater than 50%.

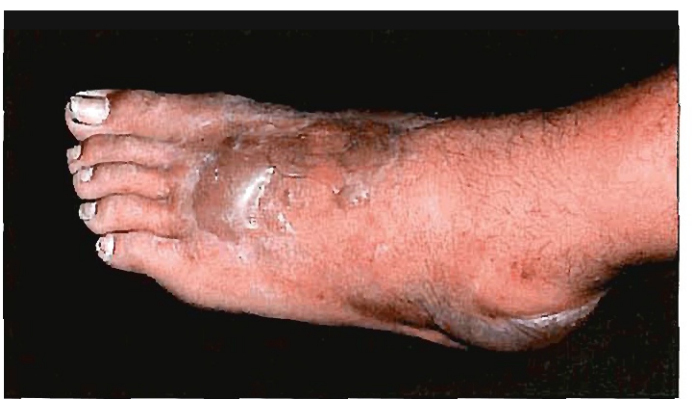

Fig. 14-41 Vibrio vulnificus infection. (Courtesy of Curt Samlaska, MD)

Treatment of this fulminant infection, which rapidly produces septic shock, includes antibiotics, surgical debridement, and appropriate resuscitative therapy. Doxycycline together with ceftazidime is the treatment of choice. In patients with preexisting hepatic dysfunction or immunocompromise and whose wounds are exposed to or acquired in saltwater, prophylactic antibiotic coverage with doxycycline 100 mg every 12 h and cleansing with 0.025% sodium hypochlorite solution may prevent progressive infection.

Borrenstein M, et al: Infections with *Vibrio vulnificus*. Dermatol Clin 2003;21:245.
Chiang SR, et al: *Vibrio bulnificus* infection. J Microbiol Immunol Infect 2003;36:81.
Oliver JD: Wound infections caused by *Vibrio vulnificus* and other marine bacteria. Epidemiol Infect 2005;133:383.
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CHROMOBACTERIOSIS AND *AEROMONAS* INFECTIONS

Chromobacteria are a genus of Gram-negative rods that produce various discolorations on gelatin broth. They have been shown to be common water and soil saprophytes of the southeastern US and Australia. Several types of cutaneous lesions are caused by chromobacteria, ranging from fluctuating abscesses and local cellulitis to anthrax-like carbuncular lesions with lymphangitis and lymphadenopathy and fatal septicemia. *Chromobacterium violaceum*, the most common organism in this genus, produces a violet pigment. Patients with chronic granulomatous disease may be at particular risk. Systemic aminoglycosides are indicated.

A Gram-negative bacterium, *Aeromonas hydrophilia*, another typical soil and water saprophyte, may cause similar skin infections manifesting as cellulitis, pustules, furuncles, gas gangrene, or ecthyma gangrenosum-like lesions, after water-related trauma and abrasions. The treatment of choice is ciprofloxacin.

Currie BJ, et al: Skin infections and infestations in Aboriginal communities in northern Australia. Australas J Dermatol 2000; 41:139.
Kienzle N, et al: Aeromonas wound infection in burns. Burns 2000;26:478.
Larka UB, et al: *Aeromonas hydrophilia* infections after penetrating foot trauma. J Foot Ankle Surg 2003;42:305.
Moore CC, et al: Successful treatment of an infant with *Chromobacterium violaceum* sepsis. Clin Infect Dis 2001;32:E107.

SALMONELLOSIS

Salmonellae are a genus of Gram-negative rods that exist in humans either in a carrier state or as a cause of active enteric

or systemic infection. Most cases of typhoid fever caused by *Salmonella typhi* are acquired by ingestion of contaminated food or water. Poultry and poultry products are the most important sources and are believed to be the cause in about half of common-source epidemics.

After an incubation period of 1 to 2 weeks, there is usually an acute onset of fever, chills, headache, constipation, and bronchitis. After 7 to 10 days of fever, diarrhea, and skin lesions, rose-colored macules or papules ("rose spots") 2 to 5 mm in diameter appear on the anterior trunk, between the umbilicus and nipples. They occur in crops, each group of 10 to 20 lesions lasting 3 to 4 days, the total duration of the exanthem being 2 to 3 weeks in untreated cases. Rose spots occur in 50% to 60% of cases. A more extensive erythematous eruption occurring early in the course, erythema typhosum, is rarely reported, as are erythema nodosum, urticaria, and ulcers or subcutaneous abscesses.

The diagnosis is confirmed by culturing the organism from blood, stool, skin, or bone marrow. If the organism is not grown on *Shigella–Salmonella* medium, or not analyzed correctly, it may be erroneously reported as a coliform. The preferred antibiotics are either ciprofloxacin or ceftriaxone.

Occasionally *S. typhi* may cause skin lesions without systemic infection. Also, infection with non-typhoid *Salmonella*, such as *S. enterica*, may cause enteric fever with rose spots.

Marzano AV, et al: Cutaneous infection caused by *Salmonella typhi*. J Eur Acad Dermatol Venereol 2003;17:575.

Nishie H, et al: Non-typhoid *Salmonella* infection associated with rose spots. Br J Dermatol 1999;140:558.

SHIGELLOSIS

Shigellae are small Gram-negative rods that cause bacillary dysentery, an acute diarrheal illness. Most cases are a result of person-to-person transmission; however, widespread epidemics have resulted from contaminated food and water. Small, blanchable, erythematous macules on the extremities, as well as petechial or morbilliform eruptions, may occur. Stoll reported a male homosexual who developed a 1-cm furuncle on the dorsal penile shaft from which a pure culture of *Shigella flexneri* was grown. Shigellosis may then occur as a purely cutaneous form of STD. *Shigella* and *Salmonella* are among the infections reported to induce the post-dysenteric form of Reiter syndrome. Therapy with a fluoroquinolone is curative.

Stoll DM: Cutaneous shigellosis. Arch Dermatol 1986;122:22.

HELICOBACTER CELLULITIS

Fever, bacteremia, cellulitis, and arthritis may all be caused by *Helicobacter cinaedi*. Generally, these manifestations occur in HIV-infected patients; however, malignancy, diabetes, and alcoholism are other predisposing conditions. The cellulitis may be multifocal and recurrent, and have a distinctive red–brown or copper color with minimal warmth. Ciprofloxacin is generally effective.

Burman WJ, et al: Multifocal cellulitis and monoarticular arthritis as manifestations of *Helicobacter cinaedi* bacteremia. Clin Infect Dis 1995;20:564.

Sullivan AK, et al: Recurrent *Helicobacter cinaedi* cellulitis and bacteremia in a patient with HIV infection. Int J STD AIDS 1997;8:59.

RHINOSCLEROMA

Rhinoscleroma is a chronic, inflammatory, granulomatous disease of the upper respiratory tract characterized by sclerosis, deformity, remission, and eventual debility. Death resulting from obstructive sequelae may occur. The infection is limited to the nose, pharynx, and adjacent structures.

The disease begins insidiously with nasal catarrh, increased nasal secretion, and subsequent crusting. Gradually there ensues a nodular or rather diffuse sclerotic enlargement of the nose, upper lip, palate, or neighboring structures (Fig. 14-42). The nodules at first are small, hard, subepidermal, and freely movable, but they gradually fuse to form sclerotic plaques that adhere to the underlying parts. Ulceration is common. The lesions have a distinctive stony hardness, are insensitive, and are of a dusky purple or ivory color. Hyperpigmentation can be expected in dark-complexioned individuals.

In the more advanced stages of rhinoscleroma, the reactive growth produces extensive mutilation of the face and marked disfigurement. Complete obstruction of the nares, superficial erosions, and seropurulent exudation may occur.

A microorganism, *Klebsiella pneumoniae*, ssp. *rhinoscleromatis*, first isolated by von Frisch, is the causative agent. The rhinoscleroma bacillus is a Gram-negative rod, short, nonmotile, round at the ends, always encapsulated in a gelatinous capsule, and measuring 2.0 to 3.0 µm. It is found in the throats of scleroma patients only.

The disease occurs in both sexes, and is most common during the third and fourth decades of life. Although endemic in Austria and southern Russia, and occasionally found in Brazil, Argentina, Chile, Spain, Italy, Sweden, and the US, it is especially prevalent in El Salvador, where many workers in the dye industry have been affected.

In the primary stage of nasal catarrh, the histologic picture is that of a mild, nonspecific inflammation. When proliferation and tumefaction develop, the granulomatous tumor is

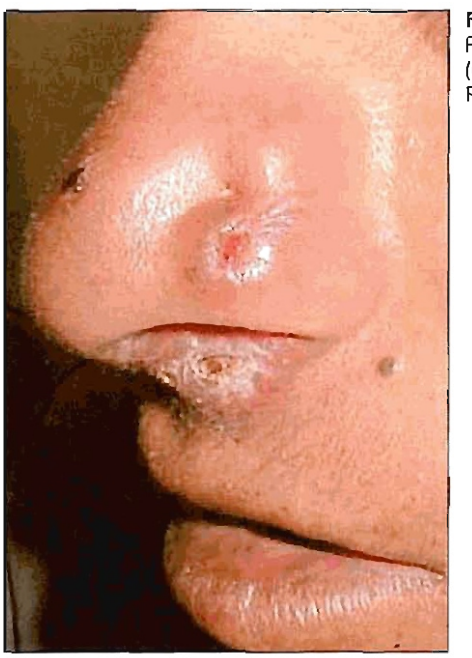

Fig. 14-42 Rhinoscleroma. (Courtesy of Jason Robbins, MD)

made up largely of plasma cells, Mikulicz cells, an occasional hyaline degenerated plasma cell (Russell body), a few spindle cells, and fibrosis. The bacilli are found within foamy macrophages (Mikulicz cells). They are best visualized with the Warthin-Starry silver stain.

Rhinoscleroma has such distinctive features that its diagnosis should not be difficult. The diagnosis depends on bacteriologic, histopathologic, and serologic tests. Heat-killed antigen gives a positive complement-fixation reaction with scleroma patients' serum. Titers run as high as 1:1280. Clinically, it can be confused with syphilitic gumma, sarcoid, leishmaniasis, frambesia, keloid, lepra, hypertrophic forms of tuberculosis, and rhinosporidiosis.

Treatment

This disease is usually progressive and resistant to therapy; however, it appears that the fluoroquinolones will prove to be the best therapy. Corticosteroids are useful in the acute phase. Surgical intervention or CO_2 laser treatments may be needed to prevent airway obstruction or to correct deformities.

Andraca R, et al: Rhinoscleroma. Mayo Clin Proc 1993;68:1151.
Badia L, et al: A case of rhinoscleroma treated with ciprofloxacin. J Laryngol Otol 2001;115:220.
Bhargava D, et al: Palatal presentation of scleroma. J Laryngol Otol 2001;115:679.
Fernandez-Vozmediano JM, et al: Rhinoscleroma in three siblings. Pediatr Dermatol 2004;21:134.

PASTEURELLOSIS

Primary cutaneous (ulceroglandular) *Pasteurella hemolytica* infection may occur in patients with skin injury and exposure to this organism. The lacerations become inflamed, lymphangitis and fever develop, and axillary lymph nodes become enlarged. Diagnosis is based on demonstration of the bacteria on culture of the lesions. *P. hemolytica* is a common pathogen of domestic animals, being associated with shipping fever in cattle and septicemia in lambs and newborn pigs.

Pasteurella Multocida Infections

Pasteurella multocida is a small, nonmotile, Gram-negative, bipolar-staining bacterium. It is known to be part of the normal oral and nasal flora of cats and dogs, but may also be an animal pathogen. The most common type of human infection follows injuries from animal bites, principally cat and dog bites, but also cat scratches. Following animal trauma, erythema, swelling, pain, and tenderness develop within a few hours of the bite, with a gray-colored serous or sanguinopurulent drainage from the puncture wounds (Fig. 14-43). There may or may not be regional lymphadenopathy or evidence of systemic toxicity such as chills and fever. Septicemia may follow the local infection in rare cases, and tenosynovitis and osteomyelitis appear with some frequency. Though a Gram-negative bacillus, treatment is with systemic penicillin G in addition to careful cleansing and tetanus prophylaxis.

Brue C, et al: *Pasteurella multocida* wound infection and cellulitis. Int J Dermatol 1994;33:471.

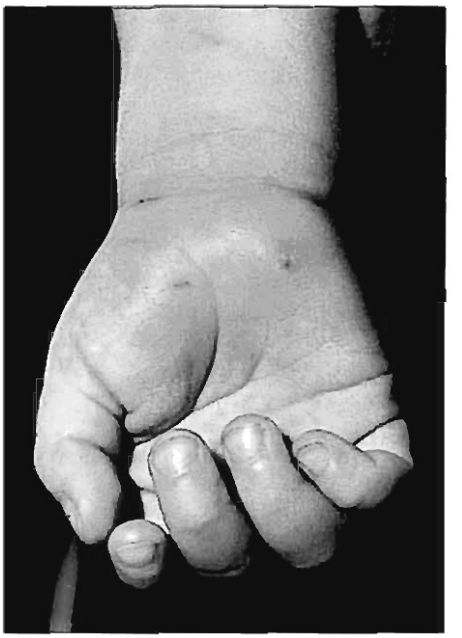

Fig. 14-43
Pasturella multocida infection.

Chun ML, et al: Postoperative wound infection with *Pasteurella multocida* from a pet cat. Am J Obstet Gynecol 2003;188:1115.
Luchansky M, et al: Cat bite in an old patient. Eur J Emerg Med 2003;10:130.

DOG AND HUMAN BITE PATHOGENS

It is recommended that all cat bites and scratches, all sutured wounds of any animal source, and any other animal injuries of an unusual type or source be treated with antibiotics in addition to careful cleansing and tetanus prophylaxis. While Pasteurella species (*canis* in dogs and *multocida* in cats) are usually present in bite site cultures, a complex mix of various other pathogens, such as streptococci, staphyloccocci, moraxella, neisseria, fusobacterium, bacteroides, and those individually discussed below, make the combination amoxicillin–clavulanate the best choice of initial therapy. Gatifloxacin and linezolid are other effective medications.

Capnocytophaga canimorsus, formerly referred to as *DF-2,* is a Gram-negative rod that is part of the normal oral flora of dogs and cats. It is associated with severe septicemia after dog bites. Patients who have undergone splenectomy are at particular risk. Alcoholism, chronic respiratory disease, and other medical conditions also predispose to infection; only one-quarter of patients were healthy before infection with *C. canimorsus*. A characteristic finding is a necrotizing eschar at the site of the bite. Fever, nausea, and vomiting occur abruptly within 1 to 3 days, and the eschar develops soon thereafter. Disseminated intravascular coagulation and extensive dry gangrene may complicate the course. Sepsis after a dog bite is another hazard faced by splenectomized patients in addition to their particular problems with pneumococcus, *H. influenzae* group B, babesiosis, *N. meningitides*, and group A streptococcus. *C. canimorsus* is difficult to identify by conventional cultures. Laboratory personnel need to be aware of the clinical suspicion of infection with this organism. A false-positive latex agglutination test for cryptococcal antigen in the spinal fluid may occur. Treatment is with intensive intravenous antibiotics. In less severely affected patients amoxicillin–clavulanate may be effective.

Eugonic fermenting bacteria (EF-4) and *Bergyella zoohelcum* are other oral and nasal commensals in dogs; thus, most reports of human disease follow animal bites. *Eikenella corrodens*, a facultative Gram-negative bacillus, is a normal inhabitant of the human mouth. Most infections are caused by human bites or fist fights. Amoxicillin–clavulanate or penicillin G are effective.

Bryson MS, et al: Purpura fulminans associated with *Capnocytophaga canimorsus* infection. Br J Haematol 2003;121:1.
Griego RD, et al: Dog, cat, and human bites. J Am Acad Dermatol 1995;33:1019.
Kravetz JD, et al: Cat-associated zoonoses. Arch Intern Med 2002;162:1945.
Talan DA, et al: Bacteriologic analysis of infected dog and cat bites. N Engl J Med 1999;340:85.

GLANDERS

Once known as *equinia*, *farcy*, and *malleus*, glanders is a rare, usually fatal, infectious disease that occurs in humans by inoculation with *Burkholderia mallei*. It is encountered in those who handle horses, mules, or donkeys.

The distinctive skin lesion is an inflammatory papule or vesicle that arises at the site of inoculation, rapidly becomes nodular, pustular, and ulcerative, and forms an irregular excavation with undermined edges and a base covered with a purulent and sanguineous exudate. In a few days or weeks other nodules (called "farcy buds") develop along the lymphatics in the adjacent skin or subcutaneous tissues; subsequently these break down. In the acute form the skin involvement may be severe and accompanied by grave diarrhea. In the chronic form there are few skin lesions and milder constitutional symptoms, but repeated cycles of healing and breakdown of nodules may occur for weeks.

The respiratory mucous membranes are especially susceptible to the disease. After accidental inhalation, first catarrhal symptoms are present and there may be epistaxis or a mucoid nasal discharge. The nasal discharge is a characteristic feature of the disease.

The diagnosis is established by finding the Gram-negative organism in this discharge or in the skin ulcers, and should be confirmed by serum agglutination. This organism has been fatal to many laboratory workers, and exposure in this setting is increasing with *Burkholderia mallei* considered a bioterrorism threat.

Treatment is chiefly by immediate surgical excision of the inoculated lesions and antibiotics. In vitro, ceftazidime, gentamicin, imipenem, doxycycline, and ciprofloxacin all have reliable activity against *B. mallei*. Imipenem and doxycycline combination cured an infected laboratory worker.

Bovine farcy also occurs and is caused by *Nocardia farcinica*. Schiff et al reported a nonimmunocompromised patient with an infected facial laceration. Osteomyelitis complicated the course. Amikacin treatment after surgical debridement resulted in complete cure.

Srinivasan A, et al: Glanders in a military research microbiologist. N Engl J Med 2001;345:256.
Schiff TA, et al: Cutaneous *Nocardia farcinica* infection in a nonimmunocompromised patient. Clin Infect Dis 1993;16:756.

MELIOIDOSIS

Melioidosis (Whitmore's disease) is a specific infection caused by a glanders-like bacillus, *Burkholderia pseudomallei*. The disease has an acute pulmonary and septicemic form where multiple miliary abscesses in the viscera occur, resulting in rapid death. Less often it runs a chronic course, with subcutaneous abscesses and multiple sinuses of the soft tissues. Its clinical characteristics are similar to glanders, disseminated fungal infections, and tuberculosis. Severe urticaria and necrotizing faciitis are uncommon complications.

Melioidosis is endemic in Southeast Asia and should be suspected in military personnel and travelers who have characteristic symptoms of a febrile illness and have been in that region. Recrudescence of disease after a long latency period may occur. Diagnosis is made from the recovery of the bacillus from the skin lesions or sputum, and by serologic tests.

Effective therapy is guided by the antibiotic sensitivity of the specific strain. For the acute septisemic phase, ceftazidime or imipenem is indicated. The majority of chronic cutaneous infections respond well to trimethoprim–sulfamethoxazole and doxycycline. Maintenance with this combination should continue for 20 weeks.

Cheng AC, et al: Melioidosis. Clin Microbiol Rev 2005;18:383.
Cochrane Database Syst Rev 2001;2:CD001263.
Dance DA: Melioidosis as an emerging global problem. Acta Trop 2000;74:115.
Tran D, et al: Cutaneous melioidosis. Clin Exp Dermatol 2002; 27:280.
White NJ, et al: Melioidosis. Lancet 2003;361:1715.

INFECTIONS CAUSED BY *BARTONELLA*

Bartonella are aerobic, fastidious, Gram-negative bacilli. Several species cause human diseases, including *Bartonella henselae* (cat-scratch disease and bacillary angiomatosis), *Bartonella quintana* (trench fever and bacillary angiomatosis), *Bartonella bacilliformis* (verruga peruana and Oroya fever), and *Bartonella clarridgeiae* (a possible cause of cat-scratch disease). These agents are transmitted by arthropod vectors in some cases. Unique to this genus is the ability to cause vascular proliferation as is seen in bacillary angiomatosis and verruga peruana. The bartonellae in affected tissue stain poorly with tissue Gram stain, and are usually identified in tissue using modified silver stains such as Warthin-Starry. They are difficult to culture, making tissue identification of characteristic bacilli an important diagnostic test. Electron microscopy and PCR can be used if routine staining is negative.

Cat-Scratch Disease

Cat-scratch disease is relatively common. About 22,000 cases are reported annually in the US, with between 60% and 90% of cases occurring in children and young adults. Cat-scratch disease is the most frequent cause of chronic lymphadenopathy in children and young adults.

B. henselae causes the vast majority of cases of cat-scratch disease. The infectious agent is transmitted from cat to cat by fleas, and from cats to humans by cat scratches or bites. The organism can be found in the primary skin and conjunctival lesions, lymph nodes, and other affected tissues. In

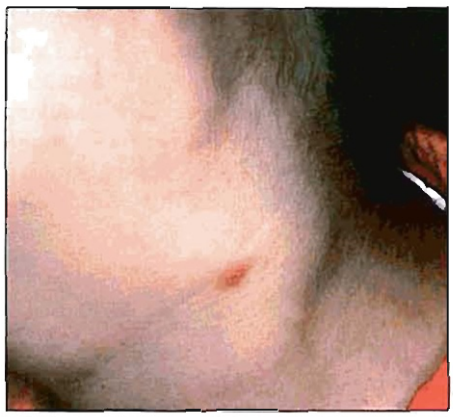

Fig. 14-44 Primary cat scratch lesion with lymphadenopathy.

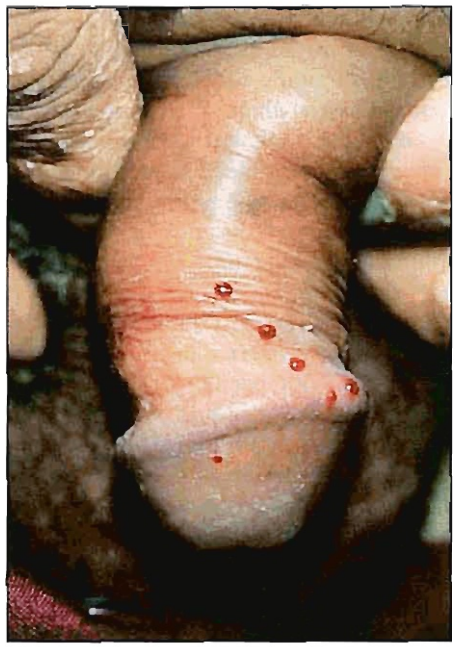

Fig. 14-45 Bacillary angiomatosis.

geographic areas where cat fleas are present, about 40% of cats are asymptomatically bacteremic with this organism.

The primary skin lesion appears within 3 to 5 days after the cat scratch, and may last for several weeks (Fig. 14-44). It is present in 50% to 90% of patients. The primary lesion is not crusted and lymphangitis does not extend from it. The primary lesion may resemble an insect bite but is not pruritic. The primary lesion heals within a few weeks, usually with no scarring.

Lymphadenopathy, the hallmark of the disease, appears within a week or two, after the primary lesions or between 10 and 50 days (average 17 days) after inoculation. Usually the lymphadenopathy is regional and unilateral. Because most inoculations occur on the upper extremities, epitrochlear and axillary lymphadenopathy is most common (50%), followed by cervical (25%) or inguinal (18%). Generalized lymphadenopathy does not occur, but systemic symptoms such as fever, malaise, and anorexia may be present. Without treatment the adenopathy resolves over a few weeks to months, with spontaneous suppuration occurring in between 10% and 50% of cases. If the primary inoculation is in the conjunctiva, there is chronic granulomatous conjunctivitis and preauricular adenopathy—the so-called oculoglandular syndrome of Parinaud. Uncommonly, acute encephalopathy, osteolytic lesions, hepatic and splenic abscesses, hypercalcemia, and pulmonary manifestations have been reported. In addition, erythema nodosum and a diffuse exanthem may accompany cat-scratch disease.

Diagnosis is made largely on clinical features. The primary skin lesion or lymph node may be biopsied and the infectious agent identified. Involved lymph nodes and skin lesions demonstrate granulomatous inflammation with central "stellate" necrosis. A serologic test is available but is not reproducibly positive early in the disease, limiting its usefulness. Cat-scratch skin testing (Hanger and Rose test) can be used but is rarely required if the history and clinical features are characteristic. Other infectious and neoplastic causes of localized lymphadenopathy, such as tularemia, sporotrichosis, atypical mycobacterial infection, and Hodgkin's disease, may need to be excluded.

The vast majority of cases of cat-scratch disease resolve spontaneously without antibiotic therapy. Such therapy has not been demonstrated to shorten the duration of the disease in most typical cases. Fluctuant lymph nodes should be aspirated, not incised and drained. In patients with severe visceral disease, azithromycin, erythromycin, tetracycline or doxycycline is effective.

Trench Fever

Trench fever is caused by *Bartonella quintana*, which is spread from person to person by the body louse. Urban cases of trench fever caused by this agent are now most commonly seen in homeless lime-infested persons.

Patients present with fever that initially lasts about a week, then recurs about every 5 days. Other symptoms are headache, neck, shin, and back pain. Endocarditis may occur. There are no skin lesions.

Treatment has not been studied systematically. Ceftriaxone for 7 days, followed by erythromycin or another macrolide for 2 to 4 months, is one effective regimen.

Bacillary Angiomatosis

Bacillary angiomatosis describes a clinical condition characterized by vascular skin lesions resembling pyogenic granulomas (Fig. 14-45). Only two organisms have been proven to cause bacillary angiomatosis: *B. henselae* (the cause of cat-scratch disease) and *B. quintana* (the cause of trench fever). The skin lesions caused by these two agents are identical. If the bacillary angiomatosis is caused by *B. henselae*, there is usually a history of cat exposure, and the same *Bartonella* can also be isolated from the blood of the source cat. Bacillary angiomatosis caused by *B. quintana* is associated with homelessness and louse infestation. The incubation period is unknown but may be years.

Bacillary angiomatosis occurs primarily in the setting of immunosuppression, especially AIDS. The helper T-cell count is usually less than 50/mL. Other immunosuppressed patients, such as those with leukemia or transplants, have been reported. Rarely, bacillary angiomatosis can occur in HIV-negative persons with no apparent immune impairment. In immunoincompetent hosts, the bacteria proliferate locally and are frequently blood-borne. The local proliferation of bacteria produces the angiogenic factor vascular endothelial growth factor (VEGF), leading to endothelial cell proliferation and the characteristic skin lesions. Immunocompetent hosts resist this bacterial proliferation, resulting in granulomatous and necrotic, rather than angiomatous, lesions.

Several different forms of cutaneous lesions occur. The most common form is lesions resembling pyogenic granulomas, which may exhibit a surrounding collarete of scale. Less commonly, subcutaneous masses, plaques, and ulcerations may occur. A single patient may exhibit several of these morphologies. Lesions are tender and bleed easily. Subcutaneous nodules are also tender and may be poorly marginated. Lesions may number from one to thousands, usually with the number gradually increasing over time if the patient is untreated.

In the setting of bacillary angiomatosis, the infection must be considered as multisystem. Bacteremia is detected in about 50% of AIDS patients with bacillary angiomatosis. This leads to dissemination of organisms to many visceral sites, but most frequently the lymph node, liver and spleen, and bone are involved. Less commonly pulmonary, gastrointestinal, muscle, oral, and brain lesions can occur. *B. henselae* is associated with lymph node and liver and spleen involvement, whereas *B. quintana* causes bone disease and subcutaneous masses. Visceral disease can be confirmed by appropriate radiologic or imaging studies. Bone lesions are typically lytic, resembling osteomyelitis. In the liver and spleen "peliosis" occurs. Liver function tests characteristically demonstrate a very elevated lactic dehydrogenase level, an elevated alkaline phosphatase level, slight elevation of the levels of hepatocellular enzymes, and a normal bilirubin level. Lesions on other epithelial surfaces, in muscle, and in lymph nodes are usually angiomatous.

Biopsies of bacillary angiomatosis skin lesions have the same low-power appearance as a pyogenic granuloma, with the proliferation of endothelial cells, forming normal small blood vessels. Bacillary angiomatosis is distinguished from pyogenic granuloma by the presence of neutrophils throughout the lesion, not just on the surface as is seen in a pyogenic granuloma. The neutrophils are sometimes aggregated around granular material that stains slightly purple. This purple material represents clusters of organisms, which can at times be confirmed by modified silver stain such as the Steiner stain. Tissue Gram stain does not routinely stain the bacteria in bacillary angiomatosis lesions. Electron microscopy may identify bacteria in cases in which special stains are negative. Bacillary angiomatosis is easily distinguished histologically from Kaposi sarcoma. In patch or plaque lesions of Kaposi sarcoma the new blood vessels are abnormal in appearance, being angulated. Endothelial proliferation in Kaposi sarcoma is seen in the dermis around the eccrine units, follicular structures, and existing normal vessels. Nodular Kaposi sarcoma is a spindle cell tumor with slits rather than well-formed blood vessels. Neutrophils and purple granular material are not found in Kaposi sarcoma, but intracellular hyaline globules are present.

The natural history of bacillary angiomatosis is extremely variable. In most patients, however, lesions either remain stable or the size or number of lesions gradually increases over time. The initial lesions are usually the largest, and multiple satellite or disseminated smaller lesions occur, representing military spread. Untreated bacillary angiomatosis can be fatal, with patients dying of visceral disease or respiratory compromise from obstructing lesions.

The diagnosis of bacillary angiomatosis is virtually always made by identifying the infectious agent in affected tissue. The organisms can also be cultured from the lesions and the patient's blood. However, these organisms grow very slowly, so cultures may not be positive for more than 1 month. Thus, tissue and blood cultures are usually confirmatory in nature. Antibodies to *Bartonella* can be detected in most bacillary angiomatosis cases by an indirect fluorescence assay. Because of its limited availability and background positivity in the general population of cat owners, this test is not generally useful in establishing the diagnosis of bacillary angiomatosis.

Treatment

Bacillary angiomatosis is dramatically responsive to treatment. Erythromycin, 500 mg four times a day, or doxycycline, 100 mg twice a day, are the treatments of choice. Minocycline, tetracycline, clarithromycin, azithromycin, roxithromycin, and chloramphenicol may also be effective. Trimethoprim–sulfamethoxazole, ciprofloxacin, penicillins, and cephalosporins are not effective. Prophylactic regimens containing a macrolide antibiotic or rifampin prevent the development of bacillary angiomatosis. Treatment duration depends on the extent of visceral involvement. In cases with skin lesions or bacteremia only, at least 8 weeks of treatment are required. For liver and spleen involvement 3 to 6 months of treatment are recommended, and for bone disease, at least 6 months of treatment should be considered. Once treatment is begun, symptoms begin to resolve within hours to days. A Jarisch–Herxheimer reaction may occur with the first dose of antibiotic. If patients relapse after an apparent adequate course of treatment, chronic suppressive antibiotic therapy should be considered.

Oroya Fever and Verruga Peruana

Oroya fever and verruga peruana represent two stages of the same infection. Oroya fever (Carrion's disease) is the acute febrile stage, and verruga peruana the chronic delayed stage. These conditions are limited to and endemic in Peru and a few neighboring countries in the Andes, and restricted to valleys between 500 and 3200 m above sea level. Both of these conditions are caused by *B. bacilliformis*, which is transmitted by a sandfly, usually *Lutzomyia verrucarum*. Humans represent the only known reservoir. Men represent about three-quarters of cases and all ages may be affected.

After an incubation period averaging 3 weeks, the acute infection, Oroya fever, develops. Symptomatology is highly variable. Some patients have very mild symptoms. Others may have high fevers, headache, and arthralgias. Severe hemolytic anemia can develop, sometimes with leukopenia, and thrombocytopenia. Untreated the fatality rate is 40% to 88%, and with antibiotic treatment is still 8%. After the acute infection resolves, a latency period follows, lasting from weeks to months. The eruptive verruga peruana then occur. They are angiomatous, pyogenic granuloma-like lesions, clinically and histologically virtually identical to the lesions of bacillary angiomatosis (Fig. 14-46). They may be large and few in number (mular form), small and disseminate (miliary form), or nodular and deep. Visceral disease has not been found in verruga peruana, which is rarely fatal. Lesions usually spontaneously heal over several weeks to months without scarring. A lasting immunity results from infection.

The diagnosis of Oroya fever is made by identifying the bacteria within or attached to circulating erythrocytes using a Giemsa stain. Verruga peruana can be diagnosed by skin

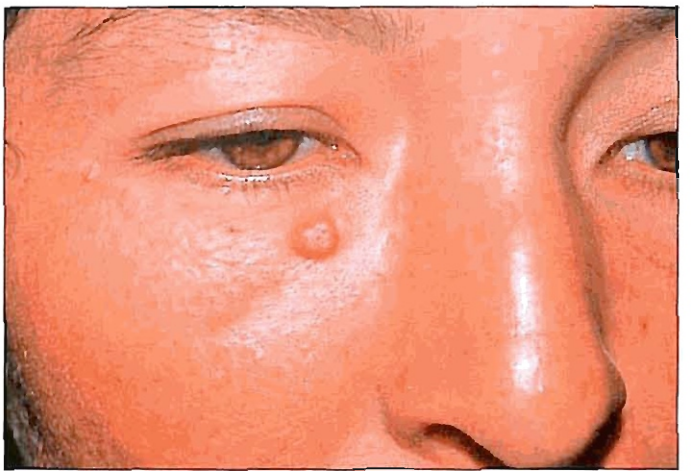

Fig. 14-46 Verruga peruana. (Courtesy of Francisco Bravo, MD)

biopsy, showing the same features as bacillary angiomatosis, but with the organisms staining with Giemsa stain.

The antibiotic treatment of choice for Oroya fever is chloramphenicol, 2 g/day, since *Salmonella* coinfection is the most frequent cause of death. Protection from sandfly bites is all important.

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PLAGUE

Plague normally involves an interaction among *Yersinia pestis*, wild rodents, and fleas parasitic on the rodents. Infection in humans with *Y. pestis* is accidental and presents usually as bubonic plague. Other clinical forms include pneumonic and septicemic plague.

In the milder form, the initial manifestations are general malaise, fever, and pain or tenderness in areas of regional lymph nodes, most often in the inguinal or axillary regions. In more severe infections, findings of toxicity, prostration, shock, and, occasionally, hemorrhagic phenomena prevail. Less common symptoms include abdominal pain, nausea, vomiting, constipation followed by diarrhea, generalized macular erythema, and petechiae. Rarely, vesicular and pustular skin lesions occur.

Plague is caused by *Y. pestis*, a pleomorphic, Gram-negative bacillus. The principal animal hosts involved have been rock squirrels, prairie dogs, chipmunks, marmots, skunks, deer mice, wood rats, rabbits, and hares. Transmission occurs through contact with infected rodent fleas or rodents, pneumonic spread, or infected exudates. *Xenopsylla cheopis* (Oriental rat flea) has traditionally been considered the vector in human outbreaks, but *Diamanus montanus*, *Chrassis bacchi*, and *Opisocrostis hirsutus* are species of fleas on wild animals responsible for spreading sylvatic plague in the US. Rodents carried home by dogs or cats are a potential source—and an important one in veterinarians—of infection. The bites, scratches or contact with other infectious material while handling infected cats is an increasing risk factor as residential development continues in areas of plague foci in the western US. In the US, 89% of cases since 1945 have occurred in the Rocky Mountain states.

Blood, bubo or parabubo aspirates, exudates, and sputum should be examined by smears stained with Gram stain or specific fluorescent antibody techniques, culture, and animal inoculation. A retrospective diagnosis can be made by serologic analysis.

The most effective drug against *Y. pestis* is streptomycin. It should be given in doses of 2 g/day intramuscularly for 10 days. Other effective drugs include gentamicin, chloramphenicol, the tetracyclines, and ciprofloxacin. Nearly all cases are fatal if not treated promptly.

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RAT-BITE FEVER

This febrile, systemic illness is usually acquired by direct contact with rats or other small rodents, which carry the Gram-negative organisms *Spirillum minor* and *Streptobacillus moniliformis* among their oropharyngeal flora. *S. moniliformis* is the principal cause in the US. Crowded living conditions or working with rats in medical research or in pet shops are predisposing factors in some infected patients. Although it usually follows a rat bite, it may follow the bites of squirrels, cats, weasels, pigs, and a variety of other carnivores that feed on rats.

There are at least two distinct forms of rat-bite fever: "sodoku," caused by *S. minus*; and septicemia, caused by *S. moniliformis*, otherwise known as *epidemic arthritic erythema* or *Haverhill fever*. The latter usually follows the bite of a

rat, but some cases have been caused by contaminated milk. The clinical manifestations of these two infections are similar in that both produce a systemic illness characterized by fever, rash, and constitutional symptoms. However, clinical differentiation is possible.

In the streptobacillary form, incubation is brief, usually lasting 10 days after the bite, when chills and fever occur. Within 2 to 4 more days the generalized morbilliform eruption appears and spreads to include the palms and soles. It may become petechial. Arthralgia is prominent, and pleural effusion may occur. Endocarditis, pneumonia, and septic infarcts may occur, and 10% of untreated cases may die from these causes.

Although infection with *S. minor* also begins abruptly with chills and fever, the incubation period is longer, ranging from 1 to 4 weeks. The bite site is often inflamed and may become ulcerated. Lymphangitis may be present. The eruption begins with erythematous macules on the abdomen, resembling rose spots, which enlarge, become purplish-red, and form extensive indurated plaques. Arthritis may rarely occur. Endocarditis, nephritis, meningitis, and hepatitis are potential complications. Six percent of untreated patients die.

In both types of disease a leukocytosis of 15,000 to 30,000/mm^3 is present, sometimes with eosinophilia. A biologic false-positive venereal disease research laboratory (VDRL) is found in 25% to 50% of cases. The course without treatment is generally from 1 to 2 weeks, though relapses may occur for months.

The diagnosis is confirmed by culturing the causative organism from the blood or joint aspirate, or demonstration of an antibody response in the streptobacillary form. *S. minus* is demonstrable by animal inoculation with the patient's blood, usually in the guinea pig or mouse. Their blood will show large numbers of organisms in Wright-stained smears. Demonstration of *S. minus* in a darkfield preparation of exudate from an infected site establishes the diagnosis.

Rat-bite fever must be differentiated from erysipelas, pyogenic cellulitis, viral exanthems, gonococcemia, meningococcemia, and Rocky Mountain spotted fever.

Prompt cauterization of bites by nitric acid may prevent the disease. Cleansing of the wound, tetanus prophylaxis, and 3 days of penicillin (2 g/day) are recommended for patients seen shortly after a bite. Both types respond readily to penicillin, tetracycline, or streptomycin therapy.

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TULAREMIA

Tularemia, also known as *Ohara's disease* or *deer fly fever*, is a febrile disease caused by *Francisella tularensis*, a short, nonmotile, non–spore-forming, Gram-negative coccobacillus. Tularemia is characterized by sudden onset, with chills, headache, and leukocytosis, after an incubation period of 2 to 7 days. Its clinical course is divided into several general types. The causative organism poses a bioterrorism threat.

The large majority are the ulceroglandular type, which begins with a primary papule or nodule that rapidly ulcerates

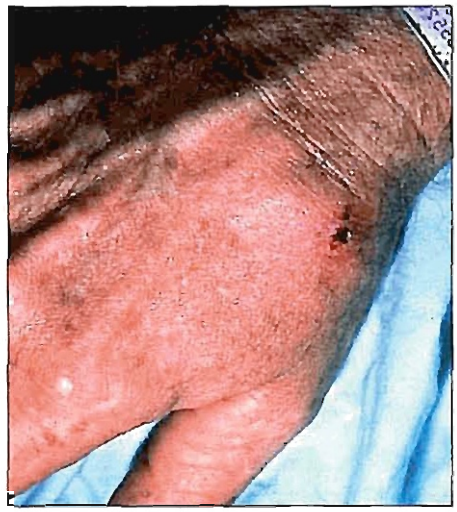

Fig. 14-47
Tularemia. (Courtesy of James Fitzpatrick, MD)

at the site of infection. This occurs usually through contact with tissues or body fluid of infected mammals, via an abrasion or scratch (Fig. 14-47), usually on the fingers, neck, or conjunctiva. The bites of a tick, *Dermacentor andersoni* or *Amblyomma americanum*, and of a deer fly, *Chrysops discalis*, transmit this disease also, and in such cases primary lesions are usually found on the legs or the perineum. The primary ulcer is tender, firm, indolent, and punched-out, with a necrotic base that heals with scar formation in about 6 weeks. A lymphangitis spreads from the primary lesion; the regional lymph glands become swollen, painful, and inflamed, and tend to break down, forming subcutaneous suppurative nodules resembling those of sporotrichosis. The ulcers extend in a chain from the ulcer to the enlarged lymphatic glands.

The course of the ulceroglandular type is marked in the early stages by headache, anorexia, and vomiting, and by articular and muscular pains. The fever is at first continuous, varying between 102 and 104° F, and later shows morning remissions, then falls by lysis to normal. Other skin lesions are encountered in the course of the disease, which are in no way characteristic and are probably of a toxic nature. A macular, papular, vesicular, or petechial exanthem may occur. Erythema multiforme and erythema nodosum often occur. The clinical similarity of the primary ulcer of tularemia to a chancre of sporotrichosis is important in the differential diagnosis.

In the typhoidal type the site of inoculation is not known and there is no local sore or adenopathy. This form of the disease is characterized by persistent fever, malaise, gastrointestinal symptoms, and the presence of specific agglutinins in the blood serum after the first week.

Other uncommon types include an oculoglandular form, in which primary conjunctivitis is accompanied by enlargement of the regional lymph nodes; the pneumonic type which occurs rarely in laboratory workers and is most severe; the oropharyngeal form which may occur after ingestion of infected and inadequately cooked meat; and the glandular type in which there is no primary lesion at the site of infection, but there is enlargement of regional lymph glands followed by generalized involvement. Several cases, mostly in children, have been acquired from cat bites, the cats having previously bitten infected rabbits.

The most frequent sources of human infection are the handling of wild rabbits and the bite of deer flies or ticks. Outbreaks of the disease occur chiefly at those times of the year when contact with these sources of infection is likely. No instance of the spread of the infection from person to person by contact has been reported. The disease occurs most often in the western and southern US, although cases have been reported in almost all parts of the US and in Japan. In Russia and other countries in the northern hemisphere it may be contracted from polluted water contaminated by infected rodent carcasses.

A definite diagnosis is made by staining smears obtained from the exudate with specific fluorescent antibody. *F. tularensis* can be cultured only on special media containing cystine glucose blood agar or other selective media. Routine culture media do not support growth. The bacilli can be identified by inoculating guinea pigs intraperitoneally with sputum or with bronchial or gastric washings, exudate from draining lymph nodes, or blood. The agglutination test is the most reliable diagnostic procedure. The titer becomes positive in the majority of patients after 2 weeks of illness. A four-fold rise in titer is diagnostic; a single convalescent titer of 1:160 or greater is diagnostic of past or current infection.

The main histologic feature of tularemia is that of a granuloma; the tissue reaction consists primarily of a massing of endothelial cells and the formation of giant cells. Central necrosis and liquefaction occur, accompanied by polymorphonuclear leukocytic infiltration. Surrounding this is a tuberculoid granulomatous zone, and peripherally lymphocytes form a third zone. Small secondary lesions may develop. These pass through the same stages and tend to fuse with the primary one.

All butchers, hunters, cooks, and others who dress rabbits should wear protective gloves when doing so. Thorough cooking destroys the infection in a rabbit, thus rendering an infected animal harmless as food. Ticks should be removed promptly, and tick repellents may be of value for people with occupations that require frequent exposure to them.

Streptomycin, 1 g intramuscularly every 12 h for 10 days, is the treatment of choice. Obvious clinical improvement occurs after 48 h, although the fever may persist for as long as a week after treatment is begun. Gentamicin is also effective, but the tetracyclines are useful only if given in high doses for 15 days. In vitro testing and numerous case reports and small case series are documenting the excellent effects of the quinolones, especially ciprofloxacin, 500 to 750 mg twice a day for 10 days, or levofloxacin 500 mg/day for 2 weeks.

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BRUCELLOSIS

Brucellosis is also known as *undulant fever*. Brucellae are Gram-negative rods that produce an acute febrile illness with headache, or at times an indolent chronic disease characterized by weakness, malaise, and low-grade fever. It is acquired primarily by contact with infected animals or animal products. Primarily, workers in the meat-packing industry are at risk; however, veterinarians, pet owners, and travelers who consume unpasteurized milk or cheese may also acquire the disease.

Approximately 5% to 10% of patients develop skin lesions. The variety of cutaneous manifestations reported is large. Erythematous papules, diffuse erythema, abscesses, erysipelas-like lesions, leukocytoclastic vasculitis, thrombocytopenic purpura and erythema nodosum-like lesions are some possible findings. Biopsy may reveal noncaseating granulomas.

Diagnosis is by culture of blood, bone marrow, or granulomas and may be confirmed by a rising serum agglutination titer. Treatment is with doxycycline and streptomycin in combination for 6 weeks.

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RICKETTSIAL DISEASES

Rickettsiae are obligate, intracellular, Gram-negative bacteria. The natural reservoirs of these organisms are the blood-sucking arthropods; when transmitted to humans through insect inoculation, the rickettsiae may produce disease. Most of the human diseases incurred are characterized by skin eruptions, fever, headache, malaise, and prostration. Diagnosis is usually made by indirect fluorescence antibody testing, which may be confirmed by Western blot, and therapy is with doxycycline 100 mg twice a day for 7 days. In addition to those discussed in the following sections, Q fever, caused by *Coxiella burnetii*, is an acute, febrile illness from this general class that uncommonly has skin manifestations, but these are nonspecific and nondiagnostic in nature.

TYPHUS GROUP

Louse-borne epidemic typhus, caused by *Rickettsia prowazekii*, mouse, cat or rat flea-borne endemic typhus, caused by *Rickettsia typhi*, and scrub typhus, a mite-borne infection caused by *Rickettsia tsutsugamushi* constitute this group.

Epidemic Typhus

Humans contract epidemic typhus from an infestation by body lice *(Pediculus humanus var. corporis)*, which harbor the rickettsiae. *R. prowazekii* is not transmitted transovarially, since it kills the louse 1 to 3 weeks after infection. For many years humans were the only known vector, but several cases of sporadic disease have been reported in which there was direct or indirect contact with the flying squirrel, and a reservoir apparently exists in this animal. While the louse feeds on the person's skin, it defecates. The organisms in the feces are scratched into the skin. Some 2 weeks after infection the prodromal symptoms of chills,

fever, aches, and pains appear. After 5 days a pink macular eruption appears on the trunk and axillary folds and rapidly spreads to the rest of the body, but usually spares the face, palms, and soles. These macules may later become hemorrhagic, and gangrene of the fingers, toes, nose, and earlobes may occur. Mortality is 6% to 30% in epidemics, with the highest death and complication rates occurring in patients over the age of 60.

Serologic testing using *immunofluorescent antibody (IFA)* and Western blot for specificity becomes positive after the eighth to twelfth day of illness.

Doxycycline, 100 mg twice a day for 7 days, is curative. Prophylaxis is by vaccination and delousing; people who succumb are usually living under miserable sanitary conditions such as occur during war and following natural disasters. Vaccination is suggested for only special high-risk groups.

Brill-Zinsser disease may occur as a recrudescence of previous infection, with a similar but milder course of illness, which more closely resembles murine typhus.

Endemic Typhus

Endemic (murine) typhus is a natural infection of rats and mice by *R. typhi*, sporadically transmitted to humans by the rat flea, *Xenopsylla cheopis*. In south Texas, *Rickettsia felis* is transmitted by cat fleas, with opposums as the natural reservoir of disease. It has the same skin manifestations as epidemic typhus (Fig. 14-48), but they are less severe, and gangrene does not supervene. Approximately 50% of patients with murine typhus had a skin eruption. Serologic testing using IFA and Western blot for specificity becomes positive in 50% of patients at 1 week and nearly all by 2 weeks. Fever and severe headache are suggestive early symptoms.

This disease occurs worldwide. In the US, the southeastern states and those bordering the Gulf of Mexico have been the most common sites of incidence. It most often occurs in urban settings, with peak incidence in the summer and fall.

Treatment is the same as that for louse-borne (epidemic) typhus.

Scrub Typhus

Also known as *tsutsugamushi fever*, scrub typhus is characterized by fever, chills, intense headache, skin lesions, and pneumonitis. The primary lesion is an erythematous papule at the site of a mite bite, most commonly on the scrotum, groin, or ankle. It becomes indurated, and a multilocular vesicle rests on top of the papule. Eventually a necrotic ulcer with eschar and surrounding indurated erythema develops and there is regional lymphadenopathy. Some 10 days after a mite bite, fever, chills, and prostration develop, and within 5 days thereafter pneumonitis and the skin eruption evolve. The erythematous macular eruption begins on the trunk, extends peripherally, and fades in a few days. Deafness and tinnitus occur in about a fifth of untreated cases.

Scrub typhus is caused by *R. tsutsugamushi*. The vector is the trombiculid red mite (chigger), which infests wild rodents in scrub or secondary vegetation in transitional terrain between forests and clearings in Far Eastern countries such as Japan, Korea, Southeast Asia, and Australia.

Serologic diagnosis and treatment is as for other forms of rickettsias; however, in areas of the world where there is reduced susceptibility to tetracyclines, such as Thailand, rifampicin is more reliable.

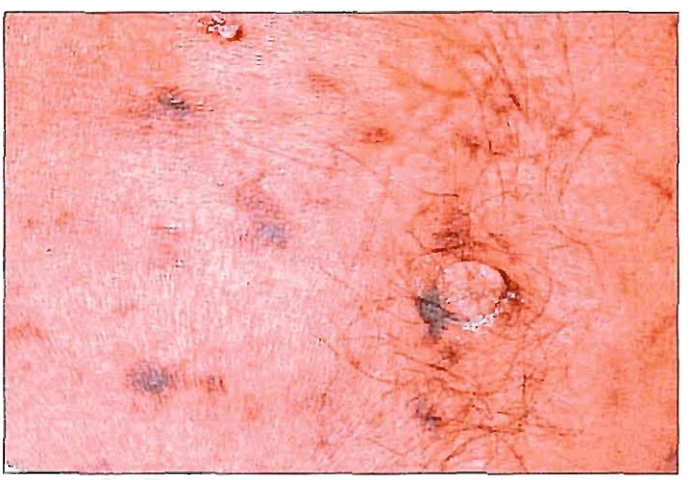

Fig. 14-48 Endemic typhus. (Courtesy of Richard DeVillez, MD)

SPOTTED FEVER GROUP

This group includes Rocky Mountain spotted fever, caused by *R. rickettsii*; Mediterranean (boutonneuse) fever, which when seen in Africa has been called Kenyan or South African tick-bite fever, caused by *Ricketssia conorii*; North Asian tick-borne rickettsiosis, caused by *Ricketssia sibirica*; Queensland tick typhus, caused by *Rickettsia australis*; African tick-bite fever, caused by *Ricketssia africae*; Flinders Island spotted fever, caused by *Rickettsia honei*; Yucatan spotted fever, caused by *Rickettsia felis* carried by the cat flea vector *Ctenocephalides felis*; Japanese spotted fever, caused by *Ricketssia japonica* and rickettsialpox; a newly reported spotted fever in the US caused by *Rickettsia parkeri*; and Russian vesicular rickettsiosis, caused by *R. akari*. Only the first two types of spotted fevers will be discussed in detail. They all are characterized by headache, fever and a rash, the latter most frequently being a pink papular eruption, which may have pethichiae, and in the case of African tick-bite fever, eschars. All are treated with doxycycline 100 mg twice a day for 7 days. Most respond well and complications are minimal. Ticks are the vectors of all but the newly recognized disease in the Yucatan. Tick prevention strategies are outlined in Chapter 21.

Rocky Mountain Spotted Fever

One to 2 weeks after the tick bite, there will be chills, fever, and weakness. An eruption appears, but unlike typhus it begins on the ankles, wrists, and forehead rather than on the trunk. The initial lesions are small, red macules, which blanch on pressure and rapidly become papular in untreated patients. Spread to the trunk occurs over 6 to 18 h, and the lesions become petechial and hemorrhagic over a period of 2 to 4 days (Fig. 14-49).

A vasculitis of the skin is the pathologic process, and *R. rickettsii* can be found in these initial macules by applying a fluorescent antibody technique to frozen sections. This is a very specific, but not very sensitive, method.

In the 10% to 20% of cases without a rash, the risk of a delay in diagnosis and a fatal outcome is greatest, with the case fatality rate rising precipitously if antibiotics are not initiated before the fifth day. An eschar will occasionally

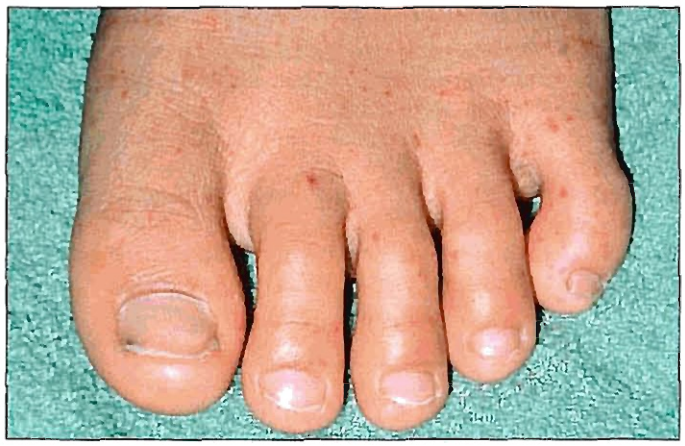

Fig. 14-49 Rocky Mountain spotted fever.

be present at the tick bite site and is a subtle clue to the diagnosis. In severe untreated cases a multisystem disorder appears, with renal, pulmonary, and central and peripheral nervous system abnormalities, and hepatomegaly most commonly found. Mortality in older persons approaches 60%; it is far lower in younger patients.

Ticks spread the causative organism, *R. rickettsii*. Principal offenders are the wood tick (*Dermacentor andersoni*), the dog tick (*D. variabilis* and *R. sanguineus* in Arizona), and the Lone Star tick (*Amblyomma americanum*).

Antibodies become positive in the second or third week of illness, too late to be of help when the decision to institute therapy is necessary. This decision is made by clinical considerations. A clue may be the recent illness of a pet dog, as *R. rickettsii* will cause symptomatic illness in infected dogs.

Treatment is with doxycycline 100 mg twice a day for 7 days.

Mediterranean Spotted Fever

Boutonneuse fever, or Mediterranean fever, is an acute febrile disease endemic in southern Europe and northern Africa, and is the prototype of the spotted fever group of diseases. It affects children mostly and is characterized by a sudden onset with chills, high fever, headache, and lassitude. The tick bite produces a small, indurated papule known as *tache noir*, which becomes a necrotic ulcer (Fig. 14-50). The erythematous macular and papular eruption develops on the trunk (Fig. 14-51), palms, and soles.

The causative organism is *R. conorii*, transmitted by the dog tick, *Rhipicephalus sanguineus*.

As with all rickettsial diseases, the diagnosis is confirmed with serology and treatment is with doxycycline. Even without therapy the prognosis is good, and complications are rare.

RICKETTSIALPOX

First recognized in New York in 1946, rickettsialpox has been found in other cities of the US and in Russia. It is an acute febrile disease characterized by the appearance of an initial lesion at the site of the mite bite about a week before the onset of the fever. This firm, 5- to 15-mm round or oval vesicle persists for 3 to 4 weeks and heals with a small pigmented scar. Regional lymphadenitis is present. The fever is remittent and lasts about 5 days. Chills, sweats, headache, and backache accompany the fever. A rash resembling

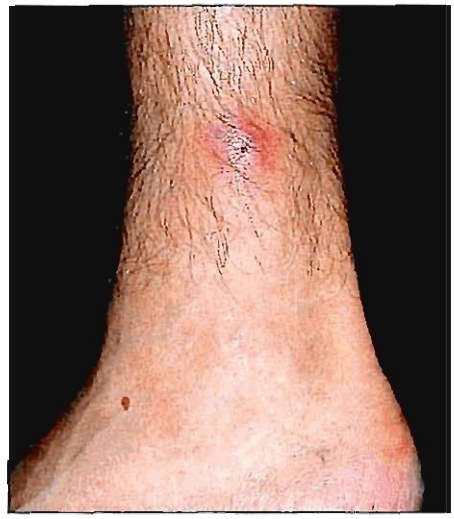

Fig. 14-50 Tache noire in Boutonneuse fever.

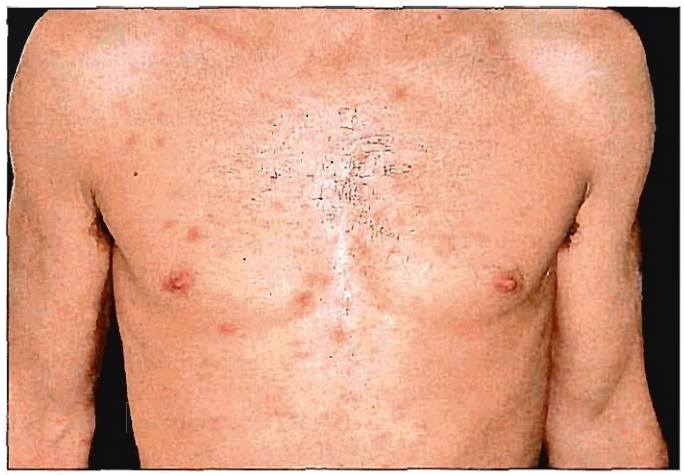

Fig. 14-51 Boutonneuse fever.

varicella develops 3 or 4 days after the onset of fever. This secondary eruption is papulovesicular, numbers approximately 5 to 50 lesions, and is generalized in distribution. It fades in about 1 week.

The rodent mite, *Allodermanyssus (Liponyssoides) sanguineus*, transmits the causative organism, *Rickettsia akari*. The house mouse (*Mus musculus*) is the reservoir. All cases have occurred in neighborhoods infested by mice, on which the rodent mite has been found.

Diagnosis is confirmed by serologic testing. The disease is self limited, and complete involution occurs in at most 2 weeks. Doxycyline is the agents of choice for treatment.

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EHRLICHIOSIS

These tick-borne organisms, which affect phagocytic cells, manifest as a febrile illness accompanied by headache and a rash. Human monocytic erhlichiosis (HME) is caused by *Ehrlichia chaffeensi*; human granulocytic erhlichiosis (HGE) by the *Ehrlichia* (Anaplasma) *phagocytophilia* groups; Sennetsu fever, a mononucleosis-type illness, by *Ehrlichia sennetsu*; and *Ehrlichia ewingii* also occasionally produces a similar symptomatic illness.

HME is transmitted by *Amblyomma americanum* or *Dermacentor variablilis*. It is most common in men between the ages of 30 and 60. The predominant regions reporting the disease are the south central, southeastern, and mid-Atlantic states. The same ixodes ticks that transmit Lyme disease and babesiosis transmit HE, and the infection occurs in the same geographic areas, the northeast and Pacific northwestern US. Coinfection with these agents occurs.

Skin eruptions are present in only about one-third of patients with HME and 10% of those with HGE. The lesions are usually present on the trunk and are nondiagnostic. A mottled or diffuse erythema, a fine petechial eruption, lower extremity vasculitis, or a macular, papular, vesicular or urticarial morphology have all been seen. Acral edema with desquamation and petechiae of the palate may be present. Involvement of the kidneys, lungs, and CNS occurs in severe cases.

If the diagnosis is suspected a complete blood count will usually show thrombocytopenia and leukopenia. The leukocytes should be inspected microscopically for intracytoplasmic microcolonies called morulae. They are seen more frequently in HGE than in HME. Indirect immunofluorescent antibodies are positive, but asymptomatic infection is frequent and seroprevalence rates are high in endemic areas. Culture of the organism is diagnostic. Doxycycline is the treatment of choice, 100 mg twice a day for 7 days. Severe life-threatening disease is usually seen in the immunosuppressed population.

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LEPTOSPIROSIS

Leptospirosis is also known as *Weil's disease*, *pretibial fever*, and *Fort Bragg fever*. It is a systemic disease caused by many strains of the genus *Leptospira*. After an incubation period of 8 to 12 days, Weil's disease (icteric leptospirosis) starts with an abrupt onset of chills, followed by high fever, intense jaundice, petechiae, and purpura on both skin and mucous membranes, and renal disease, manifested by proteinuria, hematuria, and azotemia. Death may occur in 5% to 10% of cases, as a result of renal failure, vascular collapse, or hemorrhage. Leukocytosis of 15,000 to 30,000/mm^3 and lymphocytosis in the spinal fluid are commonly present.

Pretibial fever ("Fort Bragg fever," anicteric leptospirosis) has an associated acute exanthematous infectious erythema, generally most marked on the shins. High fever, conjunctival suffusion, nausea, vomiting, and headache characterize the septicemic first stage. This lasts 3 to 7 days, followed by a 1- to 3-day absence of fever. During the second stage, when IgM antibody develops, headache is intense, fever returns, and ocular manifestations, such as conjunctival hemorrhage and suffusion, ocular pain, and photophobia, are prominent. At this time the eruption occurs. It consists of 1- to 5-cm erythematous patches or plaques that histologically show only edema and nonspecific perivascular infiltrate. The skin lesions resolve spontaneously after 4 to 7 days. There may be different clinical manifestations from identical strains of leptospira.

Leptospira interrogans, serotype *icterohaemorrhagiae*, has been the most common cause of Weil's disease, whereas pretibial fever is most commonly associated with serotype *autumnalis*. Humans acquire both types accidentally from urine or tissues of infected animals, or indirectly from contaminated soil or from drinking or swimming in contaminated water. Travelers to the tropics who enjoy water sports are at risk. In the continental US, dogs and cats are the most common animal source; worldwide, rats are more often responsible. *Leptospira* enter the body through abraded or diseased skin, and the gastrointestinal or upper respiratory tract.

Leptospirosis may be diagnosed by finding the causative spirochetes in the blood by darkfield microscopy during the first week of illness, and by blood cultures, guinea pig inoculation, and the demonstration of rising antibodies during the second week of the disease. The genus-specific hemagglutinin antibody serologic test permits relatively early diagnosis.

Treatment with tetracyclines and penicillin shortens the disease duration if given early. Doxycycline, 100 mg/day for a week is effective in mild disease; however, intravenous penicilin is necessary in severely affected patients. A dose of 200 mg once a week will prevent infection while visiting a hyperendemic area.

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BORRELIOSIS

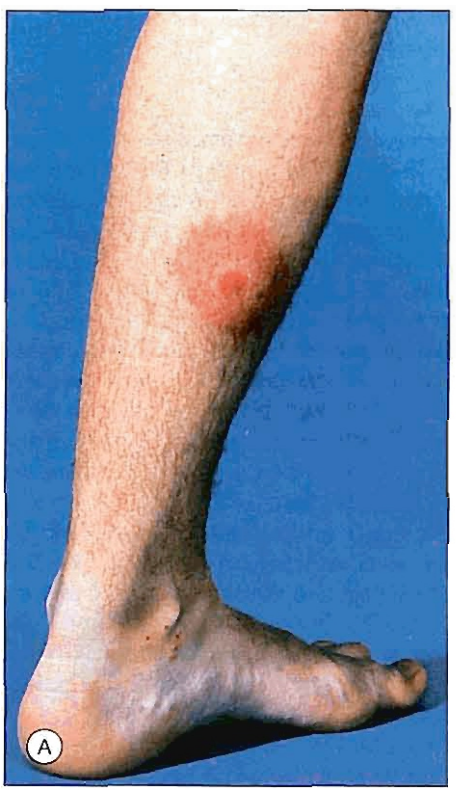
Spirochetes in the genus *Borrelia* are the cause of Lyme disease. This multisystem infection first presents with skin findings and over the course of time multiple cutaneous signs may occur. These microorganisms are also the cause of relapsing fever, an acute illness characterized by paroxysms of fever. The more common type of relapsing fever is tick-borne, occasionally being reported in the US. An unknown louse-borne type is endemic only in Ethiopia. The nonspecific macular or petechial eruption occurs near the end of the 3- to 5-day febrile crisis.

Lyme Disease

Borrelia burgdorferi sensu lato species complex are responsible for inducing Lyme disease. These spirochetes are transmitted to humans by various members of the family of hard ticks, *Ixodidae*. Four genomic subspecies are recognized to be geographically prominent and cause varying skin and systemic disease manifestations. *Borrelia burgdorferi sensu stricto* causes Lyme disease in the northeast, Midwest, and western US, and *Borrelia lonestari* causes disease in the southern US where the only skin finding is the diagnostic early manifestation, erythema migrans. *Borrelia lonestari* is the cuase of STARI, a condition characterized by erythema migrans, headache, stiff neck, myalgia, and arthralgia. *Borrelia garinii* and *Borrelia afzelii* are present in Europe, with the former being the principle agent of Lyme neuroborreliosis and the latter associated with acrodermatitis chronica atrophicans, lymphocytoma, and, in some cases, morphea and lichen sclerosis et atrophicus. If it is not treated in the early stage, chronic arthritis and neurologic and cardiac complications frequently develop.

Diagnosing early Lyme disease depends on recognition of the skin eruption. Approximately 50% of patients recall a tick bite, which leaves a small red macule or papule at the site. The areas most often involved are the legs, groins, and axilla with adults having lower extremity lesions most often and children more likely to manifest erythema migrans on the trunk. Three to 32 (median, 7) days after the bite, there is gradual expansion of the redness around the papule (Fig. 14-52A). The advancing border is usually slightly raised, warm, red to bluish-red, and free of any scale. Centrally, the site of the bite may clear, leaving only a ring of peripheral erythema, or it may remain red, become indurated, vesicular or necrotic. In Europe, the large annunlar variety is most common, while in the US the lesions are usually homogenous or have a central redness. The annular erythema usually grows to a median diameter of 15 cm, but may range from 3 to 68 cm (Fig. 14-52B). It is accompanied by a burning sensation in half the patients; rarely is it pruritic or painful. Localized alopecia may result at the site of erythema migrans.

Twenty-five to 50% of patients will develop multiple secondary annular lesions, similar in appearance to the primary lesion, but without indurated centers, and generally of smaller size (Fig. 14-53). They spare the palms and soles. Their number ranges from 2 to 100. Without treatment, erythema migrans and the secondary lesions fade in a median of 28 days, although some may be present for months. Of untreated cases, 10% experience recurrences of



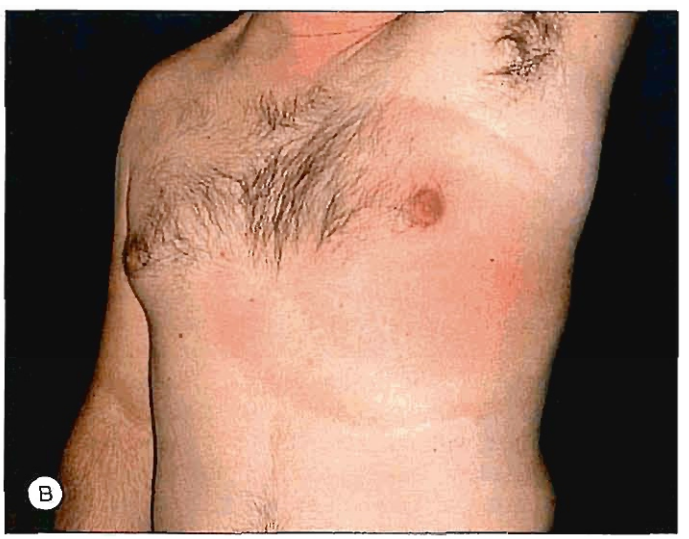


Fig. 14-52 *A* and *B*, Erythema migrans.

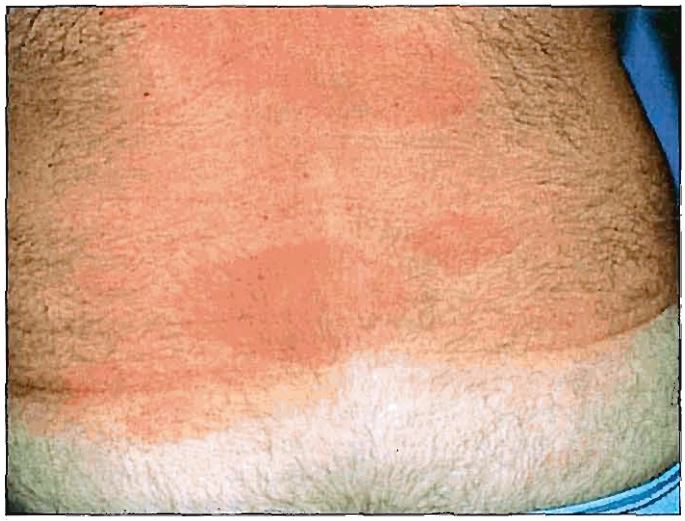


Fig. 14-53 Secondary lesions of erythema migrans.

erythema migrans over the following months. European cases of *Borrelia*-induced lymphocytoma occur generally early, from the time of erythema migrans until 10 months later. These are B-cell proliferations and present as red, indurated papules and plaques which occur most commonly on the areola or earlobe.

Diffuse urticaria, malar erythema, and conjunctivitis may be present during this early period. Malaise, fever, fatigue, headaches, stiff neck, arthralgia, myalgia, lymphadenopathy, anorexia, and nausea and vomiting may accompany early signs and symptoms of infection. Usually the symptoms are of mild severity, mimicking a slight flu-like illness, except in patients coinfected with babesiosis, as is the case in approximately 10% of cases in southern New England. Ehrlichia coinfections may also occur, as the latter two diseases are also tick-transmitted infections.

Ten percent of patients eventually develop a chronic arthritis of the knees, which in half of these leads to severe disability. Cardiac involvement occurs most often in young men, with fluctuating degrees of atrioventricular block or complete heart block occurring over a brief time (3 days to 6 weeks) early in the course of the illness. Neurologic findings include stiff neck, headache, meningitis, Bell palsy, and cranial and peripheral neuropathies, and are much more commonly manifested in European cases. Nonspecific findings include an elevated sedimentation rate in 50%, and an elevated IgM level, mild anemia, and elevated liver function tests in 20%.

Males and females are equally affected, and the age range most commonly affected is 20 to 50. Onset of illness is generally between May and November, with more than 80% of cases in the northern hemisphere identified in June, July, or August. In the US, tick transmission of Lyme disease is by *Ixodes scapularis* in the northeast and midwest, *Ixodes pacificus* is incriminated in the west, and in the south by *Amblyomma americanum*. European cases are transmitted by the tick *Ixodes ricinus*.

The different subtypes of *Borrelia* present in Europe account for the fact that the clinical illness resulting from infection is somewhat different from that seen in the US. European erythema migrans occurs more often in females. It is less likely to have multiple lesions; untreated lesions last longer; there are more laboratory abnormalities in Lyme disease; the arthritis symptoms are prominent in the US but unusual in Europe; and the neurologic manifestations differ. In Europe, infection may lead to Bannwarth syndrome, which is characterized by focal, severe, radicular pains; lymphocytic meningitis; and cranial nerve paralysis. Acrodermatitis chronica atrophicans and some cases of morphea, atrophoderma of Pasini and Pierini, anetoderma, and lichen sclerosus et atrophicus are late cutaneous sequelae of *B. afzelii* or *B. garinii* infection in Europe. Some patients with morphea-type lesions may have histopathologic features of an interstitial granulomatous dermatitis with histiocytic pseudorosettes present.

Several cases of transplacental transmission of *Borrelia*, resulting in infant death, has been reported. However, studies of Lyme disease in pregnancy have generally failed to directly implicate an association with fetal malformations.

On histologic investigation there is a superficial and deep perivascular and interstitial mixed-cell infiltrate. Lymphocytes, plasma cells, and eosinophils may be seen, the latter especially prominent when the center of the lesion is biopsied. Warthin-Starry staining may reveal spirochetes in the upper dermis.

The clinical finding of erythema migrans is the most sensitive evidence of early infection. Serologic conversion in the US is as follows: 27% when symptoms present for fewer than 7 days, 41% with symptoms for 7 to 14 days, and 88% with symptoms longer than 2 weeks. For this reason the diagnosis is made through recognition of erythema migrans. While culture and PCR analysis is specific, it is not sensitive and is not available in most areas. Serologic testing is then the confirmatory test. The screening examination is the ELISA. It is 89% sensitive and 72% specific, so when it is positive or indeterminate, a Western blot is used to confirm the result. False-positive tests occur in syphilis, pinta, yaws, leptospirosis, relapsing fever, infectious mononucleosis, and disease associated with autoantibody formation. The VDRL is negative in *B. burgdorferi* infection.

Treatment

The treatment of choice in adults is doxycycline, 100 mg twice a day for 10 to 30 days. Many authorities recommend at least 3 weeks of treatment. Amoxicillin 500 mg twice a day for 21 days or cefuroxime axetil 500 mg twice a day for 21 days are also effective. Doxycycline is also effective against *Ehrlichia* while the beta-lactams are not. Children under age 9 should be treated with amoxicillin 20 mg/kg/day in divided doses. Pregnant women with localized early Lyme disease should take amoxicillin; however, if disseminated disease is present, parenteral penicillin G or ceftriaxone is used. Immunodeficient patients may also benefit from intravenous penicillin or ceftriaxone, although the data are not robust for this recommendation.

More aggressive regimens are sometimes necessary for carditis and neurologic and arthritic involvement. For Bell palsy, first-degree heart block, and the first course of therapy for arthritis, treatment is a 28-day course of oral doxycycline or amoxicillin. For more severe manifestations in the CNS or heart and for resistant arthritis, parenteral dosing regimens are indicated.

Tick-control environmental measures and personal avoidance strategies are worthwhile when outdoor activities

are planned in tick-infested areas. Inspecting for ticks after returning from outdoor activity is a good preventive measure. The tick needs to be attached for more than 24 h to transmit disease. Nymphs are small; they may be hard to see. Beware of the freckle that moves. Prophylactic antibiotic therapy with one dose of 200 mg doxycycline after a known tick bite with a partially engorged *I. scapularis* in high incidence areas is 87% effective. An effective vaccine was withdrawn from the market due to poor sales.

Acrodermatitis Chronica Atrophicans

Also known as *primary diffuse atrophy*, acrodermatitis chronica atrophicans (ACA) is characterized by the appearance on the extremities of diffuse reddish or bluish-red, paper-thin skin. The underlying blood vessels are easily seen through the epidermis. It occurs almost exclusively in Europe.

The disease begins on the backs of the hands and feet, then gradually spreads to involve the forearms, then the arms, and on the lower extremities, knees and shins. Occasionally, even the trunk may become involved.

In the beginning the areas may be slightly edematous and scaly, but generally they are level with the skin and smooth. After several weeks to months the skin has a smooth, soft, thin, velvety feel and may easily be lifted into fine folds. It may have a peculiar pinkish gray color and a crumpled cigarette-paper appearance. Well-defined, smooth, edematous, bandlike thickenings develop and may extend from a finger to the elbow (ulnar bands) or develop in the skin over the shins. With progression of the disease, marked atrophy of the skin occurs.

Subcutaneous fibrous nodules may form, chiefly over the elbows, wrists, and knees. They may be single or multiple, and are firm and painless. Diffuse extensive calcification of the soft tissues may be revealed by radiographic examination. Xanthomatous tumors may occur in the skin. Hypertrophic osteoarthritis of the hands is frequently observed. Occasionally, atrophy of the bones of the involved extremities is encountered. Ulcerations and carcinoma may supervene on the atrophic patches. The disease is slowly progressive but may remain stationary for long periods. Patches may change slightly from time to time, but complete involution never occurs.

ACA is a spirochetosis, a late sequel of infection with *Borrelia afzelii*. It is tick-transmitted by *Ixodes ricinus*. Nearly all patients with ACA have a positive test for antibodies to the spirochete, and Warthin-Starry stains demonstrate the organism in tissue in some cases. The organism has been cultured from skin lesions of ACA.

Histologically, there is marked atrophy of the epidermis and dermis without fibrosis. The elastic tissue is absent, and the cutaneous appendages are atrophic. In the dermis a bandlike lymphocytic infiltration is seen, which varies in abundance according to the stage of the disease. The epidermis is slightly hyperkeratotic and flattened, and beneath it there is a distinctive narrow zone of connective tissue in which the elastic tissue is intact.

Antibiotic therapy cures most patients with ACA.

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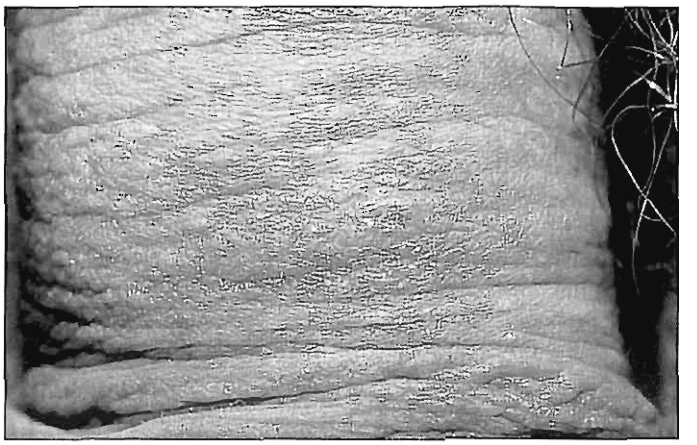

Fig. 14-54 Primary lesion of LGV. (Courtesy of James Fitzpatrick, MD)

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MYCOPLASMA

Mycoplasmas are distinct from true bacteria in that they lack a cell wall and differ from viruses in that they grow on cell-free media. *Mycoplasma pneumoniae* (Eaton agent) is an important cause of acute respiratory disease in children and young adults. It has been estimated that in the summer it may account for 50% of pneumonias.

Skin eruptions occur during the course of infection in 17% of patients. The most frequently reported is Stevens-Johnson syndrome. Erythema nodosum and Gianotti-Crosti syndrome have been occasionally reported. Other exanthems

include urticarial, vesicular, vesiculopustular, maculopapular, scarlatiniform, petechial, purpuric, and morbilliform lesions, distributed primarily on the trunk, arms, and legs. Ulcerative stomatitis and conjunctivitis may be present.

The diagnosis of *M. pneumoniae* infection is made in the acute situation by clinical means, but definitive diagnosis is made either by culture of the organism or by a rise in the specific antibody titer. The serologic procedures used are a complement fixation test and a sensitive ELISA test. Cold agglutinins with a titer of 1:128 or more are usually due to *M. pneumoniae* infection. Occasionally, acrocyanosis may occur secondary to cold agglutinin disease, which clears with antibiotic therapy.

Treatment is with either a macrolide (erythromycin, azithromycin or clarithromycin) or doxycycline for 7 days.

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CHLAMYDIAL INFECTIONS

Two species of chlamydias, *Chlamydia trachomatis* and *Chlamydia psittaci*, have been recognized. The two species share a major common antigen, and there are numerous serotypes within each species. In humans, *Chlamydia* causes trachoma, inclusion conjunctivitis, nongonococcal urethritis, cervicitis, epididymitis, proctitis, endometritis, salpingitis, pneumonia in the newborn, psittacosis (ornithosis), and lymphogranuloma venereum.

LYMPHOGRANULOMA VENEREUM

Lymphogranuloma venereum (LGV) is a STD caused by microorganisms of the *Chlamydia trachomatis* group and characterized by suppurative inguinal adenitis with matted lymph nodes, inguinal bubo with secondary ulceration, and constitutional symptoms.

After an incubation period of 3 to 20 days, a primary lesion consisting of a 2- to 3-mm herpetiform vesicle or erosion develops on the glans penis, prepuce, or coronal sulcus, or at the meatus (Fig. 14-54). In women it occurs on the vulva, vagina, or cervix. The lesion is painless and soon becomes a shallow ulceration. The primary lesion may also be a urethritis. Extragenital primary infections of LGV are rare. An ulcerating lesion may appear at the site of infection on the fingers, lips, or tongue. In patients with HIV infection, a painful perianal ulcer may occur. Primary lesions heal in a few days.

About 2 weeks after the appearance of the primary lesion, enlargement of the regional lymph nodes occurs (Fig. 14-55). In one-third of cases, the lymphadenopathy is bilateral. In the rather characteristic inguinal adenitis of LGV in men, the nodes in a chain fuse together into a large mass. The color of the skin overlying the mass usually becomes violaceous, the swelling is tender, and the bubo may break down, forming multiple fistulous openings. Adenopathy above and below

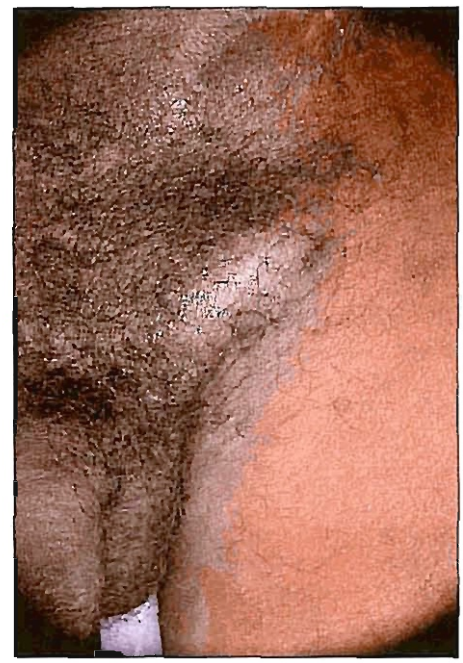

Fig. 14-55 *Lymphogranuloma venereum.*

the Poupart ligament produces the characteristic, but not diagnostic, groove sign. Along with the local adenitis there may be systemic symptoms of malaise, joint pains, conjunctivitis, loss of appetite, weight loss, and fever, which may persist for several weeks. Cases with septic temperatures, enlarged liver and spleen, and even encephalitis have occasionally been observed.

Primary lesions of LGV are rarely observed in female patients; women also have a lower incidence of inguinal buboes. Their bubo is typically pararectal in location. The diagnosis is recognized only much later when the patient presents an increasingly pronounced inflammatory stricture, which may be annular or tubular, of the lower rectal wall. Because most of the lymph channels running from the vulva drain into the nodes around the lower part of the rectum, an inflammatory reaction in these nodes results in secondary involvement of the rectal wall. The iliac nodes may also be involved.

LGV may start in the rectum as proctitis, which may then progress to the formation of a stricture. The clinical hallmark is bloody, mucopurulent rectal discharge. The stricture can usually be felt with the examining finger 4 to 6 cm above the anus. Untreated rectal strictures in men and women may eventually require colostomy. With or without rectal strictures, women may in later stages of the disease show elephantiasis of the genitals with chronic ulcerations and scarring of the vulva (esthiomene). Such a reaction is rare in men.

Cutaneous eruptions take the form of erythema nodosum, erythema multiforme, photosensitivity, and scarlatiniform eruptions. Arthritis associated with LGV involves finger, wrist, ankle, knee, or shoulder joints. Marked weight loss, pronounced secondary anemia, weakness, and mental depression are often encountered in the course of the anorectal syndrome. Colitis resulting from LGV is limited to the rectum and rectosigmoid structures. Perianal fistulas or sinuses are often seen in cases of anorectal LGV.

Among the various extragenital manifestations that occur are glossitis with regional adenitis, unilateral conjunctivitis

with edema of the lids caused by lymphatic blockage with lymphadenopathy, acute meningitis, meningoencephalitis, and pneumonia.

The complement fixation test is the most feasible and the simplest serologic test for detecting antibodies, which become detectable some 4 weeks after onset of illness. A titer of 1:64 is highly suggestive. Microhemagglutination inhibition assays are also available and not only confirm the diagnosis but also identify the strain. Three serotypes, designated L1, L2, and L3, are known for the LGV chlamydia. Characteristic surface antigens allow separation of the LGV chlamydias from the agents that cause trachoma, inclusion conjunctivitis, urethritis, and cervicitis, which also belong to the *C. trachomatis* group.

LGV occurs in all races and the highest incidence is found in the 20- to 40-year-old group. Asymptomatic female contacts who shed the organism from the cervix are an important reservoir of infection. The classic disease in men is uncommon in the US, whereas anorectal LGV has been increasing in the homosexual population.

The characteristic changes in the lymph nodes consist of an infectious granuloma with the formation of stellate abscesses. There is an outer zone of epithelioid cells with a central necrotic core composed of debris of lymphocytes, and leukocytes. In lesions of long duration plasma cells may be present. Stellate abscess also occur in cat-scratch disease, atypical mycobacterial infection, tularemia, and sporotrichosis.

As opposed to LGV, with chancroid a primary chancre or multiple chancroidal ulcers are present and may permit the demonstration of *H. ducreyi*. The skin lesions are characteristic and usually much larger and more persistent than the primary lesion of LGV. Donovan bodies are demonstrable in granuloma inguinale; however, inguinal adenitis is not characteristic. Esthiomene may also be seen in both diseases.

If the primary lesion of LGV is well developed, it may be confused with the primary lesion of syphilis. In any genital lesion, darkfield examination for *Treponema pallidum* should be made. Syphilitic inguinal adenitis shows small, hard, nontender glands. It should be emphasized again that all venereal infections may be mixed infections and that observation for simultaneous or subsequent development of another venereal disease should be unrelenting. This includes serologic testing for HIV disease. Late stages of LGV esthiomene with ulcerating and cicatrizing lesions have to be differentiated from syphilis by search for spirochetes, the serologic tests for syphilis, and complement fixation tests.

Treatment

The recommended treatment is doxycycline, 100 mg twice a day for 3 weeks. An alternative is erythromycin, 500 mg four times a day for 21 days. Sexual partners within the prior 30 days should also be treated. The fluctuant nodules are aspirated through healthy adjacent normal skin to prevent rupture.

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CHAPTER

15 Diseases Resulting from Fungi and Yeasts

SUPERFICIAL AND DEEP MYCOSES

Cutaneous infections are divided into superficial and deep mycoses. Most mycotic infections are superficial and are limited to the stratum corneum, hair, and nails. In contrast, most deep mycoses are evidence of disseminated infection, typically with a primary pulmonary focus. Although blastomycosis, histoplasmosis, and coccidioidomycosis generally appear first as skin lesions, they are almost always evidence of a systemic infection. There are a few deep mycoses that result from direct inoculation into the skin by a thorn or other foreign body. These include cutaneous lymphangitic sporotrichosis, primary cutaneous phaeohyphomycosis, and chromomycosis. Although phaeohyphomycosis generally begins as a skin infection, in immunosuppressed patients there is a great risk of dissemination and death. Even cutaneous sporotrichosis may occasionally disseminate. Although most cutaneous aspergillosis represents cutaneous embolization from a systemic (often a pulmonary) focus, in burn victims, *Aspergillus* commonly colonizes the burn eschar. This colonization may often be treated with debridement alone. Deep incisional biopsies are required to determine if there has been invasion of viable tissue beneath the eschar. Evidence of viable tissue invasion suggests a likelihood of systemic dissemination and is usually an indication for systemic antifungal therapy.

The major fungi that cause only stratum corneum, hair, and nail infection are the *dermatophytes*. They are classified in three genera: *Microsporum*, *Trichophyton*, and *Epidermophyton*. Superficial fungal infections are divided into: 1) tinea capitis (ringworm of the scalp and kerion); 2) tinea barbae (ringworm of the beard); 3) tinea faciei; 4) tinea corporis; 5) tinea manus; 6) tinea pedis; 7) tinea cruris; and 8) onychomycosis (fungus infection of the nails). Superficial mycoses are subdivided according to the causative dermatophyte. This is important because the antifungal agents vary somewhat in spectrum. For instance, higher doses of terbinafine are required to treat *Microsporum canis* infections than are needed to treat *Trichophyton spp*. The identity of the pathogen may also be important to identify a zoonotic reservoir of infection (a cat or dog for *M. canis* infections, cattle for *Trichophyton verrucosum*, rats for granular zoophilic *Trichophyton metagrophytes*).

SUSCEPTIBILITY AND PREVALENCE

Local and systemic immunosuppression may promote widespread tinea infection. Local immunosuppression is usually related to the use of a potent topical corticosteroid, but may also occur with use of a topical calcineurin inhibitor. A wide range of systemically immunocompromised states may result in severe forms of dermatophyte infection. These include primary immunodeficiency syndromes, acquired immunodeficiency syndrome (AIDS), connective tissue disease, and cancer chemotherapy. A defective cutaneous barrier, as in patients with ichthyosis, can also predispose to widespread tinea infection. Use of topical corticosteroids, occlusion, and shaving is associated with fungal folliculitis.

Genetic susceptibility to certain forms of fungal infections may be related to the types of keratin or degree or mix of cutaneous lipids produced. Surface antigens, such as the ABO system, may also be important, with patients with blood type A being somewhat more prone to chronic disease.

Data from the Icelandic population suggest a prevalence of symptomatic mycologically-determined onychomycosis of 11.1%. The prevalence doubled with a history of cancer, psoriasis, tinea pedis interdigitalis, moccasin tinea pedis, parents with onychomycosis, children with onychomycosis, spouse with onychomycosis, regular swimming, and age over 50. Fungal disease accounts for 30% to 40% of all foot disease.

Many individuals will carry *Trichophyton rubrum* asymptomatically, and this tendency may be inherited in an autosomal-dominant fashion. When they are exposed to a hot humid climate or occlusive footwear, the disease often becomes symptomatic. Reported prevalence rates are therefore heavily affected by climate, footwear, and lifestyle.

ANTIFUNGAL THERAPY

Topical agents provide safe, cost-effective therapy for limited superficial fungal infections. Available agents include clotrimazole, naftifine, miconazole, ciclopirox, econazole, oxiconazole, ketoconazole, sulconazole, tolnaftate, butenafine, and terbinafine. Clotrimazole, miconazole, tolnaftate and terbinafine are available without a prescription in the US.

When considering the use of an oral antifungal agent, considerations include the type of infection, organism, and spectrum, pharmacokinetic profile, safety, compliance, and cost of the antifungal agent. Griseofulvin has a long safety record, but requires much longer courses of therapy than newer agents. Topical antifungals remain very cost-effective for limited cutaneous disease.

Various classes of antifungals are in use. The imidazoles include clotrimazole, miconazole, econazole, sulconazole, oxiconazole, and ketoconazole. They work by inhibition of the cytochrome P450 14-α-demethylase, an essential enzyme in ergosterol synthesis. Nystatin is a polyene that works by irreversibly binding to ergosterol, an essential component of fungal cell membranes. Naftifine, terbinafine, and butenafine are allylamines, and their mode of action is inhibition of squalene epoxydation. The triazoles include itraconazole and fluconazole, which affect the cytochrome P450 system. As this system is responsible for the

metabolism of numerous drugs, interactions can occur, some of which may be life threatening.

For both itraconazole and griseofulvin, food increases absorption. For itraconazole and ketoconazole, antacids, H_2 antagonists and proton pump inhibitors lower absorption. Terbinafine is less active against *Candida* and *Microsporum spp* in vitro. In vivo, adequate doses can be effective against these organisms. Terbinafine has limited efficacy in the oral treatment of tinea versicolor but is effective topically. Although few drug interactions have been reported with terbinafine and the bioavailability is unchanged in food, hepatotoxicity, leukopenia, toxic epidermal necrolysis, and taste disturbances occur uncommonly. Ketoconazole has a wide spectrum against dermatophytes, yeasts, and some systemic mycoses. It has the potential for serious drug interactions and a higher incidence of hepatotoxicity than other available agents. The risk of liver toxicity with single doses is minimal, but for many indications, the drug has largely been replaced by fluconazole.

Fluconazole is mainly used to treat *Candida* infections, but has shown efficacy in the treatment of dermatophytoses both in daily and in weekly doses. Patients may have trouble remembering intermittent dosing schedules. In one study, daily dosing with terbinafine was rated by patients as more convenient than monthly pulsed dosing with itraconazole and was associated with higher overall satisfaction.

Both terbinafine and itraconazole have been shown to be effective and well tolerated in several studies of the treatment of tinea capitis and onychomycosis in children, but intraconazole has been associated with reports of heart failure.

Voriconazole has exceptional activity against a wide variety of yeast, as well as many other fungal pathogens. Posaconazole has significant in vitro activity against *Candida spp*, although some resistance has been reported to this drug.

The echinocandins inhibit β-(1,3)-glucan synthesis, thus damaging fungal cell walls. They are active against most *Candida spp* and fungistatic against *Aspergillus spp*. They have limited activity against zygomycetes, *Cryptococcus neoformans* or *Fusarium spp*. Caspofungin was the first drug in this class to be marketed in the US for refractory invasive aspergillosis. Micafungin also belongs to this class of antifungal agents. Adverse events are uncommon but include phlebitis, fever, elevated liver enzymes, and mild hemolysis. The drugs must be given intravenously. Metabolism is mainly hepatic. In the setting of candida sepsis, results are similar to those achieved with amphotericin B, with substantially lower toxicity. They may be used together with other antifungal agents in the treatment of life-threatening systemic fungal infections, such as disseminated aspergillosis refractory to other regimens.

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TINEA CAPITIS

Tinea capitis, also known as scalp ringworm, can be caused by all the pathogenic dermatophytes except for *Epidermophyton floccosum* and *Trichophyton concentricum*. In the US, most cases are caused by *Trichophyton tonsurans* (which has replaced *Microsporum audouinii* as the most common pathogen). Pet exposure is associated with tinea capitis caused by *M. canis*.

Tinea capitis occurs mainly in children, although it may be seen at all ages. Boys have tinea capitis more frequently than girls; however, in epidemics caused by *T. tonsurans* there is often equal frequency in the sexes. African American children have a higher incidence of *T. tonsurans* infections than Anglo Americans. The infection is also common among Latin American children.

T. tonsurans produces black-dot ringworm, as well as subtle seborrheic-like scaling and inflammatory kerion. Black dot tinea may also be caused by *Trichophyton violaceum*, an organism rarely seen in the US. Both of these organisms produce chains of large spores within the hair shaft (large spore endothrix). They do not produce fluorescence with a Wood's light.

The *M. canis* complex includes a group of organisms that produce small spores visible on the outside of the hair shaft (small spore ectothrix). These fungi fluoresce under Wood's light examination. The *M. canis* complex includes *M. canis*, *M. canis distortum*, *Microsporum ferrugineum*, and *Microsporum audouinii*. *M. canis* infections begin as scaly, erythematous, papular eruptions with loose and broken-off hairs. The lesions commonly become highly inflammatory, although *M. audouinii* has less tendency to produce inflammatory lesions. Deep tender boggy plaques exuding pus are known as *kerion celsii* (Fig. 15-1). Kerion may be followed by scarring and permanent alopecia in the areas of inflammation and suppuration. Systemic steroids for a short period along with appropriate antifungal therapy will greatly diminish the inflammatory response and reduce the risk of scarring, and should be considered in the setting of highly inflammatory lesions.

Asymptomatic carriers of *T. tonsurans* are common, and represent a source of infection for classmates and siblings. Numerous studies have shown that 5% to 15% of urban children in western countries have positive scalp dermato-

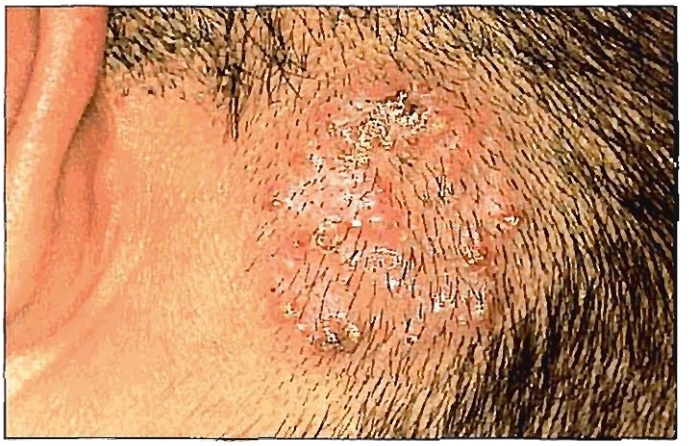

Fig. 15-1 Kerion.

phyte cultures. In one study, 60% of children with a positive scalp culture were asymptomatic. All of these children were African American. The presence of scalp scaling and the use of a dandruff shampoo were associated with an increased likelihood of carrying a fungal organism. It is unlikely that dandruff shampoos predispose to tinea. More likely, they provide incomplete treatment of minimally symptomatic tinea that produces a subtle seborrheic scale.

The prevalence of various dermatophytes varies throughout the world. Where animal herding is an important part of the economy, zoonotic fungi account for a significant proportion of cases of tinea. In Asia, organisms vary significantly by region. In a study of 204 Iraqi school children with tinea capitis, *Trichophyton verrucosum* was the most common organism. Both *T. rubrum* and *T. mentagrophytes var. mentagrophytes* were more common than *T. tonsurans*. In south central Asia, *T. violaceum* is the most common dermatophytic species isolated, with *M. audouinii* a close second. Other common organisms include *Trichophyton schoenleinii*, *T. tonsurans*, *M. gypseum*, *T. verrucosum*, and *T. mentagrophytes*. In east Asia, *T. violaceum* and *M. ferrugineum* are important pathogens. In Europe, African/Caribbean immigrants account for a large proportion of new patients with tinea capitis. Important pathogens include *T. tonsurans*, *M. audouinii var. langeronii*, *Trichophyton soudanense*, and *T. violaceum*. *Trichophyton. megninii* is a rare cause of tinea capitis largely restricted to southwest Europe. In Africa, large-scale epidemics are associated with *T. soudanense*, *T. violaceum*, *T. schoenleinii* and *Microsporum spp*. In Australia, the predominantly white population experiences infections mostly with *M. canis*, but *T. tonsurans* is now equal in prevalence in some areas of the continent.

Favus Favus, which is very rare in the US, appears chiefly on the scalp but may affect the glabrous skin and nails. On the scalp, concave sulfur-yellow crusts form around loose, wiry hairs. Atrophic scarring ensues, leaving a smooth, glossy, thin, paper-white patch. On the glabrous skin the lesions are pinhead to 2 cm in diameter with cup-shaped crusts called *scutulae*, usually pierced by a hair as on the scalp. The scutula have a distinctive mousy odor. When the nails are affected they become brittle, irregularly thickened, and crusted under the free margins.

Favus among the Bantus in South Africa is called, in Afrikaans, *witkop* (whitehead). It is also prevalent in the Middle East, southeastern Europe, and the countries bordering the Mediterranean Sea.

Pathogenesis and Natural History

The incubation period of anthropophilic tinea capitis lasts 2 to 4 days, although the period is highly variable and asymptomatic carriers are common. The hyphae grow downward into the follicle, on the hair's surface, and the intrafollicular hyphae break up into chains of spores. There is a period of spread (4 days to 4 months) during which the lesions enlarge and new lesions appear. At about 3 weeks hairs break off a few millimeters above the skin surface. Within the hair, hyphae descend to the upper limit of the keratogenous zone and here form Adamson "fringe" on about the 12th day. No new lesions develop during the refractory period (4 months to several years). The clinical appearance is constant, with the host and parasite at equilibrium. This is followed by a period of involution in which the formation of spores gradually diminishes. Zoonotic fungal infections are commonly more highly inflammatory, but undergo similar phases of evolution.

Diagnosis

Wood's Light

Ultraviolet (UV) light of 365 nm wavelength is obtained by passing the beam through a Wood's filter composed of nickel oxide-containing glass. This apparatus, commonly known as the *Wood's light*, is commonly used to demonstrate fungal fluorescence. Fluorescent-positive infections are caused by *M. audouinii*, *M. canis*, *M. ferrugineum*, *M. distortum*, and *T. schoenleinii*. In a dark room the skin under this light fluoresces faintly blue, and dandruff commonly is bright blue–white. Infected hair fluoresces bright green or yellow–green. The fluorescent substance is a pteridine. Large spore endothrix organisms (such as *T. tonsurans* and *T. violaceum*) and *T. verrucosum* (a cause of large spore ectothrix) do not fluoresce.

Laboratory Examination

For demonstration of the fungus in a highly inflammatory plaque, two or three loose hairs are carefully removed with epilating forceps from the suspected areas. If fluoresence occurs it is important to choose these hairs. Bear in mind that hairs infected with *T. tonsurans* do not fluoresce. In "black-dot" ringworm or in patients with seborrheic scale, small broken fragments of infected hair will adhere to a moist gauze pad rubbed across the scalp. The hairs are placed on a slide and covered with a drop of a 10% to 20% KOH solution. Then a coverslip is applied, and the specimen is warmed until the hairs are macerated. Dimethyl sulfoxide (DMSO) can be added to the KOH solution in concentrations up to 40%. This additive allows for rapid clearing of keratin without heating. Once the hairs have softened, they are compressed through the coverslip and examined first with a low-power objective and then with a high-power objective for detail. The patterns of endothrix and ectothrix involvement described above, together with local prevalence data, allow for identification of the organism.

Exact identification of the causative fungus is generally determined by culture, although molecular sequencing offers a more rapid alternative. For culture, several infected hairs

are planted on Sabouraud dextrose agar, Sabouraud agar with chloramphenicol, Mycosel agar or dermatophyte test medium (DTM). Cultures are best collected by rubbing the lesion vigorously with a moistened cotton swab or gauze pad, then streaking the cotton over the agar surface. On the first three media, a distinctive growth appears within 1 to 2 weeks. Most frequently the diagnosis is made by the gross appearance of the culture growth, together with the microscopic appearance. In the case of *Trichophyton spp*, growth on different nutrient agars is often required to identify the organisms beyond genus. DTM not only contains antibiotics to reduce growth of contaminants but also contains a colored pH indicator to denote the alkali-producing dermatophytes. A few nonpathogenic saprophytes will also produce alkalinization and in the occasional case of onychomycosis of toenails caused by airborne molds, a culture medium containing an antibiotic may inhibit growth of the true pathogen.

T. tonsurans

This microorganism grows slowly in culture to produce a granular or powdery yellow to red, brown, or buff colony. Crater formation with radial grooves may be produced. Swollen microconidia may be seen regularly. Diagnosis is confirmed by the fact that cultures grow poorly or not at all without thiamine.

T. mentagrophytes

The colony is velvety, granular or fluffy. It may be flat or furrowed, light buff, white, or sometimes pink. The back of the culture can vary from buff to dark red. Round microconidia borne laterally and in clusters confirm the diagnosis within 2 weeks. Spiral hyphae are sometimes prominent.

T. verrucosum

Growth is slow and cannot be observed well for at least 3 weeks. The colony is compact, glassy, velvety, heaped or furrowed, and usually white, but may be yellow or gray. The colony may crack the agar. Chlamydospores (round swellings along the hyphal structure) are present in early cultures, and microconidia may be seen.

M. audouinii

Culture typically shows a slowly growing, matted, velvety, light brown colony, the back of which is reddish brown to orange. The colony edge is generally striate, rather than smooth. Under the microscope a few large multiseptate macroconidia may be seen. Microconidia in a lateral position on the hyphae are clavate. Racquet mycelia, terminal chlamydospores, and pectinate hyphae are sometimes seen.

M. canis

The culture grossly shows profuse, cottony, aerial mycelia that are distinctly striate at the periphery, while sometimes tending to become powdery in the center. The color is buff to light brown. The back of the colony is lemon to orange-yellow. There are numerous spindle-shaped thick-walled echinulate macroconidia. Clavate microconidia may be found along with chlamydospores and pectinate bodies.

Differential Diagnosis

Tinea capitis must be differentiated clinically from chronic staphylococcal folliculitis, pediculosis capitis, psoriasis, seborrheic dermatitis, secondary syphilis, trichotillomania, alopecia areata, lupus erythematosus, lichen planus, lichen simplex chronicus, and various inflammatory follicular conditions. The distinctive clinical features of tinea capitis are broken-off stumps of hairs, often in rounded patches in which there are crusts or pustules and few hairs. The broken-off hairs are loose and when examined are found to be surrounded by, or contain, the fungus. Diffuse seborrheic scaling with hair loss is a common presentation of *T. tonsurans* infections.

In alopecia areata the affected patches are bald, and the skin is smooth and shiny without any signs of inflammation or scaling. Stumps of broken-off hairs are infrequently found, and no fungi are demonstrable. In seborrheic dermatitis the involved areas are covered by fine, dry, or greasy scales. Hair may be lost, but the hairs are not broken. Atopic dermatitis is rarely associated with localized scalp involvement, and clinical examination frequently reveals more typical generalized findings. In psoriasis, well-demarcated, sometimes diffuse, areas of erythema and white or silver scaling are noted. Lichen simplex chronicus frequently is localized to the inferior margin of the occipital scalp. In trichotillomania, as in alopecia areata, inflammation and scaling are absent. Circumscribed lesions are very rare. Serologic testing, scalp biopsies, and immunofluorescent studies may be indicated if the alopecia of secondary syphilis or lupus erythematosus is a serious consideration. It should be noted that adult patients with lupus erythematosus are susceptible to tinea capitus, which may be photosensitive and difficult to distinguish from plaques of lupus without biopsy and KOH examinations.

Treatment

Numerous clinical trials exist that demonstrate the effectiveness of itraconazole, terbinafine, and fluconazole. Despite these studies, griseofulvin remains the most commonly used antifungal agent in children. It has a long safety record, and pediatricians and family practitioners are generally comfortable with the drug. For the ultramicronized form, doses start at 10 mg/kg/day. The tablets can be crushed and given with ice cream. Grifulvin V oral suspension is less readily absorbed. The dose is 20 mg/kg/day. Treatment should continue for 2 to 4 months, or for at least 2 weeks after negative laboratory examinations are obtained. Doses much higher than those reflected in drug labeling are commonly needed. For *Trichophyton* infections, terbinafine is commonly effective in doses of 3 to 6 mg/kg/day for 1 to 4 weeks. Alternate dosing schedules for terbinafine include one 250 mg tablet for patients over 40 kg, 125 mg (half of a 250 mg tablet) for those 20 to 40 kg, and 62.5 mg (one-quarter of a 250 mg tablet) for those under 20 kg. Microsporum infections require higher doses and longer courses of therapy with terbinafine. Itraconazole has been shown to be effective in doses of 5 mg/kg/day for 2 to 3 weeks, and fluconazole at doses of 6 mg/kg/day for 2 to 3 weeks. Reports of heart failure with intraconazole have limited its use.

Selenium sulfide shampoo or ketoconazole shampoo left on the scalp for 5 min three times a week can be used as adjunctive therapy to oral antifungal agents to reduce the shedding of fungal spores. Combs, brushes, and hats should be cleaned carefully and natural bristle brushes must be discarded.

Prognosis

Recurrence usually does not occur when adequate amounts of griseofulvin, fluconazole, or terbinafine have been taken, although exposure to infected persons, asymptomatic carriers, or contaminated fomites will increase the relapse rate. Without medication there is spontaneous clearing at about the age of 15, except with *T. tonsurans*, which often persists into adult life.

DERMATOPHYTIDS

In cases of inflammatory tinea capitis, widespread "id" eruptions may appear concomitantly on the trunk and extremities. These are vesicular, lichenoid, papulosquamous or pustular. They represent a systemic reaction to fungal antigens. Although they are commonly refractory to topical corticosteroids, they typically clear rapidly after treatment of the fungal infection.

The most common type of id reaction is seen on the hands and sides of the fingers when there is an acute fungus infection of the feet. These lesions are mostly vesicular and are extremely pruritic and even tender. Secondary bacterial infection may occur; however, fungus is not demonstrable in a true dermatophytid. The onset is at times accompanied by fever, anorexia, generalized adenopathy, spleen enlargement, and leukocytosis. Dermatophytid reactions due to inflammatory tinea capitis may occasionally present as widespread eruption, usually follicular, lichenoid or papulosquamous. Rarely, the eruption may be morbilliform or scarlatiniform. The erysipelas-like dermatophytid is most commonly seen on the shin, where it appears as an elevated, sharply defined, erysipelas-like plaque about the size of the hand, usually with toe web tinea on the same side. This form of id reaction responds to systemic steroids and treatment of the tinea.

The histologic picture is characterized by spongiotic vesicles and a superficial, perivascular, predominantly lymphohistiocytic infiltrate. Eosinophils may be present. Diagnosis of a dermatophytid reaction is dependent on the demonstration of a fungus at some site remote from the suspect lesions of the dermatophytid, the absence of fungus in the id lesion, and involution of the lesion as the fungal infection subsides.

TINEA BARBAE

Ringworm of the beard, also known as *tinea sycosis* and *barber's itch*, is not a common disease. It occurs chiefly among those in agricultural pursuits, especially those in contact with farm animals. The involvement is mostly one-sided on the neck or face. Two clinical types are distinguished: deep, nodular, suppurative lesions; and superficial, crusted, partially bald patches with folliculitis (Fig. 15-2).

The deep type develops slowly and produces nodular thickenings and kerion-like swellings, usually caused by *T. mentagrophytes* or *T. verrucosum*. As a rule the swellings are confluent and form diffuse boggy infiltrations with abscesses. The overlying skin is inflamed, the hairs are loose or absent, and pus may be expressed through the remaining follicular openings. Generally, the lesions are limited to one part of the face or neck in men. The superficial crusted type is characterized by a less inflammatory pustular folliculitis, and may be associated with *T. violaceum* or *T. rubrum*. The affected hairs can sometimes be easily extracted. Rarely, *E. floccosum* may cause widespread verrucous lesions known as verrucous epidermophytosis.

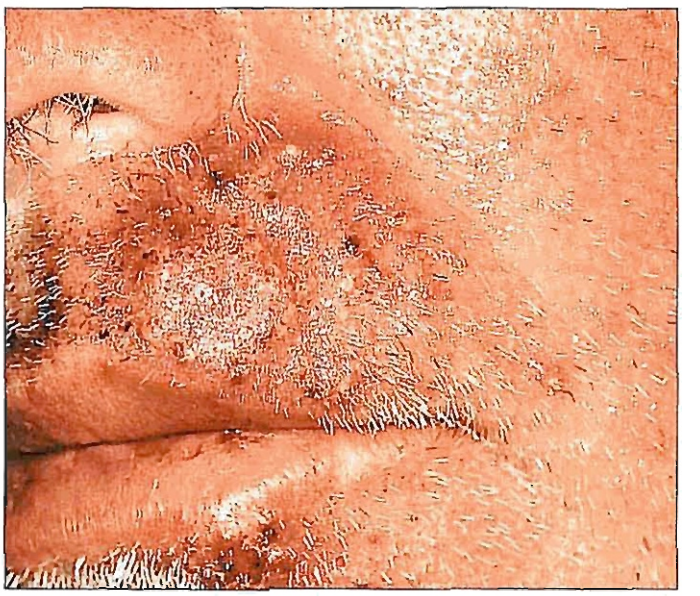

Fig. 15-2 Tinea barbae.

Diagnosis

The clinical diagnosis is confirmed by the microscopic mounts of extracted hairs or a biopsy specimen. Culture can be performed on extracted hairs or tissue homogenates of biopsy specimens.

Differential Diagnosis

The differential diagnosis includes staphylococcal folliculitis (sycosis vulgaris) and herpetic infections. Tinea barbae differs from sycosis vulgaris by usually sparing the upper lip, and by often being unilateral. In sycosis vulgaris the lesions are pustules and papules, pierced in the center by a hair, which is loose and easily extracted after suppuration has occurred. Herpetic infections usually demonstrate umbilicated vesicles. Tzanck preparations have a low diagnostic yield, but viral culture or direct fluorescent antibody are virtually always positive.

Treatment

Like tinea capitis, oral antifungal agents are required to cure tinea barbae. Topical agents are only helpful as adjunctive therapy. Oral agents are used in the same doses and for the same durations as in tinea capitis.

TINEA FACIEI

Fungal infection of the face is frequently misdiagnosed. Typical annular rings are usually lacking and the lesions are exquisitely photosensitive. Frequently a misdiagnosis of lupus erythematosus is made. Biopsies for direct immunofluorescence often demonstrate some reactants on sun-exposed skin, adding to the possible diagnostic confusion. Erythematous, slightly scaling, indistinct borders may be present at the periphery of the lesions, and are the best location for KOH examination. If topical corticosteroids have been used, fungal folliculitis is a frequent finding. A biopsy may be required to establish the diagnosis. A high index of suspicion is required, as fungal hyphae may be few in number or confined to hair follicles. The inflammatory pattern may be psoriasiform spongiotic or vacuolar interface. The latter

pattern has the potential to perpetuate confusion with lupus erythematosus.

Usually the infection is caused by *T. rubrum*, *T. mentagrophytes*, or *M. canis*. Tinea faciei caused by *Microsporum nanum* has been described in hog farmers,

If fungal folliculitis is present, oral medication is required. If no folliculitis is present, the infection generally responds well to topical therapy. Oral agents are appropriate for widespread infections.

TINEA CORPORIS (TINEA CIRCINATA)

Tinea corporis includes all superficial dermatophyte infections of the skin other than those involving the scalp, beard, face, hands, feet, and groin. This form of ringworm is characterized by one or more circular, sharply circumscribed, slightly erythematous, dry, scaly, usually hypopigmented patches. An advancing scaling edge is usually prominent (Fig. 15-3). Progressive central clearing produces annular outlines that give them the name "ringworm." Lesions may widen to form rings many centimeters in diameter. In some cases concentric circles or polycyclic lesions form, making intricate patterns. Widespread tinea corporis may be the presenting sign of acquired immunodeficiency syndrome (AIDS), or may be related to the use of a topical corticosteroid or calcineurin inhibitor.

In the US, *T. rubrum*, *M. canis*, and *T. mentagrophytes* are common causes, although it can be caused by any of the dermatophytes. Multiple small lesions are commonly caused by exposure to a pet with *M. canis*. Other zoonotic fungi, such as granular zoophilic *T. mentagrophytes* related to Southeast Asian bamboo rats, can cause widespread epidemics of highly inflammatory tinea corporis.

Tinea gladiatorum is a common problem for wrestlers. In Pennsylvania, during the 1998–1999 wrestling season, about 85% of responding teams had at least one wrestler diagnosed with ringworm, despite the fact that 97% used preventive practices. A third of these teams reported that a wrestler missed a match because of the infection. Opponents, equipment, and mats represent potential sources of infection.

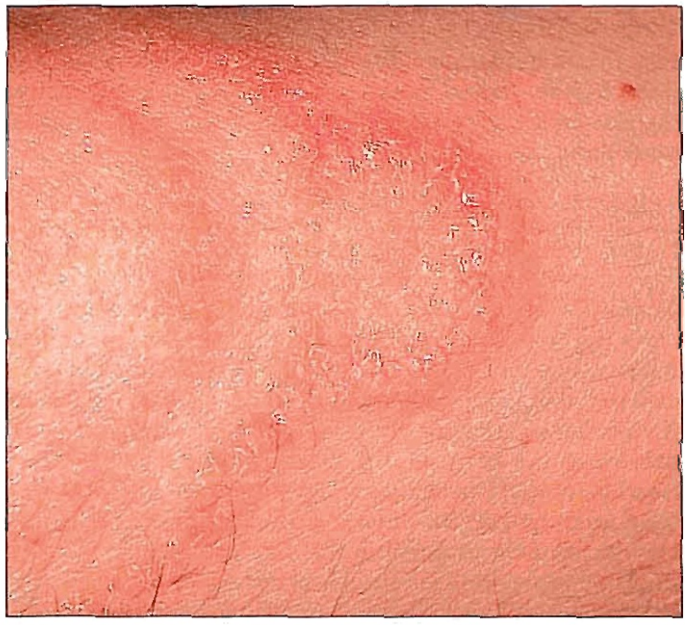

Fig. 15-3 Tinea corporis.

Diagnosis

The diagnosis is relatively easily made by finding the fungus under the microscope in skin scrapings. In addition, skin scrapings can be cultured on a suitable medium. Growth of the fungus on culture medium is apparent within a week or two at most and, in most instances, is identifiable to the genus level by the gross and microscopic appearance of the culture. Biopsy of a chronic refractory dermatosis often reveals tinea incognito.

Other diseases that may closely resemble tinea corporis are pityriasis rosea, impetigo, nummular dermatitis, secondary and tertiary syphilids, seborrheic dermatitis, and psoriasis. These are distinguished by KOH examination and culture.

Treatment

Localized disease without fungal folliculitis may be treated with topical therapy. Sulconazole (Exelderm), oxiconazole (Oxistat), miconazole (Monistat cream or lotion, or Micatin cream), clotrimazole (Lotrimin or Mycelex cream), econazole (Spectazole), naftifine (Naftin), ketoconazole (Nizoral), ciclopirox olamine (Loprox), terbinafine (Lamisil), and butenafine (Mentax) are currently available and effective. Most treatment times are between 2 and 4 weeks with twice a day use. Econazole, ketoconazole, oxiconazole, and terbinafine may be used once a day. With terbinafine the course can be shortened to 1 week. Combination products with a potent corticosteroid (such as clotrimazole/betamethasone) frequently produce widespread tinea and fungal folliculitis. Their use should be discouraged.

Extensive disease or fungal folliculitis requires systemic antifungal treatment. When tinea corporis is caused by *T. tonsurans*, *T. mentagrophytes*, or *T. rubrum*, griseofulvin, terbinafine, itraconazole, and fluconazole are all effective. Shorter courses are possible with newer antifungals. Terbinafine therapy for *M. canis* typically requires higher doses and longer courses of therapy.

The ultra-micronized form of griseofulvin may be effective in doses from 500 to 1000 mg/day for 4 to 6 weeks. Approximately 10% of individuals will experience nausea or headache with griseofulvin. These symptoms commonly respond to a temporary reduction in dosage. Absorption of griseofulvin is improved when given with whole milk or ice cream. Effective blood levels in children occur at doses of 10 to 20 mg/kg/day, although higher doses are commonly needed. Terbinafine at 250 mg/day for 1 to 2 weeks; itraconazole, 200 mg/day for 1 week; and fluconazole, 150 mg once a week for 4 weeks, have been effective doses in adults.

Other Forms of Tinea Corporis

Fungal Folliculitis (Majocchi Granuloma) and Tinea Incognito Occasionally, a deep, pustular type of tinea circinata resembling a carbuncle or kerion is observed on the glabrous skin. This type of lesion is a fungal folliculitis caused most often by *T. rubrum* or *T. mentagrophytes* infecting hairs at the site of involvement. It presents as a circumscribed, annular, raised, crusty, and boggy granuloma in which the follicles are distended with viscid purulent material. These occur most frequently on the shins or wrists. The lesions are often seen in areas of occlusion, shaving, or when a topical corticosteroid has been used. In immunosuppressed patients the lesions may be deep and nodular.

Often, patients have been treated with a shot-gun approach, using both topical corticosteroids and antifungal agents. If a topical antifungal has been used recently, KOH examination and culture may be negative. A biopsy may be required to establish the diagnosis. Oral therapy is necessary to cure the lesions.

Tinea incognito is a term applied to atypical clinical lesions of tinea, usually produced by treatment with a topical corticosteroid or occasionally a calcineurin inhibitor. The lesions are often widespread, and may lack an advancing raised scaly border. The biopsy may be established by KOH examination or biopsy.

Tinea Imbricata (Tokelau) Tinea imbricata is a superficial fungal infection limited to southwest Polynesia, Melanesia, Southeast Asia, India, and Central America. It is characterized by concentric rings of scales forming extensive patches with polycyclic borders (Fig. 15-4). Erythema is typically minimal. The eruption begins with one or several small, rounded macules on the trunk and arms. The small macular patch splits in the center and forms large, flaky scales attached at the periphery. As the resultant ring spreads peripherally, another brownish macule appears in the center and undergoes the process of splitting and peripheral extension. This is repeated over and over again. When fully developed the eruption is characterized by concentrically arranged rings or parallel undulating lines of scales overlapping each other like shingles on a roof (*imbrex* means shingle).

The causative fungus is *T. concentricum*. Microscopically, the scrapings show interlacing, septate, mycelial filaments that branch dichotomously. Polyhedral spores are also present. Griseofulvin has been used, but the recurrence rate is high. In one study, terbinafine 250 mg/day for 4 weeks was effective in all of 43 patients. Itrazonazole at a dose of 100 mg/day failed in 4 of 40 patients, but this may reflect the dose used in the study.

TINEA CRURIS

Tinea cruris, also known as *jock itch* and *crotch itch*, occurs most frequently in men on the upper and inner surfaces of the thighs, especially during the summer when the humidity is high. It begins as a small erythematous and scaling or vesicular and crusted patch that spreads peripherally and partly clears in the center, so that the patch is characterized chiefly by its curved, well-defined border, particularly on its lower edge. The border may have vesicles, pustules, or papules. It may extend downward on the thighs and backward on the perineum or about the anus. The scrotum is rarely involved.

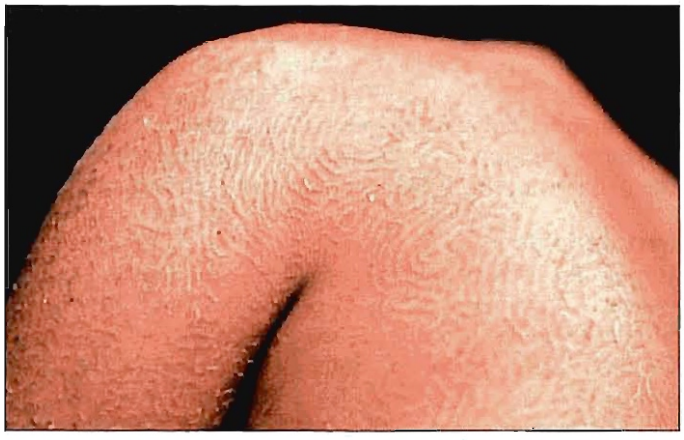

Fig. 15-4 Tinea imbricata.

Etiology and Differential Diagnosis

Ringworm of the groin usually is caused by *T. rubrum*, *T. mentagrophytes*, or *E. floccosum*. Infection with *Candida albicans* may closely mimic tinea cruris, but is usually moister, more inflammatory, and associated with satellite macules. *Candida* often produces collarette scales and satellite pustules.

The crural region is also a common site for erythrasma, seborrheic dermatitis, pemphigus vegetans, and intertriginous psoriasis. Erythrasma often has a copper color, and is diagnosed by the Wood's light examination, which produces coral-red fluorescence. Seborrheic dermatitis generally involves the central chest and axillae in addition to the groin. Pemphigus vegetans produces macerated and eroded lesions. Biopsy is established by biopsy and immunofluoresence. Inverse psoriasis may be associated with collarette scales, or with serpiginous arrays of pustules at the border of inflammatory lesions. When more typical lesions of psoriasis are lacking, a biopsy may be required to establish the diagnosis.

Treatment

The reduction of perspiration and enhancement of evaporation from the crural area are important prophylactic measures. The area should be kept as dry as possible by the wearing of loose underclothing and trousers. Plain talcum powder or antifungal powders are helpful. Specific topical and oral treatment is the same as that described earlier for tinea corporis.

TINEA OF HANDS AND FEET

Dermatophytosis of the feet, long popularly called athlete's foot, is by far the most common fungal disease. *T. rubrum* causes the majority of infections, and there may be an autosomal-dominant predisposition to this form of infection. *T. rubrum* typically produces a relatively noninflammatory type of dermatophytosis characterized by a dull erythema and pronounced silvery scaling that may involve the entire sole and sides of the foot, giving a moccasin or sandal appearance. One hand may be involved. The eruption may also be limited to a small patch adjacent to a fungus-infected toenail, or to a patch between or under the toes. Sometimes an extensive, patchy, scaly eruption covers most of the trunk, buttocks, and extremities. Rarely, there is a patchy hyperkeratosis resembling errucous epidermal nevus.

Generally, tinea infection of the hands is of the dry, scaly, and erythematous type that is suggestive of *T. rubrum* infection. Other areas are frequently affected at the same time, especially the combination of both feet and one hand.

Tinea pedis caused by anthropophylic *Trichophyton mentagrophytes (interdigitale)* presents with three distinct appearances. One is composed of multilocular bullae involving the thin skin of the plantar arch and along the sides of the feet and heel. The second presents with erythema and desquamation between the toes. The third is white superficial onychomycosis. In the human immunodeficiency (HIV)-positive population, this latter syndrome is usually caused by

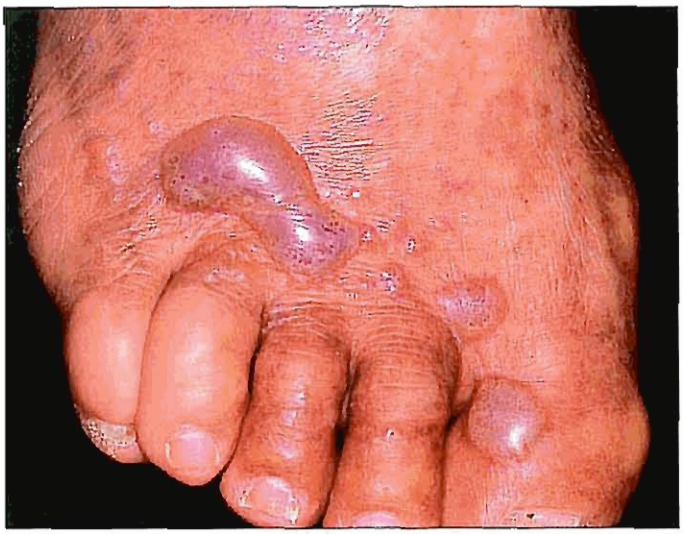

Fig. 15-5 Bullous tine.

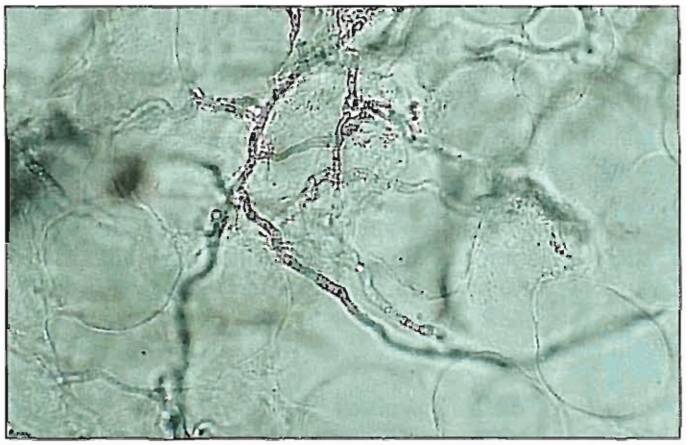

Fig. 15-6 Positive KOH examination.

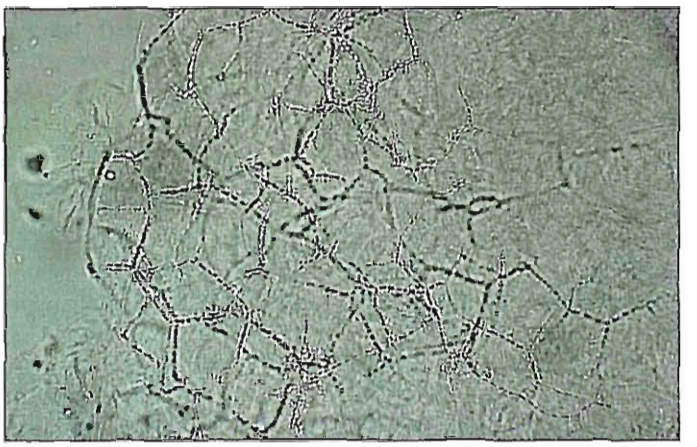

Fig. 15-7 False-positive "mosaic" hyphae (artefact).

T. rubrum. Interdigital tinea must be distinguished from simple maceration caused by a closed webspace. The latter does not respond to antifungal therapy. Interdigital tinea must also be distinguished from Gram-negative toe web infection.

Trichophyton mentagrophytes often produces acutely inflammatory multilocular bullae (Fig. 15-5). The burning and itching that accompany the formation of the vesicles may cause great discomfort, which is relieved by opening the tense vesicles. They contain a clear straw-colored tenacious fluid. Extensive or acute eruptions on the soles may be incapacitating. The fissures between the toes, as well as the vesicles, may become secondarily infected with pyogenic cocci, which may lead to recurrent attacks of lymphangitis and inguinal adenitis. Gram-negative toe-web infections may also supervene. Hyperhidrosis is frequently present in this type of dermatophytosis. The sweat between the toes and on the soles has a high pH, and damp keratin is a good culture medium for the fungi.

Dermatophytid of the hands may be associated with inflammatory tinea of the feet and begins with the appearance of groups of minute, clear vesicles on the palms and fingers. The itching may be intense. As a rule, both hands are involved and the eruption tends to be symmetrical; however, there are cases in which only one hand is affected. The dorsa and sides of the feet may also be affected.

Diagnosis

Demonstration of the fungus by microscopic examination of the scrapings taken from the involved site establishes the diagnosis. Copious dry scale from the instep, heel, and sides of the foot can be gathered by scraping with the edge of a glass microscope slide. Bullae should be unroofed and either the entire roof mounted intact or scrapings made from the underside of the roof. A drop of a 10% to 20% solution of KOH is added to the material on the glass slide. A coverslip is placed over the specimen and pressed down firmly. Gentle heat is applied until the scales are thoroughly macerated. The addition of 20% to 40% DMSO speeds clearing of keratin without the need for heating. A staining method using 100 mg of chlorazol black E dye in 10 mL of DMSO and adding it to a 5% aqueous solution of KOH can be helpful. Toluidine blue, 0.1%, can also be used on thin specimens, but contains no clearing agent to dissolve keratin.

The mycelium (Fig. 15-6) may be seen under low power, but better observation of both hyphae and spores is obtained by the use of 10× objective with the condenser cranked down or the light aperture closed by two-thirds. The lines of juncture of normal epidermal cells dissolve into a branching network that may easily be mistaken for fungus structures ("mosaic false hyphae") (Fig. 15-7). This is the most common artifact misinterpreted as a positive KOH examination. Cotton and synthetic fibers from socks may also mimic hyphae.

Material may also be placed on Sabouraud dextrose agar, Sabouraud agar with chloramphenicol, Mycosel agar, or DTM. The last three agars inhibit growth of bacterial or saprophytic contaminants. The last two may inhibit some pathogenic nondermatophytes. The alkaline metabolites produced by growth of dermatophytes change the color of the pH indicator in DTM medium from yellow to red.

Prophylaxis

Hyperhidrosis is a predisposing factor for tinea infections. Because the disease often starts on the feet, the patient should be advised to dry the toes thoroughly after bathing. Dryness of the parts is essential if reinfection is to be avoided.

The use of a good antiseptic powder on the feet after bathing, particularly between the toes, is strongly advised for

susceptible persons. Tolnaftate powder (Tinactin powder) or Zeasorb medicated powder are excellent dusting powders for the feet. Plain talc, cornstarch, or rice powder may be dusted into socks and shoes to keep the feet dry. Periodic use of a topical antifungal agent may be required, especially when hot occlusive footwear is worn.

Treatment

Clotrimazole, miconazole, sulconazole, oxiconazole, ciclopirox, econazole, ketoconazole, naftifine, terbinafine, flutrimazol, bifonazole, and butenafine are effective topical antifungal agents. When there is significant maceration between the toes, the toes may be separated by foam or cotton inserts in the evening. Aluminum chloride 10% solution or aluminum acetate, 1 part to 20 parts of water, can be beneficial. Topical antibiotic ointments, such as gentamicin (Garamycin), which are effective against Gram-negative organisms, are helpful additions in some moist interdigital lesions. In the ulcerative type of Gram-negative toe web infections, systemic antibiotic therapy is necessary. (See Chapter 14 for a discussion on Gram-negative toe-web infections.) Keratolytic agents containing salicylic acid, resorcinol, lactic acid, and urea may be useful in some cases, although all may lead to maceration if occluded.

Treatment of fungal infection of the skin of the feet and hands with griseofulvin in doses of 500 to 1000 mg/day can be effective. Dosage for children is 10 to 20 mg/kg/day. The period of therapy depends on the response of the lesions. Repeated KOH scrapings and cultures should be negative. Much shorter courses are possible with newer antifungal agents. Recommended adult dosing for terbinafine is 250 mg/day for 1 to 2 weeks; for itraconazole, 200 mg twice a day for 1 week; and for fluconazole, 150 mg once a week for 4 weeks. Abbreviated schedules and intermittent dosing with other agents may be possible, but require further study. In one small study, itraconazole was given in doses of 100 mg twice a day immediately after meals on 2 consecutive days. The regimen produced good to excellent responses in all patients within 14 days.

Onychomycosis (Tinea Unguium) Onychomycosis is defined as the infection of the nail plate by fungus and represents up to 30% of diagnosed superficial fungal infections. *T. rubrum* accounts for most cases, but many fungi may be causative. Other etiologic agents include *E. floccosum* and various species of *Microsporum* and *Trichophyton* fungi. It may also be caused by yeasts and nondermatophytic molds.

There are four classic types of onychomycosis:

1. Distal subungual onychomycosis: primarily involves the distal nailbed and the hyponychium, with secondary involvement of the underside of the nail plate of fingernails and toenails. Usually caused by *T. rubrum*.
2. White superficial onychomycosis (Fig. 15-8) (leukonychia trichophytica): this is an invasion of the toenail plate on the surface of the nail. It is produced by *T. mentagrophytes*, species of *Cephalosporium* and *Aspergillus*, and *Fusarium oxysporum* fungi. In the HIV-positive population, it is commonly caused by *T. rubrum*.
3. Proximal subungual onychomycosis (Fig. 15-9): involves the nail plate mainly from the proximal nailfold, producing a specific clinical picture. It is produced by *T. rubrum* and *T. megninii*, and may be an indication of HIV infection.
4. Candida onychomycosis produces destruction of the nail and massive nailbed hyperkeratosis. It is due to *C. albicans* and is seen in patients will chronic mucocutaneous candidiasis.

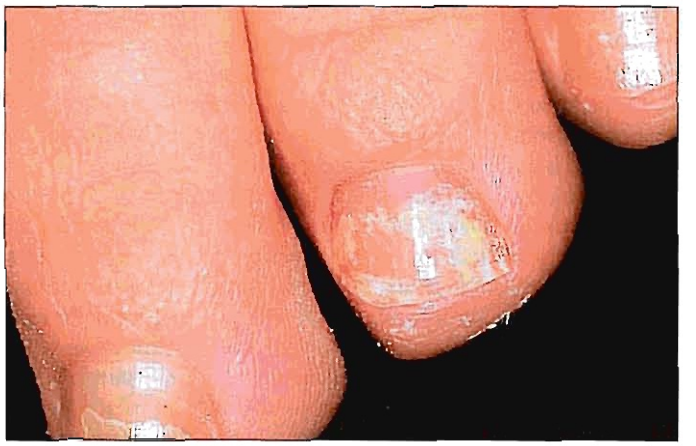

Fig. 15-8 Superficial white onychomycosis.

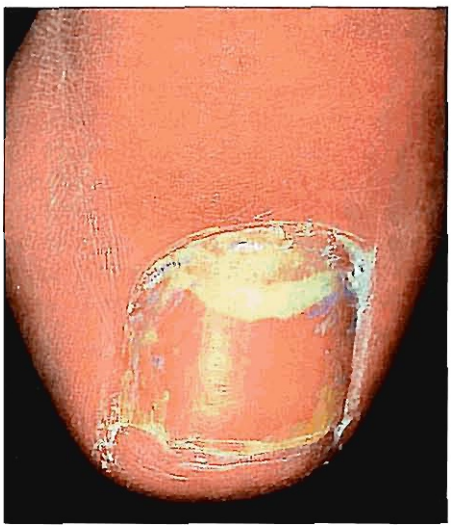

Fig. 15-9 White proximal subungual onychomycosis.

Onychomycosis caused by *T. rubrum* usually starts at the distal corner of the nail and involves the junction of the nail and its bed. A yellowish discoloration occurs, which spreads proximally as a streak in the nail. Later, subungal hyperkeratosis becomes prominent and spreads until the entire nail is affected. Gradually the entire nail becomes brittle and separated from its bed as a result of the piling up of subungual keratin. Fingernails and toenails present a similar appearance, and the skin of the soles is likely to be involved, with characteristic branny scaling and erythema.

Onychomycosis caused by *T. mentagrophytes* is usually superficial, and there is no paronychial inflammation. The infection generally begins with scaling of the nail under the overhanging cuticle and remains localized to a portion of the nail. In time, however, the entire nail plate may be involved. White superficial onychomycosis is the name given to one type of superficial nail infection caused by this fungus in which small, chalky white spots appear on or in the nail

plate. They are so superficial that they may be easily shaved off. *T. violaceum*, *T. schoenleinii*, and *T. tonsurans* occasionally invade the nails, as does *Trichosporon beigelii*.

Scopulariopsis brevicaulis has been infrequently isolated from onychomycosis. Infection usually begins at the lateral edge of the nail, burrows beneath the plate, and produces large quantities of cheesy debris. Nattrassia mangiferae (*Hendersonula toruloidea*) and *Scytalidium hyalinum* have been reported to cause onychomycosis, as well as a moccasin-type tinea pedis. In addition to the more common features of onychomycosis, such as nail-plate thickening, opacification, and onycholysis, features of infection with these fungi include lateral nail invasion alone, paronychia, and transverse fracture of the proximal nail plate. When these agents are suspected, culture must be done with a medium that does not contain cycloheximide (found in Mycosel agar). Oral ketoconazole and griseofulvin are not effective in the treatment of these organisms.

The pathogen is heavily influenced by heredity, geography, and footwear. In the US, most tinea pedis and onychomycosis are caused by *T. rubrum*. In a rural school in Mexico where most people wear nonocclusive leather sandals, *Trichosporon cutaneum*, *Candida spp* and *Trichophyton mentagrophytes* accounted for most infection. *T. rubrum* was not isolated in any patient. Cutaneous *Scytalidium* infections are common in patients from the tropics, especially the West Indies and Africa. They commonly carry the organism with them, even when they emigrate to more temperate climates.

Diagnosis

The demonstration of fungus is made by microscopic examination or by culture. The submitted clippings or curettings must include dystrophic subungual debris. Immediate examination may be made if very thin shavings or curettings are taken from the diseased nailbed and examined with KOH solution. A variety of stains such as chlorazole black E can be added to improve sensitivity. Specimens can also be sent for histologic examination or culture.

Histopathologic examination with periodic acid-Schiff stain (PAS) has been found to be 41% to 93% sensitive in various studies. It has proved more sensitive than either KOH or culture in several studies. In one study, in which histology was 85% sensitive, KOH dissolution and centrifugation combined with PAS was 57% sensitive, while calcofluor white fluorescent staining and chlorazol black E were each found to be 53% sensitive. Culture on Sabouraud agar with chloramphenicol and cycloheximide (Mycosel) agar was 32% sensitive. Other studies have shown the sensitivity of culture to be 30% to 70%. Combining KOH and culture has yielded sensitivities in the range of 80% to 85%.

Both office and central laboratories can be used to isolate fungi, but false-negative results are common in both settings. In one study, office DTM culture was positive in 102 of 184 patients (55%), while the central laboratory detected the infection in 78 of 184 (42%). The two tests were in agreement (both positive or both negative) in 114 of 184 patients (62%). In a similar study, DTM cultures were positive in 51% (n = 345), while central laboratory cultures were positive in 44% (n = 297). The two cultures were in agreement in 68% of cases. Dermatophytes accounted for about 90% of the confirmed infections in each study.

As no single method offers 100% sensitivity, a variety of methods are still in use. KOH has the advantage of being performed rapidly in the office. Histologic examination usually provides results within 24 h, while culture can take days to weeks. Identification of genus and species is only possible with culture.

Differential Diagnosis

Dystrophic nails can be produced by psoriasis, lichen planus, eczema and contact dermatitis, and may be clinically indistinguishable from fungal nails. Confirmatory tests to identify the fungus are mandatory in order to establish a diagnosis. Psoriasis may involve other nails with pitting, onycholysis, oil spots, salmon patches or by heaped-up subungual keratinization. Typical features of psoriasis may be present on other areas of skin. Lichen planus may produce rough nails or pterygium formation and may involve the oral mucosa or skin. Eczema and contact dermatitis affect the adjacent nailfold. Hyperkeratotic ("Norwegian") scabies can also produce dystrophic nails, but is associated with generalized hyperkeratosis.

Onychomycosis among psoriasis patients is reported with varying prevalence, but occurs roughly in the range of 22% compared to 13% for patients with other skin diseases. Onychomycosis occurs more frequently in men than in women with psoriasis.

Treatment

Many patients with onychomycosis are not symptomatic, and may not seek treatment. Patients with diabetes or peripheral neuropathy may be at higher risk for complications related to onychomycosis, and the benefits of treatment may be greater in this population. These factors, as well as cost and risk of recurrence, should be considered as part of the decision to treat onychomycosis.

The topical management of onychomycosis has improved with the introduction of ciclopirox and amorolfine nail lacquers. These agents are modestly effective at moderate cost. Other topical agents are of little benefit, and no topical agent achieves the cure rates possible with oral therapy.

For disease involving fingernails, terbinafine is given in doses of 250 mg/day for 6 to 8 weeks. For toenails, the course of treatment is generally 12 to 16 weeks. Itraconazole is generally given as pulsed dosing, 200 mg twice a day for 1 week of each month, for 2 months when treating fingernails and for 3 to 4 months when treating toenails. Fluconazole at doses of 150 to 300 mg once a week for 6 to 12 months appears to be effective. Around 20% of patients will not respond to treatment. The presence of a dermatophytoma within the nail may be associated with a higher risk of failure. Dermatophytomas present as yellow streaks within the nail, and may respond to unroofing and curettage. Several studies have suggested that continuous therapy with terbinafine for 4 months is cost-effective when compared with other possible agents and regimens. Most clinical trials have been industry-sponsored and little independent research is available for review. For onychomycosis in children, terbinafine, itraconazole, and fluconazole have all been shown to be effective. Dosage depends on body weight, as indicated above. Duration of treatment is the same as for adults.

Treatment with systemic antifungals is very effective in onychomycosis caused by *Aspergillus spp*. *Scopulariopsis*

brevicaulis and *Fusarium spp* infection are difficult to eradicate and treatment with systemic antifungals should always be associated with topical treatment with nail lacquers. Nail avulsion represents another option. Candida onychomycosis is always a sign of immunodepression. Systemic treatment with itraconazole or fluconazole is usually effective, but relapses are the rule. When treating *Candida* infections, combinations of topical and systemic treatment can be used for synergistic effect. The combination of topical amorolfine and oral itraconazole, which interferes with different steps of ergosterol synthesis, has been shown to exhibit substantial synergy in this setting. Combination treatment with topical amorolfine and two pulses of intraconazole may be as effective as three pulses of itraconazole, with a lower cost.

The FDA has issued a health advisory to announce serious risks associated with the use of itraconazole and terbinafine. The advisory states that both have been associated with serious liver problems resulting in liver failure, the need for transplantation, and death. There is a small but real risk of developing congestive heart failure associated with the use of intraconazole. Significant drug interactions may occur in patients on intraconazole who are also treated with drugs metabolized by the cytochrome P450 pathway. Interactions with terbinafine and the tricyclic antidepressant desimpramine have been reported.

Itraconazole pulsed treatment has been shown to have a low incidence of liver function abnormalities (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin). Product labeling recommends liver function tests for patients receiving continuous itraconazole for periods exceeding 1 month. Monitoring is required for the pulsed regimen if the patient has a history of hepatic disease, has abnormal baseline liver function tests, or development of signs or symptoms suggestive of liver dysfunction. Phenobarbital shows potential for the cytoprotection of hepatocytes to itraconazole-but not fluconazole-induced cytotoxicity in vitro, suggesting the possibility of regimens to further reduce the risk of toxicity.

Molds are sensitive to ultraviolet (UV) and visible light, and *T. rubrum* in culture has been shown to be susceptible to photodynamic therapy (PDT) as well as psoralens with UVA (PUVA). For PDT with broad-band white light, the phthalocyanines and photofrin displayed a fungistatic effect, whereas porphyrins caused photodynamic killing of the dermatophyte. 5,10,15-Tris(4-methylpyridinium)-20-phenyl-(21H,23H)-porphine trichloride and deuteroporphyrin monomethylester showed superior results in vitro. Further study of various methods of phototherapy is warranted.

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CANDIDIASIS

Candidiasis is also known as *candidosis*, *moniliasis*, *thrush*, and *oidiomycosis*.

C. albicans is a common inhabitant of the human gastrointestinal and genitourinary tracts, and skin. Under the right conditions, it becomes a pathogen, causing lesions of the skin, nails, and mucous membranes. The intertriginous areas are frequently affected. Here warmth, moisture, and maceration of the skin permit the organism to thrive. The areas most often involved are the perianal and inguinal folds, abdominal creases, inframammary creases, interdigital areas, nailfolds, and axillae.

C. albicans is largely an opportunistic organism, acting as a pathogen in the presence of impaired immune response, or where local conditions favor growth. Warmth and moisture favor candidal growth. Reductions in competing flora during antibiotic therapy can also favour candidal growth. Higher skin pH favors candidal growth. Diapers, panty liners, and other occlusive products raise skin pH and may predispose to skin infections of *C. albicans*. A topical acidic buffer may be helpful as a preventive measure for recurrent *Candida*-induced skin rash.

Diagnosis

The demonstration of the pathogenic yeast *C. albicans* establishes the diagnosis. Under the microscope the KOH preparation may show spores and pseudohyphae. On Gram stain the yeast forms dense, Gram-positive, ovoid bodies, 2 to 5 µm in diameter.

Candida proliferates in both budding and mycelial forms in the stratum corneum or superficial mucosa. Budding yeast and pseudohyphae are easier to detect in histologic section with a PAS stain. Whereas dermatophyte hyphae tend to run parallel to the skin surface, candida pseudohyphae have more of a tendency to vertical orientation.

In culture *C. albicans* should be differentiated from other forms of *Candida* that are only rarely pathogenic, such as *Candida krusei*, *Candida stellatoidea*, *Candida tropicalis*, *Candida pseudotropicalis*, and *Candida guilliermondii*. Culture on Sabouraud glucose agar shows a growth of creamy, grayish, moist colonies in about 4 days. In time the colonies form small, rootlike penetrations into the agar. Microscopic examination of the colony shows clusters of budding cells. When inoculated into cornmeal agar culture, thick-walled, round chlamydospores characteristic of *C. albicans* are produced.

Topical Anticandidal Agents

Most of the topical agents marketed for tinea are also effective for candidiasis. These include clotrimazole (Lotrimin, Mycelex), econazole (Spectazole), ketoconazole (Nizoral), miconazole (Monistat-Derm Lotion, Micatin), oxiconazole (Oxistat), sulconazole (Exelderm), naftifine (Naftin), terconazole, ciclopirox olamine (Loprox), butenafine (Mentax), Terbinafine (Lamisil), nystatin, and topical amphotericin B lotion. Older agents such as gentian violet, Castellani paint, and boric acid are still sometimes used.

Oral Candidiasis (Thrush) The mucous membrane of the mouth may be involved in healthy infants. In the newborn the infection may be acquired from contact with the vaginal tract of the mother. In older children and adults, thrush is commonly seen following antibiotic therapy. It may also be a sign of immunosuppression.

Grayish-white membranous plaques are found on the surface of the mucous membrane. The base of these plaques is moist, reddish, and macerated. In its spread the angles of the mouth may become involved, and lesions in the intertriginous areas may occur, especially in marasmic infants. The diaper area is especially susceptible to this infection. Most of the intertiginous areas and even the exposed skin may be involved, with small pustules that quickly turn into macerated and erythematous scaling patches.

In adults, the appearance may resemble that seen in children, or may be drier and more erythematous. Saliva inhibits the growth of candida, and a dry mouth predisposes to candidal growth. Broad-spectrum antibiotics also predispose to candidiasis. The papillae of the tongue may appear atrophic, with the surface smooth, glazed, and bright red. Frequently the infection extends onto the angles of the mouth to form perléche. This appearance is common in elderly, debilitated, and malnourished patients, and in patients with diabetes. It is often the first manifestation of AIDS, and is present in nearly all untreated patients with full-blown AIDS. The observation of oral "thrush" in an adult with no known predisposing factors warrants a search for other evidence of infection with HIV, such as lymphadenopathy, leukopenia, or HIV antibodies in the serum.

Various treatment options are available. Infants are commonly treated with oral nystatin suspension. An adult can let clotrimazole troches dissolve in the mouth. A single 150 mg dose of fluconazole is effective for many mucocutaneous infections in adults. In immunosuppressed patients, 200 mg/day is the starting dose, but much higher doses are often needed. Itraconazole, 200 mg/day for 5 to 10 days, can also be effective. Although terbinafine is commonly thought of as a dermatophyte drug, it can also be effective for candida infections at doses of 250 mg/day.

Perlèche Perlèche, or angular cheilitis, is characterized by maceration and transverse fissuring of the oral commissures. The earliest lesions are ill-defined, grayish-white, thickened areas with slight erythema of the mucous membrane at the oral commissure. When more fully developed this thickening has a bluish-white or mother-of-pearl color and may be contiguous with a wedge-shaped erythematous scaling dermatitis of the skin portion of the commissure. Fissures, maceration, and crust formation ensue. Soft, pinhead-sized papules may appear. Involvement usually is bilateral. Perlèche is commonly related to *C. albicans*, but may also harbor coagulase-positive *S. aureus* and Gram-negative bacteria. Similar changes may occur in riboflavin deficiency or other nutritional deficiency.

Identical fissuring occurs at the mucocutaneous junction from drooling in persons with malocclusion caused by ill-fitting dentures and in the aged in whom atrophy of the alveolar ridges ("closing" the bite) has caused the upper lip to overhang the lower at the commissures. There is sometimes a vertical shortening of the lower third of the face.

If due to *C. albicans*, anticandidal creams are effective, but the response is more rapid if they are used in combination with a mid-strength topical corticosteroid. If the perlèche is due to vertical shortening of the lower third of the face, dental or oral surgical intervention may be helpful. Injection of collagen into the depressed sulcus at the oral commissure can be beneficial.

Candidal Vulvovaginitis *C. albicans* is a common inhabitant of the vaginal tract. Overgrowth can cause severe pruritus, burning, and discharge. The labia may be erythematous, moist, and macerated, and the cervix hyperemic, swollen, and eroded, showing small vesicles on its surface. The vaginal discharge is not usually profuse and varies from watery, to thick and white or curdlike.

This type of infection may develop during pregnancy, in diabetes, or secondary to therapy with broad-spectrum antibiotics. Recurrent vulvovaginal candidiasis has also been associated with long-term tamoxifen treatment. Candidal balanitis may be present in an uncircumcised sexual partner. Diagnosis is established by the clinical symptoms and findings as well as the demonstration of the fungus by KOH microscopic examination and culture.

Oral fluconazole, 150 mg given once, is easy and effective. In some patients with predisposing factors, longer courses of fluconazole, 100 to 200 mg/day, or itraconazole, 200 mg/day for 5 to 10 days, may be needed. Topical options include miconazole, nystatin, clotrimazole, and terconazole.

Candida glabrata vaginitis may be refractory to azole drugs and can be difficult to eradicate. Topical boric acid, amphotericin B, and flucytosine may be helpful in this setting.

Candidal Intertrigo The pruritic intertriginous eruptions caused by *C. albicans* may arise between the folds of the genitals; in groins or armpits; between the buttocks; under large, pendulous breasts; under overhanging abdominal folds; or in the umbilicus. The pink to red intertriginous moist patches are surrounded by a thin, overhanging fringe of somewhat macerated epidermis ("collarette" scale). Some eruptions in the inguinal region may resemble tinea cruris, but usually there is less scaliness and a greater tendency to fissuring. Persistent excoriation and subsequent lichenification and drying may, in the course of time, modify the original appearance. Often, tiny, superficial, white pustules are observed closely adjacent to the patches. Topical anticandidal preparations are usually effective, but recurrence is common. Combinations of a topical anticandidal agent with a mid-strength corticosteroid may lead to more rapid relief. Castellani paint may also be helpful. Colorless Castellani paint is often preferred by patients.

Diaper Candidiasis The diagnosis of candidiasis may be suspected by the finding of involvement of the folds and occurrence of many small erythematous desquamating "satellite" or "daughter" lesions scattered along the edges of the larger macules. Topical anticandidal agents are effective. They are sometimes compounded in zinc oxide ointment to act as a barrier against the irritating effect of urine. Recurrent diaper candidiasis may be associated with oral and gut colonization and may respond to the addition of oral nystatin suspension.

Congenital Cutaneous Candidiasis Premature rupture of membranes together with a birth canal infected with *C. albicans* may lead to congenital cutaneous candidiasis. The eruption is usually noted within a few hours of delivery. Erythematous macules progress to thin-walled pustules, which rupture, dry, and desquamate within a week or so. Lesions are usually widespread, involving the trunk, neck, and head, and at times the palms and soles, including the nailfolds. The oral cavity and diaper area are spared, in contrast to the usual type of acquired neonatal infection. The differential diagnosis includes other neonatal vesiculopustular disorders, such as listeriosis, syphilis, staphylococcal and herpes infections, erythema toxicum neonatorum, transient neonatal pustular melanosis, miliaria rubra, drug eruption, and congenital ichthyosiform erythroderma. If suspected early the amniotic fluid, placenta, and cord should be examined for evidence of infection.

Infants with candidiasis limited to the skin have favorable outcomes; however, systemic involvement may occur. Disseminated infection is suggested by evidence of respiratory distress or other laboratory or clinical signs of neonatal sepsis. Dissemination is more common in infants who weigh less than 1500 g. Treatment with broad-spectrum antibiotics and altered immune responsiveness can also predispose to dissemination. Infants with congenital cutaneous candidiasis and any of the above factors may be considered for systemic antifungal therapy.

Perianal Candidiasis *C. albicans* infection may present as pruritus ani. Perianal dermatitis with erythema, oozing, and maceration is present. Pruritus and burning can be extremely severe. Satellite lesions may be present, but their

absence does not exclude candidiasis. Candida growth is also enhanced on abnormal tissue, such as extramammary Paget's disease or psoriasis. If the tissue does not return to normal after treating the candidiasis, a biopsy may be warranted.

Candidal Paronychia Inflammation of the nailfold produces redness, edema, and tenderness of the proximal nailfolds, and gradual thickening and brownish discoloration of the nail plates. Usually the fingernails only are affected. Patients commonly have an atopic background.

While acute paronychia is usually staphylococcal in origin, chronic paronychia is commonly multifactorial in origin. Irritant dermatitis and candidiasis may play important roles. In one study, treatment with a topical corticosteroid was superior to treatment with an anticandidal agent. Avoidance of irritants and wet work is essential. Anticandidal agents may be of use in this setting, and may be used in combination with a topical corticosteroid.

Candidal paronychia is frequently seen in patients with diabetes, and one aspect of the treatment consists of bringing the diabetes under control. The avoidance of chronic exposure to moisture and irritants is also essential in these patients. If topical treatment fails, oral fluconazole once a week or itraconazole in pulsed dosing can be effective.

Repetitive contact urticaria or allergic contact dermatitis to foods and spices may mimic candidal paronychia. Patch and radioallergosorbent (RAST) testing may be of value.

Erosio Interdigitalis Blastomycetica This form of candidiasis is seen as an oval-shaped area of macerated white skin on the web between and extending onto the sides of the fingers. Usually at the center of the lesion there are one or more fissures with raw, red bases; as the condition progresses the macerated skin peels off, leaving a painful, raw, denuded area surrounded by a collar of overhanging white epidermis. It is nearly always the third web, between the middle and ring fingers, that is affected. The moisture beneath the ring macerates the skin and predisposes to infection. The disease is also seen in patients with diabetes and those who do wet work.

Intertriginous lesions between the toes are similar. Usually the white, sodden epidermis is thick and does not peel off freely. On the feet it is the fourth interspace that is most often involved, but the areas are apt to be multiple. Clinically, this may be indistinguishable from tinea pedis. Diagnosis is made by culture.

Chronic Mucocutaneous Candidiasis The term *chronic mucocutaneous candidiasis* designates a heterogeneous group of patients whose infection with *Candida* is chronic but limited to mucosal surfaces, skin, and nails. Onset is typically before age 6. Onset in adult life may herald the occurrence of thymoma. These cases may be either inherited or sporadic. Inherited types may be associated with endocrinopathy. Oral lesions are diffuse and perlèche and lip fissures are common. The nails become thickened and dystrophic, with associated paronychia. Hyperkeratotic, hornlike, or granulomatous lesions are often seen.

Patients with mucocutaneous candidiasis have a selective defect in immunity that leaves them vulnerable to candidiasis. The underlying defect is unknown, and it is likely that this condition represents a group of disorders with a similar phenotype. Abnormalities of type 1 cytokine production in response to candida have been reported. Specifically, there may be markedly impaired production of interleukin (IL)-12 and dramatically increased levels of IL-6 and IL-10. Reductions in natural killer (NK) cells have also been noted. In a five-generation Italian family with chronic mucocutaneous candidiasis affecting only the nails, low serum intercellular adhesion molecule 1 (ICAM-1) was noted. The defect was linked to a 19 cM pericentromeric region on chromosome 11. Chronic mucocutaneous candidiasis with thyroid disease has been linked to chromosomes 2p.

Systemic fluconazole, itraconazole or ketoconazole is necessary to control the disease. Courses are typically prolonged, repeated, and given at higher than the usual recommended dose. Patients with achlorhydria may require an acidic beverage, such as cola, to enhance absorption of itraconazole and ketoconazole. Cimetidine was reported to restore deficient cell-mediated immunity in four adults from one family, at a dose of 300 mg four times a day.

Systemic Candidiasis *C. albicans* is capable of causing disseminated disease and sepsis, invariably when host defenses are compromised. Those who are at high risk include patients with malignancies, especially leukemias and lymphomas, in which there may be impaired immune defenses; patients with AIDS: debilitated and malnourished patients; patients with transplants requiring immunosuppressive drugs for prolonged periods; patients receiving oral cortisone; patients who have had multiple surgical operations, especially cardiac surgery; patients with indwelling intravenous catheters; and intravenous drug abusers.

The initial sign of systemic candidiasis may be fever of unknown origin, pulmonary infiltration, gastrointestinal bleeding, endocarditis, renal failure, meningitis, osteomyelitis, endophthalmitis, peritonitis, proximal muscle weakness and tenderness, or a disseminated maculopapular exanthema. The cutaneous lesions begin as erythematous macules that may become papular, pustular, hemorrhagic or ulcerative. Deep abscesses may occur. The trunk and extremities are the usual sites of involvement. Proximal muscle tenderness frequently accompanies the exanthema and may be a valuable clue to the correct diagnosis.

The demonstration of microorganisms or a positive culture will substantiate a diagnosis of candidiasis only if the microorganism is found in tissues or fluids ordinarily sterile for *Candida* and if the clinical picture is compatible. *Candida* colonization of endotracheal tubes used in supporting low birth weight neonates predisposes to systemic disease. If candida is cultured within the first week of life there is a high rate of systemic disease.

The mortality attributed to systemic candidosis has declined because of early empiric antifungal treatment and better prophylaxis. Although amphotericin B remains the gold standard of treatment in systemic candidiasis, other safer options are available. Amphotericin B is now available in liposome-encapsulated forms, which appear to be less toxic. Fluconazole has been shown to be effective as prophylaxis of bone marrow transplantation, as well as in the treatment of oropharyngeal candidosis and candidemia in nonneutropenic patients. At high doses, it is sometimes used for candida in neutropenic patients. Voriconazole is a new triazole antifungal that acts by inhibiting the synthesis of

ergosterol in the fungal cell membrane. Posaconazole is a triazole active against *Candida*, although some problems with resistance have been reported. Caspofungin is an echinocandin antifungal that inhibits β-1,3-D-glucan synthesis in the cell wall. Micafungin and anidulafungin are echinocandins. The newer triazoles and echinocandins have broad-spectrums and are effective against invasive *Aspergillus* and *Candida* infections. Voriconazole has produced liver abnormalities, rash, and visual disturbances, and these must be monitored during therapy.

Candidid As in dermatophytosis, patients with candidiasis may develop secondary id reactions. They are much less common than the reactions seen with acute inflammatory dermatophytosis. The reactions, which have been reported to clear with treatment of candidal infection, are usually of the erythema annulare centrifugum or chronic urticaria type.

Antibiotic (Iatrogenic) Candidiasis The use of oral antibiotics, such as the tetracyclines and their related products, may induce clinical candidiasis involving the mouth, gastrointestinal tract, or perianal area. In addition, vulvovaginitis may occur. It has been suggested that perhaps the bacterial flora in the gastrointestinal system is changed by suppression of some of the antibiotic-sensitive bacteria, thereby permitting other organisms such as *Candida* to flourish. Fluconazole, 150 mg once, will treat this adequately if antibiotic therapy is given for a limited time. For more prolonged courses of antibiotic therapy, the dose of fluconazole may have to be repeated, or a longer course of a topical agent may be used.

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GEOTRICHOSIS

Geotrichum candidum is an ascomycetous anamorph yeast-like fungus commonly found as part of the natural flora of milk. It is also found on fruit, tomatoes, and in soil. It is used commercially as a maturing agent for cheese. Individual strains may be more mold- or yeast-like. Substantial genetic polymorphism has been noted in this organism. Strains with a mold-like phenotype tend to have larger genomes than those with a yeast-like phenotype.

In immunosuppressed individuals, *G. candidum* may act as an opportunistic pathogen, causing disseminated or mucocutaneous geotrichosis. Mucocutaneous disease is characterized by erythema, pseudomembranes, and mucopurulent sputum similar to that seen in thrush. The intestinal, bronchial, and pulmonary forms are similar to candidal infection. *G. candidum* is commonly isolated as a saprophyte. If it is cultured repeatedly from diseased tissue, it should be assumed to be acting as a pathogen.

The diagnosis is made by the repeated demonstration of the organism by KOH microscopic examination and by its culture from sputum on Sabouraud dextrose agar. Direct examination shows branching septate mycelium and chains of rectangular cells. In culture there is a mealy growth at room temperature. The hyphae form rectangular arthrospores.

Treatment of mucocutaneous disease can be accomplished with oral nystatin or mycostatin suspension in some cases. For more severe or disseminated disease, liposomal amphotericin B, itraconazole, flucytosine or combinations of these agents have been effective.

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TINEA NIGRA

Hortaea werneckii (formerly *Phaeoannellomyces werneckii*) is a black yeast-like hyphomycete that is widely distributed in hot, humid environments. The organism is common in the tropics. In the US, the infection is commonly seen along the gulf coast. Tinea nigra presents as one or several brown or black spots on the palms or soles. The lesions may be mistaken for nevi or melanoma. The pigment is confined to the stratum corneum and scrapes off easily. Dermoscopy has also been used to differentiate the lesions from melanocytic

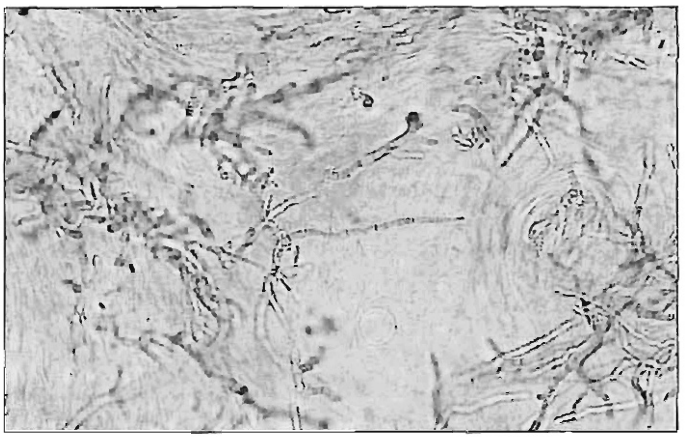

Fig. 15-10 Tinea nigra, note golden color of mycelia.

tumors. The fungus can easily be demonstrated by means of KOH or culture. In KOH preparations, the hyphae appear brown or golden in color (Fig. 15-10). Young colonies are glossy, black, and yeast-like, but older colonies are filamentous and grayish. The pigment produced by the fungal hyphae is melanin. Culture will identify the organism, and polymerase chain reaction (PCR) can be useful for rapid identification of *H. werneckii*.

Topical imidazoles and allylamines, such as clotrimazole, miconazole, ketoconazole, sulconazole, econazole, and terbinafine, have been reported as effective. *Griseofulvin* is not effective. Simply shaving away the superficial epidermis with a blade is frequently both diagnostic and curative.

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PIEDRA (TRICHOSPOROSIS)

In black piedra, dark, pinhead to pebble-sized formations occur on the hairs of the scalp, brows, lashes, or beard. These nodules are distributed irregularly along the length of the shaft. White piedra, is commonly caused by *T. beigelii* or *T. inkin*, and occurs more commonly in temperate climates. A synergistic corynebacterial infection is often present with *T. beigelii*, as demonstrated by culture and electron microscopy. *T. beigelii* has also been implicated as a cause of onychomycosis. *Trichosporon inkin* is implicated as an etiologic agent of pubic white piedra. *Trichosporon asahii* causes white piedra and onychomycosis. *Trichosporon spp* can also cause disseminated disease in immunosuppressed patients.

In white peidra, patients present with yellow or beige colored soft slimy sheaths coating the hair shafts (Fig. 15-11). The sheaths (Fig. 15-12) are composed of hyphae, arthrospores, and bacteria. The culture shows cream-colored, soft colonies composed of blastospores and septate hyphae, which fragment into arthrospores. Black piedra, caused by *Piedraia hortai*, occurs mostly in the tropics, especially in South America and Asia. The nodelike masses in KOH preparations show numerous oval asci containing two to eight ascospores

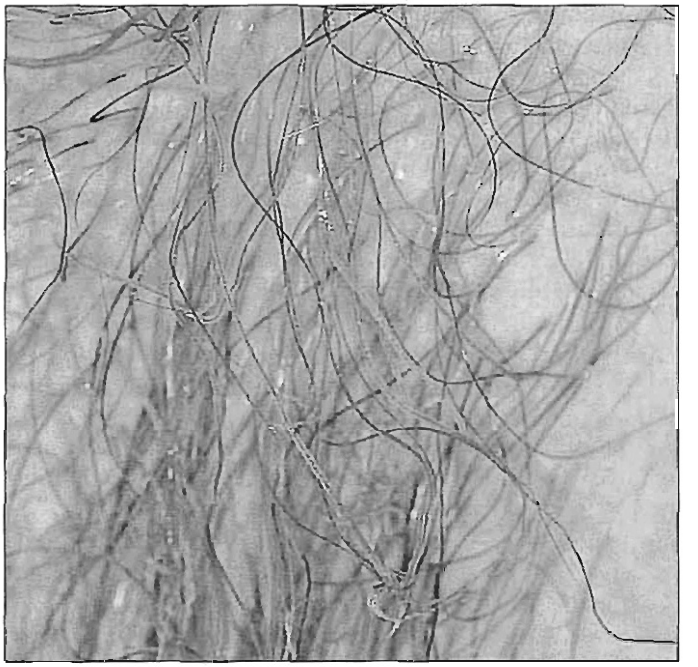

Fig. 15-11 White piedra.

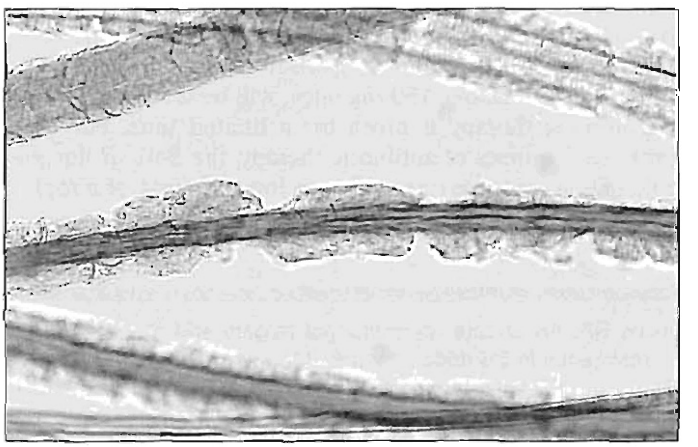

Fig. 15-12 White piedra.

and mycelium. Cultures produce black colonies composed of hyphae and chlamydospores.

Treatment may be accomplished by cutting or shaving the hair, but this may not be acceptable to the patient. Oral and topical terbinafine have been effective in black piedra. For white piedra, oral itraconazole, topical imidazoles, ciclopirox olamine, 2% selenium sulfide, 6% precipitated sulfur in petrolatum, chlorhexidine solutions, Castellani paint, zinc pyrithione, amphotericin B lotion, and 2% to 10% glutaraldehyde have all been used successfully. Unfortunately, the recurrence rate is high. Spontaneous remissions are sometimes observed.

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TINEA VERSICOLOR (PITYRIASIS VERSICOLOR)

Tinea versicolor is caused by *Malassezia furfur*. The yeast phase of this organism is classified as *Pityrosporum orbiculare*. As a yeast, the organism is part of the normal follicular flora. It produces skin lesions when it grows in the hyphal phase. Tinea versicolor commonly presents as hypo- or hyper-pigmented coalescing scaly macules on the trunk and upper arms. Pink (Fig. 15-13), atrophic, and trichrome (Fig. 15-14) variants exist and can produce striking clinical pictures. The eruption is more common during the summer months, and favors oily areas of skin. Sites of predilection are the sternal region and the sides of the chest, the abdomen, back, pubis, neck, and intertriginous areas. Mild itching and inflammation about the patches may be present. In some instances many follicular papules are present. The face and scalp may be affected. Facial lesions occur fairly commonly in infants and immunocompromised patients. In the latter, penile lesions may occur as well. The disease may even occur on the scalp, palms, and soles.

In hypopigmented tinea versicolor, abnormally small and poorly melanized melanosomes are produced, and are not transferred to keratinocytes properly. This becomes most conspicuous in dark-skinned people. This hypopigmentation may persist for weeks or months after the fungal disease is cured unless an effort is made to regain the lost pigmentation through UV exposure.

Fig. 15-13 Tinea versicolor.

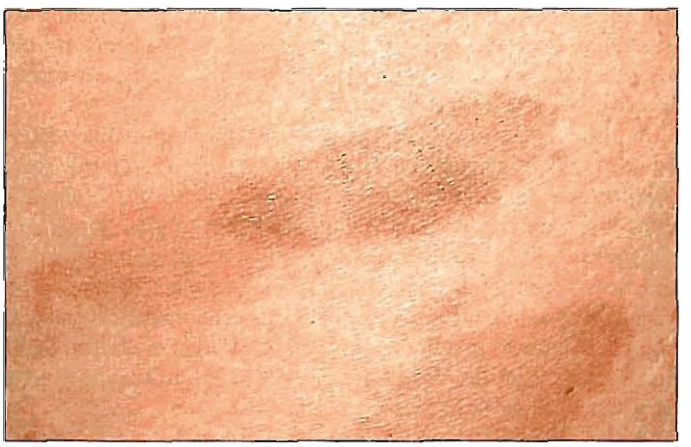

Fig. 15-14 Trichrome tinea versicolor.

Diagnosis

The fungus is easily demonstrated in scrapings of the profuse scales that cover the lesions. Tape stripping of the lesions can also be performed. Microscopically, there are short, thick fungal hyphae and large numbers of variously sized spores. This combination of strands of mycelium and numerous spores is commonly referred to as "spaghetti and meatballs". Identification by culture requires lipid enrichment of the media, and is rarely done to establish the diagnosis. Wood's light examination accentuates pigment changes, and may demonstrate yellow–green fluorescence of the lesions in adjacent follicles.

Biopsy will demonstrate a thick basket-weave stratum corneum with hyphae and spores. In the atrophic variant, epidermal colonization with hyphae and spores is accompanied by effacement of the rete ridges, subepidermal fibroplasia, pigment incontinence, and elastolysis.

Differential Diagnosis

Tinea versicolor must be differentiated from seborrheic dermatitis, pityriasis rosea, pityriasis rubra pilaris, pityriasis alba, leprosy, syphilis, and vitiligo. In the atrophic variant, the lesions may suggest parapsoriasis, mycosis fungoides, anetoderma, lupus erythematosus, or steroid atrophy.

The diagnosis in all forms of tinea versicolor is generally easily established by KOH examination. In seborrheic dermatitis the patches have an erythematous yellowish tint and the scales are soft and greasy, whereas in tinea versicolor the scales are furfuraceous. The macular syphilid consists of faint pink lesions, less than 1 cm in diameter, irregularly round or oval, which are distributed principally on the nape, sides of the trunk, and flexor aspects of the extremities. They are slightly indurated with a peripheral scale, and may be copper-colored. There may be general adenopathy. Serologic tests are positive in this phase of syphilis, but prozone reactions may occur, and the serum may have to be diluted.

Treatment

Imidazoles, triazoles, selenium sulfide, ciclopirox olamine, zinc pyrithione, sulfur preparations, salicylic acid preparations, propylene glycol, and benzoyl peroxide have been used successfully as topical agents. Selenium sulfide lotion is very cost-effective, and can be applied daily for a week, washed off after 10 min. It is also effective in a single overnight application. This can be repeated monthly as prophylaxis. The scalp can be shampooed monthly with selenium sulfide to reduce scalp colonization. Zinc pyrithione soap is also cost-effective and well tolerated for treatment and prophylaxis.

Ketoconazole in 400-mg doses repeated at monthly intervals is very effective. Oral itraconazole 200 mg once a day for 7 days is effective and can be followed by prophylactic treatment with itraconazole, 200 mg twice a day on 1 day a month. In a study of 50 patients, 400-mg single dose intraconazole was shown to be equivalent to 200 mg/day itraconazole for 7 days. Fluconazole, 400 mg once, may also be effective, and can be repeated at monthly intervals. In a study of 128 patients, weekly dosing with two 150-mg

capsules of fluconazole for 2 weeks was equivalent to weekly dosing of two 200-mg tablets of ketoconazole for 2 weeks. The effect of a single dose, not repeated in 2 weeks, was not assessed in this study, and may have proved just as effective. Although terbinafine has been shown to be ineffective via the oral route, it is effective topically. Twice a day applications are superior to once a day applications.

Patients should be informed that the hypo- and hyperpigmentation will take time to resolve and is not a sign of treatment failure. Relapse is likely if prophylactic doses are not given occasionally, but many options are available for prophylactic treatment. After initial therapy, patients may prefer weekly washing with a topical zinc pyrithione bar, single overnight applications of selenium sulfide, ketoconazole, econazole or bifonazole shampoo every 30 to 60 days, or monthly oral therapy.

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Pityrosporum Folliculitis Pityrosporum folliculitis has been a controversial entity, but its prompt response to antifungal agents suggests that pityrosporum yeast are indeed pathogenic. Criteria for diagnosis include characteristic morphology, demonstration of yellow–green Wood's light fluorescence of the papules or demonstration of pityrosporum yeast in smears or biopsies, and prompt response to antifungal treatment. Lesions tend to be chronic, moderately itchy, dome-shaped, follicular papules and tiny pustules involving the upper back and adjacent areas. The face and scalp can be involved, and the lesions are sometimes found in association with either tinea versicolor or seborrheic dermatitis. Pityrosporum folliculitis is more common in organ or marrow transplant recipients. As pityrosporum yeast are normally part of the follicular flora, alterations in flora may favour uncontrolled growth of the yeast. One such instance occurs when *Propionibacterium acnes* is suppressed by tetracycline therapy.

The eruption responds to oral fluconazole, 400 mg once, ketoconazole 400 mg once, or itraconazole, 200 mg/day for 5 to 7 days. Topical therapy with 2.5% selenium sulfide applied overnight is also generally effective. Other treatments include 30% to 50% propylene glycol in water, and topical imidazole creams. Relapses are common, but prophylaxis may be successful with monthly applications of selenium sulfide or maintenance doses of topical econazole.

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THE DEEP MYCOSES

Most deep cutaneous fungal infections are a manifestation of systemic infection from inhalation of dust contaminated with fungus. When primary infection is introduced directly into the skin from puncture wounds, abrasions, or other trauma, a chancriform or verrucous lesion will form that may be accompanied by secondary lymphangitis. Chest radiographs should be taken when investigating patients with deep mycoses except for the classic inoculation types, such as sporotrichosis, mycetoma, chromoblastomycosis, and phaeohyphomycosis.

COCCIDIOIDOMYCOSIS

Coccidioidomycosis is also known as *coccidioidal granuloma*, *valley fever*, and *San Joaquin valley fever*.

Primary Pulmonary Coccidioidomycosis Inhalation of *Coccidioides immitis*, followed by an incubation period of 10 days to several weeks, produces a respiratory infection that may be mild, with only a low-grade fever resembling a flulike illness. Approximately 60% of infected persons are entirely asymptomatic. Severe symptoms of chills, high fever, night sweats, severe headache, backache, and malaise may ensue in a minority. A large percentage of patients show lung changes on roentgenographic examination. These include hilar adenopathy, peribronchial infiltration or an infiltrate compatible with bronchopneumonia. At the time of onset a generalized maculopapular eruption may be present, which may be confused with a drug eruption, measles, or scarlet fever.

Within a few weeks the pulmonary symptoms subside. In about 30% of women and in 15% of men, allergic skin manifestations appear in the form of erythema nodosum over the shins and sometimes over the thighs, hips, and buttocks. These tender lesions may become confluent, gradually turn from purple to brown, and then disappear in about 3 weeks. Erythema nodosum is a favorable prognostic sign and occurs mostly in white individuals with transient self-limited disease. Sometimes erythema multiforme may develop in a similar clinical setting.

Although valley fever is usually self-limited and patients recover spontaneously, a small percentage steadily progress

into the chronic, progressive, disseminated form. The propensity for disseminated disease is several-fold higher in hispanics and Native Americans and many times higher for African Americans, Filipinos, and Vietnamese. In women, pregnancy may predispose to systemic disease. Infants, the elderly, persons with blood types B or AB, and immunosuppressed patients, including patients with AIDS, are also at increased risk for severe disease.

Disseminated Coccidioidomycosis (Coccidioidal Granuloma) Dissemination occurs in less than 1% of infections, but its incidence is heavily influenced by the factors listed above. Target organs include the bones, joints, viscera, brain, meninges, and skin. A single organ or multiple organs may be involved.

Skin lesions occur in 15% to 20% of patients with disseminated disease. They may appear as verrucous nodules (Fig. 15-15), pink papules resembling basal cell carcinoma, or as subcutaneous abscesses. The face is frequently involved. Some chronic lesions develop into plaques that resemble mycosis fungoides or North American blastomycosis. In patients with AIDS, umbilicated papules may mimic molluscum contagiosum. Umbilicated papules are more commonly associated with cryptococcocis, but can occur with a variety of fungi.

Primary Cutaneous Coccidioidomycosis This form occurs rarely, and skin disease should be considered a manifestation of disseminated disease unless there is a definite history of inoculation or a colonized splinter is found in the lesion. One to 3 weeks following inoculation an indurated nodule develops that may ulcerate. Later, nodules appear along the lymphatic vessels. Spontaneous recovery may result after several weeks, although most patients are treated with systemic agents.

Etiology and Pathology

The causative organism, *C. immitis,* has been isolated from the soil and from vegetation. It is commonly found in the burrows of rodents, often at a depth of about 20 cm. Epidemics occur when the soil is disrupted to a depth of 20 cm or more. This can occur as a result of road work, laying of telephone or electric cable, dust storms, and earthquakes. A large outbreak occurred in 1994 in Ventura County, California, after the Northridge earthquake. Outbreaks occur sporadically in California and Arizona. Outbreaks in military personnel are often related to training in endemic areas.

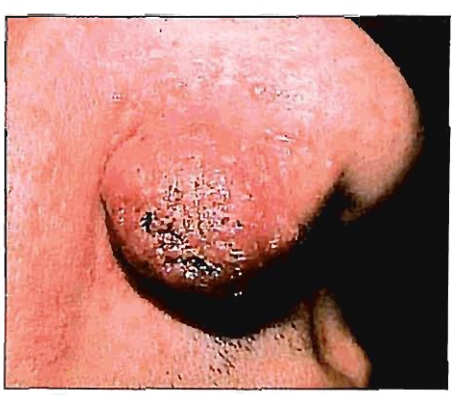

Fig. 15-15 Coccidioidomycosis. (Courtesy of Larry Anderson, MD, Brooke Army Medical Center Teaching File)

C. immitis is dimorphous, reproducing brittle mycelia at room temperature, and spherules in tissue. Spherules are unencapsulated with a thick refractile wall and a granular interior. They measure 5 to 200 µm in diameter, but average 20 µm. Endosporulation can occur, and the organism can resemble rhinosporidium. Compared to the latter organism, *Coccidiodes* is typically much smaller and more uniform in size. It also lacks the small central nucleus that is uniformly present in non-sporulating *Rhinosporidium*.

Culture

Coccidiodes is readily grown at room temperature, and is highly infectious. For this reason, culture of deep fungi should never be attempted in the office setting. Cultures should only be performed in laboratories with biocontainment hoods. The colonies appear on Sabouraud dextrose agar within 2 to 7 days as small, slightly raised disks penetrating the medium. Older cultures become covered with a dusty layer of aerial hyphae and assume a brownish color with age. In culture, spherical bodies throw out filaments of barrel-shaped arthrospores. Mycelia are branched and septate, 2 to 8 µm in diameter. PCR primers and a DNA hybridization probe test that targets organism-specific ribosomal RNA show promise for rapid identification.

Epidemiology

The disease principally occurs in limited areas in the Western Hemisphere. The original diagnosis was in a soldier from Argentina, where the disease is endemic in the Gran Chaco area. It is also endemic in northern Mexico, Venezuela, and the southwestern US (the lower Sonoran Life Zone). In highly endemic areas, most residents will have been infected, and new residents have a good chance of becoming infected within 6 months. Very few will develop disseminated disease.

Differential Diagnosis

Clinically, it is extremely difficult to differentiate this disease from blastomycosis, which it closely resembles. Definite diagnosis depends on serologic testing and the demonstration of *C. immitis* microscopically, culturally, or by animal inoculation. Guinea pigs inoculated with *C. immitis* die from the systemic infection, whereas no evidence of infection is apparent after inoculation with *Blastomyces*. Intradermal testing with coccidioidin has largely been replaced by serologic testing. A positive reaction of the delayed tuberculin type develops early and remains high in those who resist the disease well. A negative skin test occurs with dissemination.

Immunology

The first widely used skin test, coccidioidin, was developed in the 1940s. In the 1970s, spherulin was found to be more sensitive. Cross-reactions can occur with histoplasmin, blastomycin, and paracoccidioidin. In vitro tests of cellular immunity yield comparable results and skin testing has generally been replaced by serologic testing.

Precipitin, latex agglutination, immunodiffusion, and complement fixation serologic tests have been developed. The precipitin, immunodiffusion, enzyme immunoassay, and latex agglutination tests are useful in very recent infection, since a maximum titer is reached in 1 to 2 weeks. They permit detection of coccidioidal IgM in early coccidioidomycosis. In later infections, the complement fixation test is useful.

In primary coccidioidomycosis the titer is low, whereas in subsequent dissemination there is a rapid rise in titer. When the disease has disseminated, cerebrospinal, synovial, and peritoneal fluid can be tested for coccidioidal antibody.

Treatment

Amphotericin B is active against the organism, but less toxic drugs are now available. Fluconazole at doses of 400 to 800 mg/day is commonly used. Treatment must be continued for 12 months or longer. Many patients will require ongoing suppressive therapy. In patients infected with HIV, lifetime suppressive doses of 200 mg/day are advised. In coccidioidomycotic meningitis, fluconazole 400 to 600 mg/day is given indefinitely. Fluconazole and itraconazole have similar efficacies in the treatment of progressive nonmeningeal coccidioidomycosis. In meningeal disease itraconazole is not effective and amphotericin needs to be given intrathecally in addition to intravenously. Liposomal amphotericin is effective in animal models of meningeal disease without the need for intrathecal administration. Newer agents that have activity against *C. immitis* include voriconazole, caspofungin, and posaconazole. Voriconazole has been used successfully in meningeal disease.

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HISTOPLASMOSIS

Histoplasmosis is caused by inhalation of airborne spores. It may be asymptomatic or cause limited lung disease. Dissemination to other organs, including the skin, occurs in about 1 in 2000 acute infections. Immunodeficiency, old age, and systemic corticosteroids predispose to widespread disease. Cases misdiagnosed as sarcoidosis and treated with corticosteroids have disseminated widely. In disseminated disease, mucous membranes are involved much more commonly than skin. Primary cutaneous disease is exceedingly rare.

Primary Pulmonary Histoplasmosis Primary pulmonary histoplasmosis is usually a benign self-limited form of acute pneumonitis characterized by fever, malaise, night sweats, chest pain, cough, and hilar adenopathy. Resolution of the pneumonitis occurs rapidly, and the only residua may be calcifications in the lung and a positive skin test to histoplasmin. However, serious pneumonitis caused by histoplasmosis does occur. Such cases have been reported among cave workers in Mexico and travelers returning from Central America. A chronic pulmonary form may occur in patients with emphysema.

Approximately 10% of patients with acute symptomatic infection develop arthritis and erythema nodosum. During a large midwestern epidemic, about 4% of patients diagnosed with histoplasmosis presented with erythema nodosum. Erythema multiforme has also been described.

Progressive, Disseminated Histoplasmosis Most patients who develop this severe form are immunocompromised or taking systemic corticosteroids. Leukemia, lymphoma, lupus erythematosus, renal transplantation, or AIDS are frequent predisposing diseases. Cases have also been reported in patients receiving low-dose methotrexate for psoriasis. Approximately 20% have no identifiable risk factor.

The reticuloendothelial system, genitourinary tract, adrenals, gastrointestinal tract, adrenal glands, and heart may be involved. Ulcerations and granulomas of the oronasopharynx are the most common mucocutaneous lesions, occurring in about 20% of patients with disseminated disease. Beginning as solid, indurated plaques, they ulcerate and become deepseated, painful, and secondarily infected. Perianal lesions may also occur.

Skin lesions are present in approximately 6% of patients with dissemination and may be more common in patients with AIDS and in renal transplant recipients. The morphologic patterns are nonspecific and protean, including. umbilicated nodules, papules, and ulcers. Abscesses, pyoderma, pustules, and furuncles may be the first lesions on the skin. Demonstration of the organisms is readily made from histologic sections and cultures of the exudate. The most common manifestation in children is purpura. Usually it appears a few days before death and is probably caused by severe involvement of the reticuloendothelial system, with emaciation, chronic fever, and severe gastrointestinal symptoms.

In the HIV-positive population, dyspnea, a platelet count of $<100{,}000$ platelets/mm^3, and lactate dehydrogenase levels of more than two-fold the upper limit of the normal range are poor prognostic factors, and are independently associated with death during the first 30 days of antifungal treatment.

Primary Cutaneous Histoplasmosis This rare entity is characterized by a chancre-type lesion with regional adenopathy. It has been reported on the penis.

African Histoplasmosis This type is caused by *Histoplasma duboisii*, now classified as a variant of *Histoplasma capsulatum*. Skin lesions are much more common and include superficial cutaneous granulomas, subcutaneous granulomas, and osteomyelitic lesions with secondary involvement of the skin (cold abscesses). In addition, papular, nodular, circinate, eczematoid, and psoriasiform lesions may be seen. The granulomas are dome-shaped nodules, painless but slightly pruritic. There may be skin and mucous mem-

brane manifestations such as ulcerations of the nose, mouth, pharynx, genitals, and anus. These ulcers are chronic, superficial lesions with no induration or noticeable inflammatory reaction. Erythema nodosum occurs frequently. Emaciation and chronic fevers are common systemic signs.

Etiology and Pathology

Histoplasmosis was first discovered in Panama by ST Darling in 1906. It is caused by *H. capsulatum*, a dimorphic fungus that exists as a soil saprophyte. The organism is frequently found in bat and bird feces.

In tissue there are 2- to 3-μm round bodies within the cytoplasm of large macrophages. A pseudocapsule surrounds each organism. The organisms bear a striking resemblance to those of leishmaniasis, but lack a kinetoplast and are distributed evenly throughout the cytoplasm, while leishmanial organisms often line up at the periphery of the cell like light bulbs on a movie marquis. Budding forms may rarely be present, and mycelial and pleomorphic budding forms are sometimes seen in cavitary pulmonary disease, endocardial disease, aortic plaques or skin lesions. Morphologically, these forms resemble candida more than typical intracellular histoplasma. On direct examination the organism may be demonstrated in the peripheral blood, sputum, bronchial washings, spinal fluid, sternal marrow, lymph node touch smears, or ulcers when stained with Giemsa, periodic acid-Schiff or Gomori methenamine silver stains. In African histoplasmosis, the organisms are 10 to 13 μm in diameter and are typically found within multinucleated giant cells.

The mycelial phase may be demonstrated on Sabouraud dextrose agar, Mycosel medium, or brain–heart infusion agar to which blood has been added. A white, fluffy colony is found, with microconidia and echinulate macroconidia. One set of cultures should be inoculated at room temperature to demonstrate the mycelial phase and another at 37° C to produce the yeast phase. In disseminated disease the bone marrow is frequently involved. Blood, urine, and tissue from oral and skin lesions should also be cultured. PCR probes are available for rapid culture confirmation.

Epidemiology

Although histoplasmosis occurs throughout the world, it is most frequent in North America, especially in the central states of the US along the Mississippi River basin. Histoplasmosis is found frequently in river valley areas in the tropical and temperate zones. The Nile River valley seems to be one exception. Besides the Mississippi and Ohio river valleys, it has been found along the Potomac, Delaware, Hudson, and St Lawrence rivers. It has been reported in the major river valleys of South America, Central Africa, and Southeast Asia. The disease is heavily endemic in Puerto Rico and Nicaragua.

Transmission of the disease does not occur between individuals; instead, the infection is contracted from the soil by inhalation of the spores, especially in a dusty atmosphere. Feces of birds and bats contain the fungus. The spores have been demonstrated in the excreta of starlings, chickens, and bats. The disease may be contracted by persons who enter caves inhabited by bats or birds. Epidemics have been reported from exposure to silos, abandoned chicken houses, and storm cellars. Infected people throughout the world number in the many millions.

In an outbreak occurring in Indianapolis in 1978, 488 clinically recognized cases occurred, and 55 had disseminated disease. The actual number infected was probably well over 100,000. Nineteen died, none of whom were under the age of 1. Fatal or disseminated infections occurred in 74% of immunosuppressed persons, compared with 6.5% of those without immunosuppression. Age over 54 was a worse prognostic factor than chronic lung disease in nonimmunosuppressed persons. Disseminated histoplasmosis is seen as an opportunistic infection in HIV-infected individuals, reflecting impaired cellular immune function.

Immunology

The best diagnostic test is the urinary enzyme-linked immunosorbent assay (ELISA). Serologic testing for antibodies requires that the patient has normal immune responsiveness and is further limited by a high rate of false positives and false negatives. The complement fixation test, when positive at a titer of 1:32 or greater, indicates active or recent infection.

Treatment

Whereas minimal disease heals spontaneously in the majority of cases, moderate to severe disease requires therapy. Amphotericin B is the treatment of choice in severely ill patients and all immunocompromised patients. In patients infected with HIV a suppressive dose of 200 mg/day of itraconazole follows the intravenous amphotericin. Itraconazole, 200 mg/day for 9 months, may be given for moderate disease in immunocompetent patients. Most patients initially treated with amphotericin B respond quickly and can be switched to itraconazole.

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CRYPTOCOCCOSIS

Cryptococcosis generally begins as a pulmonary infection and remains localized to the lung in 90% of cases. In the remaining 10% the organisms hematogenously disseminate to other organs, with the central nervous system (CNS) and the skin the two most common secondary sites. Patients in the latter group are usually immunocompromised or debilitated. The incidence of dissemination is much higher in patients with AIDS, occurring in up to 50% of this population.

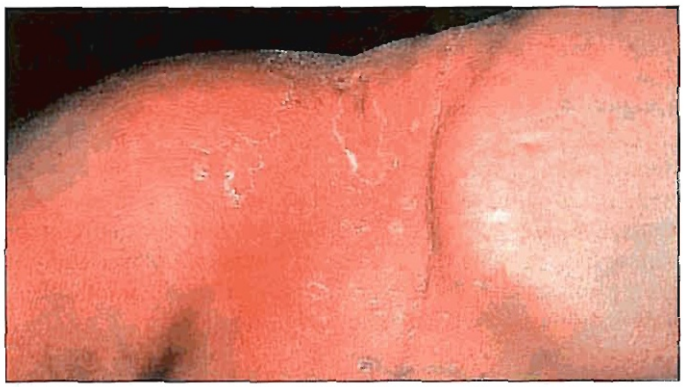

Fig. 15-16 Cryptococcal cellulitis.

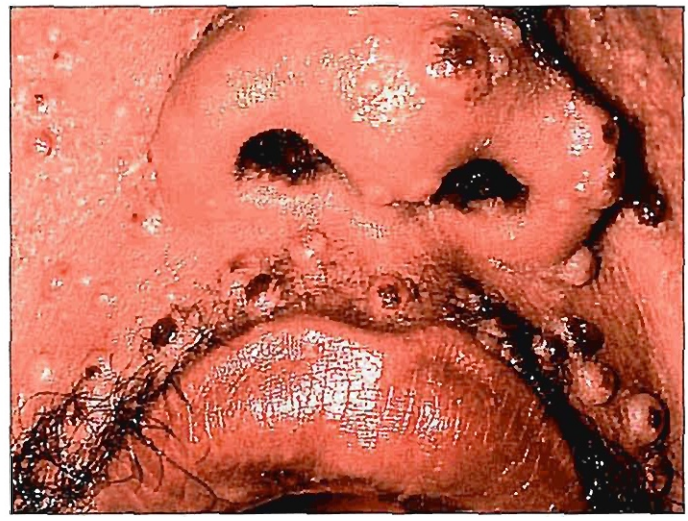

Fig. 15-17 Molluscum-like lesions of cryptococcosis.

Primary pulmonary cryptococcosis infection may be so mild that the symptoms of fever, cough, and pain may be absent. On the other hand, some cases may be severe enough to cause death. Radiographic studies will reveal disease at this stage.

When dissemination occurs the organism has a special affinity for the CNS. It is the most common cause of mycotic meningitis. There may be restlessness, hallucinations, depression, severe headache, vertigo, nausea and vomiting, nuchal rigidity, epileptiform seizures, and symptoms of intraocular hypertension. Other organs, such as the liver, skin, spleen, myocardium, and skeletal system, as well as the lymph nodes, may be involved. Disseminated cryptococcosis can present in many organ systems; hepatitis, osteomyelitis, prostatitis, pyelonephritis, peritonitis, and skin involvement have all been reported as initial manifestations of disease. The incidence of skin involvement in cases of cryptococcosis is between 10% and 15%, although it is lower in the HIV-infected population. Cutaneous lesions may precede overt systemic disease by 2 to 8 months.

Skin infection with cryptococcosis occurs most frequently on the head and neck. A variety of morphologic lesions has been reported, including subcutaneous swellings, abscesses, blisters, tumorlike masses, molluscum contagiosum-like lesions, draining sinuses, ulcers, eczematous plaques, granulomas, papules, nodules, pustules, acneiform lesions, plaques, and cellulitis (Fig. 15-16). Approximately 50% of patients with HIV will develop molluscum contagiosum-like lesions (Fig. 15-17). In these patients there is often a central hemorrhagic crust. Solitary cutaneous lesions and indolent cellulites may be the presenting signs of disseminated disease.

Primary inoculation of the skin is a very rare disease. To establish the diagnosis, there should be a clear history of implantation or a foreign body found in association with the organism. Usually, primary inoculation disease presents as a solitary skin lesion on an exposed area, frequently presenting as a whitlow. Risk factors include outdoor activities and exposure to bird droppings. *Cryptococcus neoformans* serotype D is more commonly associated with primary cutaneous disease. Although primary cutaneous disease exists, for all practical purposes, identification of cryptococci in the skin indicates disseminated disease with a poor prognosis, and it requires a search for other sites of involvement.

Etiology and Pathology

The causative organism is *C. neoformans*. The organism appears in tissue as a pleomorphic budding yeast. The organisms vary markedly in size and shape, in contrast to most other fungal organisms. The capsule is usually prominent, although it is inversely proportional to the extent of the granulomatous reaction. Generally, the capsule is easily identified in hematoxylin and eosin (H&E) sections, although mucicarmine, methylene blue or alcian blue staining can also be used. Usually multiple yeast share a common capsule. Cryptococcus stains well with the Fontana-Masson stain for melanin.

Epidemiology

Cryptococcosis has a worldwide distribution and affects both humans and animals. The organism has been recovered from human skin, soil, dust, and pigeon droppings. The latter, when deposited on window ledges in large cities are a source of infection. The patient with disseminated cryptococcosis usually has a concomitant debilitating disease, such as AIDS, cancer, leukemia, lymphoma, renal failure, hepatitis, alveolar proteinosis, severe diabetes mellitus, sarcoidosis, tuberculosis, or silicosis. Long-term oral prednisone or immunosuppressive therapy for chronic illnesses, such as renal transplantation, sarcoidosis or connective tissue disease may also be a factor. The portal of entry is the lungs. Males outnumber females 2:1. Cryptococcosis is most frequent in persons aged 30 to 60 years.

Patients with AIDS are particularly at risk for disseminated disease. Cryptococcosis is the fourth leading cause of opportunistic infection and the second most common fungal opportunist, with 5% to 9% of patients manifesting symptomatic disease. Dissemination occurs in 50% of patients with AIDS; skin involvement is reported to be present in 6% of patients with AIDS.

Immunology

The latex slide agglutination test is a sensitive and specific test. It may give false positives in the presence of rheumatoid factor. Direct microscopic examination and latex agglutination have been used with lesional skin scrapings to aid in the rapid diagnosis. The complement fixation test for cryptococcal polysaccharide, the indirect fluorescence test, and the enzyme immunoassay for cryptococcal antigen detection are all helpful, but the last is capable of detecting the presence

of antigen earlier and at a lower concentration than the other two tests.

Mycology

For direct examination, a drop of serum or exudate is placed on a slide and then covered with a coverslip. If examination shows yeast, one drop of 10% KOH can be added to half of the coverslip and one drop of India ink to the other half to demonstrate the capsule.

The organism produces a moist, shiny, white colony on Sabouraud dextrose agar. With aging the culture may turn to a cream and then a tan color. Subcultures from Sabouraud agar may be made onto cornmeal agar, and onto urea medium to aid in distinguishing the yeast from *Candida* and other yeasts. A commercially available DNA probe detection assay allows rapid culture confirmation.

Treatment

In seriously ill patients, amphotericin B intravenously initially followed by fluconazole orally is standard treatment. In less severely ill non-AIDS patients, fluconazole 400 to 600 mg/day for 8 to 10 weeks may be effective. In non-AIDS meningitis, flucytosine is given in combination with amphotericin B, and in patients infected with HIV fluconazole is given indefinitely at a suppressive dose of 200 mg/day. In one study of AIDS patients suffering from cryptococcal meningitis, 600 mg/day of either fluconazole or itraconazole showed efficacy. The availability of voriconazole has expanded the number of options available. In disease refractory to other drugs, voriconazole has shown a response rate of 38.9%. Caspofungin has limited activity against cryptococcosis.

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NORTH AMERICAN BLASTOMYCOSIS

North American Blastomycosis is also known as *Gilchrist's disease*, *blastomycosis*, and *blastomycetic dermatitis*.

Most cutaneous blastomycosis is the result of dissemination from a primary pulmonary focus. The lesions are chronic, slowly progressive, verrucous, and granulomatous lesions characterized by thick crusts, warty vegetations, discharging sinuses, and pustules along the advancing edge. The lesions are often multiple and are located mostly on exposed skin. Papillomatous proliferation is most pronounced in lesions on the hands and feet, where the patches become very thick. There is a tendency for the patches to involute centrally and to form white scars while they spread peripherally. The crusts are thick and dirty gray or brown. Beneath them there are exuberant granulations covered with a seropurulent exudate, which oozes out of small sinuses that extend down to indolent subcutaneous abscesses. Lower extremity nodules and plaques clinically and histologically suggestive of Sweet syndrome have also been described.

The primary infection is almost always in the upper or middle lobes of the lungs, and most cases never develop cutaneous dissemination. When dissemination does occur, the most frequent site is the skin, accounting for at least 80% of cases of disseminated disease. It also frequently disseminates to bone, especially the ribs and vertebrae. Other targets are the CNS, liver, spleen, and genitourinary system.

Cutaneous blastomycosis rarely occurs as a result of primary cutaneous inoculation. Such cases have a clear history of inoculation, and present with a small primary nodule and subsequent secondary nodules along the draining lymphatics, creating a picture similar to sporotrichosis. Healing takes place within several months.

Etiology and Pathology

The fungus *Blastomyces dermatitides* causes North American blastomycosis and was first described by Gilchrist in 1894. It is frequently found in soil and animal habitats. *B. dermatitides* is a dimorphic fungus with a mycelial phase at room temperature and a yeast phase at 37° C. Direct microscopic examination of a KOH slide of the specimen should always be made, since culture of the fungus is difficult and the organism may be found in purulent exudates obtained from skin lesions. The specimen should be cultured by a qualified laboratory on Sabouraud dextrose agar, Mycosel, and brain–heart infusion agar to which blood has been added. Aerial mycelium will develop in 10 to 14 days, forming a white, cottony growth that turns tan with age. The structures are septate mycelia with characteristic conidia on the sides of hyphae. The conidia are 3 to 5 µm and variously shaped from round to oval forms. Culture at 37° C produces a slow-growing, wrinkled yeast with spherules, single budding cells, and some abortive hyphae. A DNA probe detection assay is commercially available for rapid culture confirmation.

Cutaneous blastomycosis usually demonstrates marked pseudoepitheliomatous hyperplasia of the epidermis with neutrophilic abscesses. Giant cells are frequently present in the dermal infiltrate. Organisms are typically few in number and are most commonly found within giant cells or intraepidermal abscesses. The organism is a thick-walled yeast, usually 5 to 7 µm in diameter, although giant forms have been reported in tissue. The organism lacks a capsule, but has a thick and distinctly asymmetrical refractile wall. Broad-based budding may occasionally be noted. Rarely, acute skin lesions may lack pseudoepitheliomatous hyperplasia and demonstrate a diffuse neutrophilic dermal infiltrate.

Primary cutaneous blastomycosis demonstrates a neutrophilic infiltrate with many budding cells of blastomycetes. In later lesions, a granulomatous infiltrate is found. The lymph nodes may show marked inflammatory changes, giant cells containing the organisms, lymphocytes, and plasma cells.

Lung involvement may show many changes that are suggestive of tuberculosis with tubercle formation. Purulent abscesses may occur in the lungs and bone. The abscesses may sometimes contain many organisms.

Epidemiology

North American blastomycosis is prevalent in the southeastern US and the Ohio and Mississippi river basins, reaching epidemic proportions in Kentucky and Mississippi; the latter has the highest prevalence of blastomycosis in North America. There is a male-to-female ratio of approximately 6:1, and most patients are over the age of 60. Often the cutaneous form occurs without a known history of pulmonary lesions.

Outdoor activity after periods of heavy rain is a risk factor for acute pulmonary disease. Beaver lodges are a common site for the fungus, and some reports have linked outbreaks of disease with outings near a beaver lodge. Blastomycosis has also been reported from the bite of a dog suffering from pulmonary blastomycosis. Transmission has been reported between men with prostatic involvement and their sexual partners.

Risk factors for symptomatic disease include preexisting illness. In one study, one-quarter of patients with blastomycosis had underlying immunosuppression, and 22% had diabetes mellitus. In the south, African Americans have a higher incidence than whites and the mortality rate is also higher among African Americans.

Immunology

Serologic tests are performed by immunodiffusion or ELISA. Commercial antigen test kits are available for rapid diagnosis.

Differential Diagnosis

Blastomycosis may closely resemble halogenoderma, blastomycosis-like pyoderma, pemphigus vegitans, tuberculosis verrucosa cutis, syphilis, granuloma inguinale, drug eruptions, and trichophytic granuloma. The diagnosis is established by demonstration of the organism or serologic testing. The course of blastomycosis is more rapid and involvement is more extensive than in the verrucous type of tuberculosis. Vegetative lesions of tertiary syphilis usually are accompanied by other signs of the disease and have a predilection for the scalp and mucocutaneous junctions. Bromide and iodide eruptions are generally more acutely inflammatory, but may be indistinguishable from blastomycosis. Biospy, drug history, and blood iodine or bromine levels may be required to distinguish the two.

Treatment

Itraconazole, at a dose of 200 to 400 mg/day for 6 months, is the treatment of choice. Amphotericin B for a total dose of 1.5 g may be required for very ill patients. Fluconazole, 400 to 800 mg/day for at least 6 months, is effective in 85% of patients with non-life-threatening disease. Voricanazole has also been used.

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SOUTH AMERICAN BLASTOMYCOSIS

Mucocutaneous involvement in South American blastomycosis, also known as *paracoccidioidal granuloma* and *paracoccidioidomycosis*, is almost always a sign of disseminated disease, primary in the lungs. Rare cases may arise from inoculation. In Brazil, the disease causes about 200 deaths per year.

The mucocutaneous type usually begins in the mouth (Fig. 15-18), where small papules and ulcerations appear. Gingival lesions are most common, followed by lesions of the tongue and lips. With time, adjacent tissues are affected, and ultimately extensive ulcerations destroy the nose, lips, and face (Fig. 15-19). Skin lesions may show ulcerations, pseudoepitheliomatous hyperplasia, and microabscesses. The lymphangitic type manifests itself by enlargement of the regional lymph nodes soon after the appearance of the initial lesions about the mouth. The adenopathy may extend to the supraclavicular and axillary regions. Nodes may become greatly enlarged and break down with ulcerations that secondarily involve the skin, causing severe pain and dysphagia with progressive cachexia and death. It may closely simulate Hodgkin's disease, especially when the suprahyoid, preauricular, or retroauricular groups of lymph nodes are involved.

There is a visceral type, caused by hematogenous spread of the disease to the liver, adrenal glands, spleen, intestines, and other organs. There is also a mixed type that has the combined symptomatology of the mucocutaneous, lymphangitic, and visceral types. The disease may present either as a rapidly progressive, acute disease or follow a subacute course, or occur as a chronic, slowly advancing form.

Etiology and Pathology

Lutz first described South American blastomycosis in Brazil in 1908. It is caused by the fungus *Paracoccidioides brasiliensis*, a member of the phylum Ascomycota, order Onygenales, and family Onygenaceae.

Biopsies may demonstrate pseudoepitheliomatous hyperplasia, abscess formation, or ulceration. A granulomatous inflammatory infiltrate is frequently present, consisting of lymphocytes, epithelioid cells, and Langerhans giant cells. The organism appears as a round cell, 10 to 60 μm in diameter, with a delicate wall. Multiple buds may be present, creating a resemblance to a mariner's wheel (Fig. 15-20).

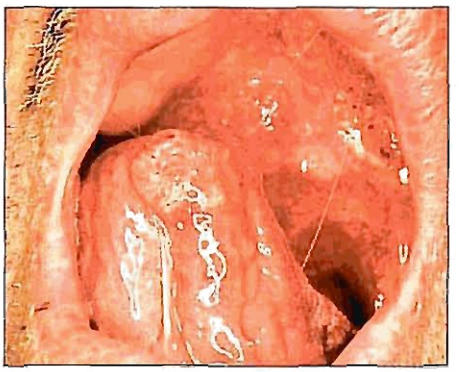

Fig. 15-18 Paracoccidioidomycosis. (Courtesy of Maria Silvia Negrao, MD)

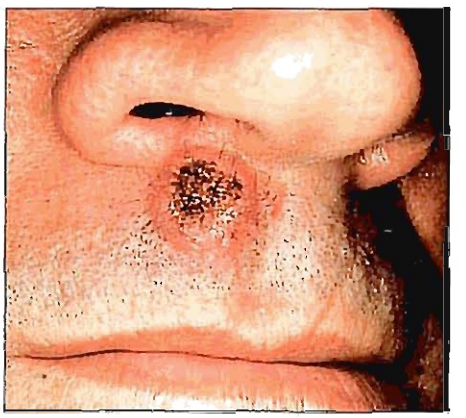

Fig. 15-19 Paracoccidioidomycosis. (Courtesy of Maria Silvia Negrao, MD)

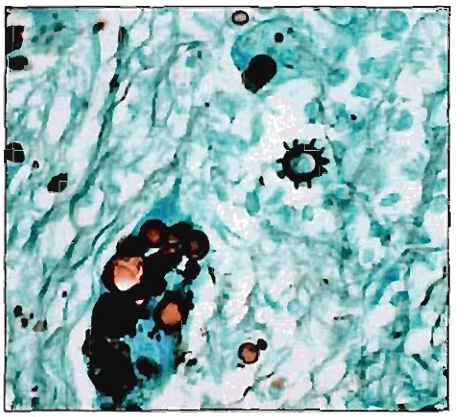

Fig. 15-20 Paracoccidioidomycosis. (Courtesy of Maria Silvia Negrao, MD)

This chronic granulomatous disease is endemic in Brazil and also occurs in Argentina and Venezuela. Occasional cases have been reported in the US, Mexico, Central America, Europe, and Asia. Most of these patients have a travel history to endemic areas. The disease is generally found among laborers, mostly in men. Although the initial infection is usually respiratory, some individuals may become infected by picking their teeth with twigs or from chewing leaves. Armadillos may harbor the disease.

The fact that the disease is 15 times more common in men is of particular interest, since it has been shown that 17β-estradiol inhibits transition from the mycelial to the tissue-invasive yeast form. *P. brasiliensis* can lodge in periodontal tissues and some cases start after extraction of teeth. Many cases have been reported in patients with AIDS, where the course is usually acute and severe.

Mycology

In culture the colony is cream-colored, compact, and powdery. Chlamydospores are round or oval. Elongate lateral conidia may be present.

Immunology

Complement fixation tests are positive in 97% of severe cases, and the titer rises as the disease becomes more severe. With improvement, the titer decreases. Immunodiffusion tests are commonly employed for diagnosis and post-therapy follow-up. The test is highly specific but only about 90% sensitive. IgG1 antibodies usually bind well. False-negative tests are commonly related to low-avidity IgG2 antibodies directed against fungal carbohydrate epitopes. Antibody responses to different antigens vary during the course of the disease. Sera from patients with severe acute or chronic disease recognized a greater number of antigens. Reactivity with BAT-exoAg persists after clinical recovery, and IgG reactivity against the 160-kD antigen is the most persistent marker of *P. brasiliensis* infection.

Bronchoalveolar lavage fluid demonstrates low but detectable amounts of IL-6, tumor necrosis factor (TNF)-α, and macrophage inflammatory protein (MIP)-1α produced by alveolar macrophages. Specific antibodies are mainly of the immunoglobulin G2 isotype. MIP-1α selectively attracts CD8+ T-cells. In skin lesions, Langerhans cells have short and irregular dendrites and are decreased in number. FXIIIa-positive dendrocytes are increased in number and have prominent dendrites. The organism is frequently found within FXIIIa-positive dendrocytes.

Treatment

Itraconazole, 200 mg/day for 6 months, is the treatment of choice for most patients as it is well tolerated and shows an excellent response in 90%. Ketoconazole, 400 mg/day for 6 to 18 months, is equally effective, but not as well tolerated. Fluconazole, amphotericin B, and the sulfonamides also have activity against the yeast, although sulfa resistance has been reported. Many patients, especially those with AIDS, are given long-term suppressive therapy with a sulfa drug, so the emergence of resistance is of concern. In a randomized trial, itraconazole, ketoconazole, and sulfadiazine showed similar efficacy in the initial treatment of the disease. In vitro, terbinafine is highly active against isolates of *P. brasiliensi,* and may have a role as an alternate agent. IFN-γ and granulocyte–macrophate colony-stimulating factor enhance the antifungal effect of fluconazole in animal models.

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SPOROTRICHOSIS

Sporotrichosis usually occurs as a result of direct inoculation by a thorn, cat's claw or other minor penetrating injury. The earliest manifestation may be a small nodule which may heal

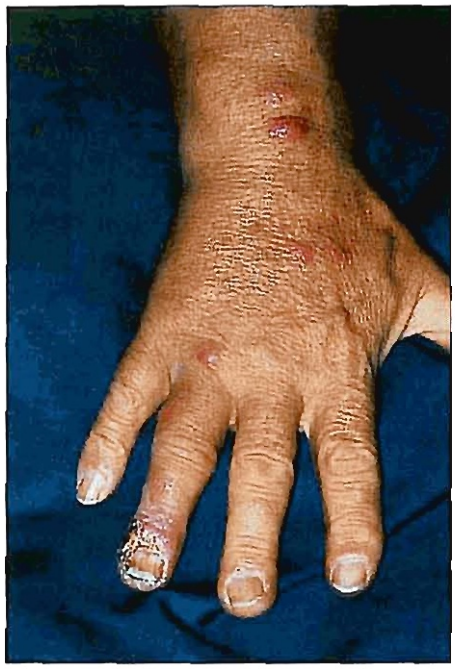

Fig. 15-21
Sporotrichosis.

and disappear before the onset of other lesions. In the course of a few weeks nodules generally develop along the draining lymphatics (Fig. 15-21). These lesions are at first small, dusky red, painless, and firm. In time the overlying skin becomes adherent to them and may ulcerate. When the lesions occur on the face, the lymphatic drainage is radial, rather than linear, and secondary nodules occur as rosettes around the primary lesion.

Regional lymphangitic sporotrichosis is the common type, accounting for 75% of cases. Fixed cutaneous sporotrichosis is seen in 20% of cases and is characterized by a solitary ulcer, plaque or crateriform nodule without regional lymphangitis. It may also present as localized rosacea-like lesions of the face without regional lymphangitis. Increased host resistance, a smaller inoculum, facial location, and variations in strain pathogenicity have all been suggested as reasons for the fixed cutaneous form.

Disseminated disease is the least common form. Factors that predispose to extracutaneous disease include oral prednisone therapy, other immunosuppressive drugs including TNF-α inhibitors, chronic alcoholism, diabetes mellitus, hematologic malignancies, and AIDS. Systemic invasion may produce cutaneous, pulmonary, gastrointestinal, articular lesions, and brain lesions. Arthritis or bone involvement occurs in most cases. The cutaneous lesions are reddish, tender nodules, which soften, form cold abscesses, and eventually suppurate, leaving chronic ulcers or fistulas. These are usually around arthritic joints and the face and scalp, but may occur anywhere on the skin. At times only internal involvement, such as of the lungs, brain, or bones, is apparent.

Etiology and Pathology

Sporotrichosis is caused by *Sporothrix schenckii*, a dimorphic fungus that grows in a yeast form at 37° C and in a mycelial form at room temperature. Cutaneous disease typically presents with palisading granulomatous dermatitis surrounding a stellate suppurative abscess. Organisms appear as cigar-shaped yeast in tissue, but are rare in North American cases. In Asian cases of sporotrichosis, the organisms are frequently more numerous. Asteroid bodies and mycelial elements are prevalent in regional lymphangitic sporotrichosis. PCR methods of detection have been developed.

Epidemiology

There seems to be no geographic limitation to the occurrence of sporotrichosis. Most often the primary invasion is seen as an occupational disease in gardeners, florists, and laborers following injuries by thorns, straw or sphagnum moss. The pathogen commonly lives as a saprophyte on grasses, shrubs, and other plants. Carnations, rose bushes, barberry shrubs, and sphagnum moss are common sources. Infection may also be noted after insect stings. High humidity and high temperature favor infection. An epidemic of sporotrichosis among South African diamond miners was ascribed to inoculation of the organism by rubbing against the supporting wooden beams in the mines. Experimentally, it has been produced in many laboratory animals, and spontaneous cases have been observed in horses, mules, dogs, cats, mice, and rats. In cats, sporotrichosis commonly produces disseminated disease. The organism may be found on the claws, and transmitted to humans through cat scratches. Epidemics related to cat exposure have been documented.

Mycology

On Sabouraud agar a moist, white colony develops within 3 to 7 days. The surface becomes wrinkled and folded. Later the culture turns tan and, ultimately, black, as the organism is capable of producing melanin. In slide culture preparations, the colony shows septate branching mycelia. Conidia are found in clusters or in sleevelike arrangements on delicate sterigmata. If the culture is grown at 37° C, grayish-yellow, velvety yeast-like colonies are produced. Cigar-shaped, round, oval and budding cells, hyphae, and conidia may be seen microscopically.

Immunology

Culture extracts from *S. schenckii*, known as *sporotrichins*, will produce a delayed tuberculin-type reaction in persons who have had sporotrichosis. The test is fairly reliable, but only indicates previous exposure. Agglutination testing has been developed, but clinical diagnosis, biopsy, and culture remain the most common means of establishing a diagnosis.

Differential Diagnosis

Demonstration by culture establishes the diagnosis, and it is important to differentiate sporotrichosis from other lymphangitic infections. Atypical mycobacteriosis (especially *Mycobacterium marinum*), leishmaniasis, and nocardiosis all produce lymphangitic spread. In contrast, tuberculosis, cat-scratch disease, tularemia, glanders, melioidosis, lymphogranuloma venereum, and anthrax produce ulceroglandular syndromes (an ulcer with regional lymphadenopathy rather than an ulcer with nodules along the lymphatic vessels).

Treatment

Itraconazole is effective at a dose of 100 to 200 mg/day for several months. For cutaneous forms, potassium iodide in doses of 2 to 6 g/day remains an effective and inexpensive

therapeutic option, and may be effective in cases where intraconazole therapy fails. Iodide therapy generally requires 6 to 12 weeks of treatment. Generally, it is best to begin with five drops of the saturated solution in grapefruit or orange juice three times a day after meals. The drops can also be put in milk, but strong flavored citrus juices are better at masking the taste. The dose should be gradually increased until 30 to 50 drops are taken three times a day. The drug is not suitable for pregnant women. Adverse effects of iodide therapy include nausea, vomiting, parotid swelling, acneiform rash, coryza, sneezing, swelling of the eyelids, hypothyroidism, a brassy taste, increased lacrimation and salivation, flares of psoriasis, and occasionally, depression. Most of the side effects can be controlled by stopping the drug for a few days and reinstituting therapy at a reduced dosage. Application of local hot compresses, hot packs, or a heating pad twice a day has been advocated as a useful adjunct, as *S. schenckii* is intolerant to temperatures above 38.5° C (101° F).

In adult disseminated cases, itraconazole, 300 mg twice a day for 6 months, followed by 200 mg twice a day is the treatment of choice. In children, the drug is dosed based on weight and therapeutic response. The drug may have to be continued for many months. Amphotericin B, 0.5 mg/kg/day, is an alternative, but sensitivity to this is strain-dependent. *S. schenckii* is more sensitive to itraconazole than voriconazole, but the latter drug may also represent a therapeutic option.

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CHROMOBLASTOMYCOSIS

Chromoblastomycosis usually affects one of the lower extremities (Fig. 15-22). It occurs as a result of direct inoculation of the organism into the skin. As a rule, lesions begin as a small, pink, scaly papule or warty growth on some part of the foot or lower leg, then slowly spreads through direct extension and satellite lesions. With time, lesions develop a verrucous or nodular border and central atrophy and scarring. Small lesions may resemble common warts. Regional lymphadenitis may occur as a result of secondary bacterial infection. In rare instances the disease begins on an upper extremity or the face. Rarely, CNS involvement has been reported, both with and without associated skin lesions.

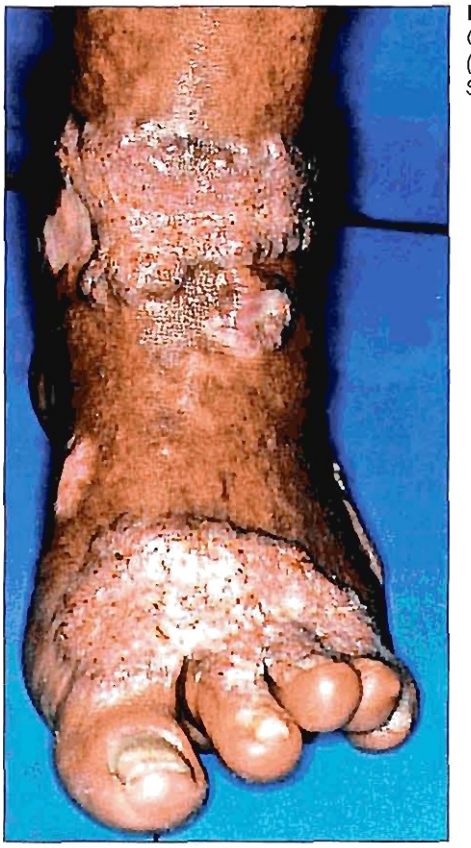

Fig. 15-22
Chromomycosis. (Courtesy of Maria Silvia Negrao, MD)

There is a 4:1 male predominance, and farmers account for almost 75% of patients with the disease. The disease is slowly progressive, and the average time between the appearance of lesions and diagnosis is almost 15 years. Lesions occur at sites of minor trauma. A thorn injury is remembered in about 16% of patients. Squamous cell carcinoma may occur in long-standing cases.

Etiology and Pathology

Most cases are caused by one of five dematiaceous fungi. *Fonsecaea pedrosoi* is the most common cause, and accounts for 90% or more of the cases reported in South America. It has also been reported as the most common cause in other parts of the world. Other agents include *Phialophora verrucosa*, *Fonsecaea compacta*, *Cladosporium carrionii*, and *Rhinocladiella aquaspersa*. *Exophiala spinifera* and *Exophilia jeanselmei* have been reported in isolated cases. Patients may have more than one organism, and cutaneous lesions caused by both paracoccidioidomycosis and chromoblastomycosis have been reported in the same patient. Patients may also have chromoblastomycosis concurrently with mycetoma or invasive phaeohyphomycosis. CNS lesions have been associated with *Cladosporium trichoides* (*Xylohypha or Cladophialophora bantiana*), as well as other organisms to include *Fonsecaea pedrosoi*. Most of the reported cases are really phaeohyphomycosis, rather than chromoblastomycosis, because the organism grows in the hyphal form.

Histopathologically, lesions are characterized by pseudoepitheliomatous hyperplasia with intraepidermal abscess, a dermal granulomatous reaction, and the presence of pigmented fungal sclerotic bodies. The fungi often appear in clusters that reproduce by equatorial septation, rather than

by budding. The presence of sclerotic bodies (Medlar bodies, "copper pennies") rather than hyphae distinguish the infection from invasive phaeohyphomycosis. The organisms are often seen in association with an embedded splinter.

Staining for fungal antigens has demonstrated that they accumulate in macrophages and occasionally in factor XIIIa-positive dendrocytes or Langerhans cells. The immune response to the organism appears to affect the clinical and histologic presentation. Patients with verrucous plaques demonstrate a type T-helper 2 (Th2) immunologic response, while those with erythematous atrophic plaque have a type Th1 response.

Epidemiology

Chromoblastomycosis was first recognized in Brazil by Pedroso in 1911. Since then it has been found in other parts of South America and the Caribbean, Madagascar, South Asia, East Asia, the US, Russia, and many other countries. Barefooted farm workers bear the largest burden of infection. Trauma from wood products and soil exposure results in implantation of the organism, and dissemination is rare.

Mycology

The microorganisms produce black, slowly growing, heaped-up colonies. The genera differ according to the type of conidiophore produced. All produce melanin.

Treatment

Treatment is difficult, and the disease often affects those who can ill afford medication. In some series, only about 30% of patients were cured, although almost 60% improved. About 10% fail therapy outright, and recrudescence of the disease is noted in more than 40% of patients.

Smaller lesions of chromoblastomycosis are best treated by surgical excision or cryotherapy. In one study of 22 patients, the number of cryosurgeries varied from 1 to 22, and treatment lasted for up to 126 months. Only three patients did not respond. If the lesions are extensive, itraconazole, 100 mg/day or more is given for at least 18 months. Terbinafine, 500 mg/day for 6 to 12 months, has been effective in some patients. In refractory cases, itraconazole may be combined with cryotherapy, application of heat (local hyperthermia), or CO_2 laser vaporization. Alternate-week therapy with itraconazole and terbinafine has also been reported. Local hyperthermia alone has been reported as effective in some cases, and has been combined with CO_2 laser vaporization. Despite these options, some lesions remain resistant, and amputation may be unavoidable in some patients.

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PHAEOHYPHOMYCOSIS

This heterogeneous group of mycotic infections is caused by dematiaceous fungi whose morphologic characteristics in tissue include hyphae, yeast-like cells, or a combination of these. This contrasts with chromomycosis where the organism forms round sclerotic bodies.

There are many types of clinical lesions caused by these organisms. Tinea nigra is an example of superficial infection. Alternariosis can also present as a superficial pigmented fungal infection in immunocompetent patients. Subcutaneous disease occurs most commonly as indolent abscesses at the site of minor trauma (so called "phaeomycotic cyst"). *E. jeanselmei* is the most common cause of this presentation in temperate climates. Systemic phaeohyphomycosis is largely a disease of immunocompromised patients, although primary cerebral forms occur in immunocompetent patients. Localized forms occur primary as a result of primary inoculation of the organism into the skin. Disseminated disease may also begin as a skin infection, although catheter sepsis is being recognized as a cause of disseminated infection. The lesions commonly appear as dry black leathery eschars with a scalloped erythematous edematous border (Fig. 15-23).

Biopolaris specifera is the most common cause of disseminated disease, although *Scedosporium prolificans* has been reported as the most common organism in some areas. The presence of melanin in the cell wall may be a virulence factor for these fungi. Eosinophilia is noted in about 10% of patients with disseminated disease. The disease often disseminates to many organs. Endocarditis is mostly reported on porcine valves. In some series, the mortality rate of disseminated disease is about 80%. More than a half of patients with primary CNS disease have no known underlying immunodeficiency. Mortality rates from CNS infections are high regardless of immune status.

Etiology and Pathology

Many black molds are capable of causing phaeohyphomycosis. Among them are *E. jeanselmei*, *Dactylaria gallopava*, *Phialophora parasitica*, *P. wemeckii*, *H. toruloidea*, *Wangiella dermatitidis*, *Exserohilum rostratum*, *Bipolaris spicifera*, *C.*

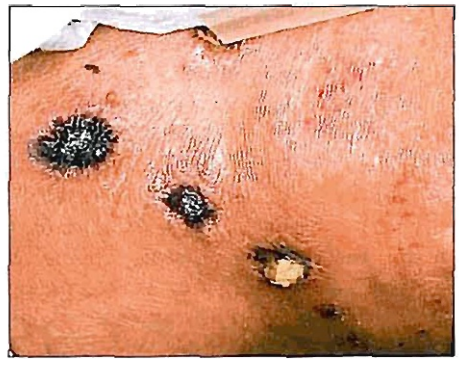

Fig. 15-23 Phaeohyphomycosis.

bantiana, *Chaetomium globosum*, and *X. bantiana*. Some fungi, such as *P. verrucosa*, can cause both phaeohyphomycosis and chromoblastomycosis. Some fungi, such as *E. jeanselmei*, may cause mycetoma (characterized by grain formation) in some patients, and phaeohyphomycosis or chromoblastomycosis in others.

All these organisms produce pigmented hyphae in tissue and culture, although the pigment may only be visible focally in some histologic sections. Melanin can be stained with the Fontana-Masson method, but many organisms produce enough melanin to stain positive, and a positive stain should not be misinterpreted as proof of phaeohyphomycosis. Organisms as diverse as zygomycetes and dermatophytes can stain with the Fontana-Masson stain. When hyphae appear brown in tissue, there is little question as to the diagnosis, but when the organism appears hyaline in tissue, the presence of melanin staining must be interpreted in the context of the fungal morphology. Most organisms of phaeohyphomycosis produce thick refractile walls, and have prominent bubbly cytoplasm. This contrasts with the thin, delicate walls of organisms such as aspergillus, fusarium, and dermatophytes. Zygomycetes are aseptate, and usually appear hollow in tissue sections. Their thick refractile wall usually stains intensely red with H&E, contrasting with the pale wall of a phaeomycotic organism. Some organisms, like *Bipolaris*, produce round, dilated structures that resemble spores is tissue. The mix of round structures and hyphae is a helpful clue to the presence of a black mold in tissue.

Treatment

Phaeomycotic cysts are best treated with excision. Superficial phaeohyphomycosis may respond to topical antifungal agents and superficial debridement. For invasive and disseminated disease, surgical excision should generally be combined with antifungal therapy. Itraconazole has the best record of treating this group of infections, and doses of 400 mg/day or higher are commonly needed. Reproducible fungal sensitivity studies are now available through a few reference laboratories, but the process is slow, and patients with disseminated disease have little time to spare. Some organisms respond to amphotericin B or terbinafine. Combinations of terbinafine and triazoles have been successful clinically, and the combination of terbinafine and fluconazole has shown promise in vitro. For CNS disease, combinations of amphotericin B, flucytosine, and itraconazole may improve survival rates. Voriconazole has a broad spectrum of activity against these fungi, but clinical experience is limited. Complete excision of primary brain lesions may be prudent when possible. In widely disseminated disease, excision of lesions becomes impractical, but debulking of skin disease may be of some value.

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MYCETOMA

Mycetoma, also known as *Madura foot* and *maduromycosis*, is a chronic, granulomatous, subcutaneous, inflammatory disease caused by filamentous bacteria (actinomycetoma) or true fungi (eumycetoma). The organisms enter the skin by traumatic inoculation. Both forms of mycetoma present as progressive subcutaneous swelling with sinus tracts that discharge grains (Fig. 15-24).

The disease progresses slowly. Mycetomas generally begin on the instep or the toe webs. The lesion is commonly relatively painless, nontender, and firm. The overlying skin may be normal or attached to the underlying tumor. Mature lesions often have nodules and draining sinuses. Not only the skin and subcutaneous tissues but also the underlying fascia and bone are involved. Other parts of the body, such as the hands, arms, chest, jaw, and buttocks, may be involved. Exposed sites are most common, and lesions in covered areas are nearly always actinomycetomas.

Etiology and Pathology

Mycetoma is divided into actinomycetoma, produced by bacteria, and eumycetoma, produced by true fungi. Actinomycetomas are caused by *Nocardia*, *Actinomadura*, or *Actinomyces spp*. Eumycetomas are caused by true fungi including pigmented fungi such as *Madurella spp*, and hyaline fungi such as *Pseudallescheria* and *Acremonium (Cephalosporium)*. Organisms include *Pseudallescheria boydii* (which may occasionally disseminate as the anamorph or asexual form, *Scedosporium apiospermum*), *Madurella grisea*, *Madurella mycetomati*, *Acremonium falciforme*, *Acremonium recifei*, *Leptosphaeria senegalensis*, *eptosphaeria tompkinsii*, *E. jeanselmei*, *Pyrenochaeta romeri*, and *P. verrucosa*. Examples of actinomycetomas are those caused

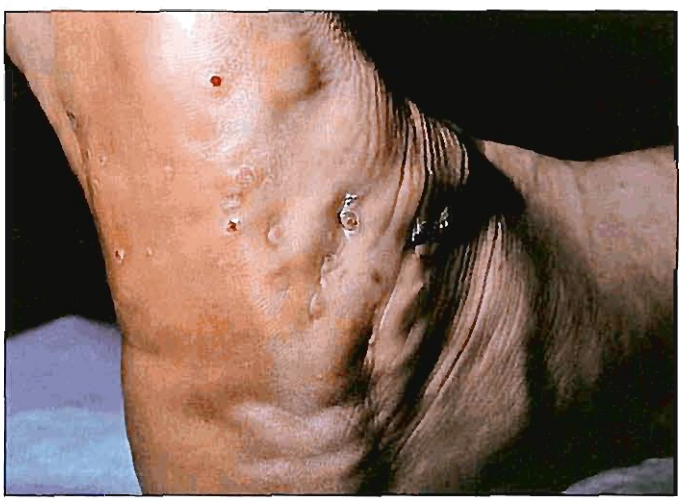

Fig. 15-24 Mycetoma.

by *Nocardia asteroides*, *Nocardia brasiliensis*, *Nocardia caviae*, *Actinomadura madurae*, *Actinomadura pelletieri*, *Actinomyces israelii*, and *Streptomyces somaliensis*. *A. israelii* is the major cause of lumpy jaw, a form of mycetoma.

Almost all actinomycetomas produce light colored grains, as do hyaline fungi. The list of light-grain organisms includes *A. israelii*, *A. madurae*, *Nocardia spp*, *S. somaliensis*, *P. boydii*, *Acremonium spp*, *Aspergillus nidulans*, *Fusarium spp*, and *Neotestudina rosatii*. Red grains are usually produced by *A. pelletieri*, although red pigment-producing colonies that differed from this organism (they were positive for casein hydrolysis and negative for nitrate reduction and hydrolysis tests of xanthine, hypoxanthine, and tyrosine) have been described and provisionally identified as *Actinomadura vinacea*. Pigmented fungi produce dark grains. These organisms include *M. grisea*, *M. mycetomatis*, *Curvularia geniculata*, *Helminthosporium speciferum*, *L. senegalensis*, *E. jeanselmei*, *P. verrucosa*, and *P. romeri*.

Histologic sections demonstrate stellate abscesses containing grains. Gram stain of an actinomycotic grain shows Gram-positive, thin filaments, 1 to 2 μm thick, embedded in a Gram-negative amorphous matrix. Club formation in the periphery of a grain may be seen. Special stains for demonstration of fungi, such as PAS and Gomori methenamine silver, will clearly show hyphae and other fungal structures within the grain. Hyphae of 2 to 5 μm in thickness suggest true fungal mycetoma.

Epidemiology

The mycetoma belt stretches between the latitudes of 15° south and 30° north. Relatively arid areas have higher rates of infection than humid areas. In the Western Hemisphere the incidence is highest in Mexico, followed by Venezuela and Argentina. In Africa it is found most frequently in Senegal, Sudan, and Somalia. Mycetomas are also reported in large numbers in India. Actinomycetomas outnumber eumycetomas by 3:1, which is a blessing as the former is much more responsive to therapy. The male-to-female ratio varies from 2:1 to 5:1.

Mycology

For true fungi (eumycetoma), cultures are made from the grains on Sabouraud dextrose agar containing 0.5% yeast extract and suitable antibiotics. Cultures should be incubated at 37° C and room temperature. For actinomycetes grains, culture should be made in brain–heart infusion agar, incubated aerobically and anaerobically at 37° C, and on Sabouraud dextrose agar with 0.5% yeast extract incubated aerobically at 37° C and room temperature. The specimen for culture should be taken from a deep site, preferably from the base of a biopsy. Cultures should be processed by a reference laboratory and should not be grown in an office laboratory.

Diagnosis

Mycetoma may be diagnosed by keeping in mind a triad of signs, namely: tumefaction, sinuses, and granules. Pus gathered from a deep sinus will show the granules when examined with the microscope. The slide containing the specimen should have a drop of 10% NaOH added and a coverslip placed on top. A biopsy may be required. Radiographs will show the bone involvement and MRI images may show the "dot in a circle" sign, corresponding to grains.

Treatment

Actinomycetomas generally respond to antibiotic therapy, although advanced cases may also need surgery. In *A. israelii* infection, penicillin in large doses is curative. *N. asteroides* or *N. brasiliensis* is usually treated with sulfonamides.

Patients in the early stage of eumycetoma may be successfully treated by surgical removal of the area. In the more advanced stages, a combination of antifungal therapy and surgery may be successful. In some cases of eumycetoma, amputation will be necessary. Surgical excision combined with itraconazole, 200 mg twice a day until clinically well, may be effective in cases caused by *P. boydii*. *P. boydii* is not generally responsive to amphotericin, although liposome-encapsulated forms may have an effect. In one study, 30 isolates of *P. boydii* were tested for activity of posaconazole, fluconazole, and itraconazole in a mouse model of disseminated disease. Posaconazole was as effective as fluconazole and more effective than itraconazole.

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KELOIDAL BLASTOMYCOSIS (LOBOMYCOSIS)

Keloidal blastomycosis was originally described by Jorge Lobo in 1931. Most cases have occurred in countries in Central and South America. One occurred in an aquarium attendant in Europe who cared for an infected dolphin. One occurred in an American who had walked under the pounding water of Angel Falls on a trip to South America.

The disease may involve any part of the body and the lesions appear characteristically keloidal (Figs 15-25 and 15-26). Fistulas may occur. The nodules increase in size gradually by invasion of the surrounding normal skin or through the superficial lymphatics. Long-standing cases may involve the regional lymph nodes. A common location is the ear, which may resemble the cauliflower ear of a boxer.

The fungus is probably acquired from water, soil, or vegetation in forested areas where the disease is prevalent. Dolphins may be infected. Agricultural laborers have been most frequently affected, but the sex distribution is almost equal.

The causative organism, *Lacazia loboi* (formerly *Loboa loboi* and *Paracoccidioides loboi*), is an obligate parasite. Culture has not been successful, but the organism can grow in mouse footpads.

Histologically, the epidermis is atrophic. The organisms are thick-walled, refractile spherules, larger than those of

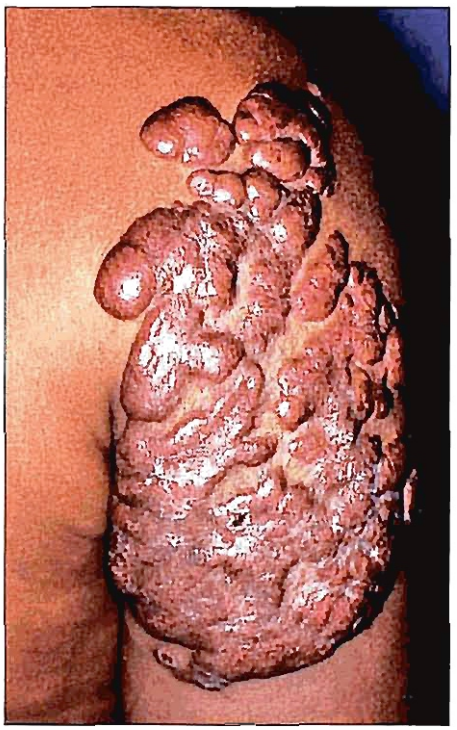

Fig. 15-25 Lobomycosis. (Courtesy of Maria Silvia Negrao, MD)

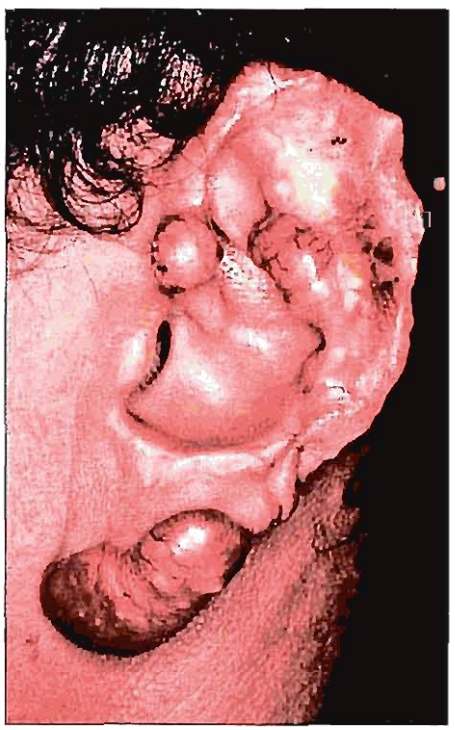

Fig. 15-26 Lobomycosis. (Courtesy of Maria Silvia Negrao, MD)

P. brasiliensis. One or two buds may be seen, but never multiple budding as in *P. brasiliensis*. The organisms are typically numerous and appear in chains of spheres connected by short narrow tubes like a child's pop beads (Fig. 15-27). The cellular infiltrate is composed of histiocytes, giant cells, and lymphocytes. In dolphin tissue, the organism appears significantly smaller than in human tissue. This may be a manifestation of the host response, or may indicate that the organism in the two hosts may not be identical.

Surgical excision of the affected areas may be curative when the lesions are small, but recurrence is common.

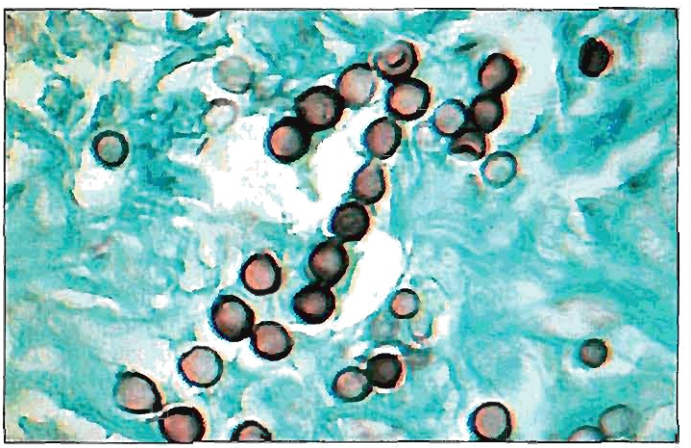

Fig. 15-27 Lobomycosis. (Courtesy of Maria Silvia Negrao, MD)

Complete resolution has been reported in a patient treated for 1 year with a combination of itraconazole (100 mg/day) and clofazimine (100 mg/day).

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RHINOSPORIDIOSIS

Rhinosporidiosis is a polypoid disease usually involving the nasal mucosa. Conjunctival, lacrimal, oral, and urethral tissues may also be involved, and genital lesions may resemble condylomata. The lesions begin as small papillomas and develop into pedunculated tumors with fissured and warty surfaces. Grayish-white flecks may be noted on the tissue, corresponding to transepithelial elimination of large sporangia. Bleeding occurs easily. Conjunctival lesions begin as small, pinkish papillary nodules. Later they become larger, dark, and lobulated. Rectal and vaginal lesions have been reported. Like penile lesions, they may resemble condylomata or polyps. Widespread dissemination rarely occurs, and bone involvement has been described. The disease is endemic in Ceylon and India, but it also occurs in parts of East Asia, and in Latin America. It has been seen in southern US, England, and Italy.

Rhinosporidium seeberi, an organism found in stagnant water, is the causative organism. It has been characterized as either a fungus or protist. The organisms appear as spherules 7 to 10 μm in diameter, which are contained within large cystic sporangia that may be as large as 300 μm in diameter. When the organism does not form endospores, it resembles *C. immitis* spherules, but differs by the regular presence of a central nucleus within each organism. The organisms are usually present within a polypoid structure. A granulomatous response is seen in about 50% of cases, and suppurative

inflammation may be observed at the site of rupture of sporangia. Transepithelial elimination of sporangia is common.

Destruction of the involved area by excision or electrosurgery is the most common method of treatment. Antifungal agents have been of little value. Culture of the organism is easiest when it is grown together with the cyanobacterium *Microcystis aeruginosa*. These are unicellular prokaryotic organisms found in pond water together with *R. seeberi*. The two organisms have also been shown to grow together in tissue, suggesting that rhinosporidiosis may represent a synergistic infection of the fungus and cyanobacterium. As drugs such as ciprofloxacin are active against *M. aeruginosa*, trials of antibiotic therapy may be of value.

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ZYGOMYCOSIS (PHYCOMYCOSIS)

There are a number of important pathogens in the class Zygomycetes. The two orders within this class that cause cutaneous infection most often are the Mucorales and Entomophthorales.

Entomophthoromycosis Infections caused by the order Entomophthorales have been named entomophthoromycosis, rhinoentomophthoromycosis, conidiobolomycosis, or basidiobolomycosis. They occur usually in healthy individuals, and, unlike mucormycosis, often run an indolent course. The infections may be classified as cutaneous, subcutaneous, visceral, and disseminated.

Subcutaneous lesions occur in two basic types, each involving different anatomic sites. They occur either as well-circumscribed subcutaneous masses involving the nose, paranasal tissue, and upper lip, or as nodular, subcutaneous lesions located on the extremities, buttocks, and trunk.

Etiology

Conidiobolus coronatus typically causes the perinasal disease, whereas *Basidiobolus ranarum* causes the type of subcutaneous disease seen on the face.

Epidemiology

Occurrence is worldwide. It was first reported in Indonesia, where it is prevalent. Since then reports have come from Africa, Asia, and the Americas. Generally, infection occurs in a belt between 15° north and south of the equator.

Diagnosis

Isolation and identification of the causative fungus are fundamental to the diagnosis. Culture on Sabouraud dextrose agar is made of nasal discharge, abscess fluid, or biopsy specimens. Biopsy specimens will show fibroblastic proliferation and an inflammatory reaction with lymphocytes, plasma cells, histiocytes, eosinophils, and giant cells. The organisms appear as broad, thin-walled hyphae that are generally aseptate and may be branched at right angles. The Splendore-Hoeppli phenomenon is common and appears as eosinophilic sleeves around the hyphae. *Pythiosis*, a primitive aquatic hyphal organism that acts as a zoonotic pathogen, may affect man and has a similar appearance.

Treatment

Potassium iodide has been the drug of choice, although amphotericin B, cotrimoxazole, ketoconazole, itraconazole, and fluconazole have also been used successfully. Excision of small lesions is an alternative method of management, but the recurrence rate is significant. Rare human cases of pythiosis have responded to amphotericin B.

Mucormycosis *Mucormycosis* refers to infections caused by the order Mucorales of the class Zygomycetes. They characteristically are acute, rapidly developing, and often fatal. In some series, the death rate is about 80%. Most infections occur in ketoacidotic diabetics, but leukemia, lymphoma, AIDS, iatrogenic immunosuppression, burns, chronic renal failure, and malnourishment all predispose to these infections. Occasionally, healthy individuals have been reported to develop these infections. Some have occurred as a result of contaminated surgical dressings.

The five major clinical forms (rhinocerebral, pulmonary, cutaneous, gastrointestinal, and disseminated) all demonstrate vasculotropism of the organisms. This leads to infarction, gangrene, and the formation of black, necrotic, purulent debris. Ulceration, cellulitis, ecthyma gangrenosum-like lesions, and necrotic abscesses may occur. The infection may involve the skin through traumatic implantation or by hematogenous dissemination.

Etiology

The fungi that cause this infection are ubiquitous molds common in the soil, on decomposing plant and animal matter, and in the air. The pathogenic genera include *Rhizopus*, *Absidia*, *Mucor*, *Cunninghamella*, *Apophysomyces*, *Rhizomucor*, *Saksenaea*, *Mortierella*, and *Cokeromyces*.

Diagnosis

Tissue obtained by biopsy or curettage is examined microscopically and cultured. Prompt diagnosis is essential in this rapidly fatal infection. Histologically, the organism generally appears as eosinophilic, thick-walled hyphae that appear hollow in cross-section. The organism is quite irregular in outline and right-angle branching is common. The presence of thin-walled hyphae with bubbly cytoplasm should suggest aspergillosis or fusariosis. Thick refractile hyphal walls that do not stain avidly with eosin, but contain bubbly cytoplasm, should suggest a black mold. All of these organisms are highly vasculotropic and dissect along the media of muscular vessels, resulting in infarction of tissue.

Treatment

A combination of excision of affected tissue and antifungal therapy, usually with amphotericin B, is necessary in most cases. Very limited disease may be treated with excision alone,

but this approach may be risky. Liposomal amphotericin B is more effective than conventional amphotericin B in animal models of infection. Clinical data also suggest the superiority of liposomal forms of amphotericin B. Arterial infusion of liposomal amphotericin B may be superior to intravenous therapy in some serious limb infections.

In both animal models and human disease, other antifungal agents have proved to be effective, but their effectiveness varies from one zygomycete to another. Itraconazole has been shown to be inactive against *Rhizopus microsporus* and *Rhizopus oryzae*, but partially active against *Absidia corymbifera*. Posaconazole has been shown to be inactive against *R. oryzae* but partially activity against *A. corymbifera*. Posaconazole has activity against *R. microsporus*, and has been effective in some human infections. Echinocandins have limited activity against zygomycetes, but FK463, a new echinocandin, and even caspofungin, have been used successfully. As these drugs have spotty coverage against zygomycetes, they are best used in combination with other agents, or when other agents have failed.

Mohs micrographic surgery has been used for margin control during excision of infected tissue. The speed of interpretation of each stage and the potential for tissue conservation are advantages of this method. Fungal stains, such as Gomori methenamine silver, have been used in this setting, but zygomycetes show variable staining with fungal stains. Often H&E is the optimal stain, and sometimes the organisms stain avidly with a tissue Gram stain.

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HYALOHYPHOMYCOSIS

The term *hyalohyphomycosis* contrasts with phaeohyphomycosis and refers to those opportunistic mycotic infections caused by nondematiaceous molds. Most of these organisms are septate, and, compared with black molds, most have delicate walls. Organisms include *Penicillium* and *Paecilomyces*. Disseminated infections with *Scedosporium apiospermum* (the asexual form of *Pseudallescheria boydii*) are grouped in this category. Some authors use the term broadly to encompass infections with all light colored molds, including *Fusarium*. Although *Aspergillus* is a light colored mold that appears similar in tissue to other form of hyalohyphomycosis, it is usually grouped separately, as organisms other than *Aspergillus* are more likely to cause wide dissemination and CNS disease in some reported series.

These organisms are ubiquitous; they occur as saprophytes in soil or water or on decomposing organic debris. They generally do not cause disease except in immunocompromised patients. *Fusarium solani* (keratomycosis) and *Fusarium oxysporum* (white superficial onychomycosis) are exceptions. Localized hyalohyphomycosis has also occurred in immunocompetent patients following traumatic implantation. There is no classic clinical morphology to the lesions, but keratotic masses, ulcerations, ecthyma gangrenosum-like lesions, erythematous nodules, dark eschars, and disseminated erythema have been described.

Penicillium marneffei infection is an indicator of HIV disease, especially in Southeast Asia. This organism is dimorphic and appears in tissue as small intracellular organisms within histiocytes. The histologic similarity to histoplasmosis is striking.

Most of these infections are treated with a combination of excision and amphotericin B. Some organisms respond well to itraconazole alone or with an echinocandin.

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FUSARIOSIS

Fusariosis has emerged as an important pathogen, especially in neutropenic patients. It is a significant opportunistic pathogen in patients with hematologic malignancy. Skin involvement is present in about 70% of patients, and the infec-

tion may sometimes begin in the skin and then disseminate. Many cases disseminate to the skin and skin biopsies provide the diagnosis more commonly than any other test. Contaminated hospital plumbing may be a source of fusariosis. *Fusarium* has been cultured from drains, water tanks, sink faucet aerators, and shower heads. Aerosolization of *Fusarium spp* by shower heads has been documented.

The mortality rate is high, but has improved with the availability of new antifungal agents. Neutropenia, a factor predicting mortality, must be controlled with colony-stimulating factors. Liposomal encapsulated amphotericin has good activity against *Fusarium*. Voriconazole and posaconazole have been used successfully. Pentamidine is active in vitro against many *Fusarium spp*. Some data suggest that the judicious use of a corticosteroid along with an effective antifungal agent may improve outcome.

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ASPERGILLOSIS

Aspergillosis is second only to candidiasis in frequency of opportunistic fungal disease in patients with leukemia and other hematologic neoplasia. Neutropenia remains the key risk factor for invasive aspergillosis in this population. Lymphocytes, especially NK cells, are also critical in host defense, and immunosuppressive agents create a risk of infection. Other risk factors include prolonged corticosteroid therapy, graft-versus-host disease, and cytomegalovirus infection. Solid organ transplant patients are also predisposed to *Aspergillus* infections. Pulmonary involvement is usually present in invasive aspergillus disease, but skin lesions are present in only about 10% of cases. Biopsy of a skin lesion may establish the diagnosis when other studies have failed. Blood culture is an insensitive method of diagnosis. Serum antigenic assays are being developed, but suffer from limited sensitivity and specificity.

Aspergillus fumigatus is the most common cause of disseminated aspergillosis with cutaneous involvement. The organism grows on media without cycloheximide in 24 h or longer. In tissue, the organisms appear as slender hyphae with delicate walls and bubbly cytoplasm. The appearance is identical to that of *Fusarium*. The hyphae in both are septate with 45° branching. Both tend to be vasculotropic and are associated with cutaneous necrosis. In third-degree burns, aspergillus commonly colonizes the eschar. Deep incisional biopsies are required to distinguish invasive disease from colonization.

Primary Cutaneous Aspergillosis Primary cutaneous aspergillosis is a rare disease. Most cases occur at the site of intravenous cannulas in immunosuppressed patients. Hemorrhagic bullae and necrotic ulcers may be present. *Aspergillus flavus* is most commonly associated with this form of infection. Patients must be treated aggressively as the fungus may disseminate from the skin lesion.

Aspergillus is a frequent contaminant in cultures from thickened, friable, dystrophic nails, and various *Aspergillus spp* have been implicated as true etiologic agents of onychomycosis. Nail infection may respond to itraconazole.

Otomycosis The ear canal may be infected by *Aspergillus fumigatus, A. flavus*, and *Aspergillus niger*. Pathogenic bacteria, especially *Pseudomonas aeruginosa*, are often found concurrently. The colonization may be benign, but malignant otitis may occasionally occur, especially in diabetic or iatrogenically immunosuppressed patients. Invasive disease must be treated with systemic agents.

Treatment

Amphotericin B has been the drug of choice in invasive aspergillosis, but triazoles have activity against the fungus. Voriconazole shows excellent activity against *Aspergillus spp.*, including itraconazole- and amphotericin B-resistant strains of *A. fumigatus*. Some data suggest it is superior to amphotericin B, with lower overall toxicity, although visual disturbances and skin rash can be a problem with this drug. Echinocandins are fungistatic against *Aspergillus spp.*, but have also proved clinically useful.

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ALTERNARIOSIS

Alternaria is a genus of molds recognized as common plant pathogens but very rare causes of human infection. Most reported cases of invasive infection have occurred in

immunocompromised patients. Cutaneous alternariosis usually presents as focal ulcerated papules and plaques or pigmented patches on exposed skin of the face, forearms and hands, or knees of immunocompetent patients. Topical corticosteroids may predispose to local infection. Localized disease in immunocompetent patients may respond to local debridement or wide surgical excision. Itraconazole has been successful, although resistance has also been reported. Terbinafine, ketoconazole, and intralesional miconazole have also been used successfully.

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DISEASE CAUSED BY ALGAE (PROTOTHECOSIS)

Protothecosis is caused by the *Prototheca* genus of saprophytic, achloric (nonpigmented) algae. These organisms reproduce asexually via internal septation or morulation. This reproductive method, along with the absence of glucosamine and muramic acid in the cell wall, separates the genus from the bacteria and fungi. Two *Prototheca spp* cause disease in humans, *Prototheca wickerhamii* and *Prototheca zopfi*. Stagnant water, tree slime, and soil appear to be the source of infection in most cases.

Skin lesions may present as verrucous lesions, ulcers, papulonodular lesions, or crusted papules with umbilication. Protothecosis of the olecranon bursa is usually seen in healthy individuals, but cutaneous infections have been most often reported in patients receiving immunosuppressive therapy and in those with renal failure, AIDS, hematologic malignancy, or diabetes mellitus. Neutropenia is not a common risk factor.

Prototheca spp are easily recognized in PAS-stained tissue specimens when the characteristic morulating cells are visible. These are more common in *P. wickerhamii*. The organism also appears with a single black nucleus and a slightly asymmetrical thick refractile wall. It grows on most routine mycologic media, but cycloheximide will suppress growth of *Prototheca spp*. Colonies on Sabouraud agar are smooth, creamy, and yeast-like. The use of fluorescent antibody reagents makes possible the rapid and reliable identification of *Prototheca spp* in culture and tissue.

Intravenous amphotericin B remains the most effective agent for *Prototheca* infections. Triazoles appear to be less effective. Surgery, as well as topical amphotericin B and tetracycline have been used for isolated cutaneous disease.

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CHAPTER

16 Mycobacterial Diseases

TUBERCULOSIS

No ideal classification scheme exists for cutaneous tuberculosis, but the system below is logical and takes into account both the mechanism of disease acquisition and the host immunity. There are four major categories of cutaneous tuberculosis:

1. Inoculation from an exogenous source (primary inoculation tuberculosis and tuberculosis verrucosa cutis)
2. Endogenous cutaneous spread contiguously or by autoinoculation (scrofuloderma, tuberculosis cutis orificialis)
3. Hematogenous spread to the skin (lupus vulgaris; acute miliary tuberculosis; tuberculosis ulcer, gumma, or abscess; tuberculous cellulitis)
4. Tuberculids (erythema induratum [Bazin disease], papulonecrotic tuberculid, and lichen scrofulosorum)

The finding of mycobacterial DNA by polymerase chain reaction in tuberculids suggests that tuberculids also represent hematogenous dissemination of tuberculosis, which is quickly controlled by the host, usually resulting in the absence of detectable organisms.

Epidemiology

Tuberculosis in the US had declined at a rate of 5% to 6% per year until 1984. From 1985 until 1991, there was an 18% increase in the number of cases of tuberculosis. Similar increases were seen in some European countries. This increase was associated with three phenomena: large numbers of immigrants from high-prevalence countries, the acquired immunodeficiency syndrome (AIDS) epidemic, and an increasing number of persons in congregative facilities (shelters for the homeless and prisons). Asians, black persons, and Hispanics have the greatest risk for developing tuberculosis in the US. Tuberculosis is also increasing worldwide, especially in developing countries where 30% to 60% of adults are infected with *Mycobacterium tuberculosis*. The global increase in tuberculosis is related to human immunodeficiency virus (HIV) infection, since many regions of the developing world where tuberculosis is common are also areas of high HIV infection rate. Cutaneous tuberculosis is still uncommon in North America. However, with the increase in the number of cases of tuberculosis globally in both developed and developing countries, an increase in cutaneous tuberculosis may be anticipated.

Tuberculin Testing

The tuberculin test is designed to detect a cell-mediated immune response to *M. tuberculosis*. It remains the most useful method of identifying infected persons. The test becomes positive between 2 and 10 weeks following infection and remains positive for many years, although it may wane with age. Purified protein derivative (PPD) preparations are currently used for testing in the US and Canada at a dose of 5 TU. The intradermal, or Mantoux, test is the standard, and it offers the highest degree of consistency and reliability. The test is read 48 to 72 h after intradermal injection. Induration measuring 5 mm or more is considered positive in HIV-infected patients, those with risk factors, recent close contacts, or those with chest x-ray findings consistent with healed tuberculosis. Because children are at increased risk of developing active tuberculosis after exposure, a 5-mm or larger reaction in contact investigations is considered positive. If it measures more than 10 mm, it is considered positive in injection drug users, low income patients, those born in foreign countries of high prevalence, nursing home patients, and those with medical conditions that predispose to tuberculosis. If induration is more than 15 mm, it is positive in all others; 0 to 4 mm induration is negative. This means that 10 mm or more induration most likely represents specific sensitivity to *M. tuberculosis* (i.e. infection). As the amount of induration becomes progressively smaller, the likelihood that this represents true infection decreases. Many intermediate responses may represent cross-reaction with atypical mycobacteria. Although tuberculins and PPDs have been prepared for other mycobacteria, they are less sensitive and less specific and are not currently recommended for diagnostic purposes. Bacillus Calmette-Guérin (BCG) immunization leads to a positive tuberculin result in immunized children, but this reaction usually does not persist beyond 10 years. Therefore, positive reactions in adults should not automatically be attributed to childhood BCG administration.

Reactivity to the tuberculin protein is impaired in certain conditions in which cellular immunity is impaired. Lymphoproliferative disorders, sarcoidosis, corticosteroids and immunosuppressive medications, severe protein deficiency, chronic renal failure, and numerous infectious illnesses, including HIV infection, are capable of diminishing tuberculin reactivity. Because of the frequent anergy of such persons to skin testing, at least two controls should be administered along with the tuberculin. Failure to react to all antigens documents anergy. In overwhelming tuberculosis (miliary disease), more than 50% of patients have a negative skin test before beginning therapy. A negative or doubtful reaction to a PPD preparation does not rule out tuberculosis infection, particularly in the face of suggestive symptoms and signs. Testing with higher concentrations of tuberculin and repeated testing increase the number of false-positive reactions and are not recommended.

BCG Vaccination

BCG is a living attenuated bovine tubercle bacillus used in many parts of the world to enhance immunity to tuberculosis. Vaccination is given only to tuberculin-negative persons. It is effective in reducing childhood tuberculosis if given to neonates, but its efficacy when given to adults is less clear. Once the patient has been vaccinated, the tuberculin test becomes positive, and remains so for a variable length of time. In an adult who was vaccinated as a child in a foreign country with a high prevalence of tuberculosis and whose tuberculin test measures more than 10 mm, active tuberculosis should be assumed.

Dermatologic complications of BCG vaccination are rarely seen. Dostrowsky et al reported skin reactions in 27 of more than 200,000 individuals vaccinated with BCG. Among reactions attributed to the vaccination were exaggerated or persistent regional lymphadenitis, scrofuloderma, lupus vulgaris, and lichen nitidus-like lesions. Excessive ulceration may occur if the BCG is inoculated too deeply. Nonspecific reactions were noted in 33 patients. These included urticaria, erythema nodosum, erythema multiforme, and granuloma annulare.

Occasionally, BCG will cause progressive local, disseminated, or even fatal disease in the immunocompetent host. In the immunodeficient host, however, progressive disease is much more common. BCG should be given only to HIV-infected neonates if they are asymptomatic and live in a region where the risk of acquiring tuberculosis is high. HIV-infected persons living in areas of low tuberculosis prevalence or who are symptomatic from HIV disease should not receive BCG vaccine. The value of vaccinating adult HIV-infected persons is unproven.

Inoculation Cutaneous Tuberculosis from an Exogenous Source

Primary Inoculation Tuberculosis (Primary Tuberculous Complex, Tuberculous Chancre) Primary inoculation tuberculosis develops at the site of inoculation of tubercle bacilli into a tuberculosis-free individual (Fig. 16-1). Regional lymphadenopathy usually occurs, completing the "complex." It occurs chiefly in children and affects the face or extremities. Usually the inoculation occurs in previously traumatized skin, including sites of tattoos and nose-piercing, or mucosa. The earliest lesion, appearing 2 to 4 weeks after inoculation, is a painless brown–red papule, which develops into an indurated nodule or plaque that may ulcerate. This is the tuberculous chancre. Prominent regional lymphadenopathy appears 3 to 8 weeks after infection and, occasionally, cold, suppurative, and draining lesions may appear over involved lymph nodes. Primary tuberculous complex occurs on the mucous membranes in about one-third of patients. It also may occur after BCG vaccination in tuberculin-negative children. Spontaneous healing usually occurs within a year or less, with the skin lesion healing first, then the lymph node, which is often persistently enlarged and calcified. Delayed suppuration of the affected lymph node, lupus vulgaris overlying the involved node, and occasionally dissemination may follow this form of cutaneous tuberculosis.

Histologically, there is a marked inflammatory response during the first 2 weeks, with many polymorphonuclear leukocytes and tubercle bacilli. During the next 2 weeks, the picture changes. Lymphocytes and epithelioid cells appear and replace the polymorphonuclear leukocytes. Distinct tubercles develop not only at the site of inoculation but also in the regional lymph nodes within 3 or 4 weeks after inoculation. Simultaneously, with the appearance of epithelioid cells, the number of tubercle bacilli decreases rapidly.

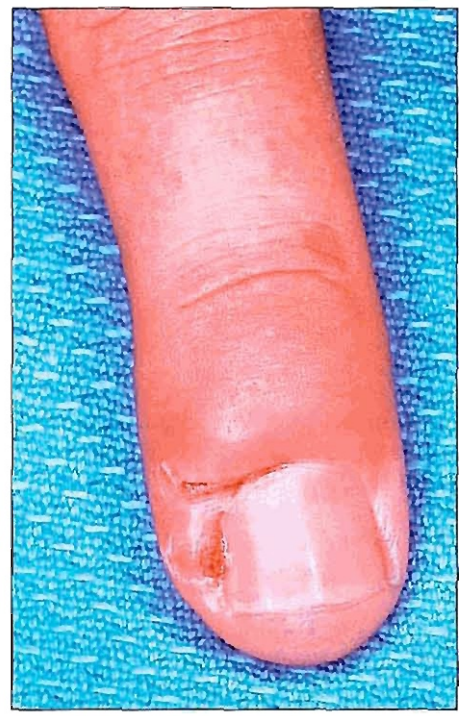

Fig. 16-1 Primary inoculation tuberculosis.

The differential diagnosis of primary inoculation tuberculosis extends over the spectrum of chancriform conditions of deep fungal or bacterial origin, such as sporotrichosis, blastomycosis, histoplasmosis, coccidioidomycosis, nocardiosis, syphilis, leishmaniasis, yaws, tularemia, and atypical mycobacterial disease. Pyogenic granuloma and cat-scratch disease must also be considered.

Tuberculosis Verrucosa Cutis Tuberculosis verrucosa cutis occurs from exogenous inoculation of bacilli into the skin of a previously sensitized person with strong immunity against *M. tuberculosis*. The tuberculin test is strongly positive. The prosector's wart resulting from inoculation during an autopsy is the prototype of tuberculosis verrucosa cutis.

Clinically, the lesion begins as a small papule, which becomes hyperkeratotic, resembling a wart. The lesion enlarges by peripheral expansion, with or without central clearing, sometimes reaching several centimeters or more in diameter (Fig. 16-2). Fissuring of the surface may occur, discharging purulent exudate. Lesions are almost always solitary, and regional adenopathy is usually present only if secondary bacterial infection occurs. Frequent locations for tuberculosis verrucosa cutis are on the dorsa of the fingers and hands in adults, and the ankles and buttocks in children.

The lesions are persistent, although usually superficial and limited in their extent. They may be separated by exudative or suppurative areas, but they seldom ulcerate and may heal spontaneously.

Histologically, there is pseudoepitheliomatous hyperplasia of the epidermis and hyperkeratosis. Suppurative and

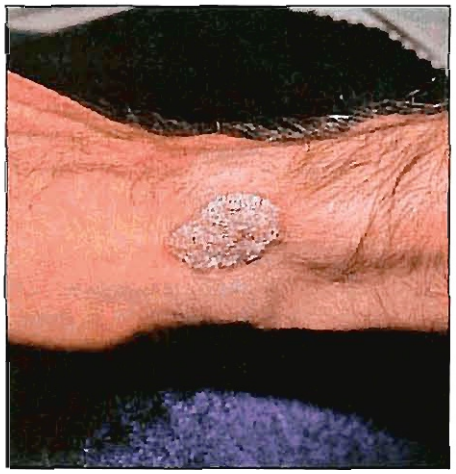

Fig. 16-2
Tuberculosis verrucosa cutis.

granulomatous inflammation is seen in the upper and mid dermis, sometimes perforating through the epidermis. The number of acid-fast bacilli is usually scant.

Differential Diagnosis

Tuberculosis verrucosa cutis is differentiated only by culture from atypical mycobacteriosis caused by *Mycobacterium marinum*. It must also be distinguished from North American blastomycosis, Majocchi granuloma, chromoblastomycosis, verrucous epidermal nevus, hypertrophic lichen planus, iododerma, bromoderma, and verruca vulgaris.

Cutaneous Tuberculosis from Endogenous Source by Direct Extension or Autoinoculation

Scrofuloderma Scrofuloderma is tuberculous involvement of the skin by direct extension, usually from underlying tuberculous lymphadenitis. It occurs most frequently over the cervical lymph nodes but also may occur over bone or around joints if these are involved. Clinically, the lesions begin as subcutaneous masses, which enlarge to form nodules (Fig. 16-3). Suppuration occurs centrally. They may be erythematous or skin colored, and usually the skin temperature is not increased over the mass. Lesions may drain, forming sinuses, or they may ulcerate with reddish granulation at the base (Fig. 16-4). Scrofuloderma heals with characteristic cordlike scars, frequently allowing the diagnosis to be made many years later.

Tuberculosis fistulosa subcutanea is characterized by a chronic anal fistula in adults between 30 and 50 years of age. Involvement of the intestinal tract, especially the rectum, is present in most of these cases. Anal strictures and involvement of the scrotum are frequently observed. The lesions consist of one or more fistulas extending into the deep tissue, infiltrated nodules, and swelling of the affected area.

Histologically, in scrofuloderma, the tuberculous process begins in the underlying lymph node or bone and extends through the deep dermis. Necrosis occurs with formation of a cavity filled with liquefied debris and polymorphonuclear leukocytes. At the periphery, more typical granulomatous inflammation is seen, along with acid-fast bacilli.

Scrofuloderma is to be differentiated from atypical mycobacterial infection; sporotrichosis, which is usually along a lymphatic of an extremity; actinomycosis; and coccidioidomycosis. Lymphogranuloma venereum (LGV) favors the inguinal and perineal areas, and has positive serologic tests for LGV.

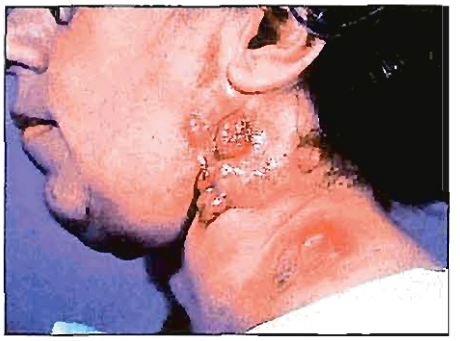

Fig. 16-3
Scrofuloderma. (Courtesy of James WD (ed): Textbook, of Military Medicine, Office of the Surgeon General, United States Army, 1994)

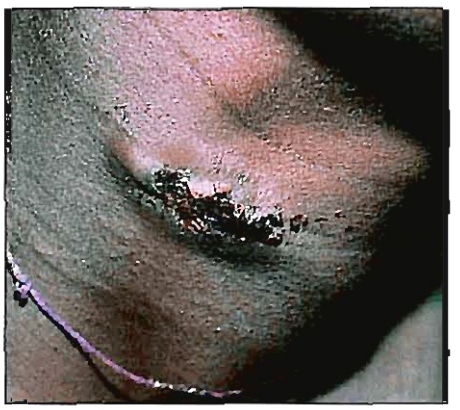

Fig. 16-4
Scrofuloderma. (Courtesy of James Fitzpatrick, MD)

Tuberculosis Cutis Orificialis Tuberculosis cutis orificialis is a form of cutaneous tuberculosis that occurs at the mucocutaneous borders of the nose, mouth, anus, urinary meatus, and vagina, and on the mucous membrane of the mouth or tongue. It is caused by autoinoculation from underlying active visceral tuberculosis, particularly of the larynx, lungs, intestines, and genitourinary tract. It indicates failing resistance to the disease. Consequently, tuberculin positivity is variable but usually present. Lesions ulcerate from the beginning and extend rapidly, with no tendency to spontaneous healing. The ulcers are usually soft, punched out, and have undermined edges.

Histologically, the ulcer base is usually composed largely of granulation tissue infiltrated with polymorphonuclear leukocytes. Deep to the ulcer, granulomatous inflammation may be found and acid-fast bacilli are numerous.

Cutaneous Tuberculosis from Hematogenous Spread

Lupus Vulgaris Lupus vulgaris may appear at sites of inoculation, in scrofuloderma scars, or most commonly at distant sites from the initial infectious focus. Approximately half of such cases will have evidence of tuberculosis elsewhere, so a complete evaluation is mandatory. Because lupus vulgaris is associated with moderately high immunity to tuberculosis, most patients will have a positive tuberculin test.

Lupus vulgaris typically is a single plaque composed of grouped red–brown papules, which, when blanched by diascopic pressure, have a pale brownish yellow or "apple-

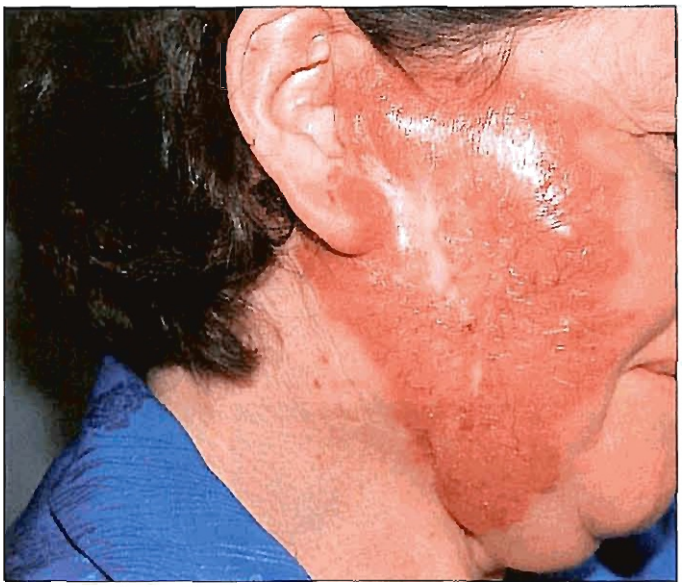

Fig. 16-5 Lupus vulgaris. (Courtesy of Dr Tavares-Bello, MD)

jelly" color. The papules tend to heal slowly in one area and progress in another. They are minute, translucent, and embedded deeply and diffusely in the infiltrated dermis, expanding by the development of new papules at the periphery, which coalesce with the main plaque (Fig. 16-5). The plaques are slightly elevated and often are covered by adherent scales. The disease is destructive, frequently causes ulceration, and on involution leaves deforming scars as it slowly spreads peripherally over the years. Ninety percent of lupus vulgaris lesions occur on the head and neck. At times there may be associated lymphangitis or lymphadenitis. If lesions involve the nose or the lobes of the ears, after involution of the lesions, these structures are shrunken and scarred, as if nibbled away. Atrophy is prominent, and ectropion and eclabion may occur. The tip of the nose may be sharply pointed and beaklike, or the whole nose may be destroyed, and only the orifices and the posterior parts of the septum and turbinates visible. The upper lip, a site of predilection, may become diffusely swollen and thickened, with fissures, adherent thin crusts, and ulcers, or granulations on the mucous aspect. On the trunk and extremities, lesions may be annular or serpiginous or may form gyrate patterns. On the hands and feet and around the genitals or buttocks, lesions may cause mutilation by destruction, scar formation, warty thickenings, and elephantiasic enlargement.

When the mucous membranes are involved, the lesions become papillomatous or ulcerative. They may appear as circumscribed, grayish, macerated, or granulating plaques. On the tongue, irregular, deep, painful fissures occur, sometimes associated with microglossia to the degree that nutrition is compromised.

The rate of progression of lupus vulgaris is slow, and a lesion may remain limited to a small area for several decades. The onset may be in childhood and persist throughout a lifetime. It may slowly spread, and new lesions may develop in other regions. In some instances, the lesions become papillomatous, vegetative, or thickly crusted so that they have a rupioid appearance.

Histologically, classic tubercles are the hallmark of lupus vulgaris. Caseation within the tubercles is seen in about half the cases and is rarely marked. Sarcoidosis may be simulated. The epidermis is affected secondarily, sometimes flattened and at other times hypertrophic. Acid-fast bacilli are found in 10% or less of cases with standard acid-fast stains. Polymerase chain reaction (PCR) may identify mycobacterial DNA in these cases, confirming the diagnosis. In paucibacillary tuberculosis, however, PCR may be negative. Cultures of the skin lesions grow *M. tuberculosis* in about half the cases.

Colloid milia, acne vulgaris, sarcoidosis, or rosacea may simulate lupus vulgaris. Differentiation from tertiary syphilis, chronic discoid lupus erythematosus, leprosy, systemic mycoses, and leishmaniasis may be more difficult, and biopsy and tissue cultures may be required.

Miliary (Disseminated) Tuberculosis Miliary tuberculosis appears in the setting of fulminant tuberculosis of the lung or meninges. Generally, patients have other unmistakable signs of severe miliary tuberculosis. It is most common in children but may occur in adults. Most reported instances of cutaneous tuberculosis seen in patients with AIDS are of this type. Miliary tuberculosis may also follow infectious illnesses that reduce immunity, especially measles. Because this represents uncontrolled hematogenous infection, the tuberculin test is negative. Lesions are generalized and may appear as erythematous macules or papules, pustules, subcutaneous nodules, and purpuric "vasculitic" lesions. Ulceration may occur, and the pain in the infarctive lesions may be substantial. The prognosis is guarded.

Skin biopsies show diffuse suppurative inflammation of the dermis or subcutis with predominantly polymorphonuclear leukocytes. Caseating granulomas may be seen. Vasculitis or abscesses may be seen. Acid-fast bacilli are abundant.

Metastatic Tuberculous Abscess or Ulceration The hematogenous dissemination of mycobacteria from a primary focus may result in firm, nontender erythematous nodules, which soften, ulcerate, and form sinuses. These are usually seen in children, and most patients have decreased immunity from malnutrition, intercurrent infection, or an immunodeficiency state. Patients presenting with tuberculous skin ulcers may or may not have other foci of tuberculosis identified. Aerosolization of mycobacteria may occur during incision and drainage and dressing changes, leading to secondary cases among surgical and nursing staff treating these ulcers. Chronic mastitis with abscess and sinus formation is another presentation of tuberculosis. Histologically, abscess formation and numerous acid-fast bacilli are seen.

Tuberculous Cellulitis An unusual manifestation of tuberculosis was reported in a patient who had been on chronic oral corticosteroids and developed clinical cellulitis. On biopsy, granulomas and acid-fast bacilli were seen and four-drug treatment resulted in cure. She had a past history of pulmonary tuberculosis.

Tuberculids

Tuberculids are a group of skin eruptions associated with an underlying or silent focus of tuberculosis. They are diagnosed by their characteristic clinical features, histologic findings, a positive tuberculin reaction, sometimes the finding of tuberculosis at a distant site, and resolution of the eruption with

antituberculous therapy. Tuberculids represent cutaneous lesions induced by hematogenous dissemination of tubercle bacilli to the skin. Lupus vulgaris may develop at the sites of tuberculids, and *M. tuberculosis* DNA may be found in tuberculid lesions by PCR. Tuberculids usually occur in persons with a strong immunity to tuberculosis (and thus have a positive PPD). This results in rapid destruction of the bacilli and autoinvolution of individual lesions in many cases. New lesions continue to appear, however, since hematogenous dissemination from the underlying focus continues. Tuberculids tend to be bilaterally symmetrical eruptions because they result from hematogenous dissemination.

Papulonecrotic Tuberculid Papulonecrotic tuberculid is usually an asymptomatic, chronic disorder, presenting in successive crops. Lesions are symmetrically distributed on the extensor extremities, especially on the tips of the elbows, and the knees; dorsal surfaces of the hands and feet; buttocks; face and ears; and glans penis. Lesions may favor pernio-prone sites and may be worse during winter months. Two-thirds of cases occur before the age of 30, and females are favored 3:1. Evidence of prior or active tuberculosis is found in between one- and two-thirds of patients, especially in the lymph nodes. The tuberculin skin test is positive and may generate a necrotic reaction.

Typical lesions vary in size from 2 to 8 mm, and are firm, inflammatory papules that become pustular or necrotic. Lesions resolve slowly over several weeks, but occasional ulcers persist longer. Varioliform scarring follows the lesions. Crops recur over a course of months to years.

Papulonecrotic tuberculids may appear in association with other cutaneous manifestations of tuberculosis, particularly erythema induratum or scrofuloderma. Associated clinical phenomena have included tuberculous arteritis with gangrene in young adult Africans and the development of lupus vulgaris from lesions of papulonecrotic tuberculid.

Histologically, the epidermis is ulcerated in well-developed lesions. A palisaded collection of histiocytes surrounds an ovoid or wedge-shaped area of dermal necrosis. Well-formed tubercles are not seen, except in nonhealing lesions evolving into lupus vulgaris. Vascular changes are prominent, ranging from a mild lymphocytic vasculitis to fibrinoid necrosis and thrombotic occlusion of vessels. This is not a neutrophilic leukocytoclastic vasculitis, but rather a chronic granulomatous small vessel vasculitis. Capillaries, venules, and arterioles may be involved. By PCR, mycobacterial DNA can be found in 50% of cases of papulonecrotic tuberculid.

Papulopustular secondary syphilis, pityriasis lichenoides et varioliformis acuta, Churg-Strauss granuloma, lymphomatoid papulosis, perforating granuloma annulare, perforating collagenosis, and necrotizing or septic vasculitis share clinical and histologic features with papulonecrotic tuberculid.

Lichen Scrofulosorum Also known as *tuberculosis cutis lichenoides*, lichen scrofulosorum consists of groups of indolent, minute, keratotic, discrete papules, scattered over the trunk. The lesions are 2 to 4 mm and yellow–pink to reddish brown. They are firm and flat-topped, or surmounted by a tiny pustule or thin scale. The lesions are arranged in nummular or discoid groups, where they persist unchanged for months and cause no symptoms. They may slowly undergo spontaneous involution, followed at times by recurrences. As a rule, they appear in children, adolescents, or adults who have tuberculosis of the bones or lymph nodes. The tuberculin test is always positive.

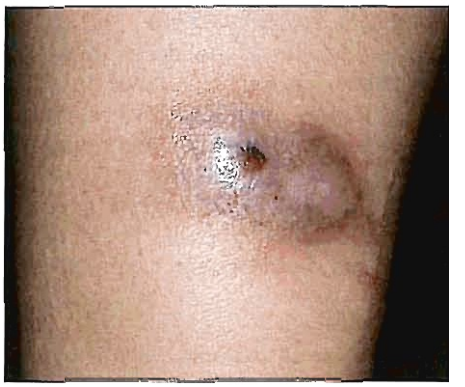

Fig. 16-6 Erythema induratum. (Courtesy of Curt Samlaska, MD)

Histologically, lichen scrofulosorum shows noncaseating tuberculoid granulomas, situated just beneath the epidermis, between and surrounding hair follicles. Normally, tubercle bacilli are not seen in the pathologic specimens, nor can they be cultured from biopsy material.

Lichen nitidus, lichen planus, secondary syphilis, and sarcoidosis should be considered in the differential diagnosis.

Erythema Induratum Erythema induratum (Bazin disease) is chronic and occurs predominantly (80%) in women of middle age. Lesions favor the posterior lower calf, which may also show acrocyanosis. Individual lesions are tender, erythematous or violaceous, 1 to 2 cm subcutaneous nodules (Fig. 16-6). Lesions resolve spontaneously, with or without ulceration, over several months and often heal with scarring. The tuberculin skin test is positive. Idiopathic nodular vasculitis unassociated with tuberculosis may have identical clinical and histologic features, and this diagnosis is made when the PPD is negative.

The primary pathology occurs in the subcutaneous fat, which shows lobular panniculitis with fat necrosis. Granulomatous inflammation occurs in two-thirds of cases and is noncaseating. In addition, a vasculitis of arterioles is present in the fat and is the apparent cause of the fat necrosis. Acid-fast bacilli are not found on special stains or cultures of the biopsy. PCR may help to confirm the diagnosis, however the positve PPD obviates the need for it. At times necrotizing granulomatous vasculitis is present at the dermo-hypodermal junction. This reaction has been termed nodular tuberculid.

Erythema induratum must be distinguished from erythema nodosum, nodular vasculitis, polyarteritis nodosa, tertiary syphilis, and other infectious and inflammatory panniculitides. Erythema nodosum is of relatively short duration and of rapid development and affects chiefly the anterior rather than the posterior calves. It produces tender, painful, scarlet or contusiform nodules that appear simultaneously and do not ulcerate; in erythema induratum, the pain is less, and the lesions tend to evolve serially or in crops. A syphilitic gumma is usually unilateral and single, or may appear as a small, distinct group of lesions. Serologic tests and histology are useful in the differential diagnosis.

Diagnosis of Cutaneous Tuberculosis

Biopsy with acid-fast staining should be done when the history and physical examination suggest cutaneous tuberculosis. PCR testing is increasingly used to identify mycobacterial DNA in tissue specimens and other biologic samples. It may be positive when both stains and cultures are negative; however, in paucibacllary disease it is not reliably positive. Culture remains the gold standard and provides the means to determine antibiotic sensitivity and response to treatment.

Treatment

HIV testing is recommended for all patients diagnosed with tuberculosis, because they may require longer courses of therapy. In addition, every effort should be made to culture the organism for sensitivity testing, since multidrug-resistant tuberculosis is common in some communities. For all forms of cutaneous tuberculosis, multidrug chemotherapy is recommended. Four-drug regimens are recommended for initial empiric treatment. Directly observed therapy is a strategy designed to ensure cure. Priority patients are those with prior treatment failure, pulmonary tuberculosis with a positive smear, HIV co-infection, current or prior drug use, drug-resistant disease, psychiatric illness, memory impairment, or prior nonadherence. Surgical excision is useful for the treatment of isolated lesions of lupus vulgaris and tuberculosis verrucosa cutis, and surgical intervention also may benefit some cases of scrofuloderma.

The initial phase of treatment is intensive, with the goal being rapid destruction of mycobacteria. During this 8-week period isoniazid, rifampin, pyrazinamide, and ethambutol are given. The continuation phase of therapy consists of a two-drug combination, either isoniazid and rifampin or, in non-HIV patients, isoniazid and rifapentine. The usual minimal duration is 18 weeks. Longer duration continuation phase therapy is indicated in several circumstances. Because the drug resistance patterns for tuberculosis vary by region and over time, and because these guidelines change, consultation with your local health department is strongly recommended.

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ATYPICAL MYCOBACTERIOSIS

Many facultative pathogens and saprophytes, which are acid-fast mycobacteria but do not cause tuberculosis or leprosy, are grouped under the designation "atypical" mycobacteria. Several of them were recognized as a cause of human disease nearly 70 years ago. They exist in a wide variety of natural sources, such as soil, water, and animals; most human disease is acquired from the environment. *Mycobacterium marinum*

is the most common cause of skin mycobacterial infections in the US, and *Mycobacterium ulcerans* produces a characteristic clinical picture. Rapid growing mycobacteria of the *Mycobacterium fortuitum* group and the *Mycobacterium chelonae/abscessus* group are usually associated with localized post-traumatic wound infection. In addition to skin disease, pulmonary infections, adenitis, osteomyelitis, and disseminated involvement may occur from a wide variety of other species, especially in immunocompromised patients. *Mycobacterium avium–intracellulare* complex is the most common cause of systemic infection.

Classification of Mycobacteria

The number of new species of non-tuberculous mycobacteria has been growing dramatically in the past several years. Systems which analyze the 16S rRNA gene sequence use PCR-restriction fragment length polymorphism typing analysis of the heat shock protein 65 as well as tools such as chromatography to define new taxa. The expanding number of newly defined organisms has resulted in a complex classification system. Many of these organisms do not cause infection and are simply commensals or saprophytes. They are found in water and soil, and their identification after contamination of clinical specimens has at times been responsible for pseudo-outbreaks of infection.

The clinical care of the patient depends on the recovery and identification of the responsible agent from tissue specimens. The laboratory should be familiar with the special media, necessary incubation times and temperature, and identification characteristics of these organisms. While most laboratories still use a combination of phenotypic characteristics such as the presence or absence of pigment, biochemical properties, and temperature requirements, there are increasing numbers of laboratories which employ both probe assay hybridization and sequence analysis to specify the species. This chapter will focus on the major atypical mycobacteria causing clinical skin infections.

Swimming Pool Granuloma (Aquarium Granuloma)

Swimming pool granuloma is caused by *M. marinum*, which grows optimally at 30° C. The usual source is an aquarium, swimming pool, lagoon, or lake. History of an injury preceding or simultaneous with exposure to contaminated water is usually present. An indolent lesion usually starts about 3 weeks after exposure as a small papule located on the hands, knees, elbows, or feet. More infections in the US are acquired from home aquariums than from other sources, and in such cases, the fingers and hands are the sites of the lesion. A sporotrichoid pattern with a succession of nodules ascending the arm is common (Fig. 16-7). The lesions may be erosions or verrucous papules or plaques (Fig. 16-8). Multiple primary lesions occur infrequently. Usually there is no ulceration or necrosis. Synovitis, draining sinuses, bursitis, arthritis, and osteomyelitis may be seen, however. The tendon sheaths of the dorsal hands and less commonly the palms may be affected, limiting range of motion and resulting in a thickening and induration. Such cases may require surgical, as well as medical, management. The natural history is for slow progression, and lesions may be relatively indolent for years. Spontaneous resolution may occur in 10% to 20% of patients after a period of many months.

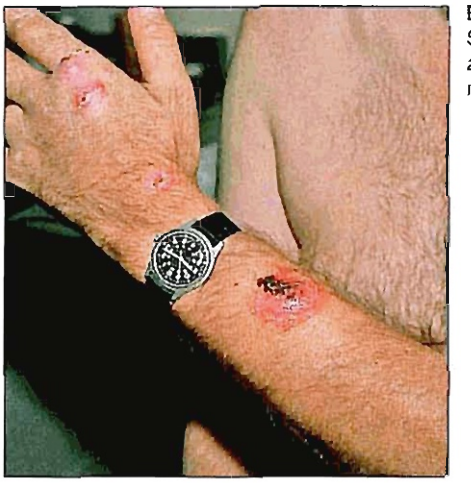

Fig. 16-7 Sporotrichoid atypical mycobacteriosis.

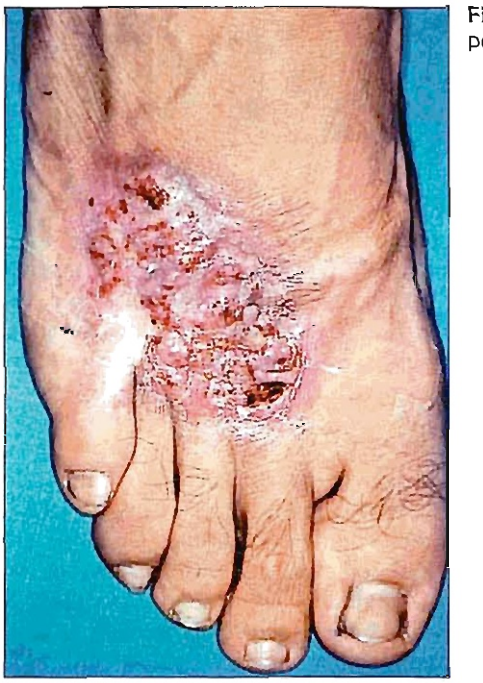

Fig. 16-8 Swimming pool granuloma.

Immunosuppressed patients may develop widely disseminated lesions that are progressive (Fig. 16-9).

Histopathologically, there is an initial mixed inflammatory reaction with overlying hyperkeratosis and acanthosis. Later, epithelioid cell tubercles with giant cells are present. Central necrosis and stellate abscess formation may occur. Acid-fast organisms occasionally may be seen. The organisms are longer and thicker than *M. tuberculosis*. The tuberculin reaction to *M. tuberculosis* usually becomes positive in those who have had *M. marinum* infection.

Excision of the lesion, when feasible, may be effective. Minocycline, 100 mg twice a day, is curative in the majority of cases but may leave a long-lasting blue–black discoloration. Doxycycline, 100 mg twice a day, trimethoprim–sulfamethoxazole (Bactrim, Septra) given as one double strength dose twice a day, or clarithromycin 500 mg twice a day are other excellent alternatives. Treatment with levofloxacin or 600 mg/day of rifampin combined with 15 mg/kg/day of ethambutol may be curative in those patients who do not respond to other medications. The duration of any of

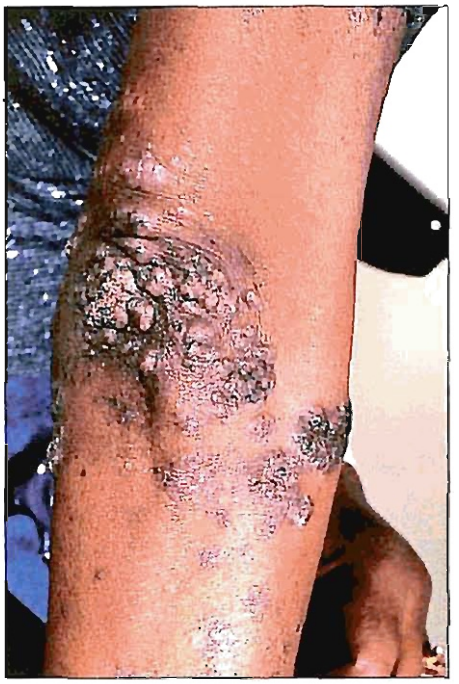

Fig. 16-9 Disseminated *Mycobacterium marinum* infection in systemic lupus erythematosus. (Courtesy of Curt Samlaska, MD)

these treatments is for at least 1 to 2 months after resolution of lesions, which is usually 3 to 4 months. No current recommendation for a drug of choice is available, and the clinician may choose from a number of effective options. When empiric therapy fails, multidrug treatment should be based on laboratory sensitivities.

Buruli Ulcer

Buruli ulcer is also known as Bairnsdale ulcer and *Searl ulcer*. This is the third most common type of mycobacerial skin infection in immunocompetent people. Children are affected most often and females predominate. The lesion begins as a solitary, hard, painless, subcutaneous nodule that subsequently ulcerates and becomes undermined (Fig. 16-10). There is a predilection for the occurrence of these ulcers on the extremities. They may become very large, exposing muscle and tendon over a large portion of an affected extremity. A rare disseminated nonulcerative form *is characterized* by widespread edema and diffuse induration. Histologically, there is extensive coagulative necrosis, little cellular infiltrate, and numerous clumps of acid-fast bacilli.

Mycobacterium ulcerans is the cause of Buruli ulcer. This organism occurs in Australia, Nigeria, Zaire, the Buruli district of Uganda, Mexico, and Malaysia. The source may be water, soil, animals, or an insect vector. *M. ulcerans* produces a toxin, mycolactone, responsible for the extensive necrosis and ulceration seen in these infections. It also has an immunosuppressive property. Antibody production occurs in patients with Buruli ulcer; however, a T-cell anergy to mycobacterial antigens is present.

When feasible, wide and deep excision is the best therapy. There are no clinical trials supporting the use of antimycobacterial drugs. A combination of rifampin and amikacin or ethambutol and trimethoprim–sulfamethoxazole for 4 to 6 weeks have been recommended, but these are best combined with surgery. BCG vaccination provides some protection from infection. Local hyperthermia may be of some benefit.

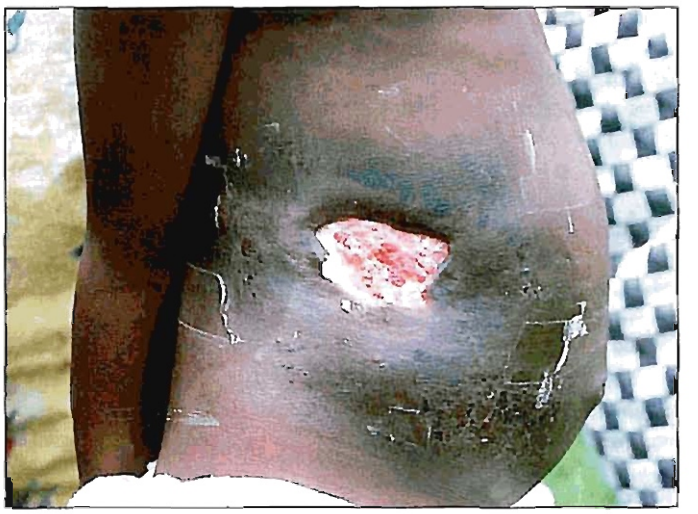

Fig. 16-10 Buruli ulcer.

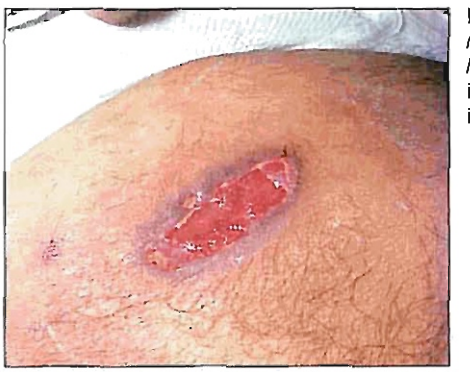

Fig. 16-11 *Mycobacterium haemophilum* infection in HIV infection.

Other Atypical Mycobacterial Infections

Mycobacterium Haemophilum *M. haemophilum* may cause multiple ulcers on the extremities, often overlying joints (Fig. 16-11). Patients with AIDS, transplants, or leukemia and lymphoma are most often infected. Because *M. haemophilum* has specific growth requirements, isolation is not possible using routine laboratory culture techniques. If acid-fast stains of tissue are positive and cultures are *negative, the laboratory should be alerted to utilize appro*priate media and culture conditions for this organism. Isolated lesions may be cured by surgical excision. When systemic infection is present in an HIV patient, institution of antiretroviral therapy may lead to involution. Usually, however, these infections require combination therapy with rifabutin or rifampin, ciprofloxacin, and amikacin.

Rapid Growing Mycobacterium The organisms of the *M. fortuitum* group and *M. chelonae/abscessus* group usually cause subcutaneous abscesses or cellulitis following trauma in immunocompetent patients (Fig. 16-12). Wounds may be caused by a variety of plastic procedures, skin piercings, or following catherterization or injections. Outbreaks of leg abscesses caused by *M. fortuitum* have been acquired in nail salon whirlpool foot baths. Sporotrichoid or disseminated disease may occur in immunocompromised patients (Fig. 16-13). In renal transplant cases, tender, nodular lesions of the legs are most common. Clarithromycin, 500 mg twice a day for 4 to 9 months, is effective and well

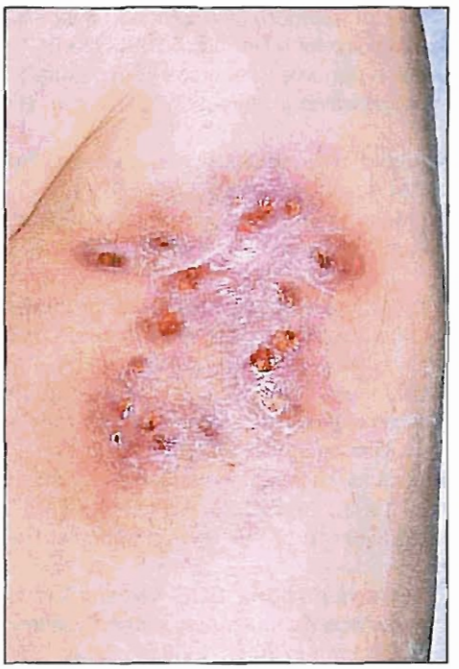

Fig. 16-12
Mycobacterial fortuitum infection.

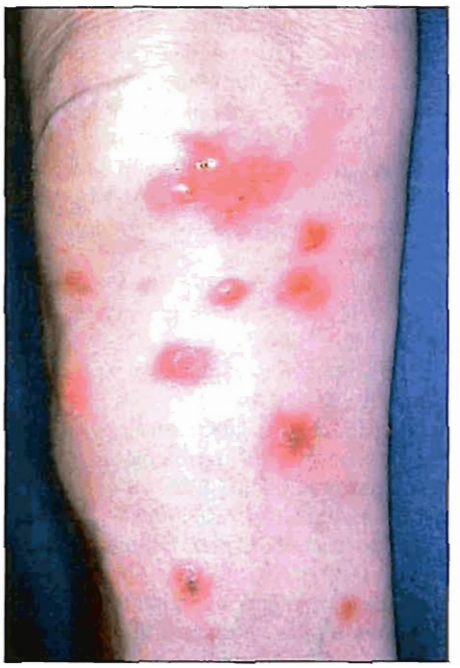

Fig. 16-13
Disseminated *Mycobacterium chelonei* infection.

tolerated in the many patients with disseminated cutaneous infection caused by *M. chelonea*. Unfortunately, monotherapy may allow resistance to occur. The optimal regimen for treatment of *M. fortuitum* likewise has not been defined. This organism is resistant to standard antituberculous therapy, but in vitro sensitivites include doxycycline, minocycline, trimethoprim–sulfamethoxazole, ciprofloxacin, and clarithromycin. A strategy that begins therapy with 2 weeks of amikacin plus either cefoxitin or imipenem (and for *M. chelonae*, tobramycin is instituted in place of amikacin), allows a successful switch to long-term monotherapy.

Mycobacterium Avium–Intracellulare *Complex* This was an uncommon causes of skin infection before the AIDS epidemic. In patients with AIDS who develop disseminated *M. avium–intracellulare* complex infections, the skin may be involved by hematogenous dissemination and may present as nodules, ulcers, or pustules, or have a cellulitis-like appearance (Fig. 16-14). Immunocompromised children with chronic pulmonary infections are also at risk. Only occasional reports of immunocompetent patients with inoculation-type lesions have been reported. Therapy for disseminated infection is undertaken with at least three agents, most commonly clarithromycin, ethambutol, and rifampin. Amikacin may additionally be required. The treatment time is 18 to 24 months.

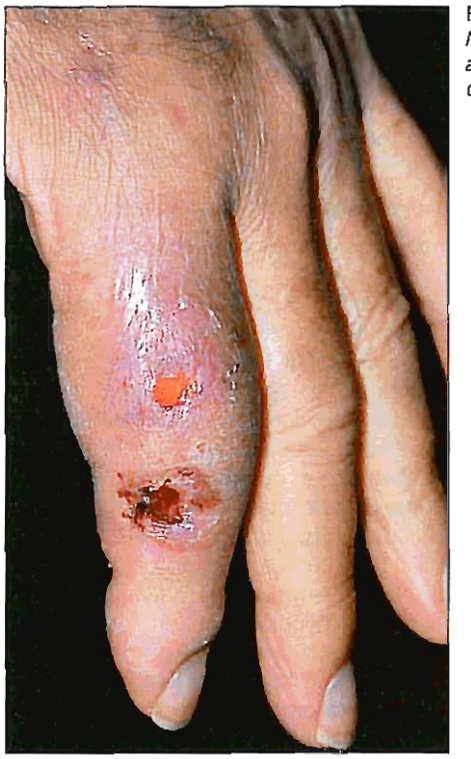

Fig. 16-14
Mycobacterium avium–intracellulare complex ulceration.

Mycobacterium Kansasii *M. kansasii* occasionally involves the skin in a sporotrichoid pattern. Localized granulomatous or cellulitis-like lesions also may be seen. Inoculation is usually by minor trauma. Minocycline, trimethoprim–sulfamethoxazole, or clarithromycin may be given if the infection is limited to the skin and if excision is impractical. Immunosuppressed patients may develop disseminated disease. If pulmonary involvement or resistant cutaneous disease is present, especially if in immune-compromised patients, rifampin and ethambutol, sometimes combined with clarithomycin or isoniazid, is necessary. They are continued for 9 months. This organism may be resistant to rifampin, and in this case ciprofloxacin is combined with ethambutol and clarithromycin. In patients with extensive disease, amikacin is added and therapy continued for 15 to 18 months. In patients with AIDS, antiretroviral treatment should be encouraged as the outcome is improved.

Less Common or Emerging Species *Mycobacterium scrofulaceum* may produce a scrofulodermatous appearance. *Mycobacterium szulgae*, *Mycobacterium genavense*, *Mycobacterium gordonae*, *Mycobacterium xenopi*, as well as other newly described species may occasionally give rise

to cutaneous disease, usually as a wound infection or part of disseminated disease in an immunocompromised patient. Surgical excision in the former, if feasible, is recommended. Multidrug antibacterial therapy appropriate for the susceptibility determination for the organism is given for the latter.

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CHAPTER

17 Hansen's Disease

EPIDEMIOLOGY

The World Health Organization (WHO) committed itself to eliminating Hansen's disease as a public health problem by the year 2000. Elimination (not eradication) is considered as a prevalence of <1 case in 10,000 persons in any country. Although this target was not met, and was extended to the year 2005, substantial progress has been made. Of the 122 countries with Hansen's disease in 1985, 98 reached this elimination goal, and global prevalence has been reduced by 86%. Globally the prevalence is about 1.25 cases per 10,000 persons. Hansen's disease remains a public health problem in 24 countries, and the top 11 countries represent 92% of cases detected worldwide. India accounts for 80% of cases worldwide, with Brazil, Indonesia, Myanmar, Madagascar, and Nepal being the other countries with highest prevalence. Although 90% of cases diagnosed in the US are imported, Hansen's disease is endemic in the coastal southeastern US and in Hawaii. In the southeastern US cases may be related to exposure to armadillos, a natural host for the infectious agent.

In leprosy-endemic areas, 1.7% to 31% of the population is seropositive for antibodies to leprosy-specific antigens, suggesting widespread exposure to the bacillus. It appears that while many persons can be transiently infected, they are able to resist overt clinical infection. Monozygotic twins have concordant disease in 60% to 85% of cases, and dizygotic twins 15% to 25%, suggesting a genetic susceptibility to development of clinical disease. Numerous genes have been identified as possibly conferring susceptibility to infection with *Mycobacterium leprae*. These genes are either components of the adaptive immune response (HLA, TAP2 [transporter 2, ATP binding]) or involved in the innate and adaptive immune responses (toll-like receptor 2, tumor necrosis factor-α). Different genes have been identified in different populations, suggesting there may be multiple genetic causes of susceptibility to infection with *M. leprae*.

In adults, cases in men outnumber those in women 1.5:1. Although leprosy occurs at all ages, most cases appearing or acquired in endemic areas present before the age of 35. Patients exposed to armadillos present on average at age 50. The latency period between exposure and overt signs of disease is usually 5 years for paucibacillary cases, but may be up to 20 years in multibacillary cases. Infected women are likely to present during or immediately after pregnancy.

The mode of transmission remains controversial. Except for cases associated with armadillo exposure, other cases of Hansen's disease are felt to be the only possible source of infection. Multibacillary cases are much more infectious than paucibacillary cases, so the nature of the source case is the most important factor in transmission. Infectious droplets from nasal secretions of active multibacillary cases with nasal erosions were felt initially to be the sole source of spread of the disease via the respiratory route. PCR sampling from nasal secretions, however, has shown that in leprosy-endemic areas, nasal carriage of leprosy bacilli occurs even in persons who can not be identified as clinically infected. Thus, in endemic areas, not all transmission may be directly from active multibacillary cases. Clearly, close contact is associated with acquiring infection. Household contacts represent only 28% of the source cases for new leprosy patients, but 80% of patients are infected by neighbors and social contacts. Insects have never been documented as vectors.

THE INFECTIOUS AGENT

All cases of human and animal leprosy are caused by the same organism, *M. leprae*. *M. leprae* is a weakly acid-fast organism that has not been successfully cultured in vitro. It grows best at temperatures (30° C) below the core body temperature of humans. This explains the localization of leprosy lesions to cooler areas of the body and the sparing of the midline and scalp. The organism may be cultivated in mouse foot pads and most effectively in armadillos, whose lower body temperature is more optimal for growth of *M. leprae*. Phenolic glycolipid-1 (PGL-1) is a surface glycolipid unique to the leprosy bacillus. In infected tissues, the leprosy bacillus favors intracellular locations, within macrophages and nerves. The genome of the leprosy bacillus has been sequenced and compared to its close relative, the tuberculous bacillus. The genome of *M. leprae* contains only 50% functional genes, apparently the result of reductive evolution. Like other intracellular parasites, and in the absence of the ability to share DNA with other bacteria, *M. leprae* has lost many nonessential genes. This may explain the extremely long generation time, 12 to 14 days, and the inability to culture *M. leprae* in vitro.

DIAGNOSIS

A diagnosis of leprosy must be considered in any patient with neurologic and cutaneous lesions. The diagnosis is frequently delayed in the developed world; clinicians do not readily think of Hansen's disease, since they may not have seen it before. In the US, this diagnostic delay averages 1½ to 2 years.

Leprosy is diagnosed, as with other infectious diseases, by identifying the infectious organism in affected tissue. Because the organism cannot be cultured, this may be very difficult. Skin biopsies from skin or nerve lesions, stained for the bacillus with Fite-Faraco stain, are usually performed in the developed world. In some Hansen's disease clinics, and in the developing world where disease is endemic, organisms are identified in slit smears of the skin. Smears are taken

from lesions and cooler areas of the skin, such as the earlobes, elbows, and knees, and stained with acid-fast stains. If organisms are found on skin smears, the patients are said to be *multibacillary*. If the results of skin smears are negative (and they have five or fewer lesions), they are called *paucibacillary*.

Serologic tests to detect antibodies against *M. leprae*-unique antigens (PGL-1) and PCR to detect small numbers of organisms in infected tissue have not improved diagnosis. They are universally positive in patients with multibacillary disease in whom the diagnosis is not difficult. In paucibacillary patients, these tests are often negative, and in endemic areas there is a high background rate of positivity of serologic tests. These tests are, therefore, of no real value in the diagnosis of patients with cutaneous Hansen's disease. In pure neural leprosy, however, about 50% of patients are seropositive, and serologic testing might be of use in that setting. Seropositivity might also be used to identify persons in endemic areas at risk to develop leprosy, and chemoprophylaxis could be directed at these persons. Also, seropositivity may be used as a surrogate field marker for high bacterial load (multibacillary status) and identify those patients who might require longer therapy to cure their infection.

CLASSIFICATION

Leprosy may present with a broad spectrum of clinical diseases. The Ridley and Jopling classification or modifications to it have classified cases based on clinical, bacteriologic, immunologic, and histopathologic features (Table 17-1). In many exposed patients the infection apparently spontaneously clears and no clinical lesions develop. Patients who do develop clinical disease are broadly classified into two groups: patients with few organisms in their tissue are termed *paucibacillary*, and patients with large number of organisms are termed *multibacillary*. In the developing world this determination is made by skin smears and lesion count. The individual's cell-mediated immune response to the organism determines the form Hansen's disease will take in the individual. If the cell-mediated immune response against *M. leprae* is strong, the number of organisms will be low (paucibacillary), and conversely if this response is inadequate, the number of organisms will be high (multibacillary).

The most common outcome after exposure is probably spontaneous cure. If skin disease does appear, the initial clinical lesion may be a single hypopigmented patch, perhaps with slight anesthesia. This is called *indeterminate* disease, since the course of the disease cannot be predicted at this stage. The lesion may clear spontaneously or may progress to any other form of leprosy.

The spectrum of leprosy has two stable poles, the tuberculoid and lepromatous forms (see Table 17-1). These so-called polar forms do not change; the patient remains in one or the other form throughout the course of the disease. The polar tuberculoid form (called TT), the form of high cell-mediated immunity, is characterized by less than five lesions (often only one) and very few organisms (paucibacillary disease). The patients have strong cell-mediated immunity against the organism. The natural history of many TT leprosy patients is for spontaneous cure over several years. The polar lepromatous form (called LL) has very limited cell-mediated immunity against the organism, lesions are numerous, and they contain many organisms (multibacillary). Between these two poles is every possible degree of infection, forming the borderline spectrum. Cases near the tuberculoid pole are called *borderline tuberculoid* (BT), those near the lepromatous pole are called *borderline lepromatous* (BL), and those in the middle are called *borderline borderline* (BB). Borderline disease is characteristically unstable, and with time cases move from the TT to the LL pole, a process called *downgrading*. Leprosy may involve only the nerves. This pure neural disease may be indeterminate, tuberculoid, or lepromatous (paucibacillary or multibacillary) and is so classified.

Early and Indeterminate Leprosy

Usually the onset of leprosy is insidious. Prodromal symptoms are generally so slight that the disease is not recognized until the appearance of a cutaneous eruption. Actually, the first clinical manifestation in 90% of patients is numbness, and years may elapse before skin lesions or other signs are identified. The earliest sensory changes are loss of the senses of cold and light touch, most often in the feet or hands. The sense of cold may be lost before pinprick sensibility. Such dissociation of sensibility is especially suspicious. The distribution of these neural signs and their intensity will depend on the type of disease that is evolving.

Often the first lesion noted is a solitary, ill-defined, hypopigmented macule that merges into the surrounding normal skin. Less often, erythematous macules may be present. Such lesions are most likely to occur on the cheeks, upper arms, thighs, and buttocks. Examination reveals that sensory functions are either normal or minimally altered. Peripheral nerves are not enlarged, and plaques and nodules do not occur. Histologically, a variable lymphocytic infiltrate (without granulomas) is seen, sometimes with involvement

Table 17-1 Spectrum of host–parasite resistance

	High resistance		*Unstable resistance*		*No resistance*
	Tuberculoid (TT)	Borderline tuberculoid (BT)	Borderline (BB)	Borderline lepromatous (BL)	Lepromatous (LL)
Lesions	1–3	Few	Few or many asymmetrical	Many	Numerous and symmetrical
Smear for bacilli	0	1+	2+	3+	4+
Lepromin test	3+	2+	+	+	0
Histology	Epithelioid cells decreasing → Nerve destruction, sarcoid-like granuloma			Increasing histiocytes, foam cells, granuloma, xanthoma-like	

Adapted from Dr JH Petit.

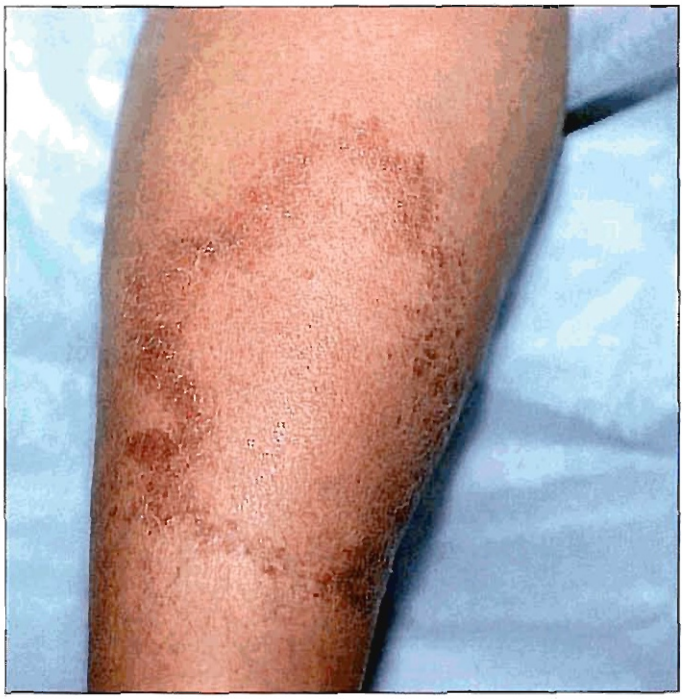

Fig. 17-1 Tuberculoid leprosy.

of the cutaneous nerves. Usually no bacilli, or only a few, are seen on biopsy of this indeterminate form. It is the classification, not the diagnosis, that is indeterminate. Few cases remain in this state; they evolve into lepromatous, tuberculoid, or borderline types, or (if cell-mediated immunity is good) often spontaneously resolve and never develop other signs or symptoms of leprosy.

Tuberculoid Leprosy

Tuberculoid lesions are solitary or few in number (usually five or less) and asymmetrically distributed. Lesions may be hypopigmented or erythematous, and are usually dry, scaly, and hairless (Fig. 17-1). The typical lesion of tuberculoid leprosy is the large, erythematous plaque with a sharply defined and elevated border that slopes down to a flattened atrophic center. This has been described as having the appearance of "a saucer right side up." Lesions may also be macular and hypopigmented or erythematous, resembling clinically indeterminate lesions. The presence of palpable induration and neurologic findings distinguishes indeterminate lesions from tuberculoid lesions clinically. The most common locations are the face, limbs, or trunk; the scalp, axillae, groin, and perineum are not involved. As the lesions clear, they tend to become annular, arciform, or circinate, with borders of variable thickness.

A tuberculoid lesion is anesthetic or hypesthetic and anhidrotic, and superficial peripheral nerves serving or proximal to the lesion are enlarged, tender, or both. The greater auricular nerve and the superficial peroneal nerve may be visibly enlarged. Nerve involvement is early and prominent in tuberculoid leprosy, leading to characteristic changes in the muscle groups served. There may be atrophy of the interosseous muscles of the hand, with wasting of the thenar and hypothenar eminences, contracture of the fingers, paralysis of the facial muscles, and foot drop.

The evolution of the lesions is generally slow. There is often spontaneous remission of the lesions in about 3 years,

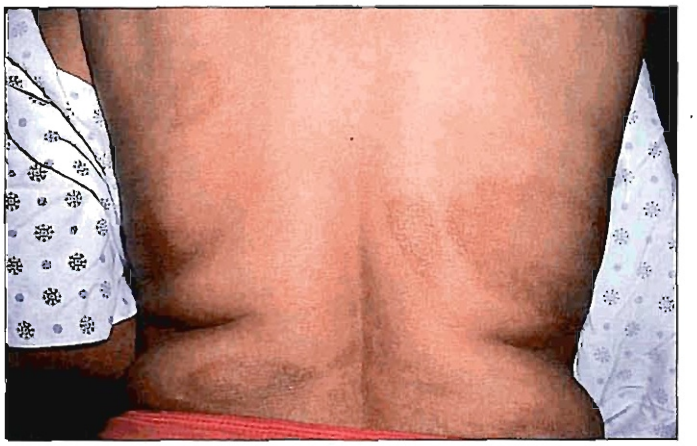

Fig. 17-2 Borderline tuberculoid leprosy.

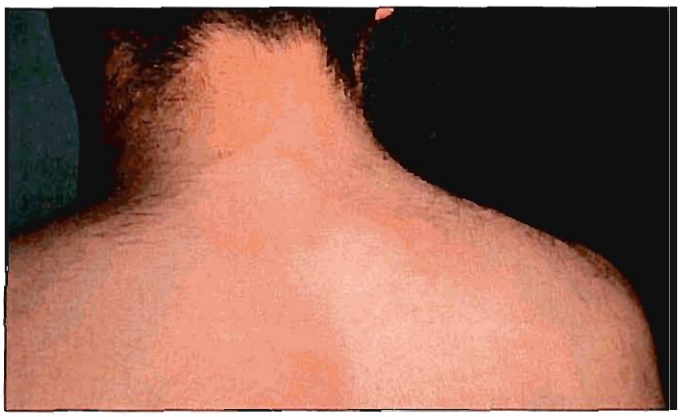

Fig. 17-3 Borderline leprosy.

or remission may result sooner with treatment. Spontaneous involution may leave pigmentary disturbances.

Borderline Tuberculoid Leprosy

Borderline tuberculoid lesions are similar to tuberculoid lesions, except that they are smaller and more numerous (Fig. 17-2). Satellite lesions around large macules or plaques are characteristic.

Borderline Leprosy

In borderline leprosy, the skin lesions are numerous (but countable) and consist of red, irregularly shaped plaques (Fig. 17-3). Small satellite lesions may surround larger plaques. Lesions are generalized but asymmetrical. The edges of lesions are not so well defined as the ones seen in the tuberculoid pole. Nerves may be thickened and tender, but anesthesia is only moderate in the lesions.

Borderline Lepromatous Leprosy

In borderline lepromatous leprosy, the lesions are symmetrical, numerous (too many to count), and may include macules, papules, plaques, and nodules (Fig. 17-4). The number of small lepromatous lesions outnumbers the larger borderline-type lesions. Nerve involvement appears later; nerves are enlarged, tender, or both; it is important to note that involvement is symmetrical. Sensation and sweating over individual lesions is normal. Patients usually do not show the features of full-blown lepromatous leprosy, such as madarosis, keratitis, nasal ulceration, and leonine facies.

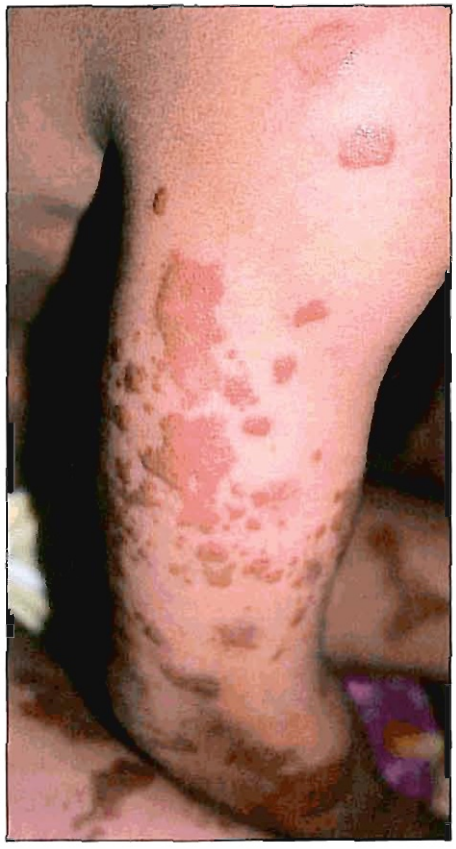

Fig. 17-4
Lepromatous leprosy, hyperpigmentation due to clofazamine.

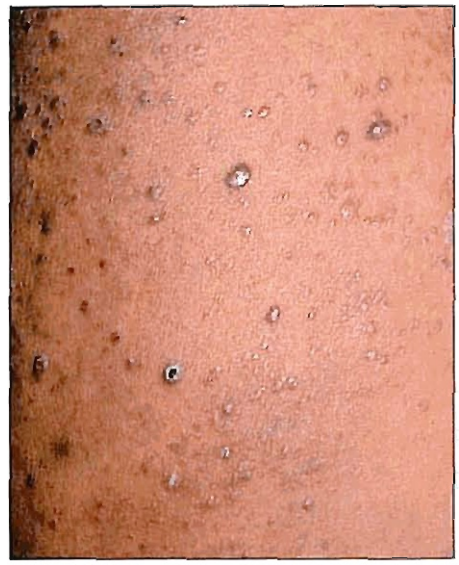

Fig. 17-5
Lepromatous leprosy, multiple papules and nodules.

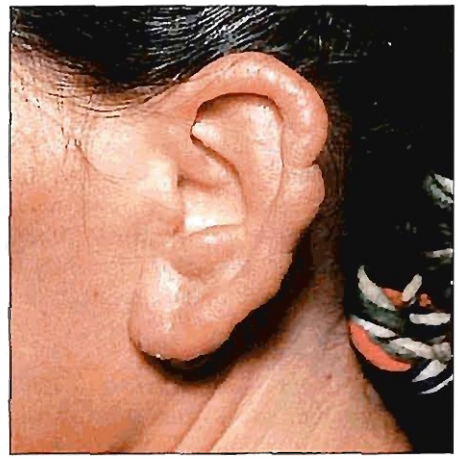

Fig. 17-6
Lepromatous leprosy, enlargement of the earlobe.

Lepromatous Leprosy

Lepromatous leprosy may begin as such or develop following indeterminate leprosy or from downgrading of borderline leprosy. The cutaneous lesions of lepromatous leprosy consist mainly of pale lepromatous macules or lepromatous infiltrations, with numerous bacilli in the lesions. There is a tendency for the disease to become progressively worse without treatment. Lepromatous leprosy may be divided into a polar form (LL_p) and a subpolar form (LL_s): these forms may behave differently.

Macular lepromatous leprosy lesions are diffusely and symmetrically distributed over the body. Tuberculoid macules are large and few in number, whereas lepromatous macules are small and numerous. Lepromatous macules are ill defined, show no change in skin texture, and blend imperceptibly into the surrounding skin. There is little or no loss of sensation over the lesions, there is no nerve thickening, and there are no changes in sweating. A slow, progressive loss of hair takes place from the outer third of the eyebrows, then the eyelashes, and finally, the body; however, the scalp hair usually remains unchanged.

Lepromatous infiltrations may be divided into the diffuse, plaque, and nodular types (Figs 17-5 and 17-6). The diffuse type is characterized by the development of a diffuse infiltration of the face, especially the forehead, loss of the eyebrows (madarosis), and a waxy and shiny appearance of the skin, sometimes described as a "varnished" appearance. Diffuse leprosy of Lucio is a striking form, uncommon except in western Mexico and certain other Latin American areas, where nearly one-third of lepromatous cases may be of this type. This form of lepromatous leprosy is characterized by diffuse lepromatous infiltration of the skin: localized lepromas do not form. A unique complication of this subtype is the reactional state referred to as *Lucio's phenomenon* (erythema necroticans).

The infiltrations may be manifested by the development of nodules called *lepromas*. The early nodules are ill defined and occur most often in acral parts: ears, brows, nose, chin, elbows, hands, buttocks, or knees. Nerve involvement invariably occurs, but develops very slowly. Like the skin lesions, nerve disease is bilaterally symmetrical, usually in a stocking-glove pattern. This is frequently misdiagnosed as diabetic neuropathy in the US if it is the presenting manifestation.

Histoid Leprosy

Histoid leprosy is an uncommon form of multibacillary leprosy in which skin lesions appear as yellow–red, shiny, large papules and nodules in the dermis or subcutaneous tissue (Fig. 17-7). Lesions appear on a background of normal skin. They vary in size from 1 to 15 mm in diameter and may appear anywhere on the body but favor the buttocks, lower back, face, and bony prominences. This pattern may appear de novo, but was mostly described in patients with resistance to long-acting dapsone resistance.

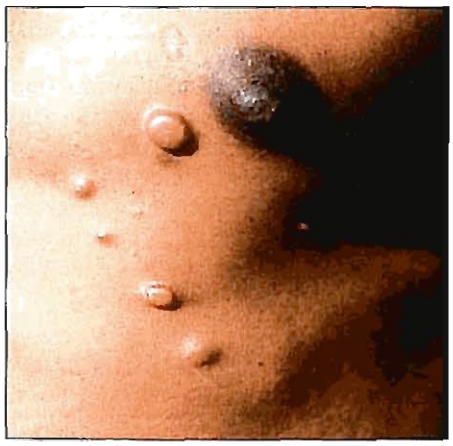

Fig. 17-7 Histoid leprosy.

NERVE INVOLVEMENT

Nerve involvement is characteristic and unique to leprosy. This neural predilection or neurotropism is a histopathologic hallmark of leprosy. Nerve involvement is responsible for the clinical findings of anesthesia within lesions (paucibacillary and borderline leprosy), and of a progressive "stocking-glove" peripheral neuropathy (lepromatous leprosy). The neuropathy is termed "primary impairments" (WHO grade 1). Secondary (or visible) impairments (WHO grade 2) are a consequence of the neuropathy and include skin fissures, wounds, clawing of digits, contractures, shortening of digits, and blindness. Neural damage leads to deformities and results in leprosy being a major cause in leprosy-endemic regions of "limitations of activity" (formerly called disability) and "restrictions in social participation" (formerly termed handicap). Neuropathy is present in 1.3% to 3.5% of paucibacillary cases and 7.5% to 24% of multibacillary cases undergoing multidrug therapy. Secondary impairments occur in 33% to 56% of multibacillary cases. Neuropathy may progress, even after effective multidrug therapy, and secondary impairments may continue to appear for years as a consequence of the neuropathy.

Nerve enlargement is rare in other skin diseases, so the finding of skin lesions with enlarged nerves should raise the possibility of leprosy. Nerve involvement tends to occur with skin lesions, and the pattern of nerve involvement parallels the skin disease. Tuberculoid leprosy is characterized by asymmetrical nerve involvement localized to the skin lesions. Lepromatous nerve involvement is symmetrical and not associated with skin lesions. Nerve involvement without skin lesions, called *pure neural leprosy*, can occur and may be either tuberculoid (paucibacillary) or lepromatous (multibacillary). Nerve disease can be symptomatic or asymptomatic.

Leprosy bacilli may be delivered to the nerves via the perineural and endoneural blood vessels. Once the bacilli transgress the endothelial basal lamina and are in the endoneurium, they either enter resident macrophages or selectively enter Schwann cells. Damage to the nerves could then occur by several mechanism: 1) obstruction of neural vessels: 2) vasculitis of neural vessels; 3) interference with the metabolism of the Schwann cell making it unable to support the neuron; 4) immunologic attack of endothelium or nerves; or 5) infiltration and proliferation of *M. leprae* in the closed and relatively nonexpandable endoneural and perineural spaces. Different and multiple mechanisms may occur in different forms of leprosy and in the same patient over time. The selective ability of *M. leprae* to enter Schwann cells is unique among bacteria. The *M. leprae*-unique PGL-1 phenolic glycolipid, expressed abundantly on the surface of leprosy bacilli, binds selectively to the α2 G module of laminin 2. This α2 chain is tissue restricted and specifically expressed on Schwann cells. The binding of *M. leprae* to laminin 2 places it in apposition to the Schwann cell basement membrane when laminin 2 binds to the dystroglycan complex on the Schwann cell membrane. These bound *M. leprae* are endocytosed into the Schwann cells, giving *M. leprae* selective access to the inside of Schwann cells. Other accessory binding molecules may facilitate the binding and endocytosis. The nerves become immunologic targets when they present *M. leprae* antigens on their surface in the context of major histocompatibility (MHC) class II molecules. Schwann cells and hence nerves are usually protected from immunologic attack mediated by the adaptive immune system since they rarely present MHC class II antigens on their surface. In leprosy, expression of these immunologic molecules occurs on the surface of Schwann cells, making them potential targets for CD4+ cytotoxic T-cells. This mechanism may be important in the nerve damage that occurs in type I (reversal) reactions.

The neural signs in leprosy are dysesthesia, nerve enlargement, muscular weakness and wasting, and trophic changes. The lesions of the vasomotor nerves accompany the sensory disturbances or may precede them. Dysesthesia develops in a progressive manner. The first symptom is usually an inability to distinguish hot and cold. Subsequently, the perception of light touch is lost, then that of pain, and lastly the sense of deep touch. At times the sensory changes in large leprosy lesions are not uniform because of the variation in the involvement of the individual neural filaments supplying the area. Therefore, the areas of dysesthesia may not conform to the distribution of any particular nerve, nor (except in lepromatous cases) are they symmetrical.

Nerve involvement affects chiefly (and is most easily observed in) the more superficial nerve trunks, such as the ulnar, median, radial, peroneal, posterior tibial, fifth and seventh cranial nerves, and especially the great auricular nerve. Beaded enlargements, nodules, or spindle-shaped swellings may be found, which at first may be tender. Neural abscesses may form. The ulnar nerve near the internal condyle of the humerus may be as thick as the little finger, round and stiff, and often easily felt several centimeters above the elbow.

As a result of the nerve damage, areas of anesthesia, paralysis, and trophic disorders in the peripheral parts of the extremities gradually develop. Muscular paralysis and atrophy generally affect the small muscles of the hands and feet or some of the facial muscles, producing weakness and progressive atrophy. Deeper motor nerves are only rarely involved. The fingers develop contractures, with the formation of a claw hand, and, as the result of resorption of phalangeal bones, fingers and toes become shorter. Ptosis, ectropion, and a masklike appearance occur from damage to the fifth and seventh cranial nerves.

Subsequent to nerve damage ulceration, hyperkeratosis, bullae, alopecia, anhidrosis, and malum perforans pedis can develop. Trophic ulceration usually manifests as a perforating ulcer on the ball or heel of the foot.

OCULAR INVOLVEMENT

Corneal erosions, exposure keratitis, and ulcerations may occur as a result of involvement of the seventh nerve. Specific changes may include corneal opacity, avascular keratitis, pannus formation, interstitial keratitis, and corneal lepromas. The corneal opacities enlarge and finally form visible white flecks called pearls. When (in borderline lepromatous or lepromatous cases only) the iris and the ciliary body become involved, miliary lepromata (iris pearls), nodular lepromata, chronic granulomatous iritis, and acute diffuse iridocyclitis may result. Of multibacillary patients, 2.8% to 4.6% are blind at diagnosis and 11% will have a potentially blinding process.

MUCOUS MEMBRANE INVOLVEMENT

The mucous membranes may also be affected, especially in the nose, mouth, and larynx. The nasal mucosa is most commonly involved, and lepromatous patients, if queried, frequently complain of chronic nasal congestion. By far the most common lesions in the nose are infiltrations and nodules. Perforation of the nasal septum may occur in advanced cases, with collapse of the nasal bridge (Fig. 17-8). Saddle-nose deformities and loss of the upper incisor teeth can occur.

Nodules occurring on the vocal cords will produce hoarseness.

VISCERAL INVOLVEMENT

In lepromatous leprosy, the body is diffusely involved and bacteremia occurs. Except for the gastrointestinal tract, lungs, and brain, virtually every organ can contain leprosy bacilli. The lymph nodes, bone marrow, liver, spleen, and testicles are most heavily infected. Visceral infection is restricted mostly to the reticuloendothelial system, which despite extensive involvement rarely produces symptoms or findings. Testicular atrophy with resultant gynecomastia or premature osteoporosis is an exception. Secondary amyloidosis with renal impairment may complicate multibacillary leprosy. Glomerulonephritis occurs in more than 5% and perhaps as many as 50% of leprosy patients and is not correlated with bacillary load or the presence of erythema nodosum leprosum.

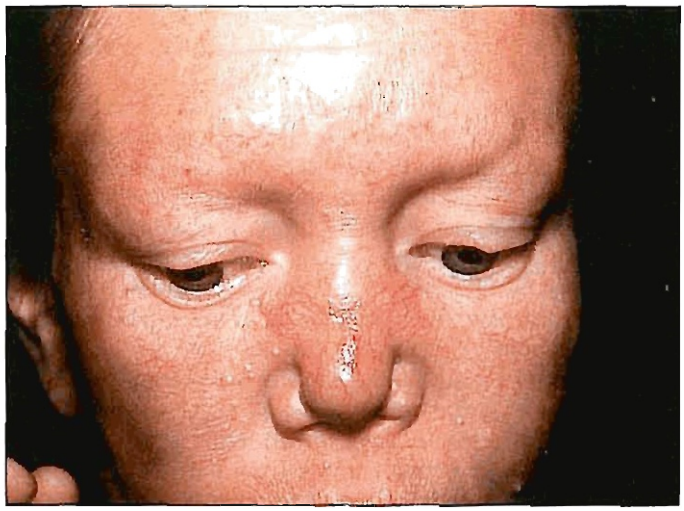

Fig. 17-8 Lepromatous leprosy with collapse of nasal bridge.

PREGNANCY AND HANSEN'S DISEASE

Hansen's disease may be complicated in several ways by pregnancy. As a state of relative immunosuppression, pregnancy may lead to an exacerbation or reactivation after apparent cure. In addition, pregnancy may induce reactional states in patients with Hansen's disease. Pregnant patients with Hansen's disease cannot be given certain medications used to treat Hansen's disease, such as thalidomide, ofloxacin, and minocycline. Multidrug therapy is tolerated by pregnant women if these restricted agents are avoided.

HUMAN IMMUNODEFICIENCY VIRUS AND HANSEN'S DISEASE

HIV infection, while a cause of profound immunosuppression of the cell-mediated immune system, does not seem to adversely affect the course of Hansen's disease. Patients are treated with the same agents and can be expected to have similar outcomes in general. Duration of treatment with multidrug therapy may need to be extended in patients with HIV infection. Treatment of HIV-infected patients with Hansen's disease with effective antiretroviral treatment may be associated with the appearance of reactional states as part of the immune reconstitution syndrome.

PATHOGENESIS

The patient's immune reaction to the leprosy bacillus is a critical element in determining the outcome of infection. Tuberculoid patients make well-formed granulomas that contain helper T-cells, where as lepromatous patients have poorly formed granulomas and suppressor T-cells predominate. The cytokine profile in tuberculoid lesions is that of good cell-mediated immunity with interferon (IFN)-γ and interleukin (IL)-2 being present. In lepromatous patients, these cytokines are reduced and IL-4, -5, and -10, cytokines that downregulate cell-mediated immunity and enhance suppressor function and antibody production, are prominent. Lepromatous leprosy thus represents a classic helper T-cell type 2 (Th-2) response to *M. leprae*. Lepromatous lesions contain high levels of cyclooxygenase type 2 and prostaglandin E. Lepromatous patients have polyclonal hypergammaglobulinemia, and may have false-positive syphilis serology, rheumatoid factor, and antinuclear antibodies as a result.

Although the cell-mediated immune response of lepromatous patients to *M. leprae* is reduced, these patients are not immune suppressed for other infectious agents. Tuberculosis behaves normally in patients with lepromatous leprosy.

HISTOPATHOLOGY

Ideally, biopsies should be performed from the active border of typical lesions and should extend into the subcutaneous tissue. Punch biopsies are usually adequate. Fite-Faraco stain is optimal for demonstrating *M. leprae*. Because the diagnosis of leprosy is associated with significant social implications, evaluation must be complete, to include evaluation of multiple sections in paucibacillary cases, and consultation with a pathologist experienced in the diagnosis of leprosy can be helpful if the diagnosis is suspected, but organisms cannot be identified in the affected tissue, especially in paucibacillary disease and reactional states. PCR testing can be of value if

the tissue is preserved in alcohol rather than formalin, or if it processed within hours of fixation in formalin.

The histologic features of Hansen's disease correlate with the clinical pattern of disease. Nerve involvement is characteristic of leprosy, and histologic perineural and neural involvement should raise the possibility of leprosy.

Tuberculoid Leprosy

Dermal tuberculoid granulomas, consisting of groups of epithelioid cells with giant cells, are found in tuberculoid leprosy. The granulomas are elongated and generally run parallel to the surface, following neurovascular bundles. The epithelioid cells are not vacuolated or lipidized. The granulomas extend up to the epidermis, with no grenz zone. Lymphocytes are found at the periphery of the granulomas. Acid-fast bacilli are rare. The most important specific diagnostic feature, next to finding bacilli, is selective destruction of nerve trunks and the finding of perineural concentric fibrosis. An S-100 stain may demonstrate this selective neural destruction by demonstrating unrecognizable nerve remnants in the inflammatory foci. Bacilli are most frequently found in nerves, but the subepidermal zone and arrector pili muscles are other fruitful areas.

Borderline Tuberculoid Leprosy

The histopathology of the borderline tuberculoid type is similar to that seen in the tuberculoid variety, but epithelioid cells may show some vacuolation, bacilli are more abundant, and a grenz zone separates the inflammatory infiltrate from the overlying epidermis.

Borderline Leprosy

In borderline leprosy granulomas are less well organized, giant cells are not seen, the macrophages have some foamy cytoplasm, and organisms are abundant.

Borderline Lepromatous Leprosy

In borderline lepromatous lesions, foamy histiocytes, rather than epithelioid cells, make up the majority of the granuloma. Lymphocytes are still present and may be numerous in the granulomas, but are dispersed diffusely within them, not organized at the periphery. Perineural involvement with lymphocyte infiltration may be present. Organisms are abundant and may be found in clumps.

Lepromatous Leprosy

In lepromatous leprosy, granulomas are composed primarily of bacilli- and lipid-laden histocytes. These are the so-called lepra cells or foam cells of Virchow. The infiltrate is localized in the dermis and may be purely perivascular or sheetlike and separated from the epidermis by a well-defined grenz zone. Acid-fast bacilli are typically abundant and appear as round clumps (globi). Pure polar lepromatous leprosy differs from the subpolar type primarily by the paucity of lymphocytes in the pure polar form.

REACTIONAL STATES

Reactions are a characteristic and clinically important aspect of Hansen's disease. Fifty percent of patients will experience a reaction after the institution of multidrug therapy. In addition to antibiotic therapy, intercurrent infections, vaccination, pregnancy, vitamin A, iodides, and bromide may trigger reactions. Reactions can be severe and are an important cause of permanent nerve damage in borderline patients. Reactional states are frequently abrupt in their appearance, as opposed to Hansen's disease itself, which changes slowly. It is therefore a common reason for patients to seek consultation. In addition, if the patient feels that the chemotherapy is triggering the reaction, he/she will tend to discontinue the treatment, leading to treatment failure.

Reactional states are divided into two forms, called type 1 and type 2 reactions. Type 1 reactions are caused by cell-mediated immune inflammation within existing skin lesions. They generally occur in patients with borderline leprosy (BT, BB, BL). Type 2 reactions are mediated by immune complexes and occur in lepromatous patients (BL, LL).

Type 1 Reactions (Reversal, Lepra, and Downgrading Reactions)

Type 1 reactions represent an enhanced cell-mediated immune response to *M. leprae*, and commonly occur after treatment is initiated. If the reactions occur with antibiotic chemotherapy, they are called *reversal reactions*, and if they occur as borderline disease shifts toward the lepromatous pole (downgrading), they are called *downgrading reactions*. These two reaction types are clinically identical. Patients in all parts of the borderline spectrum may be affected by type 1 reactions, but these are most severe in patients with borderline lepromatous leprosy who have a large amount of *M. leprae* antigen and therefore have prolonged and repeated reactions during treatment.

Type 1 reactions clinically present with inflammation of existing lesions. There are no systemic symptoms (such as fever, chills, and arthralgias). Lesions swell, become erythematous, and are sometimes tender, simulating cellulitis. In severe cases, ulceration can occur (Fig. 17-9). Patients may state that new lesions appeared with the reaction, but these probably represent subclinical lesions that were highlighted by the reaction. The major complication of type 1 reactions is nerve damage. As the cell-mediated inflammation attacks *M. leprae* antigen, any infected tissue compartment can be damaged. Because bacilli are preferentially in nerves, neural symptoms and findings are often present. Reversal reaction

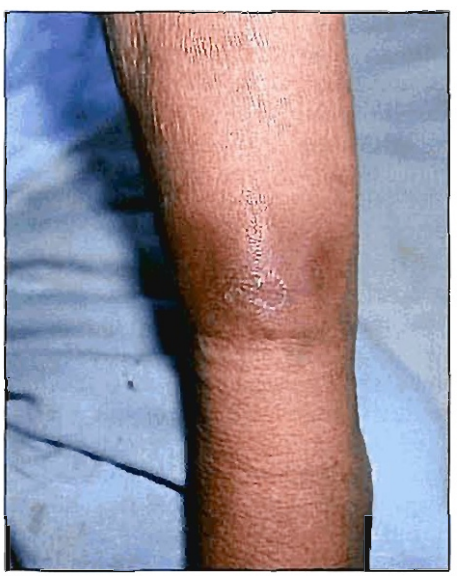

Fig. 17-9 Type I reaction.

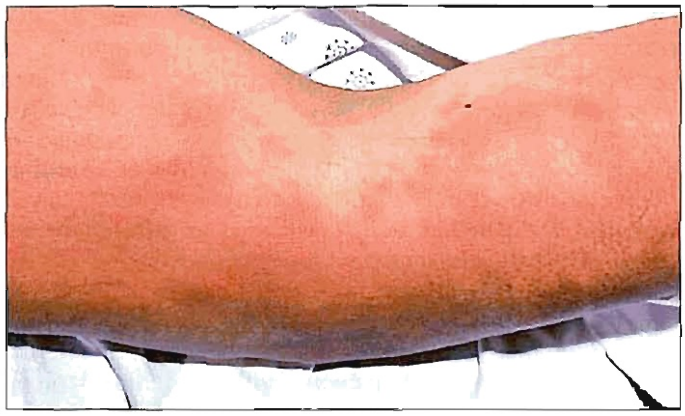

Fig. 17-10 Erythema nodosum leprosum.

occurring within a nerve may lead to sudden loss of nerve function and to permanent damage to that nerve. This makes type 1 reactions an emergency. In this setting, affected nerves are enlarged and tender. In other patients the neuritis may be subacute or chronic and of limited acute symptomatology, but may still result in severe nerve damage. Histologically, skin lesions show perivascular and perineural edema and large numbers of lymphocytes. Severe reactions may demonstrate tissue necrosis. Bacilli are reduced.

Type 2 Reactions (Erythema Nodosum Leprosum)

Erythema nodosum leprosum (ENL) occurs in half of patients with borderline lepromatous or lepromatous leprosy, 90% of the time, within a few years of institution of antibiotic treatment for Hansen's disease or during pregnancy. ENL is an circulating immune complex-mediated disease, with most of the complexes forming in sites of heavy bacterial burden. As such, in contrast to type 1 reactions, it can result in multisystem involvement and is usually accompanied by systemic symptoms (fever, myalgias, arthralgias, anorexia). Skin lesions are characteristically erythematous subcutaneous and dermal nodules that are widely distributed (Fig. 17-10). They do not occur at the sites of existing skin lesions. Severe skin lesions can ulcerate. Unlike classic erythema nodosum, lesions are generalized and favor the extensor arms and medial thighs.

ENL is a multisystem disease and can produce conjunctivitis, neuritis, keratitis, iritis, synovitis, nephritis, hepatosplenomegaly, orchitis, and lymphadenopathy. The intensity of the reaction may vary from mild to severe and it may last from a few days to weeks, months, or even years. Histologically, ENL demonstrates a leukocytoclastic vasculitis.

Lucio's Phenomenon

Lucio's phenomenon is an uncommon and unusual reaction that occurs in patients with diffuse lepromatous leprosy of the "la bonita" type, most commonly found in western Mexico. Some consider it a subset of ENL, but it differs in that it lacks neutrophilia and systemic symptoms. It is not associated with institution of antibiotic treatment as is ENL, but it is commonly the reason for initial presentation in affected patients. Purpuric macules evolve to bullous lesions that rapidly ulcerate, especially below the knees (Fig. 17-11). They may be painful, but may also be relatively asymptomatic. Histologically, bacilli are numerous, and in addition to being in the dermis, are seen within blood vessel walls with thrombosis of mid-dermal vessels resulting in cutaneous infarction. Fever, splenoegaly, lymphadenopathy, gloverulnephritis, anemia, hypoalbuminemia, polyclonal gammopathy, and hypocalcemia can be associated. If the patient is diagnosed early, before significant metabolic and infectious complications occur, the outcome is favorable. In advanced cases, even with aggressive treatment, death may occur.

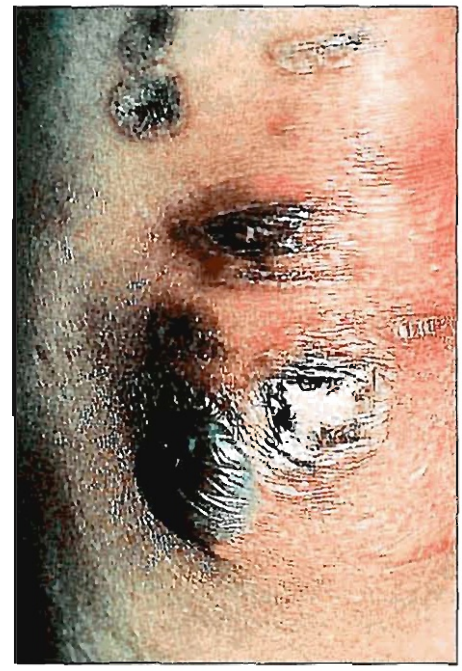

Fig. 17-11 Lucio's phenomenon, early bullous lesions.

TREATMENT

Before 1982, dapsone monotherapy was the standard treatment for Hansen's disease, and while it was effective in many patients, primary and secondary dapsone-resistant cases occurred. In addition, multibacillary patients required lifelong treatment, which had inherent compliance problems. To circumvent these problems and shorten therapeutic courses, WHO proposed multidrug therapy. This has been very effective in treating active cases of Hansen's disease. Relapse rates range from 0.01% to 2% annually (averaging 0.1% per annum overall). A common cause of failure is initial misdiagnosis, i.e. diagnosing multibacillary patients as having paucibacillary disease. This occurs for three reasons: 1) failure or inability to do a skin biopsy; 2) classifying patients with more than five lesions as "tuberculoid" and hence "paucibacillary;" and 3) failure to understand that although the patient has histologic and clinical features of "tuberculoid" disease, organisms are identified on skin biopsy. All patients with more than five lesions and those with organisms identified on skin biopsy should be treated for multibacillary leprosy. Failure may also result from noncompliance, drug resistance, relapse after apparent clinical and bacteriologic cure, and persistence. *Persisters* are viable organisms that by mouse footpad testing are sensitive to the antimicrobial agents given but persist in tissue despite bactericidal tissue levels in the patient. They are usually found in macrophages or nerves. These persisters correlate with relapse occurring 6 to 9 years following multidrug therapy. Since relapses may occur many years after multidrug therapy, where adequate

healthcare resources exist, multibacillary patients should be followed annually to examine for evidence of relapse, reaction, or progression of neuropathy.

There are several different multidrug therapy recommendations, but only two are given here—those recommended by the Gillis W Long Hansen's Disease Center for patients in the US and those recommended by WHO. Because dapsone resistance is less common in the US, and effective compliance programs can be developed to enhance monotherapy, dapsone monotherapy may still be considered after multidrug therapy in the US. For paucibacillary cases (no organisms found on skin smears or skin biopsy; five lesions or less; indeterminate and tuberculoid leprosy) in the US, the recommendation is 600 mg/day of rifampin and 100 mg/day of dapsone for 12 months. Paucibacillary patients who relapse with paucibacillary disease are treated with an appropriate regimen for multibacillary disease. In the US, multibacillary cases receive 100 mg/day of dapsone, 50 mg/day of clofazamine, and 600 mg/day of rifampin, or a standard WHO regimen (see below) for 2 years. For multibacillary patients who refuse clofazimine, 100 mg of minocycline or 400 mg/day of ofloxacin may be substituted. Clarithromycin 500 mg/day may also be used in treatment regimens but is not currently a recommended agent. Multibacillary relapses, whether the initial diagnosis was paucibacillary or multibacillary disease, should have a mouse footpad sensitivity study carried out, treated with an appropriate multidrug regimen for 2 years, followed by daily life-long dapsone or clofazamine, depending on sensitivity testing.

The WHO-recommended protocols are shorter and cheaper than those recommended in the US. There is concern that the reduction of multidrug therapy from 2 years to 1 year may lead to increased numbers of relapses, especially among patients with high bacillary loads (bacillary index >4 on skin smear). This group of multibacillary patients already have a 4% to 7% annual relapse rate an average of 5 years after multidrug therapy. There is insufficient long-term data at this time to evaluate the efficacy of the shorter treatment regimens (12 months or less) for multibacillary leprosy. The recommendation for paucibacillary disease (no bacilli on smears or biopsy; five or less lesions; indeterminate and tuberculoid patients) is 600 mg of rifampin under supervision once a month for 6 months and 100 mg/day of dapsone for 6 months, unsupervised. For single-lesion paucibacillary disease a single dose of 600 mg of rifampin, 400 mg of ofloxacin, and 100 mg of minocycline (ROM), all at one time, is recommended (this regimen demonstrates a 47% cure rate at 18 months). Multibacillary patients (BT, BB, BL, and LL; more than five lesions; any bacilli seen on smears or biopsies) are treated with four drugs. Rifampin 600 mg and clofazimine 300 mg, once a month under supervision, are taken with dapsone 100 mg/day and clofazimine 50 mg/day. Treatment is for 12 months. For patients intolerant of clofazamine, the regimen is: rifampin 600 mg, ofloxacin 400 mg, and minocycline 100 mg all once monthly for 24 doses. Clofazamine 50 mg, ofloxacin 400 mg, and minocycline 100 mg daily for 6 months followed by 18 months of clofazamine plus daily oflxacin or minocycline for 18 months is an alternative.

At the end of treatment, visible skin lesions may still be present, especially with the WHO short-duration treatments. Paucibacillary lesions tend to clear 1 to 2 years after the 6-month treatment course. In the US, treatment could be continued until skin lesions are clear, even if the recommended duration of treatment has been passed. With short-duration multidrug therapy, it is very difficult to distinguish clinical relapse (failure of treatment) from late type 1 reactions causing skin lesions to reappear. Pathologic examination (biopsy) or an empiric trial of prednisone for several months may be considered in these cases.

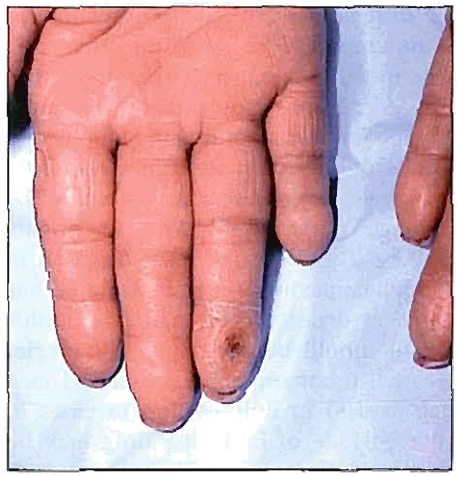

Fig. 17-12 Acral burns due to peripheral sensory neuropathy, lepromatous leprosy.

Adjunctive Treatments

Once neurologic complications have occurred, patients with Hansen's disease should be offered occupational therapy. This should include training on how to avoid injury to insensitive skin of the hands and feet (Fig. 17-12). Special shoes may be required. Ocular complications are frequent, and an ophthalmologist with specific skill in treating patients with leprosy is an invaluable member of the treatment team.

MANAGEMENT OF REACTIONS

Even though reactions may appear after drug treatment is instituted, it is not advisable to discontinue or reduce antileprosy medication because of these. In mild reactions—those without neurologic complications or severe systemic symptoms or findings—treatment may be supportive. Bed rest and administration of aspirin or nonsteroidal anti-inflammatory agents may be used.

Type 1 reactions are usually managed with systemic corticosteroids. Prednisone is given orally, starting at a dose of 40 to 60 mg/day. Neuritis and eye lesions are urgent indications for systemic steroid therapy. Nerve abscesses may also need to be surgically drained immediately to preserve and recover nerve function. The corticosteroid dose and duration are determined by the clinical course of the reaction. Once the reaction is controlled, the prednisone may need to be tapered slowly—over months to years. The minimum dose required and alternate-day treatment should be used in corticosteroid treatment courses of more than 1 month in duration. Clofazimine appears to have some activity against type 1 reactions and may be added to the treatment in doses of up to 300 mg/day if tolerated. Cyclosporin can be used if steroids fail or as a steroid-sparing agent. The starting dose would be 5 to 10 mg/kg. If during treatment the function of some nerves fails to improve while the function of others normalizes, the possibility of mechanical compression

should be evaluated by surgical exploration. Transposition of the ulnar nerve does not seem to be more effective than immunosuppressive treatment for ulnar nerve dysfunction.

Thalidomide has been demonstrated to be uniquely effective against erythema nodosum leprosum and is the treatment of choice. Thalidomide is a potent teratogen and should *not* be given to women of childbearing potential. The initial recommended dosage is up to 400 mg/day in patients weighing more than 50 kg. This dose is highly sedating in some patients, and patients may complain of central nervous system side effects, even at doses of 100 mg/day. For this reason, such a high dose should be used for only a brief period, or in milder cases, treatment may be started at a much lower dose, such as 100 to 200 mg/day. In cases in which there is an acute episode of ENL, the drug may be discontinued after a few weeks to months. In chronic type 2 reactions, an attempt to discontinue the drug should be made every 6 months. Systemic corticosteroids are also effective in type 2 reactions, but long-term use may lead to complications. Clofazimine in higher doses (up to 300 mg/day) is effective in ENL, and may be used alone or to reduce corticosteroid or thalidomide doses. The combination of pentoxifylline 400 to 800 mg twice a day and clofazamine 300 mg/day can be used in ENL when thalidomide can not be used or to avoid the use of systemic steroids to manage severe ENL. Pentoxyfylline alone is inferior to steroids and thalidomide.

Lucio's phenomenon is poorly responsive to both corticosteroids and thalidomide. Effective antimicrobial chemotherapy for lepromatous leprosy is the only recommended treatment, combined with wound management for leg ulcers.

PREVENTION

Because a defect in cell-mediated immunity is inherent in the development of leprosy, vaccine therapies are being tested. Bacillus Calmette-Guérin (BCG) vaccination alone provides about 34% protection against infection, and combining this with heat-killed *M. leprae* increases the protection to 64%. ICRC vaccination was 65% effective. If the prevalence of leprosy continues to fall, vaccination would be limited to those areas (such as South India) where multidrug therapy might prove to be ineffective in reducing prevalence of infection. Since 80% of patients have close contact with multibacillary patients, prevention depends on treating active multibacillary patients and examining exposed persons on an annual basis to detect early evidence of infection. Several trials of chemoprophylaxis (once yearly multidrug therapy with single-dose rifampin, minocycline, and clofazamine) have shown early promise and may be useful in hyperendemic regions.

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CHAPTER

18 Syphilis, Yaws, Bejel, and Pinta

SYPHILIS

Syphilis, also known as *lues*, is a contagious, sexually-transmitted disease caused by the spirochete *Treponema pallidum* subspecies *pallidum*. The spirochete enters through the skin or mucous membranes, on which the primary manifestations are seen. In congenital syphilis the treponeme crosses the placenta and infects the fetus. Syphilis results in multiple patterns of skin and visceral disease and is potentially lifelong.

T. pallidum is a delicate spiral spirochete that is actively motile. The number of spirals varies from 4 to 14 and the entire length is 5 to 20 μm. It can be demonstrated in preparations from fresh primary or secondary lesions by darkfield microscopy or by fluorescent antibody techniques. The motility is characteristic, consisting of three movements: a projection in the direction of the long axis, a rotation on its long axis, and a bending or twisting from side to side. The precise uniformity of the spiral coils is not distorted during these movements. Microscopic characteristics of *T. pallidum* cannot be distinguished from commensal oral treponemes, so darkfield examination of oral lesions is untrustworthy. Direct fluorescent antibody testing can be used for confirmation. The electron microscope shows the organism to have an axial filament with several fibrils, a protoplasmic cylinder, and a thin membranaceous envelope called the *periplast*. The organism is pathogenic for the anthropoid apes and produces a primary sore and secondary skin eruption closely simulating the disease in humans. It is also pathogenic for rabbits.

Syphilis remains a major health problem throughout the world. Using serologic testing, contact tracing, and penicillin treatment, the health departments in the US reduced the incidence of syphilis dramatically from the turn of the century through the mid-1950s. Then the incidence gradually increased through the next two decades and into the 1980s. In the early 1980s, half the cases of syphilis diagnosed were in homosexual men. Changes in sexual behavioral patterns among gay men in response to the acquired immunodeficiency syndrome (AIDS) epidemic reduced the number of these cases, but in the late 1980s syphilis again began to increase dramatically, associated with drug usage, especially crack cocaine. The incidence of syphilis increased disproportionately among socioeconomically disadvantaged minority populations, especially in major cities. Throughout the 1990s the rate of syphilis fell in the US, so that by 1999 the national rate of 2.6 cases in 100,000 was the lowest level ever recorded. In addition, half of new cases were concentrated in 28 counties, mainly in the southeastern US and in selected urban areas. Despite the optimism of the late 1990s that syphilis might be eradicated in the US, epidemics continue to occur. Vancouver experienced an outbreak beginning in 1997, primarily in heterosexuals, linked to professional sex workers. A worrisome trend is increasing numbers of cases of syphilis in San Francisco in men who have sex with men and who are infected with human immunodeficiency virus (HIV). In Western Europe syphilis rates have risen as well. Syphilis in Europe and the Indian subcontinent is reported as commonly presenting as early or late latent disease diagnosed only by serologic testing, often during prenatal visits. This suggests that syphilis screening should continue, especially in high-risk groups such as military personnel, professional sex workers, men who have sex with men, patients with other sexually-transmitted infections, and pregnant women.

Syphilis and other genital ulcer diseases enhance the risk of transmission and acquisition of HIV. This may be due to the fact that early lesions of syphilis contain mononuclear cells with enhanced expression of CCR5, the coreceptor for HIV-1. HIV testing is recommended in all patients with syphilis. Syphilis is a reportable disease, and contact tracing and treatment of contacts are critical in reducing the incidence of syphilis.

Serologic Tests

Serologic tests for syphilis (STS) reveal the individual's immunologic status, but not (unless in rising titer) whether the patient is currently infected. Serum containing the antibody against *T. pallidum* forms aggregates with a cardiolipin–cholesterol–lecithin antigen that can be viewed directly in tubes or on cards or slides, or can be examined in an autoanalyzer. Because these tests use lipoidal antigens rather than *T. pallidum* or components of it, they are called *nontreponemal antigen tests*. Most widely used are the rapid plasma reagin (RPR) and venereal disease research laboratory (VDRL) tests. Tests yield a positive result, as a rule, within 5 to 6 weeks after infection, shortly before the chancre heals. Tests are generally strongly positive throughout the secondary phase, except in rare patients with AIDS, whose response is less predictable, and usually become negative during therapy, especially if therapy is begun within the first year. Results may also become negative after a few decades, even without treatment.

By diluting the serum serially, the strength of the reaction can be stated in dilutions, the number given being the highest dilution giving a positive test result. In primary infection the titer may be only 1:2; in secondary syphilis it is regularly high, 1:32 to 1:256 or higher; in late syphilis, much lower as a rule, perhaps 1:4 or 1:8. The rise of titer in early infection is of great potential diagnostic value, as is the fall after proper treatment or the rise again if there is reinfection or relapse.

Patients with very high antibody titers, as occur in secondary syphilis, may have a false negative result when undiluted

serum is tested. This "prozone" phenomenon will be overcome by diluting the serum.

To improve sensitivity and specificity, tests have been devised using a specific treponemal antigen. Foremost among these are the microhemagglutination assay for *T. pallidum* (MHA-TP) and the fluorescent treponemal antibody absorption (FTA-ABS) test, which reliably identify seroreactivity caused by treponemal diseases (syphilis, yaws, bejel, or pinta). All positive nontreponemal test results should be confirmed with a specific treponemal test. Treponemal test results may be positive in borreliosis, but Lyme disease is not a common cause of false-positive nontreponemal test results, so it is not clinically important.

The treponemal tests become positive early, before the nontreponemal tests and may be useful in confirming primary syphilis. They usually remain positive for life and are therefore not useful in diagnosing other than the initial episode of syphilis. However, effective treatment of syphilis leads to loss of positivity of both the FTA-ABS and MHA-TP in between 13% and 24% of patients, regardless of stage of syphilis and HIV status. Because the nontreponemal tests tend to become negative in late syphilis, the specific treponemal tests are useful in diagnosing late disease.

Biologic False-Positive Test Results

The term *biologic false-positive* (BFP) is used to denote a positive STS in persons with no history or clinical evidence of syphilis. Ninety percent of BFP test results are of low titer (<1:8). Acute BFP reactions are defined as those that revert to negative in less than 6 months; those that persist for more than 6 months are categorized as chronic. Acute BFP reactions may result from vaccinations, infections (infectious mononucleosis, hepatitis, measles, typhoid, varicella, influenza, lymphogranuloma venereum, malaria), and pregnancy. Chronic BFP reactions are seen in connective tissue diseases, especially systemic lupus erythematosus (SLE) (44%), chronic liver disease, multiple blood transfusions/intravenous drug usage, and advancing age.

False-positive results to specific treponemal tests are less common but have been reported to occur in lupus erythematosus, drug-induced lupus, scleroderma, rheumatoid arthritis, smallpox vaccination, pregnancy, and genital herpes simplex infections. A pattern of beaded fluorescence associated with FTA-ABS testing may be found in the sera of patients without treponemal disease who have SLE. The beading phenomenon, however, is not specific for SLE or even for connective tissue diseases.

Cutaneous Syphilis

Chancre (Primary Stage)

The chancre is usually the first cutaneous lesion, appearing 18 to 21 days after infection. The typical incipient chancre is a small red papule or a crusted superficial erosion. In a few days to weeks it becomes a round or oval, indurated, slightly elevated papule, with an eroded but not ulcerated surface that exudes a serous fluid (Figs 18-1 and 18-2). On palpation it has a cartilage-like consistency. The lesion is usually, but not invariably, painless. This is the uncomplicated or classic Hunterian chancre. The regional lymph nodes on one or both sides are usually enlarged, firm, and nontender, and do not suppurate. Adenopathy begins 1 or 2 weeks after the appearance of the chancre. The Hunterian chancre leaves no scar when it heals.

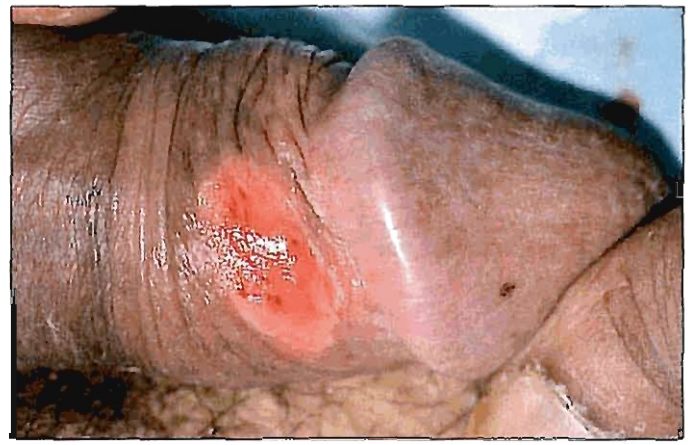

Fig. 18-1 Primary syphilis, chancre.

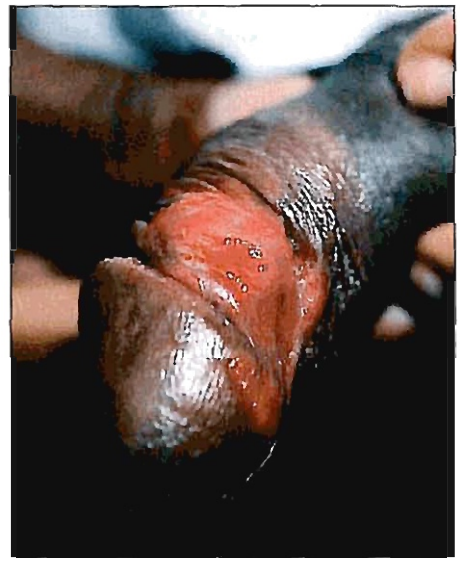

Fig. 18-2 Primary syphilis, chancre with induration and erosion.

Chancres generally occur singly, although they may be multiple; they vary in diameter from a few millimeters to several centimeters. In women the genital chancre is less often observed because of its location within the vagina or on the cervix. Extensive edema of the labia or cervix may occur. In men the chancre is common in the coronal sulcus or on either side of the frenum. A chancre in the prepuce, being too hard to bend, will flip over all at once when the prepuce is drawn back, a phenomenon called a *dory flop*, from the resemblance to the movement of a broad-beamed skiff or dory as it is being turned upside down. Untreated, the chancre tends to heal spontaneously in 1 to 4 months. About the time of its disappearance, or usually a little before, constitutional symptoms and objective signs of generalized (secondary) syphilis occur.

Extragenital chancres may be larger than those on the genitalia. They affect the lips (Fig. 18-3), tongue, tonsil, female breast, index finger, and, especially in men who have sex with men, the anus. The presenting complaints of an anal chancre include an anal sore or fissure and irritation or bleeding on defecation. Anal chancre must be ruled out in any anal fissure not at the 6 or 12-o'clock positions. When

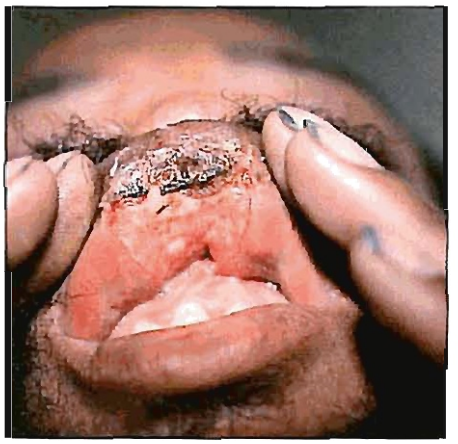

Fig. 18-3 Primary syphilis, chancre of the upper lip.

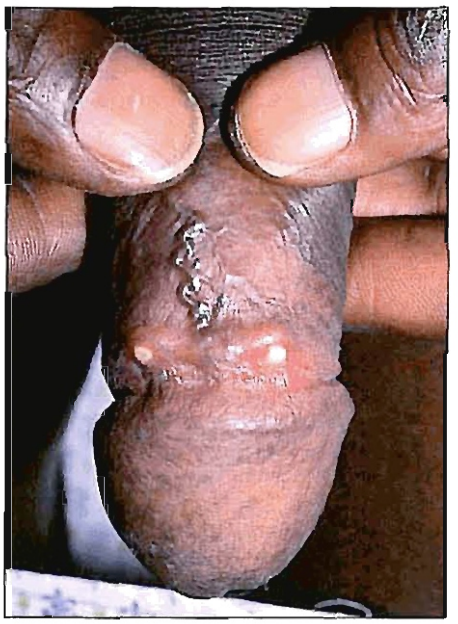

Fig. 18-4 Primary syphilis, atypical chancres, diagnosis confirmed by biopsy.

there is a secondary eruption, no visible chancre, and the glands below Poupart's ligament are markedly enlarged, anal chancre should be suspected.

Atypical chancres are common (Fig. 18-4). Simultaneous infection by a spirochete and another microbial agent may produce an atypical chancre. The mixed chancre caused by infection with *Haemophilus ducreyi* and *T. pallidum* will produce a lesion that runs a course different from either chancroid or primary syphilis alone. Such a sore begins a few days after exposure, since the incubation period for chancroid is short, and later the sore may transform into an indurated syphilitic lesion. A phagedenic chancre results from the combination of a syphilitic chancre and contaminating bacteria that may cause severe tissue destruction and result in scarring. Edema indurativum, or penile venereal edema, is marked solid edema of the labia or the prepuce and glans penis accompanying a chancre. Chancre redux is relapse of a chancre with insufficient treatment. It is accompanied by enlarged lymph nodes. Pseudochancre redux is a gumma occurring at the site of a previous chancre. It is distinguished from relapsing chancre by the absence of lymphadenopathy and a negative darkfield examination. Syphilitic balanitis of Follmann may occur in the absence of a chancre. The lesions may be exudative, circinate or erosive.

Histologic evaluation of a syphilitic chancre reveals an ulcer covered by neutrophils and fibrin. Subjacent there is a dense infiltrate of lymphocytes and plasma cells. Blood vessels are prominent with plump endothelial cells, but these vascular changes, while helpful in evaluation, are nonspecific. Spirochetes are numerous in untreated chancres of primary syphilis and can be demonstrated with an appropriate silver stain, such as the Warthin-Starry, Levaditi, or Steiner methods, or by immunoperoxidase staining. They are best found in the overlying epithelium or adjacent or overlying blood vessels in the upper dermis. The direct fluorescent antibody tissue test for *T. pallidum* (DFAT-TP) may be used in combination with histologic stains to demonstrate pathogenic treponemes in formalin-fixed tissues.

In a patient who presents with an acute genital ulceration, a darkfield examination should be performed if this investigation is available. The finding of typical *T. pallidum* in a sore on the cutaneous surface establishes a diagnosis of syphilis. *Treponema pertenue*, which causes yaws, and *Treponema carateum*, which causes pinta, are both indistinguishable morphologically from *T. pallidum*, but the diseases that they produce are usually easy to recognize. Commensal spirochetes of the oral mucosa are indistinguishable from *T. pallidum*, making oral darkfield examinations unreliable. If the darkfield examination results are negative, the examination should be repeated daily for several days, especially if the patient has been applying any topical antibacterial agents.

The lesion selected for examination is cleansed with water and dried. It is grasped firmly between the thumb and index finger and abraded sufficiently to cause clear or faintly blood-stained plasma to exude when squeezed. In the case of an eroded chancre, a few vigorous rubs with dry gauze are usually sufficient. If the lesion is made to bleed, it is necessary to wait until free bleeding has stopped to obtain satisfactory plasma. The surface of a clean coverslip is touched to the surface of the lesion so that plasma adheres. Then it is dropped on a slide and pressed down so that the plasma spreads out in as thin a film as possible. Immersion oil forms the interface between the condenser and slide and between the coverslip and objective. The specimen must be examined quickly, before the thin film of plasma dries.

An alternative to darkfield microscopy is the direct fluorescent antibody test (DFAT-TP) for the identification of *T. pallidum* in lesions. Serous exudate from a suspected lesion is collected as described above, placed on a slide, and allowed to dry. Many health departments will examine such specimens with fluorescent antibodies specific to *T. pallidum*. The method, unlike the darkfield examination, can be used for diagnosing oral lesions. Multiplex polymerase chain reaction (PCR) is also an accurate and reproducible method for diagnosing genital ulcerations. It has the advantage of being able to diagnose multiple infectious agents simultaneously. In genital ulcer disease outbreaks it should be made available.

The results of serologic tests for syphilis are positive in 50% (nontreponemal tests) to 90% (treponemal tests) of patients with primary syphilis; these tests should be performed in every patient with suspected syphilis. The likelihood of positivity depends on the duration of infection. If the chancre has been present for several weeks, test results are usually positive.

A syphilitic chancre must be differentiated from chancroid. The chancre has an incubation period of 3 weeks; is usually

a painless erosion, not an ulcer; has no surrounding inflammatory zone; and is round or oval. The edge is not undermined, and the surface is smooth and at the level of the skin. It has a dark, velvety red, lacquered appearance, is without an overlying membrane, and is cartilage-hard on palpation. Lymphadenopathy may be bilateral and is nontender and nonsuppurative. Chancroid, on the other hand, has a short incubation period of 4 to 7 days; the ulcer is acutely inflamed, is extremely painful, and has a surrounding inflammatory zone. The ulcer edge is undermined and extends into the dermis. It is covered by a membrane, and is soft to the touch. Lymphadenopathy is usually unilateral, tender, and may suppurate. Chancroid lesions are usually multiple and extend into each other. Darkfield examination and cultures for chancroid confirm the diagnosis. However, since a combination of a syphilitic chancre and chancroid (mixed sores) is indistinguishable from chancroid alone, appropriate direct and serologic testing should be performed to investigate the presence of syphilis. Multiplex PCR allows for the simultaneous diagnosis of multiple infectious agents in genital ulcer diseases.

The primary lesion of granuloma inguinale begins as an indurated nodule that erodes to produce hypertrophic, vegetative granulation tissue. It is soft, beefy-red, and bleeds readily. A smear of clean granulation tissue from the lesion stained with Wright or Giemsa stain reveals Donovan bodies in the cytoplasm of macrophages.

The primary lesion of lymphogranuloma venereum (LGV) is usually a small, painless, transient papule or a superficial nonindurated ulcer. It most commonly occurs on the coronal sulcus, prepuce, or glans in men, or on the fourchette, vagina, or cervix in women. A primary genital lesion is noticed by about 30% of infected heterosexual men, but less frequently in women. Primary lesions are followed in 7 to 30 days by adenopathy of the regional lymph nodes. LGV is confirmed by serologic tests.

Herpes simplex begins with grouped vesicles, often accompanied or preceded by burning pain. After rupture of the vesicles, irregular, tender, soft erosions form.

Secondary Syphilis

Cutaneous Lesions

The skin manifestations of secondary syphilis have been called *syphilids* and occur in 80% or more of cases of secondary syphilis. The early eruptions are symmetrical, more or less generalized, superficial, nondestructive, exanthematic, transient, and macular; later they are maculopapular or papular eruptions, which are usually polymorphous, and less often scaly, pustular, or pigmented. The early manifestations are apt to be distributed over the face, shoulders, flanks, palms and soles, and anal or genital regions. The severity varies widely. The presence of lesions on the palms and soles is strongly suggestive. However, a generalized syphilid can spare the palms and soles. The individual lesions are generally less than 1 cm in diameter, except in the later secondary eruptions or in relapsing secondary eruptions.

Macular Eruptions. The earliest form of macular secondary syphilis begins with the appearance of an exanthematic erythema 6 to 8 weeks after the development of the chancre, which may still be present. The syphilitic exanthem extends rapidly, so that it is usually pronounced a few days after onset. It may be evanescent, lasting only a few hours or days, or it may last several months, or partially recur after having disappeared. This macular eruption appears first on the sides of the trunk, about the navel, and on the inner surfaces of the extremities.

Individual lesions of macular secondary syphilis consist of round indistinct macules that are nonconfluent and may rarely be slightly elevated or urticarial. The color varies from a light pink or rose to brownish-red. The macular eruption may not be noticed on black skin and may be so faint that it is not recognized on other skin colors also. Pain, burning, and itching are usually absent, although pruritus may be present in 10% to 40% of cases. Simultaneous with the onset of the eruption there is a generalized shotty adenopathy most readily palpable in the posterior cervical, axillary, and epitrochlear areas. Rarely, secondary syphilis may cause livedo reticularis. The macular eruption may disappear spontaneously after a few days or weeks without any residuum, or may result in postinflammatory hyperpigmentation. After a varying interval, macular syphilis may be followed by other eruptions.

Papular Eruptions. The papular types of eruption usually arise a little later than the macular. The fully developed lesions are of a raw-ham or coppery shade, round, and from 2 to 5 mm or more in diameter (Figs 18-5 to 18-8). They are often only slightly raised, but a deep, firm infiltration

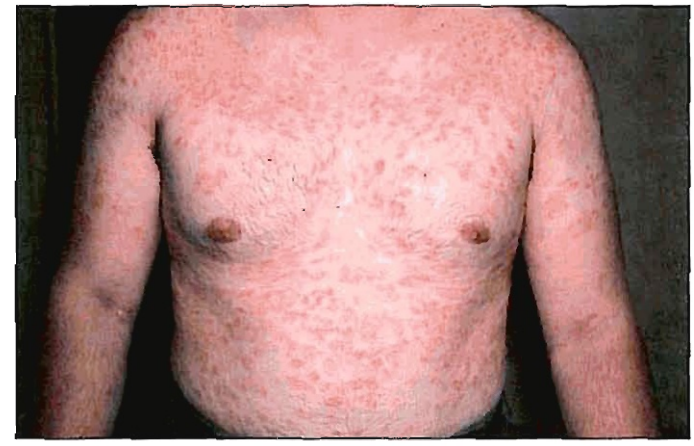

Fig. 18-5 Secondary syphilis, macules, papules and annular lesions.

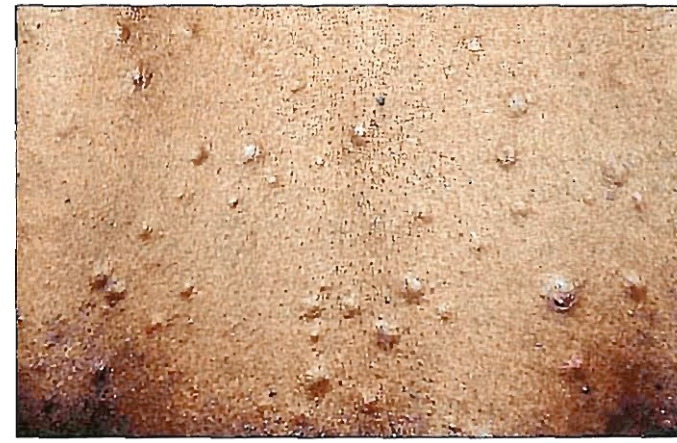

Fig. 18-6 Secondary syphilis.

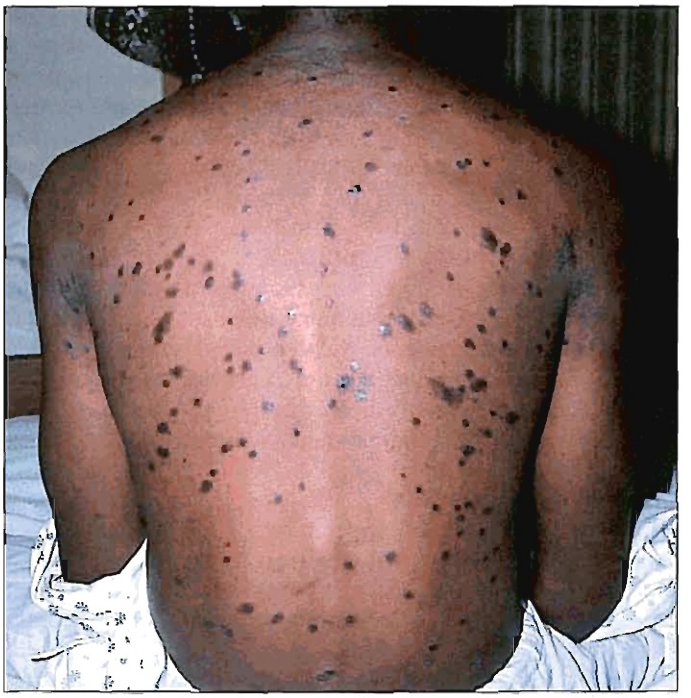

Fig. 18-7 Secondary syphilis, lichenoid lesions.

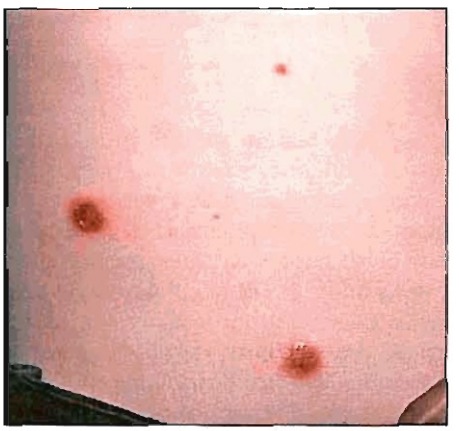

Fig. 18-8
Secondary syphilis, late, larger lesions.

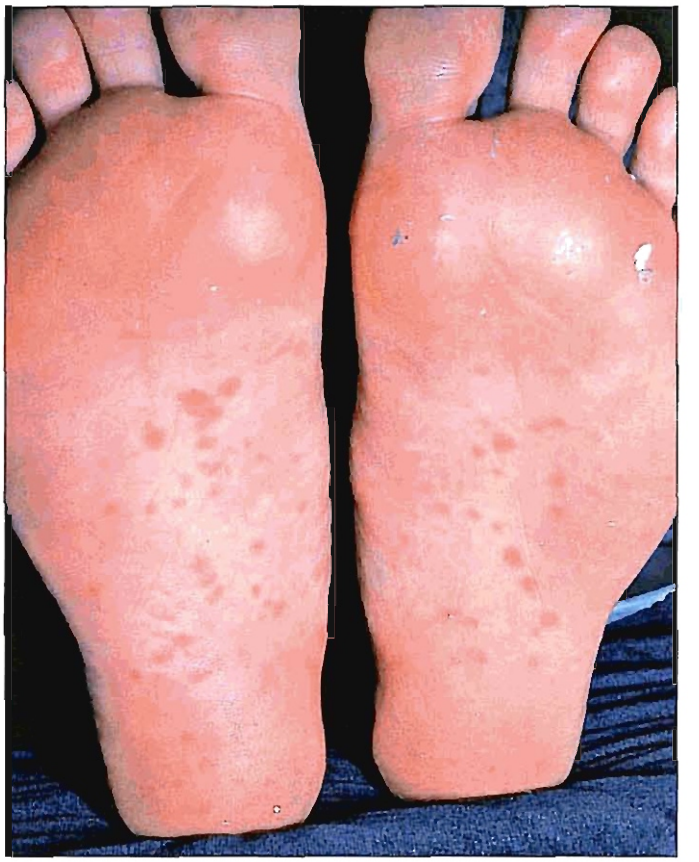

Fig. 18-9 Secondary syphilis, red flat-topped papules of the soles.

is palpable. The surface is smooth, sometimes shiny, at other times covered with a thick, adherent scale. When this desquamates, it leaves a characteristic collarette of scales overhanging the border of the papule.

Papules are frequently distributed on the face and flexures of the arms and lower legs but are often distributed all over the trunk. Palmar and plantar involvement characteristically appears as indurated, yellowish-red spots (Fig. 18-9). Ollendorf's sign is present: the papule is exquisitely tender to the touch of a blunt probe. Healing lesions frequently leave hyperpigmented spots that, especially on the palms and soles, may persist for weeks or months. Split papules are hypertrophic, fissured papules that form in the creases of the alae nasi and at the oral commissures. These may persist for a long period. The papulosquamous syphilids, in which the adherent scales covering the lesions more or less dominate the picture, may produce a psoriasiform eruption (Fig. 18-10). Follicular or lichenoid syphilids, which occur much less frequently, appear as minute scale-capped papules. If they are at the ostia of hair follicles, they are likely to be conical; elsewhere on the skin, they are domed. Often they are grouped to form scaling plaques in which the minute coalescing papules are still discernible.

Like the other syphilids, papular eruptions tend to be disseminated but may also be localized, asymmetrical, configurate, hypertrophic, or confluent. The arrangement may be corymbose or in patches, rings, or serpiginous patterns.

The annular syphilid, like sarcoidosis (which it may mimic), is more common in blacks. It is often located on the cheeks, especially close to the angle of the mouth. Here it may form annular, arcuate, or gyrate patterns of delicate, slightly raised, infiltrated, finely scaling ridges. These ridges are made up of minute, flat-topped papules, and the boundaries between ridges may be difficult to discern. An old term for annular syphilids was *nickels and dimes*.

The corymbose syphilid is another infrequent variant, usually occurring late in the secondary stage, in which a large central papule is surrounded by a group of minute satellite papules. The pustular syphilids are among the rarer manifestations of secondary syphilis. They occur widely scattered over the trunk and extremities, but they usually involve the face, especially the forehead. The pustule usually arises on a red, infiltrated base. Involution is usually slow, resulting in a small, rather persistent, crust-covered, superficial ulceration. Lesions in which the ulceration is deep are called *ecthymatous*. Closely related is the rupial syphilid, a lesion in which a relatively superficial ulceration is covered with a pile of terraced crusts resembling an oyster shell. Lues maligna is a rare form of secondary syphilis with severe ulcerations, pustules, or rupioid lesions, accompanied by severe constitutional symptoms.

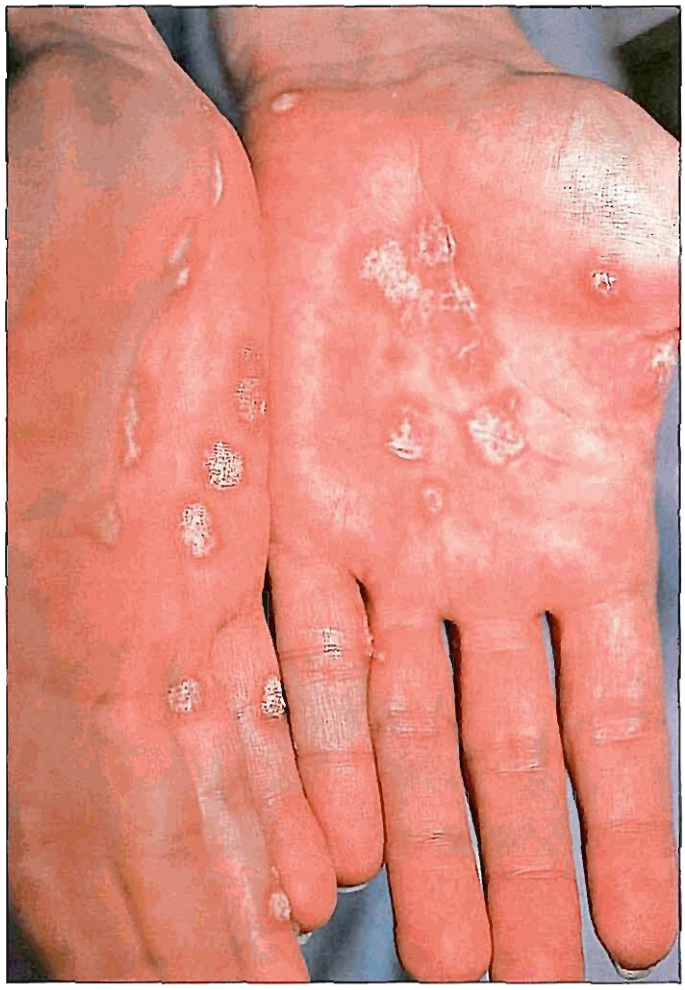

Fig. 18-10 Secondary syphilis, psoriasiform papules.

Condylomata lata are papular lesions, relatively broad and flat, located on folds of moist skin, especially about the genitalia and anus; they may become hypertrophic and, instead of infiltrating deeply, protrude above the surface, forming a soft, red, often mushroom-like mass 1 to 3 cm in diameter, usually with a smooth, moist, weeping, gray surface. Condyloma lata may be lobulated but are not covered by the digitate elevations characteristic of venereal warts (*condylomata acuminata*).

Syphilitic alopecia is irregularly distributed so that the scalp has a moth-eaten appearance. It is unusual, occurring in about 5% of patients with secondary syphilis. Smooth circular areas of alopecia mimicking alopecia areata may occur in syphilis, and an ophiasis pattern may rarely be seen.

Mucous membrane lesions are present in one-third of patients with secondary syphilis. The most common mucosal lesion in the early phase is the syphilitic sore throat, a diffuse pharyngitis that may be associated with tonsillitis or laryngitis. Hoarseness and sometimes complete aphonia may be present. On the tongue, smooth, small or large, well-defined patches devoid of papillae may be seen, most frequently on the dorsum near the median raphe. Ulcerations may occur on the tongue and lips during the late secondary period.

Mucous patches are the most characteristic mucous membrane lesions of secondary syphilis. They are macerated, flat, grayish, rounded erosions covered by a delicate, soggy membrane. These highly infectious lesions are about 5 mm in diameter and teem with treponema. They occur on the tonsils, tongue, pharynx, gums, lips, and buccal areas, or on the genitalia, chiefly in women. In the latter they are most common on the labia minora, vaginal mucosa, and cervix. Such mucous erosions are transitory and change from week to week, or even from day to day.

Relapsing Secondary Syphilis

The early lesions of syphilis undergo involution either spontaneously or with treatment. Relapses occur in about 25% of untreated patients, 90% within the first year. Such relapses may take place at the site of previous lesions, on the skin or in the viscera. Recurrent eruptions tend to be more configurate or annular, larger, and asymmetrical.

Systemic Involvement

The lymphatic system in secondary syphilis is characteristically involved. The lymph nodes most frequently affected are the inguinal, posterior cervical, postauricular, and epitrochlear. The nodes are shotty, firm, slightly enlarged, nontender, and discrete.

Acute glomerulonephritis, gastritis or gastric ulceration, proctitis, hepatitis, acute meningitis, sensorineural hearing loss, iritis, anterior uveitis, optic neuritis, Bell palsy, multiple pulmonary nodular infiltrates, periostitis, osteomyelitis, polyarthritis, or tenosynovitis may all be seen in secondary syphilis.

Histopathology

Macules of secondary syphilis feature superficial and deep perivascular infiltrates of lymphocytes, macrophages, and plasma cells without epidermal change, or accompanied by slight vacuolar change at the dermoepidermal junction.

Papules and plaques of secondary syphilis usually show dense superficial and deep infiltrates of lymphocytes, macrophages, and plasma cells. These cells are usually distributed in a bandlike pattern in the papillary dermis and cuffed around blood vessels, accompanied by psoriasiform epidermal hyperplasia and hyperkeratosis. Clusters of neutrophils are commonly present within the stratum corneum. The presence of numerous macrophages often gives the infiltrates a pallid appearance under scanning magnification. Vacuolar degeneration of keratinocytes is often present, giving the lesions a "psoriasiform and lichenoid" histologic pattern with slender elongated rete ridges. Plasma cells are said to be absent in 10% to 30% of cases. As lesions age, macrophages become more numerous, so that in late secondary lues, granulomatous foci are often present, mimicking sarcoidosis. Condylomata lata show spongiform pustules within areas of papillated epithelial hyperplasia and spirochetes are numerous. Spirochetes are most numerous within the epidermis and around superficial vessels. PCR and immunoperoxidase may identify *T. pallidum* infection when silver stains are negative.

Diagnosis and Differential Diagnosis

The nontreponemal serologic tests for syphilis are almost invariably strongly reactive in secondary syphilis. An exception occurs when very high titers of antibody are present, producing a false-negative result (prozone phenomenon). The true positivity of the serum is detected on dilutional testing. Also, rarely, seronegative secondary syphilis may occur in

patients with AIDS. Identification of spirochetes by darkfield examination or histologic examination of affected tissues may be used to confirm the diagnosis, especially in patients who are seronegative.

Syphilis has long been known as the "great imitator," because the various cutaneous manifestations may simulate almost any cutaneous or systemic disease. Pityriasis rosea may be mistaken for secondary syphilis, especially since both begin on the trunk. The herald patch, the oval patches with a fine scale at the edge, patterned in the lines of skin cleavage, the absence of lymphadenopathy, and infrequent mucous membrane lesions help to distinguish pityriasis rosea from secondary syphilis. Drug eruptions may produce a similar picture; however, they tend to be scarlatiniform or morbilliform. Drug eruptions are often pruritic, whereas secondary syphilis usually is not. Lichen planus may resemble papular syphilid. The characteristic papule of lichen planus is flat topped, polygonal, has Wickham's striae, and exhibits the Koebner's phenomenon. Pruritus is severe in lichen planus and less common and less severe in syphilis. Psoriasis may be distinguished from papulosquamous secondary syphilis by the presence of adenopathy, mucous patches, and alopecia in the latter. Sarcoidosis may produce lesions morphologically identical to secondary syphilis. Histologically, multisystem involvement, adenopathy, and granulomatous inflammation are common to both diseases. Serologic testing and biopsy specimens will distinguish these two disorders.

The differential diagnosis of mucous membrane lesions of secondary syphilis is of importance. Infectious mononucleosis may cause a biologic false-positive test for syphilis but is diagnosed by a high heterophile antibody titer. Geographic tongue may be confused with the desquamative patches of syphilis or with mucous patches. Lingua geographica occurs principally near the edges of the tongue in relatively large areas, which are often fused and have lobulated contours. It continues for several months or years and changes in extent and degree of involvement from day to day. Recurrent aphthous ulceration produces one or several painful ulcers, 1 to 3 mm in diameter, surrounded by hyperemic edges, with a grayish covering membrane, on nonkeratinized mucosal epithelium, especially in the gingival sulcus. A prolonged, recurrent history is characteristic. Syphilis of the lateral tongue may resemble oral hairy leukoplakia.

Latent Syphilis

After the lesions of secondary syphilis have involuted, a latent period occurs. This may last for a few months or continue for the remainder of the infected person's life. Sixty to 70% of untreated infected patients remain latently asymptomatic for life. During this latent period there are no clinical signs of syphilis, but the serologic tests for syphilis are reactive. During the early latent period infectivity persists: for at least 2 years a woman with early latent syphilis may infect her unborn child. For treatment purposes it is important to distinguish early latency (<1 year's duration) from late latency (of >1 year or unknown duration).

Late Syphilis

Late syphilis is defined by the Centers for Disease Control (CDC) as infection of greater than 1 year in duration, or by the World Health Organization (WHO) as greater than 2 years in duration. Only about one-third of patients with late syphilis will develop complications of their infection.

Tertiary Cutaneous Syphilis

Tertiary syphilids most often occur 3 to 5 years after infection. Sixteen percent of untreated patients will develop tertiary lesions of the skin, mucous membrane, bone, or joints. Skin lesions tend to be localized, to occur in groups, to be destructive, and to heal with scarring. Treponema are usually not found by silver stains or darkfield examination but may be demonstrated by PCR.

Two main types of tertiary syphilids are recognized, the nodular syphilid and the gumma, although the distinction is sometimes difficult to make. The nodular, noduloulcerative, or tubercular type consists of reddish-brown or copper-colored firm papules or nodules, 2 mm in diameter or larger. The individual lesions are usually covered with adherent scales or crusts. The lesions tend to form rings and to undergo involution as new lesions develop just beyond them, so that characteristic circular or serpiginous patterns are produced. A distinctive and characteristic type is the kidney-shaped lesion. These frequently occur on the extensor surfaces of the arms and on the back of the trunk. Such patches are composed of nodules in different stages of development so that it is common to find scars and pigmentation together with fresh and also ulcerated lesions. On the face the nodular eruption closely resembles lupus vulgaris. When the disease is untreated, the process may last for years, slowly marching across large areas of skin. The nodules may enlarge and eventually break down to form painless, rounded, smooth-bottomed, ulcers, a few millimeters deep. These punched-out ulcers arise side by side and form serpiginous syphilitic ulcers, palm-sized in aggregate, enduring for many years.

Gummas may occur as unilateral, isolated, single or disseminated lesions, or in serpiginous patterns resembling those of the nodular syphilid. They may be restricted to the skin or, originating in the deeper tissues, break down and secondarily involve the skin. The individual lesions, which begin as small nodules, slowly enlarge to several centimeters. Central necrosis is extensive and may lead to the formation of a deep punched-out ulcer with steep sides and a gelatinous, necrotic base. Again, progression may take place in one area while healing proceeds in another. Perhaps the most frequent site of isolated gummas is the lower legs, where deep punched-out ulcers are formed, often in large infiltrated areas.

Histologically, nodular lesions of late syphilis usually have changes that resemble those of secondary lesions, with the addition of tuberculoid granulomas containing varying numbers of multinucleate giant cells. The epidermis is often atrophic rather than hyperplastic. In gummas, there is necrosis within granulomas and fibrosis as lesions resolve. Spirochetes are scant.

For diagnosis of late syphilis clinicians rely heavily on the serologic tests for syphilis. The nontreponemal tests, such as the VDRL and RPR, are positive in approximately 75% of cases. The treponemal tests, such as the FTA-ABS, and MHA-TP, are positive in nearly 100% of patients. When there are mucous membrane lesions for which a diagnosis of carcinoma must also be considered, histologic examination is performed. Darkfield examination is not indicated, since it is always negative, but PCR of biopsy material may be positive.

In late syphilis the mucous membranes are attacked; the tongue is a frequent site. Gumma of the tongue usually involves the edge, toward the back, and rapidly breaks down to form a punched-out ulcer with irregular, soft edges.

When not ulcerated, lesions of tertiary syphilis must be distinguished from malignant tumors, leukemids, and sarcoidosis. The ulcerated tertiary syphilids must be differentiated from other infections such as scrofuloderma, atypical mycobacterial infection, and deep fungal infections. Wegners and ulcerative cutaneous malignancies must be considered in the differential diagnosis. Histology and appropriate cultures may be required. On the lower extremities gummas are frequently mistaken for erythema induratum.

A superficial glossitis may cause irregular ulcers, atrophy of the papillae, and smooth, shiny scarring, a condition known as *smooth atrophy*. In interstitial glossitis there is an underlying induration. In the advanced stages, tertiary syphilis of the tongue may lead to a diffuse enlargement (macroglossia). Perforation of the hard palate from gummatous involvement is a characteristic tertiary manifestation. It generally occurs near the center of the hard palate. Destruction of the nasal septum may also occur.

Late Osseous Syphilis

Not infrequently, gummatous lesions involve the periosteum and the bone. Skeletal tertiary syphilis affects most commonly the head and face, and the tibia. Late manifestations of syphilis may produce periostitis, osteomyelitis, osteitis, and gummatous osteoarthritis. Osteocope (bone pain), most often at night, is a suggestive symptom.

Syphilitic joint lesions also occur, with the Charcot joint being the most prevalent manifestation. They are often associated with tabes dorsalis and occur most frequently in men. Although any joint may be involved, the knees and ankles are the most frequently affected. There is hydrops, then loss of the contours of the joint, hypermobility, and no pain. It is readily diagnosed by x-ray examination.

Neurosyphilis

Central nervous system (CNS) involvement can occur at any stage of syphilis, even the primary stage. Most persons with CNS involvement have no symptoms, but the disease can be detected by finding cerebrospinal fluid (CSF) pleocytosis or a positive CSF serology. From this group of persons with "asymptomatic" neurosyphilis, symptomatic disease will occur in some. Persons with negative CNS examinations have almost no risk of developing neurosyphilis. Four to 9% of persons with untreated syphilis will develop neurosyphilis. Symptomatic neurosyphilis occurs from early in the secondary phase through the tertiary phase. It is divided into early and late forms, which do not directly correlate with early and late syphilis as defined above.

CSF evaluation is recommended in all patients with syphilis with any neurologic, auditory, or ophthalmic signs or symptoms, possibly resulting from syphilis, independent of stage. Patients with latent syphilis should have CSF evaluation if they are HIV positive, fail initial therapy, or if therapy other than penicillin is planned for syphilis of more than 1 year in duration. Patients with tertiary syphilis should have CSF evaluation before treatment to exclude neurosyphilis.

Early Neurosyphilis

Early neurosyphilis is mainly meningeal, occurring in the first year of infection, and spinal fluid abnormalities herald the early changes. CSF examination shows a positive serology and a pleocytosis with lymphocytosis. Meningeal neurosyphilis manifests as meningitis, with headache, stiff neck, cranial nerve disorders (loss of hearing, facial weakness, visual disturbances), seizures, and delirium, with increased intracranial pressure indicated by papilledema.

Meningovascular Neurosyphilis

Meningovascular neurosyphilis most frequently occurs 4 to 7 years after infection. It is caused by thrombosis of vessels in the CNS and presents as in other CNS ischemic events. Hemiplegia, aphasia, hemianopsia, transverse myelitis, and progressive muscular atrophy may occur. Cranial nerve palsies may also occur, such as eighth nerve deafness and eye changes. The eyes may show fixed pupils, Argyll Robertson pupils, or anisocoria.

Late (Parenchymatous) Neurosyphilis

Parenchymatous neurosyphilis tends to occur more than 10 years after infection. There are two classic clinical patterns: tabes dorsalis and general paresis.

Tabes dorsalis is the degeneration of the dorsal roots of the spinal nerves and of the posterior columns of the spinal cord. The symptoms and signs are numerous. Gastric crisis with severe pain and vomiting is the most frequent symptom. Other symptoms are lancinating pains, urination difficulties, paresthesias (numbness, tingling, and burning), spinal ataxia, diplopia, strabismus, vertigo, and deafness. The signs that may be present are Argyll Robertson pupils, absent or reduced lower cord reflexes, Romberg sign, sensory loss (deep tendon tenderness, vibration, and position), atonic bladder, trophic changes, malum perforans pedis, Charcot joints, and optic atrophy.

Paresis has prodromal manifestations of headache, fatigability, and inability to concentrate. Later, personality changes occur, along with memory loss and apathy. Grandiose ideas, megalomania, delusions, hallucinations, and finally dementia may occur.

Late Cardiovascular Syphilis

Late cardiovascular syphilis occurs in about 10% of untreated patients. Aortitis is the basic lesion of cardiovascular syphilis, resulting in aortic insufficiency, coronary disease, and ultimately aortic aneurysm.

Congenital Syphilis

Prenatal syphilis is acquired in utero from the mother, who usually has early syphilis. Infection through the placenta usually does not occur before the fourth month, so treatment of the mother before this time will almost always prevent infection in the fetus. If the mother has early syphilis and prenatal infection occurs soon after the fourth month, fetal death and miscarriage occur in about 40% of pregnancies. During the remainder of the pregnancy, infection is equally likely to produce characteristic developmental physical stigmata or, after the eighth month, active, infectious congenital syphilis. Forty percent of pregnancies in women with untreated early syphilis will result in a syphilitic infant. In utero infection of the fetus is rare when the pregnant mother

has had syphilis for 2 or more years. Most neonates with congenital syphilis are normal at birth. Lesions occurring within the first 2 years of life are called *early congenital syphilis* and those developing thereafter are called *late congenital syphilis*. The clinical manifestations of these two syndromes are different.

Early Congenital Syphilis

Early congenital syphilis describes those cases presenting within the first 2 years of life. Most neonates with congenital syphilis are normal at birth. Cutaneous manifestations appear most commonly during the third week of life, but sometimes occur as late as 3 months after birth. Neonates born with findings of congenital syphilis are usually severely affected. They may be premature, are often marasmic, fretful, and dehydrated. The face is pinched and drawn, resembling that of an old man or woman. Multisystem disease is characteristic.

Snuffles, a form of rhinitis, is the most frequent and often the first specific finding. The nose is blocked, often with blood-stained mucus, and a copious discharge of mucus runs down over the lips. The nasal obstruction often interferes with the child's nursing. In persistent and progressive cases ulcerations develop that may involve the bones and ultimately cause perforation of the septum or development of saddle nose, which are important stigmata later in the disease.

Cutaneous lesions of congenital syphilis resemble those of acquired secondary syphilis and occur in 30% to 60% of infants with syphilis. The early skin eruptions are usually morbilliform, and more rarely, purely papular. The lesions are at first a bright or violaceous red, later fading to a coppery color. The papules may become large and infiltrated; frequently scaling is pronounced. There is secondary pustule formation with crusting, especially in lesions that appear 1 or more years after birth. The eruption shows a marked predilection for the face, arms, buttocks, legs, palms, and soles.

Syphilitic pemphigus, a bullous eruption, usually on the palms and soles, is a relatively uncommon lesion. Lesions are present at birth or appear in the first week of life. They are teeming with spirochetes. The bullae quickly become purulent and rupture, leaving weeping erosions. They are found also on the eponychium, wrists, ankles, and, infrequently, other parts of the body. Even in the absence of bullous lesions, desquamation is common, often preceded by edema and erythema, especially on the palms and soles.

Various morphologies of cutaneous lesions occur on the face, perineum, and intertriginous areas. They are usually fissured lesions resembling mucous patches. In these sites radial scarring often results, leading to rhagades. Condylomata lata, large, moist, hypertrophic papules, are found about the anus and in other folds of the body. They are more common around the first year of life than in the newborn period. In the second or third year, recurrent secondary eruptions are likely to take the papulopustular form. Annular lesions similar to those in adults occur. Mucous patches in the mouth or on the vulva are seen infrequently.

Bone lesions occur in 70% to 80% of cases of early congenital syphilis. Epiphysitis is common and apparently causes pain on motion, leading to the infant's refusing to move (Parrot pseudoparalysis). Radiologic features of the bone lesions in congenital syphilis during the first 6 months after birth are quite characteristic, and x-ray films are an important part of the evaluation of a child suspected of having congenital syphilis. Bone lesions occur chiefly at the epiphyseal ends of the long bones. The changes may be classified as osteochondritis, osteomyelitis, and osteoperiostitis.

A general enlargement of the lymph nodes usually occurs, with enlargement of the spleen. Clinical evidence of involvement of the liver is common, manifested both by hepatomegaly and elevated liver function test results, and interstitial hepatitis is a frequent finding at autopsy. The nephrotic syndrome, and less commonly, acute glomerulonephritis have been reported in congenital syphilis.

Symptomatic or asymptomatic neurosyphilis, as demonstrated by a positive CSF serologic test may be present. Eighty-six percent of infants with congenital syphilis diagnosed by clinical and laboratory findings born to mothers with untreated early syphilis will have CNS involvement, compared with only 8% of those with no clinical or laboratory findings. Clinical manifestations may not appear until the third to sixth month of life and are meningeal or meningovascular in origin. Meningitis, obstructive hydrocephalus, cranial nerve palsies, and cerebrovascular accidents may all occur.

Late Congenital Syphilis

Although no sharp line can be drawn between early and late congenital syphilis, children who appear normal at birth and develop the first signs of the disease after the age of 2 years show a different clinical picture. Lesions of late congenital syphilis are of two types: malformations of tissue affected at critical growth periods (stigmata) and persistent inflammatory foci.

Inflammatory Late Congenital Syphilis

Lesions of the cornea, bones, and CNS are the most important. Interstitial keratitis, which begins with intense pericorneal inflammation and persists to characteristic diffuse clouding of the cornea without surface ulceration, occurs in 20% to 50% of cases of late congenital syphilis. If persistent, it leads to permanent partial or complete opacity of the cornea. Syphilitic interstitial keratitis must be differentiated from Cogan syndrome, consisting of nonsyphilitic interstitial keratitis, usually bilateral, associated with vestibuloauditory symptoms, such as deafness, tinnitus, vertigo, nystagmus, and ataxia. It is congenital.

Perisynovitis (Clutton joints), which affects the knees, leads to symmetrical, painless swelling. Gummas may also be found in any of the long bones or in the skull. Ulcerating gummas are frequently seen. They probably begin more often in the soft parts or in the underlying bone than in the skin itself, and when they occur in the nasal septum or palate, may lead to painless perforation.

The CNS lesions in late congenital syphilis are, as in late adult neurosyphilis, usually parenchymatous (tabes dorsalis or generalized paresis). Seizures are a frequent symptom in congenital cases.

Malformations (Stigmata)

The destructive effects of syphilis in young children often leave scars or developmental defects called *stigmata*, which persist throughout life and enable a diagnosis to be made of congenital syphilis. Hutchinson emphasized the diagnostic

importance of changes in the incisor teeth, opacities of the cornea, and eighth nerve deafness, which have since become known as the *Hutchinson triad*. Hutchinson's teeth, corneal scars, saber shins, rhagades of the lips, saddle nose, and mulberry molars are of diagnostic importance.

Hutchinson's teeth are a malformation of the central upper incisors that appear in the second or permanent teeth. The characteristic teeth are cylindrical rather than flattened, the cutting edge is narrower than the base, and in the center of the cutting edge a notch may develop. The mulberry molar (usually the first molar, appearing about the age of 6 years) is a hyperplastic tooth, the flat occlusal surface of which is covered with a group of little knobs representing abortive cusps. Nasal chondritis in infancy results in flattening of the nasal bones forming a so-called saddle nose.

The unilateral thickening of the inner third of one clavicle (Higouménaki's sign) is a hyperostosis resulting from syphilitic osteitis in individuals who have had late congenital syphilis. The lesion appears typically on the right side in right-handed persons and on the left side in left-handed persons.

Diagnosis

Infants of women who meet the following criteria should be evaluated for congenital syphilis:

1. Maternal untreated syphilis, inadequate treatment, or no documentation of adequate treatment
2. Treatment of maternal syphilis with erythromycin
3. Treatment less than 1 month before delivery
4. Inadequate maternal response to treatment
5. Appropriate treatment before pregnancy, but insufficient serologic follow-up to document adequacy of therapy.

The results of serologic tests for syphilis for every woman delivering a baby must be known before the discharge of that baby from the hospital. Serologic testing of the mother and child at delivery are recommended.

Evaluation of the children noted above might include:

A. A complete physical examination for findings of congenital syphilis
B. Nontreponemal serology of the infant's sera (not cord blood)
C. CNS evaluation
D. Pathologic evaluation of the placenta using specific antitreponemal antibody staining

Treatment

Penicillin remains the drug of choice for treatment of all stages of syphilis. Erythromycin is not recommended for treatment of any stage or form of syphilis. HIV testing is recommended in all patients with syphilis. Treatment for HIV-infected patients is discussed later. Patients with primary, secondary, or early latent syphilis known to be of less than 1 year in duration can be treated with a single intramuscular injection of 2.4 MU of benzathine penicillin G. The addition of a second dose 1 week later has been recommended by some. In nonpregnant, penicillin-allergic, HIV-negative patients, tetracycline 500 mg orally four times a day or doxycycline 100 mg orally twice a day for 2 weeks is recommended. Ceftriaxone 1 g intramuscularly or intravenously for 8 to 10 days, or azithromycin 2 g as a single oral dose, may be effective alternatives. Close follow-up is recommended for all patients treated with non-penicillin-based regimens. These alternative agents are not recommended for persons with HIV infection and early syphilis.

The recommended treatment of late or late latent syphilis of more than 1 year in duration in an HIV-negative patient is benzathine penicillin G 2.4 MU intramuscularly once a week for 3 weeks. In a penicillin-allergic, nonpregnant, HIV-negative patient, tetracycline 500 mg orally four times a day or doxycycline 100 mg orally twice a day for 30 days is recommended. CSF evaluation is recommended if neurologic or ophthalmologic findings are present, if there is evidence of active late (tertiary) syphilis, if treatment has previously failed, if the nontreponemal serum titer is 1:32 or higher, or if any regimen not based on penicillin is planned.

Recommended treatment regimens for neurosyphilis include penicillin G crystalline, 3 to 4 MU intravenously every 4 h for 10 to 14 days, or penicillin G procaine, 2.4 MU/day intramuscularly plus probenecid 500 mg orally four times a day, both for 10 to 14 days. These regimens are shorter than those for treatment of late syphilis, so they may be followed by benzathine penicillin G, 2.4 MU intramuscularly, once a week for 3 weeks. Patients allergic to penicillin should have their allergy confirmed by skin testing. If allergy exists, desensitization and treatment with penicillin are recommended.

Treatment of congenital syphilis in the neonate is complex. Therapy should be undertaken in consultation with a pediatric infectious disease specialist. Management strategies can be found in the CDC Guidelines for the Management of Sexually Transmitted Diseases (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5106a1.htm). Older children with congenital syphilis should have a CSF evaluation and be treated with aqueous crystalline penicillin G, 200,000 to 300,000 U/kg/day intravenously or intramuscularly (50,000 U every 4–6 h) for 10 to 14 days.

Pregnant women with syphilis should be treated with penicillin in doses appropriate for the stage of syphilis. A second dose of benzathine penicillin 2.4 MU intramuscularly may be administered 1 week after the initial dose in pregnant women with primary, secondary or early latent syphilis. Sonographic evaluation of the fetus in the second half of pregnancy for signs of congenital infection may facilitate management and counseling. Expert consultation should be sought in cases where evidence of fetal syphilis is found, as fetal treatment failure is increased in this scenario. Follow-up quantitative serologic tests should be performed monthly until delivery. Pregnant women who are allergic to penicillin should be skin tested and desensitized if test results are positive.

Jarisch-Herxheimer or Herxheimer Reaction A febrile reaction often occurs after the initial dose of antisyphilitic treatment, especially penicillin, is given. It occurs in about 60% of patients treated for seronegative primary syphilis, 90% of those with seropositive primary or secondary syphilis, and 30% of those with neurosyphilis. The reaction generally occurs 6 to 8 h after treatment and consists of shaking chills, fever, malaise, sore throat, myalgia, headache, tachycardia, and exacerbation of the inflammatory reaction at sites of localized spirochetal infection. A vesicular Herxheimer reaction can occur. A Herxheimer reaction in pregnancy may induce premature labor and fetal distress. Every effort should be made to avoid this compli-

cation. Early in pregnancy, women should rest and take acetaminophen for fever. Women treated after 20 weeks of pregnancy should seek obstetric evaluation if they experience fever, decreased fetal movement or regular contractions within 24 h of treatment. An increase of inflammation in a vital structure may have serious consequences, as when there is an aneurysm of the aorta or iritis. When the CNS is involved, special importance is attached to avoiding the Herxheimer reaction, even though the paralyses that may result are often transitory. It is important to distinguish the Herxheimer reaction from a drug reaction to penicillin or other antibiotics. The reaction has also been described in other spirochetal diseases, such as leptospirosis and louse-borne relapsing fever.

Treatment of Sex Partners Sexual partners of persons with syphilis should be identified. Persons who are exposed within 90 days of the diagnosis of primary, secondary or early latent syphilis, even if seronegative, should be treated presumptively. If the exposure was longer than 90 days ago, but follow-up is uncertain, presumptive treatment should be given. If the infectious source has a serologic titer of greater than 1:32, they should be presumed to have early syphilis and sexual partners should be treated. At-risk partners are identified as those exposed for 3 months plus the duration of the primary lesions, for 6 months plus the duration of the secondary lesions, or 1 year for latent syphilis. Treatment of sexual partners is based on their clinical and serologic findings. If they are seronegative but had exposures as outlined above, treatment would be as for early syphilis, with benzathine penicillin 2.4 MU intramuscularly as one dose. Single-dose azithromycin, as used to treat nongonococcal urethritis, is effective in treating incubating syphilis. Therefore, contacts of syphilis cases who have been so treated may be serologically tested and followed, and additional penicillin therapy is not required.

Serologic Testing After Treatment Before therapy and then regularly thereafter, quantitative VDRL or RPR testing should be performed on patients who are to be treated for syphilis to ensure appropriate response. For primary and secondary syphilis in an HIV-negative nonpregnant patient, testing is repeated every 3 months in the first year, every 6 months in the second year, and yearly thereafter. At least a four-fold decrease in titer would be expected 6 months after therapy, but 15% of patients with recommended treatment will not achieve this serologic response by 1 year. Patients with prior episodes of syphilis may respond more slowly. If response is inadequate, HIV testing (if HIV status is unknown) and CSF evaluation are recommended. For HIV-negative patients who fail to respond and who have a normal CSF evaluation, optimal management is unclear. Close follow-up must be assured. If it is decided to retreat the patient, 3-weekly injections of benzathine penicillin G 2.4 MU are recommended. A four-fold increase in serologic titer clearly indicates treatment failure or reinfection. These patients should have HIV testing and CSF analysis, with treatment determined by the results of these tests. Patients with documented neurosyphilis should also have a repeat CSF evaluation at 6 months and at 6-month intervals thereafter until response can be documented by resolution of pleocytosis and/or fall in the CSF nontreponemal titer.

The response for patients with latent syphilis is slower, but a four-fold decrease in titer should be seen by 12 to 24 months. If no such response occurs, HIV testing and CSF evaluation are recommended. Patients treated for latent or late syphilis may be serofast, so that failure to observe a titer fall in these patients does not in itself indicate a need for retreatment. If the titer is less than 1:32, the possibility of a serofast state exists, and retreatment should be planned on an individual basis.

Seroreversion in specific treponemal tests can occur. By 36 months 24% of patients treated for early syphilis had a negative FTA-ABS and 13% a negative MHA-TP

Syphilis and Human Immunodeficiency Virus Disease

Most HIV-infected patients with syphilis exhibit the classic clinical manifestations with appropriate serologic titers for that stage of disease. Response to treatment, both clinical and serologic in HIV-infected patients with syphilis, generally follow the clinical and serologic patterns seen in patients without coexisting HIV infection. In a large study that compared HIV-positive with HIV-negative patients with syphilis, the former were more likely to present with secondary syphilis (53% vs 33%) and were more likely to have a chancre that persisted when they had secondary syphilis (43% vs 15%). Unusual clinical manifestations of syphilis in HIV include florid skin lesions to few atypical ones, but these are exceptions, not the rule.

In general, the nontreponemal tests are of higher titer in HIV-infected persons. Rarely, the serologic response to infection may be impaired or delayed, and seronegative secondary syphilis has been reported. Biopsy of the skin lesions and histopathologic evaluation with silver stains will confirm the diagnosis of syphilis in such cases. This approach, along with darkfield examination of appropriate lesions, should be considered if the clinical eruption is characteristic of syphilis and the serologic tests yield negative results.

Neurosyphilis has been frequently reported in HIV-infected persons, even after appropriate therapy for early syphilis. Manifestations have been those of early neurosyphilis or meningeal or meningovascular syphilis. These have included headache, fever, hemiplegia, and cranial nerve deficits especially deafness (cranial nerve VIII), decreased vision (cranial nerve II), and ocular palsies (cranial nerves III and VI). Whether HIV-infected persons are at increased risk for these complications or whether they occur more quickly is unknown. It is known that spirochetes are no more likely to remain in the CSF after treatment in HIV-infected persons than in HIV-negative persons. Whether the impaired host immunity allows these residual spirochetes to more frequently or more quickly cause clinical relapse in the setting of HIV is unknown.

HIV-infected patients who have primary or secondary syphilis, who are not allergic to penicillin, and who have no neurologic or psychiatric findings, should be treated with benzathine penicillin G 2.4 MU intramuscularly each week for a minimum of two doses, preferably three. The third dose, while it may be unnecessary, will not harm the patient and reassures the physician that the patient's treatment was adequate. Patients who are allergic to penicillin should be desensitized and treated with penicillin. Following treatment, the patient should have serologic follow-up with quantitative

nontreponemal tests at 3, 6, 9, 12, and 24 months. Failure of the titer to fall is an indication for reevaluation, including lumbar puncture.

Because of the concerns of neurologic relapse in the setting of HIV disease, more careful CNS evaluation is recommended. Lumbar puncture is recommended in HIV-infected persons with latent syphilis (of any duration), late syphilis (even with a normal neurologic examination), and HIV-infected persons with any neurologic or psychiatric signs or symptoms. Treatment in these patients will be determined by the result of their CSF evaluation. HIV-infected persons with primary and secondary syphilis should be counseled about their possible increased risk of CNS relapse and the possibility of a lumbar puncture should be explored.

Azithromycin does not appear to treat incubating or early syphilis adequately in persons with HIV infection. Benzathine penicillin 2.4 MU intramuscularly should be used to treat all HIV-infected contacts of persons with syphilis who are at risk to acquire infection, even if prior azithromycin therapy was given.

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NONVENEREAL TREPONEMATOSES: YAWS, ENDEMIC SYPHILIS, AND PINTA

This group of diseases is called the endemic or nonvenereal treponematoses. They share many epidemiological and pathologic features. Like venereal syphilis, the clinical manifestations are divided into early and late stages. Early disease is considered infectious, and lasts for approximately 5 years. There are periods of latency. The histology is very similar in all the diseases, and similar to venereal syphilis. Cutaneous manifestations are prominent. The bones and mucosa may also be involved in some cases (except in pinta). The involvement of other organs systems and congenital disease is not seen. Children younger than 15 years are primarily affected. Person-to-person contact, or sharing of a drinking vessel, are the modes of transmission. The endemic treponematoses are closely related to poverty and a lack of available health services. They are described as occurring where the road ends. These diseases tend to occur in the tropics, especially yaws, and the wearing of few clothes and a hot, humid climate enhance them. In endemic areas, as hygiene improves, "attenuated" forms of yaws and endemic syphilis appear. A larger percentage of the population is latently infected, secondary lesions are fewer in number,

drier, and limited to moist skinfolds. Instead of several "crops" of eruptions lasting months to years, infected persons have only a single crop. Transmission is thus reduced, although a large percentage of the population may be infected.

Yaws (Pian, Frambesia, Bouba)

Yaws is caused by *T. pallidum* subsp *pertenue*, which is endemic in some tropical, rainforest regions. It is transmitted nonsexually, by contact with infectious lesions. Yaws predominantly affects children younger than 15 years of age. The disease has a disabling course, affecting the skin, bones, and joints, and is divided into early (primary and secondary) and late (tertiary) disease.

Early Yaws

A primary papule or group of papules appears at the site of inoculation after an incubation period of about 3 weeks (10 days to 3 months), during which there may be headache, malaise, and other mild constitutional symptoms. The initial lesion becomes crusted and larger, and is known as the mother yaw (*maman pian*). The crusts are amber–yellow. They may be knocked off, forming an ulcer with a red, pulpy, granulated surface, but quickly reform, so that the typical yaws lesion is crusted. The lesion is not indurated. There may be some regional adenopathy.

Exposed parts are most frequently involved—the extremities, particularly the lower legs, feet, buttocks, and face—although the mother's breasts and trunk may be infected by her child. The lesion is practically always extragenital, and when genital, is a result of accidental contact rather than intercourse. After being present for about 3 to 6 months, the mother yaw spontaneously disappears, leaving slight atrophy and depigmentation.

Weeks or months after the primary lesion appears, secondary yaws develops. Secondary lesions resemble the mother yaw, but they are smaller and may appear around the primary lesions or in a generalized pattern. The secondary lesions may clear centrally and coalesce peripherally, forming annular lesions (ringworm yaws). The palms and soles may be involved, resembling secondary syphilis. In some sites, especially around the body orifices, and in the armpits, groins, and gluteal crease, condylomatous lesions may arise, resembling condyloma lata of secondary syphilis. In drier endemic regions and during drier seasons, lesions tend to be fewer, less papillomatous, and more scaly, and instead of being generalized, favor the folds of the axillae, groin, and oral cavity. Yaws in the dry seasons and regions closely resembles endemic syphilis. The palms and soles may develop thick, hyperkeratotic plaques that fissure. They are painful, resulting in a crablike gait (crab yaws). At times there is paronychia.

In the course of a few weeks or months the secondary lesions may undergo spontaneous involution, leaving either no skin changes or hypopigmented macules that later become hyperpigmented. However, the eruption may persist for many months as a result of fresh recurrent outbreaks. The course is slower in adults than in children, in whom the secondary period rarely lasts longer than 6 months.

Painful osteoperiostitis and polydactylitis may present in early yaws as fusiform swelling of the hands, feet, arms and legs.

Late Yaws

The disease usually terminates with the secondary stage, but in about 10% it progresses to the late stage, in which gummatous lesions occur. These present as indolent ulcers with clean-cut or undermined edges, which tend to fuse to form configurate and, occasionally, serpiginous patterns clinically indistinguishable from those of tertiary syphilis. On healing, these sores cause scar tissue, leading to contractures and deformities.

Similar processes may occur in the skeletal system and other deep structures, leading to painful nodes on the bones, or destruction of the palate and nasal bone (gangosa). There may be periostitis, particularly of the tibia (saber shin, saber tibia), epiphysitis, chronic synovitis, and juxta-articular nodules. Goundou is a rare proliferative osteitis affecting initially the nasal aspects of the maxilla. Two large hard tumors form on the lateral aspects of the nose. These can significantly obstruct vision. The process may extend into other bones of the central face, affecting the palate and nose, resulting in protrusion of the whole central face as a mass. Although classically felt to spare the eye and nervous system, abnormal CSF findings in early yaws and scattered reports of eye and neurologic findings in patients with late yaws suggest that yaws, like syphilis, has the potential to cause neurologic or ophthalmic sequelae, although very rarely.

Histopathology

Early yaws shows epidermal edema, acanthosis, papillomatosis, neutrophilic intraepidermal microabscesses, and a moderate-to-dense perivascular infiltrate of lymphocytes and plasma cells. Treponema are usually demonstrable in the primary and secondary stages with the use of the same silver stains used in diagnosing syphilis. Tertiary yaws shows features identical to the gumma of tertiary syphilis.

Diagnosis

The diagnosis should be suspected by the typical clinical appearance in a person living in an endemic region. The presence of keratoderma palmaris et plantaris in such a person is highly suggestive of yaws. Darkfield demonstration of spirochetes in the early lesions and a reactive VDRL or RPR test can be used to confirm primary and secondary yaws.

Endemic Syphilis (Bejel)

Bejel is a Bedouin term for this nonvenereal treponematosis, which occurs primarily in the seminomadic tribes who live in the arid regions of North Africa, Southwest Asia, and the Eastern Mediterranean. The etiologic agent of bejel is considered to be *T. pallidum* subsp *endemicum*. It occurs primarily in childhood and is spread by skin contact or from mouth to mouth by kissing or use of contaminated drinking vessels. The skin, oral mucosa, and skeletal system are primarily involved.

Primary lesions are rare, probably occurring undetected in the oropharyngeal mucosa. The most common presentation is with secondary oral lesions resembling mucous patches. These are shallow, relatively painless ulcerations, occasionally accompanied by laryngitis. Split papules, angular cheilitis, condylomatous lesions of the moist folds of the axillae and groin, and a nonpruritic generalized papular eruption may be seen. Generalized lymphadenopathy is common. Osteoperiostitis of the long bones may occur, causing nocturnal leg pains.

Untreated secondary bejel heals in 6 to 9 months. In the tertiary stage, leg pain and gummatous ulcerations of the skin, nasopharynx, and bone occur. Gangosa (rhinopharyngitis mutilans) can result. Rarely reported neurologic sequelae seem to be restricted to the eye, including uveitis, choroiditis, chorioretinitis, and optic atrophy. The diagnosis of bejel is confirmed by the same means as for venereal syphilis.

Pinta

Pinta is an infectious, nonvenereal, endemic treponematosis caused by *Treponema carateum*. The mode of transmission is unknown, but repeated, direct lesion-to-skin contact is likely. Only skin lesions occur. By contrast with yaws and bejel, pinta affects persons of all ages. While once prevalent in the forests and rural areas of Central and South America, and Cuba, it is now found only in scattered areas of the Brazilian rainforest. The manifestations of pinta may be divided into primary, secondary (early), and tertiary (late) stages, but historically patients may describe continuous evolution from secondary dyspigmented lesions to the characteristic achromic lesions of tertiary pinta.

Primary Stage

It is believed that the initial lesion appears 7 to 60 days after inoculation. The lesion begins as a tiny red papule that becomes an elevated, ill-defined, erythematous, infiltrated plaque up to 10 to 12.5 cm in diameter in the course of 2 to 3 months. Expansion of the primary lesion may occur by fusion with surrounding satellite macules or papules. Ultimately, it becomes impossible to distinguish the primary lesion from the secondary lesions. At no time is there erosion or ulceration such as occurs in the syphilitic chancre. Most initial lesions of pinta develop on the legs and other uncovered parts. The STS is nonreactive in the primary stage. Darkfield examination may be positive.

Secondary Stage

The secondary stage appears from 5 months to 1 year or more after infection. It begins with small, scaling papules that may enlarge and coalesce, simulating psoriasis, ringworm, eczema, syphilis, or leprosy. They are located mostly on the extremities and face and frequently are somewhat circinate. Over time, the initially red to violaceous lesions show postinflammatory hyperpigmentation in shades of gray, blue, or brown, or hypopigmentation. Secondary lesions are classified as erythematous, desquamative, hypochromic or hyperchromic. Multiple different morphologies may be present simultaneously, giving a very polymorphous appearance. Nontreponemal tests for syphilis are reactive in the secondary stage in about 60% of patients. Darkfield examination may show spirochetes.

Late Dyschromic Stage

Until the 1940s, the late pigmentary changes were the only recognized clinical manifestations of pinta. These have an insidious onset, usually in adolescents or young adults, of widespread depigmented macules resembling vitiligo. The lesions are located chiefly on the face, waistline, wrist flexures, and trochanteric region, although at times diffuse involvement occurs, so that large areas on the trunk and extremities are affected. The lesions are symmetrical in over one-third of patients. Hemipinta is a rare variety of the disease in which the pigmentary disturbances affect only half of the body. In the late dyschromic stage of pinta, the STS is positive in nearly all patients.

Histopathology

Skin lesions in early pinta show moderate acanthosis; occasionally, lichenoid changes with basal layer vacuolization; and an upper dermal perivascular infiltrate of lymphocytes and plasma cells. Melanophages are prominent in the upper dermis. Spirochetes may be demonstrated in the epidermis by special stains in primary, secondary, and hyperpigmented lesions of tertiary pinta. In tertiary pinta the depigmented skin shows a loss of basal pigment, pigmentary incontinence, and virtually no dermal inflammatory infiltrate. Spirochetes are rarely found in depigmented tertiary lesions.

Treatment

The treatment of choice is benzathine penicillin G, 1.2 to 2.4 MU intramuscularly (0.6–1.2 MU for children under 10 years of age). In penicillin-allergic patients, tetracycline 500 mg four times a day for adults (and erythromycin for children, 8 to 10 mg/kg four times a day for 15 days) are recommended. Penicillin-resistant yaws has been reported from New Guinea. In tertiary pinta, the blue color gradually disappears, as do the areas of partial depigmentation. The vitiliginous areas, if present for more than 5 years, are permanent. Eradication of these diseases is possible with persistent and effective treatment strategies. These include: 1) screening of the whole population in endemic areas; 2) diagnosis of patients seen at health services and by community outreach; 3) health education; and 4) improved hygiene (soap and water). If more than 10% of the population is affected, the whole population is treated (mass treatment). If 5% to 10% of the population is affected, treat all active cases, all children under the age of 15, and all contacts (juvenile mass treatment). If under 5% of the population is infected, treat all active cases and all household and close personal contacts (selective mass treatment). Unfortunately, with the areas affected by the endemic treponematoses also struggling with epidemics of HIV, tuberculosis, and malaria, eradication programs have been largely discontinued.

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CHAPTER

19 Viral Diseases

Viruses are obligatory intracellular parasites. The structural components of a viral particle (virion) consist of a central core of nucleic acid, a protective protein coat (capsid), and (in certain groups of viruses only) an outermost membrane or envelope. The capsid of the simplest viruses is made up of many identical polypeptides (structural units) that fold and interact with one another to form morphologic units (capsomeres). The number of capsomeres is believed to be constant for each virus with cubic symmetry, and it is an important criterion in the classification of viruses. The protein coat determines serologic specificity, protects the nucleic acid from enzymatic degradation in biologic environments, controls host specificity, and increases the efficiency of infection. The outermost membrane of the enveloped viruses is essential for the attachment to, and penetration of, host cells. The envelope also contains important viral antigens.

Two main groups of viruses are distinguished: DNA and RNA. The DNA virus types are parvovirus, papovavirus, adenovirus, herpesvirus, and poxvirus. RNA viruses are picornavirus, togavirus, reovirus, coronavirus, orthomyxovirus, retrovirus, arenavirus, rhabdovirus, and paramyxovirus. Some viruses are distinguished by their mode of transmission: arthropod-borne viruses, respiratory viruses, fecal–oral or intestinal viruses, venereal viruses, and penetrating wound viruses.

HERPESVIRUS GROUP

The herpesviruses are medium-sized viruses that contain double-stranded DNA and replicate in the cell nucleus. They are characterized by the ability to produce latent, but lifelong infection by infecting immunologically protected cells (immune cells and nerves). Intermittently they have replicative episodes with amplification of the viral numbers in anatomic sites which are conducive to transmission from one host to the next (genital skin, orolabial region). The vast majority of infected persons remain asymptomatic. Viruses in this group are varicella zoster virus (VZV); herpes simplex virus (HSV)-1 and -2; cytomegalovirus (CMV); Epstein-Barr virus (EBV); human herpesviruses (HHV)-6, -7, and -8; *Herpesvirus simiae* (B virus); and other viruses of animals.

Herpes Simplex

Infection with HSV is one of the most prevalent infections worldwide. HSV-1 infection, the cause of most cases of orolabial herpes, is more common than infection with HSV-2, the cause of most cases of genital herpes. Between 30% and 95% of adults (depending on the country and group tested) are seropositive for HSV-1. Seroprevalence for HSV-2 is lower, and it appears at the age of onset of sexual activity. In Scandinavia, the rate of infection with HSV-2 increases from 2% in 15-year-olds to 25% in 30-year-olds. About 2.4% of adults become infected annually with HSV-2 in their third decade of life. In the US about 25% of adults are infected with HSV-2. In sexually-transmitted disease (STD) clinic patients, the infection rate is between 30% and 50%. In sub-Saharan Africa, infection rates are between 60% and 95%. Worldwide, the seroprevalence is higher in human immunodeficiency virus (HIV)-infected persons. Serologic data have demonstrated that many more people are infected than give a history of clinical disease. For HSV-1, about 50% of infected persons give a history of orolabial lesions. For HSV-2, 20% of infected persons are completely asymptomatic (latent infection), 20% have recurrent genital herpes they recognize, and 60% have clinical lesions that they do not recognize as genital herpes (subclinical or unrecognized infection). Most persons with HSV-2 infection are symptomatic, but the majority do not recognize that their symptoms are caused by HSV. All persons infected with HSV-1 and -2 infection are potentially infectious.

HSV infections are classified as either "first episode" or "recurrent." Most patients have no lesions or findings when they are initially infected with an HSV. When the patient has his/her first clinical lesion, this is usually a recurrence. Since the initial clinical presentation is not associated with a new infection, the old terminology of "primary" infection has been abandoned. Instead the initial clinical presentation is called a "first episode" and may represent a true primary infection or a recurrence. Persons with chronic or acute immunosuppression may have prolonged and atypical clinical courses.

Infections with HSV-1 or -2 are diagnosed by specific and nonspecific methods. The most common procedure used in the office is the Tzanck smear. It is nonspecific since both HSV and VZV infections result in the formation of multinucleate epidermal giant cells. The multiple nuclei are molded or fit together like pieces of a puzzle. Although the technique is rapid, its success depends heavily on the skill of the interpreter. The accuracy rate is between 60% and 90%, with a false-positive rate of 3% to 13%. The direct fluorescent antibody (DFA) test is more accurate, will identify virus type, and results can be available in hours if a virology laboratory is nearby. Viral culture is very accurate and rapid, since HSV is stable in transport and grows readily and rapidly in culture. Results are often available in 48 to 72 h. Polymerase chain reaction (PCR) is as accurate as viral culture and can be performed on dried or fixed tissue. Skin biopsies of lesions can detect viropathic changes caused by HSV, and with specific HSV antibodies, immunoperoxidase techniques can accurately diagnose infection. The accuracy of various tests is dependent on lesion morphology. Only acute, vesicular lesions are likely to be positive with Tzanck smears. Crusted, eroded, or ulcerative lesions are best diagnosed by viral culture, fluorescent antibody, histologic methods, or PCR.

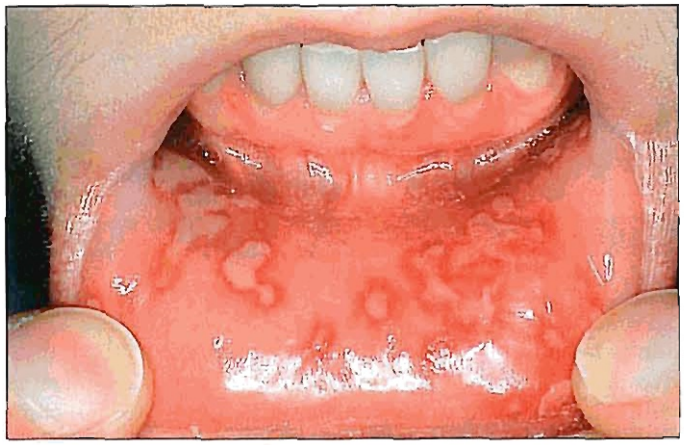

Fig. 19-1 Herpetic gingivostomatitis, extensive erosions of the oral mucosa.

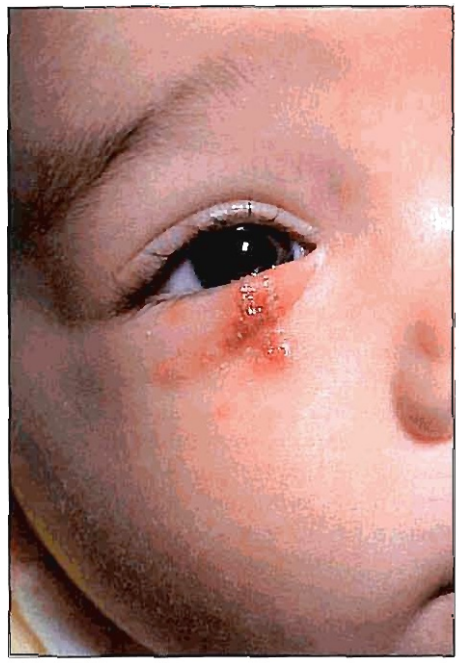

Fig. 19-2 HSV-1, *eyelid infection from* a "kiss" from an infected adult.

Serologic tests are generally not used in determining whether a skin lesion is due to HSV infection. A positive serologic test indicates only that the individual is infected with that virus, not that the viral infection is the cause of the current lesion. Second-generation enzyme-linked immunosorbent assay (ELISA) tests and G protein-specific Western blot serologic tests can detect specific infection with HSV-1 and -2 but cannot determine the duration or source of that infection. In addition to determining the infection rate in various populations, serologic tests are most useful in evaluating couples in which only one partner gives a history of genital herpes (*discordant couples*), *in couples at risk for* neonatal herpes infection, and for possible HSV vaccination when it becomes available.

Orolabial Herpes Orolabial herpes is virtually always caused by HSV-1. In 1% or less of newly infected persons, herpetic gingivostomatitis develops, chiefly in children and young adults (Fig. 19-1). The onset is often accompanied by high fever, regional lymphadenopathy, and malaise. The herpetic lesions in the mouth are usually broken vesicles that appear as erosions or ulcers covered with a white membrane. The erosions may become widespread on the oral mucosa, tongue, and tonsils, and produce pain, foul breath, and dysphagia. In young children, dehydration may occur. It may cause pharyngitis, with ulcerative or exudative lesions of the posterior pharynx. The duration, untreated, is 1 to 2 weeks.

The most frequent clinical manifestation of orolabial herpes is the "cold sore" or "fever blister." Recurrent HSV-1 is the cause 95% or more of the time, and typically presents as grouped blisters on an erythematous base. The lips near the vermilion are most frequently involved. Lesions may, however, occur wherever the virus was inoculated or proliferated during the initial episode (Fig. 19-2). Recurrences may be seen on the cheeks, eyelids, and earlobes. Outbreaks are variable in severity, partly related to the trigger of the outbreak. Some outbreaks are small and resolve rapidly, while others may be severe, involving both the upper and lower lips (Fig. 19-3). In severe outbreaks, lip swelling is often present. Patient symptomatology is variable. A prodrome of up to 24 h of tingling, itching, or burning may precede the outbreak. Local discomfort as well as headache, nasal congestion, or mild flu-like symptoms may occur. Ultraviolet (UV) exposure, especially UVB, is a frequent trigger of

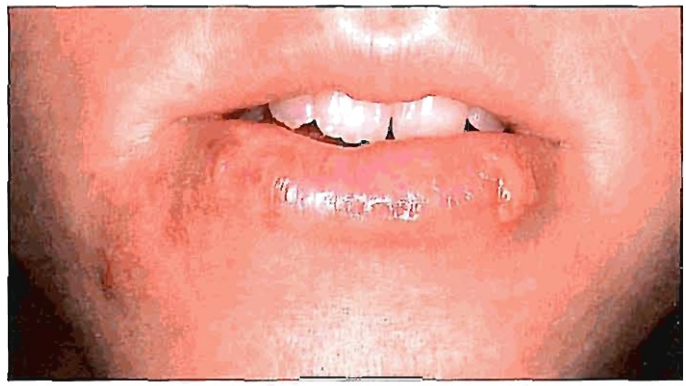

Fig. 19-3 Orolabial herpes simplex, severe outbreak triggered by a sunburn.

recurrent orolabial HSV, and the severity of the outbreak may correlate with the intensity of the sun exposure. HSV may also recur intraorally, usually on fixed, keratinized mucosa of the gingiva or hard palate.

In most patients recurrent orolabial herpes represents more of a nuisance than a disease. Because UVB radiation is a common trigger, use of a sunblock daily on the lips and facial skin may reduce recurrences. All therapies for the acute treatment of recurrent orolabial herpes have limited efficacy, reducing disease duration and pain by one day or less. Topical treatment with tetracaine cream and penciclovir cream has modest affects on reduction of lesion number, healing time, and discomfort. Acyclovir cream (not ointment) has some efficacy. Topical acyclovir ointment and docosanol cream provide minimal to no reduction in healing time or discomfort. If oral therapy is contemplated for patients with severely symptomatic recurrences of orolabial HSV, it must be remembered that much higher doses of oral antivirals are required than for the treatment of genital herpes. Intermittent treatment with valacyclovir 2 g twice a day for 1 day, starting at the onset of the prodrome is a simple and effective oral regimen. Since the patient's own inflammatory reaction against the virus contributes substantially to the severity

of lesions of orolabial herpes simplex, topical therapy with a high-potency topical steroid (fluocinonide gel 0.05% three times a day) in combination with an oral antiviral (famciclovir 500 mg three times a day) was studied. The combination therapy was superior, reducing pain, maximum lesion area, and time of healing. If episodic treatment for orolabial HSV is recommended, and an oral agent is used, the addition of a high-potency topical steroid should be considered.

Although most patients with orolabial herpes simplex do not require treatment, certain medical and dental procedures may trigger outbreaks of HSV. If the cutaneous surface has been damaged by the surgical procedure (such as a dermabrasion, chemical peel, or laser resurfacing procedure) the surgical site can be infected by the virus and result in prolonged healing and possible scarring. Prophylaxis is regularly used before such surgeries in patients with a history of orolabial herpes simplex. Famciclovir 250 mg twice a day and valacyclovir 500 mg twice a day are prophylactic options, to be begun 24 h before the procedure, or the morning of the procedure and continued for 10 to 14 days. Prophylaxis could also be considered before skiing or tropical vacations and extensive dental procedures at the same dosages. In persons with frequent orolabial recurrences, chronic suppressive acyclovir therapy in a dose of 400 mg twice a day can reduce the number of outbreaks by 50%.

Herpetic Sycosis Recurrent or initial herpes simplex infections (usually due to HSV-1) may affect primarily the hair follicle. The clinical appearance may vary from a few eroded follicular papules (resembling acne excoree) to extensive lesions involving the whole beard area. Close razor blade shaving immediately prior to initial exposure or in the presence of an acute orolabial lesion may be associated with a more extensive eruption. The onset may be very acute (over days) or more subacute or chronic. Diagnostic clues include the tendency for erosions, a self-limited course of 2 to 3 weeks, and an appropriate risk behavior. The diagnosis may be confirmed by biopsy. Although the herpes infection is primarily in the follicle, surface cultures of eroded lesions will usually be positive in the first 5 to 7 days of the eruption.

Herpes Gladiatorum HSV-1 infection is highly contagious to susceptible persons who wrestle with an infected individual with an active lesion. One-third of susceptible wrestlers will get infected after a single match. In tournaments and wrestling camps, outbreaks can be epidemic, affecting up to 20% of all participants. Lesions usually occur on the lateral side of the neck, side of the face, and the forearm, all areas in direct contact with the face of the infected wrestler (Fig. 19-4). Vesicles appear 4 to 11 days after exposure, often preceded by 24 h of malaise, sore throat, and fever. Lesions are frequently misdiagnosed as a bacterial folliculitis. Any wrestler with a confirmed history of orolabial herpes should be on suppressive antiviral therapy during all periods of training and competition. Rugby players, especially forwards who participate in scrums, are also at risk.

Herpetic Whitlow HSV infection may uncommonly occur on the fingers or periungually. Lesions begin with tenderness and erythema usually of the lateral nailfold or on the palm. Deep-seated blisters develop 24 to 48 h after symptoms begin (Fig. 19-5). The blisters may be very small, requiring careful inspection to detect them (Fig. 19-6). Deep-seated lesions that appear unilocular may be mistaken for a paronychia or other inflammatory process. Lesions may progress to erosions, or heal without ever impairing epidermal integrity due to the thick stratum corneum in this location. Herpetic whitlow may simulate a felon. Swelling of the affected hand is not uncommon. Lymphatic streaking and swelling of the epitrochlear or axillary lymph nodes may occur, mimicking a bacterial cellulitis. Repeated episodes of herpetic lymphangitis may lead to persistent lymphedema of the affected hand. Herpetic whitlow is much less frequent among healthcare workers since the institution of universal precautions and glove use during contact with the oral mucosa. Currently, most cases are seen in persons with herpes elsewhere. Children may be infected while thumb sucking or nail biting during their initial herpes outbreak or by touching an infectious lesion of an adult. Herpetic whitlow is bimodal in distribution, with about 20% of cases occurring in children younger than 10 years old, and 55% of cases between the ages of 20 and 40. All cases in children are caused by HSV-1, but in adults up to three-quarters of cases are caused by HSV-2. Among adults, herpetic whitlow is twice as common in females. Herpetic whitlow in healthcare workers can be transmitted to patients. In patients whose oropharynx is exposed to the ungloved hands of healthcare workers with herpetic whitlow, 37% develop herpetic pharyngitis.

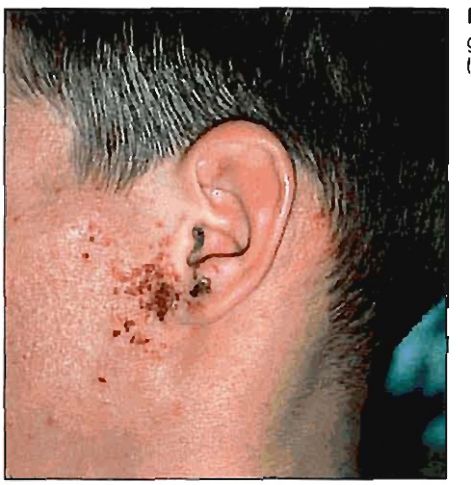

Fig. 19-4 Herpes gladiatorum, neck lesions of HSV-1.

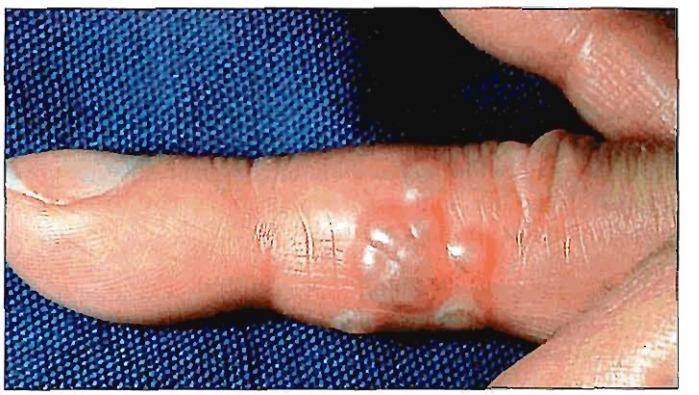

Fig. 19-5 Herpetic whitlow, classic grouped blisters.

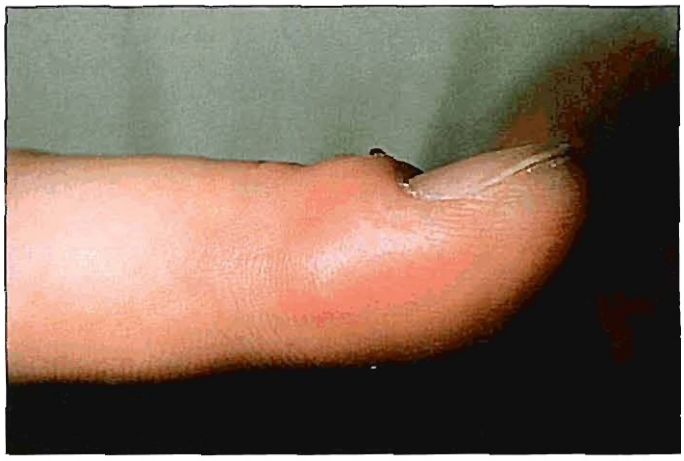

Fig. 19-6 Herpetic whitlow.

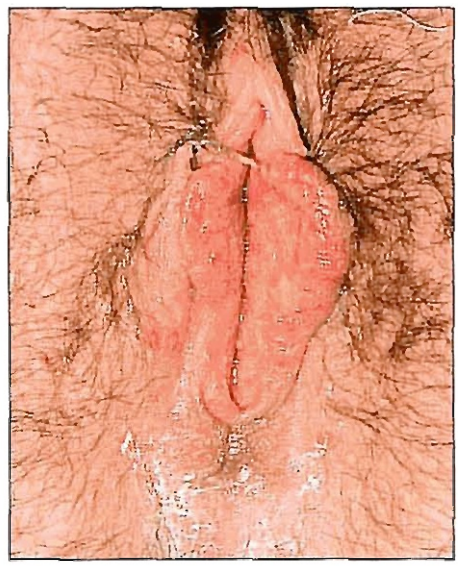

Fig. 19-7 Initial episode of genital herpes, HSV-2.

Herpetic Keratoconjunctivitis Herpes simplex infection of the eye is a common cause of blindness in the US. It occurs as a punctate or marginal keratitis, or as a dendritic corneal ulcer, which may cause disciform keratitis and leave scars that impair vision. Topical corticosteroids in this situation may induce perforation of the cornea. Vesicles may appear on the lids, and preauricular nodes may be enlarged and tender. Recurrences are common.

Genital Herpes Genital herpes infection is usually due to HSV-2, causing 85% of initial infections and up to 98% of recurrent lesions. In the mid-1980s, the prevalence of genital herpes caused by HSV-1 began to increase because of changes in sexual habits, so that in some developed countries HSV-1 has caused up to 40% of anogenital herpes in women. HSV-1 in the genital area is much less likely to recur than HSV-2.

Genital herpes is spread by skin-to-skin contact, usually during sexual activity. The incubation period averages 5 days. Active lesions of HSV-2 contain live virus and are infectious. Persons with recurrent genital herpes shed virus asymptomatically between outbreaks (asymptomatic shedding). Asymptomatic shedding occurs simultaneously from several anatomic sites (penis, vagina, cervix, and rectum) and can occur through normally appearing intact skin and mucosae. In addition, persons with HSV-2 infection may have lesions they do not recognize as being caused by HSV (unrecognized outbreak) or have recurrent lesions that do not cause symptoms (subclinical outbreak). Most transmission of genital herpes occurs during subclinical or unrecognized outbreaks, or while the infected person is shedding asymptomatically.

The risk of transmission in monogamous couples, in which only one partner is infected, is about 5% to 10% annually, with women being at much greater risk than men for acquiring HSV-2 from their infected partner. Prior HSV-1 infection does not reduce the risk of being infected with HSV-2 but does make it more likely that initial infection will be asymptomatic. There is no strategy that absolutely prevents herpes transmission. All prevention strategies are more effective in reducing the risk of male-to-female transmission than female-to-male transmission. Condom use for all sexual exposures and avoiding sexual exposure when active lesions are present have been shown to be effective strategies. Chronic suppressive therapy of the infected partner with valacyclovir 500 mg/day reduces the risk of transmission to a susceptible partner by about 50%.

The symptomatology during acquisition of infection with HSV-2 has a broad clinical spectrum from totally asymptomatic to severe genital ulcer disease (erosive vulvovaginitis or proctitis). Only 57% of new HSV-2 infections are symptomatic. Clinically, the majority of symptomatic initial herpes lesions are classic grouped blisters on an erythematous base. At times the initial clinical episode is that of typical grouped blisters, but with a longer duration of 10 to 14 days. While uncommon and representing 1% or fewer of new infections, severe first-episode genital herpes can be a significant systemic illness. Grouped blisters and erosions appear in the vagina, rectum, or on the penis with continued development of new blisters over 7 to 14 days. Lesions are bilaterally symmetrical, often extensive, and the inguinal lymph nodes can be enlarged bilaterally (Fig. 19-7). Fever and flu-like symptoms may be present, but in women the major complaint is vaginal pain and dysuria (herpetic vulvovaginitis). The whole illness may last 3 weeks or more. If the inoculation occurs in the rectal area, severe proctitis may occur from extensive erosions in the anal canal and on the rectal mucosa. The initial clinical episode of genital herpes is treated with oral acyclovir 200 mg five times a day or 400 mg three times a day, famciclovir 250 mg three times a day, or valacyclovir 1000 mg twice a day, all for 7 to 10 days.

Virtually all persons infected with HSV-2 will have recurrences, even if the initial infection was subclinical or asymptomatic. HSV-2 infection results in recurrences in the genital area six times more frequently than HSV-1. Twenty percent of persons with HSV-2 infection are truly asymptomatic, never having had either an initial lesion or recurrences. Twenty percent of patients have lesions they recognize as recurrent genital herpes and 60% have clinical lesions that are culture positive for HSV-2, but are unrecognized by the patient as being caused by genital herpes. This large group of persons with subclinical or unrecognized genital herpes is infectious, at least intermittently, and represents one factor in the increasing number of new HSV-2 infections.

Typical recurrent genital herpes begins with a prodrome of burning, itching, or tingling. Usually within 24 h, red papules

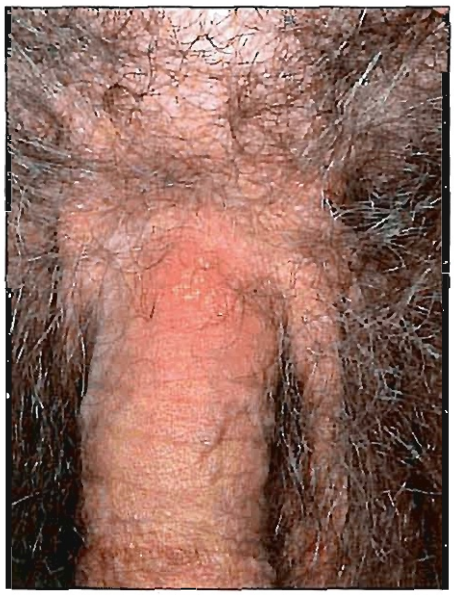

Fig. 19-8 Recurrent genital herpes.

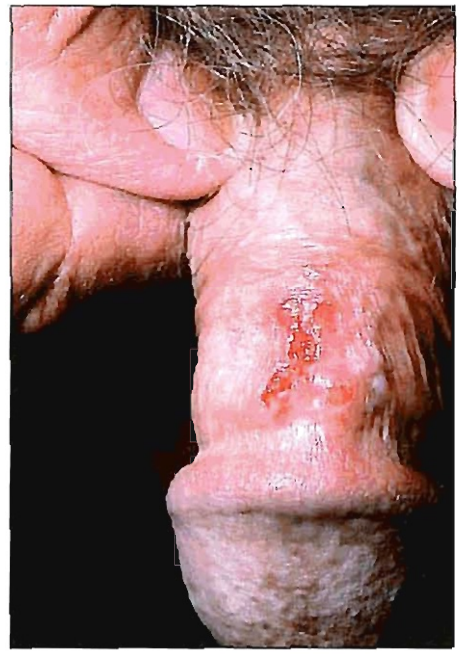

Fig. 19-9 Recurrent genital herpes.

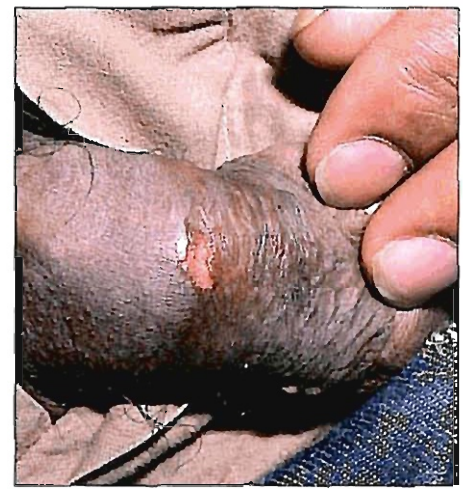

Fig. 19-10 Genital herpes, solitary ulceration.

appear at the site, progress to blisters filled with clear fluid over 24 h, form erosions over the next 24 to 36 h, and heal in another 2 to 3 days (Figs 19-8 to 19-10). The total duration of a typical outbreak of genital herpes is 7 days. Lesions are usually grouped blisters, and the coalescent grouped erosions they evolve into characteristically have a scalloped border. Erosions or ulcerations from genital herpes are usually very tender and not indurated (as opposed to the chancre of primary syphilis). Lesions tend to recur in the same anatomic region, although not at exactly the same site (as opposed to a fixed drug eruption). Less classic clinical manifestations are tiny erosions or linear fissures on the genital skin. Lesions occur on the vulva, vagina, and cervical mucosa, as well as the penile and vulval skin. The upper buttock is a common site for recurrent genital herpes in both men and women. Intraurethral genital herpes may present with dysuria and a clear penile discharge, and is usually misdiagnosed as a more common, nongonococcal urethritis such as *Chlamydia* or *Ureaplasma*. Inguinal adenopathy may be present. Looking into the urethra and culturing any erosions will establish the diagnosis. Recurrent genital herpes heals without scarring unless the lesion is secondarily infected.

The natural history of untreated recurrent genital herpes is not well studied. Over the first several years of infection, the frequency of recurrences often stays the same. Over longer periods (more than 3 to 5 years) the frequency of outbreaks decreases.

Recurrent genital herpes is a problematic disease due to the social stigma associated with it. Because it is not curable, patients frequently demonstrate a significant emotional response when they are first diagnosed. These include anger (at the presumed source of the infection), depression, guilt, and the feeling they are not worthy. During the visit the healthcare worker should ask about a patient's feelings surrounding the diagnosis and any psychological complications that have occurred. This psychological component of genital herpes must be recognized, addressed directly with the patient, and managed for the therapy of recurrent genital herpes to be successful.

Management of recurrent genital herpes should be individualized. A careful history, including a sexual history, should be obtained. Examination should include seeing the patient during an active recurrence, so that the infection can be confirmed. The diagnosis of recurrent genital herpes should not be made on clinical appearance alone because of the psychological impact of the diagnosis. The diagnosis is best confirmed by a viral culture or DFA examination, allowing for typing of the causative virus.

Treatment depends on several factors including the frequency of recurrences, severity of recurrences, infection status of the sexual partner, and psychological impact of the infection on the patient. For patients with few or mildly symptomatic recurrences, treatment is often not necessary. Counseling regarding transmission risk is required. In patients with severe but infrequent recurrences or in those who have severe psychological complications, intermittent therapy may be useful. To be effective, intermittent therapy must be initiated at the earliest sign of an outbreak. The patient must be given the medication before the recurrence, so treatment can be started by the patient when the first symptoms appear. Intermittent therapy only reduces the duration of the average recurrence by about 1 day. However, it is a powerful tool in the patient who is totally overwhelmed by each outbreak. The treatment of recurrent genital herpes is acyclovir 200 mg five times a day or 800 mg twice a day, or famciclovir 125 mg twice a day, both for 5 days. Valacyclovir may be used at a dose of 500 mg twice a day for 3 days.

For patients with frequent recurrences (more than 6 to 12 per year), suppressive therapy is more reasonable. Acyclovir, 400 mg twice a day, 200 mg three times a day, or 800 mg once a day will suppress 85% of recurrences, and 20% of patients will be recurrence-free during suppressive therapy.

Valacyclovir, 500 mg/day (or 1000 mg/day for persons with >10 recurrences per year), or famciclovir, 250 mg twice a day, are equally effective alternatives. In addition, chronic suppressive therapy reduces asymptomatic shedding by almost 95%. After 10 years of suppressive therapy a large number of patients can stop treatment with a substantial reduction in frequency of recurrences. Chronic suppressive therapy is very safe and laboratory monitoring is not required.

Intrauterine and Neonatal Herpes Simplex Neonatal herpes infections occurs in between 1 in 1400 and 1 in 30,000 pregnancies, resulting in 1500 to 2200 cases of neonatal herpes annually in the US. Eighty-five percent of cases of neonatal herpes simplex infections occur at the time of delivery, 5% occur in utero with intact membranes, and 10% to 15% occur from nonmaternal sources after delivery. In utero infection may result in fetal anomalies to include skin lesions and scars, limb hypoplasia, microcephaly, microphthalmos, encephalitis, chorioretinitis, and intracerebral calcifications. It is either fatal or complicated by permanent neurologic sequelae.

Seventy percent of cases of neonatal herpes simplex are caused by HSV-2. Neonatal HSV-1 infections are usually acquired postnatally through contact with a person with orolabial disease, but can also occur intrapartum if the mother is genitally infected with HSV-1. The clinical spectrum of perinatally acquired neonatal herpes can be divided into three forms: 1) localized infection of the skin, eyes and/or mouth (SEM); 2) central nervous system (CNS) disease; and 3) disseminated disease (encephalitis, hepatitis, pneumonia, and coagulopathy). The pattern of involvement at presentation is important prognostically. With treatment, localized disease (skin, eyes, or mouth) is rarely fatal, whereas brain or disseminated disease is fatal in 15% to 50% of neonates so affected. In treated neonates, long-term sequelae occur in 10% of neonates with localized disease. More than 50% of cases of CNS or disseminated neonatal herpes suffer neurologic disability.

In 68% of infected babies, skin vesicles are the presenting sign, and are a good source for virus recovery. However, 39% of neonates with disseminated disease, 32% with CNS disease, and 17% with SEM disease never develop vesicular skin lesions. Because the incubation period may be as long as 3 weeks, and averages about 1 week, skin lesions and symptoms may not appear until the child has been discharged from hospital.

The diagnosis of neonatal herpes is confirmed by viral culture or preferably immediate DFA staining of material from skin or ocular lesions. CNS involvement is detected by PCR of the cerebrospinal fluid (CSF). PCR of the CSF is negative in 24% of cases of neonatal CNS herpes infection, so empiric therapy pending other testing may be required. Neonatal herpes infections are treated with intravenous acyclovir 60 mg/kg/day for 14 days for SEM disease and 21 days for CNS and disseminated disease.

Seventy percent of mothers of infants with neonatal herpes simplex are asymptomatic at the time of delivery and have no history of genital herpes. Thus, extended history taking is of no value in predicting which pregnancies may be complicated by neonatal herpes. The most important predictors of infection appear to be the nature of the mother's infection at delivery (first episode versus recurrent), and the presence of active lesions on the cervix, vagina, or vulvar area. The risk of infection for an infant delivered vaginally when the mother has active *recurrent* genital herpes infection is between 2% and 5%, whereas it is 26% to 56% if the maternal infection at delivery is a first episode. One strategy to prevent neonatal HSV would be to prevent transmission of HSV to at-risk women during pregnancy, eliminating initial HSV episodes during pregnancy. To accomplish this, pregnant women and their partners would be tested to identify discordant couples for HSV-1 and -2. If the woman is HSV-1 negative and the man is HSV-1 positive, orogenital contact during pregnancy should be avoided, and a condom should be used for all episodes of sexual contact. Valacyclovir suppression of the infected male could also be considered, but might have limited efficacy. If the woman is HSV-2 seronegative and her partner is HSV-2 seropositive, barrier protection for sexual contact during gestation is recommended, and valacyclovir suppression of the man could be considered. This strategy has not been tested and could not be guaranteed to prevent all cases of neonatal HSV. At a minimum, discordant couples should be made aware of the increased risk to the fetus that acquisition of HSV by the mother during pregnancy presents.

The appropriate management of pregnancies complicated by genital herpes is complex and there are still areas of controversy. Routine prenatal cultures are not recommended for women with recurrent genital herpes, as they do not predict shedding at the time of delivery. Such cultures may be of value in women with primary genital herpes during pregnancy. Scalp electrodes should be avoided in deliveries where cervical shedding of HSV is possible as they have been documented to increase the risk of infection of the newborn by up to seven-fold (Fig. 19-11). Vacuum-assisted delivery also increases the relative risk of neonatal transmission of HSV by between 2 and 27 times. Genital HSV-1 infection appears to be much more frequently transmitted intrapartum than HSV-2. The current recommendation is still to perform cesarean section in the setting of active genital lesions or prodromal symptoms. This will reduce the risk of transmission of HSV to the infant from 8% to 1% for women who are culture positive from the cervix at time of delivery. However, this approach will not prevent all cases of neonatal herpes, is expensive, and has a high maternal

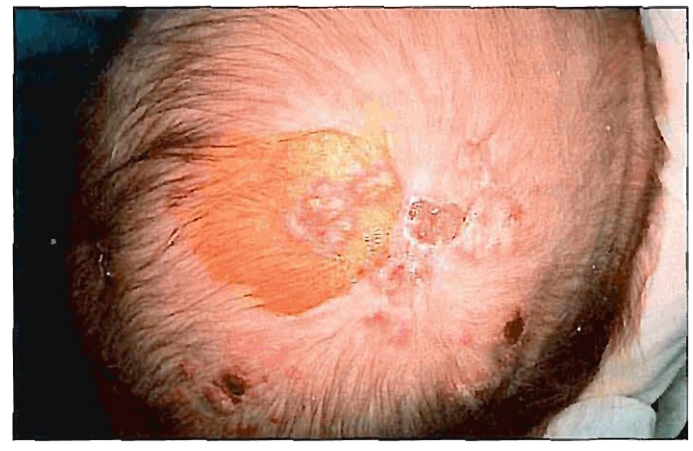

Fig. 19-11 Neonatal herpes, a scalp monitor was associated with infection of this neonate.

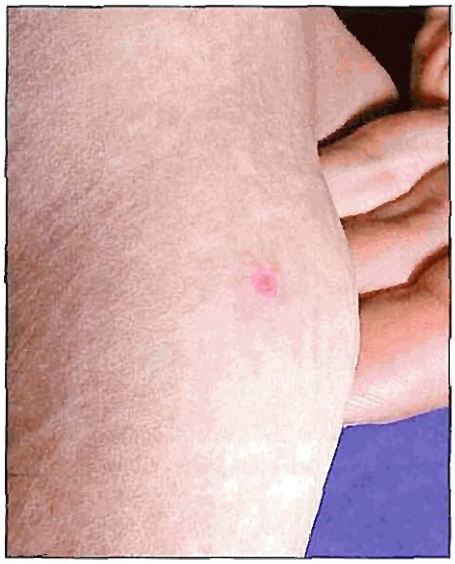

Fig. 19-12 Extensive congenital erosions and vesicles healing with reticulate scarring (the erosion on the arm was culture positive for HSV-1).

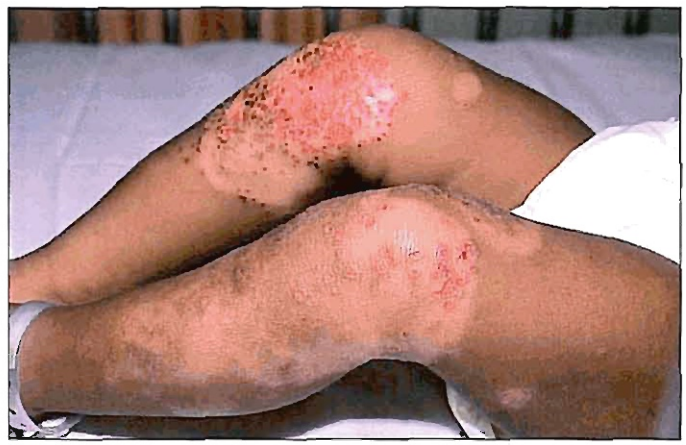

Fig. 19-13 Eczema herpeticum, sudden appearance of uniform erosions, accentuated in areas of active dermatitis.

morbidity. (US$2.5 million to prevent each case of neonatal herpes, 1580 excess cesarian sections for every poor outcome case of neonatal HSV prevented, and 0.57 maternal deaths for every neonatal death prevented.) Because the risk of neonatal herpes is much greater in mothers who experience their initial episode during pregnancy, antiviral treatment of all initial episodes of genital HSV in pregnancy is recommended (except in the first month of gestation where there may be an increased risk of spontaneous abortion). Standard acyclovir doses for initial episodes (acyclovir 400 mg twice a day for 10 days) are recommended. This is especially true for all initial episodes in the third trimester. Chronic suppressive therapy with acyclovir has been used from 36 weeks gestation to delivery in women with an initial episode of genital HSV during pregnancy to reduce outbreaks and prevent the need for cesarean section. This approach has been recommended by the American College of Obstetrics and Gynecology, and may also be considered for women with recurrent genital herpes, although this has not been documented to reduce the need for cesarean section.

The condition of extensive congenital erosions and vesicles healing with reticulate scarring may represent intrauterine neonatal herpes simplex (Fig. 19-12). The condition is rare due to the rarity of intrauterine HSV infections, and usually fatal. Only a few children probably survive to present later in life with the characteristic widespread reticulate scarring of the whole body. This may explain the associated CNS manifestations seen in many affected children. One of the authors (TB) has seen a child with this condition who developed infrequent widespread cutaneous blisters from which HSV could be cultured. Modern obstetric practices which screen for herpes in pregnant women and prophylactic treatment with acyclovir in the third trimester may prevent the condition, explaining the lack of recent cases.

Eczema Herpeticum Infection with herpesvirus in patients with atopic dermatitis may result in spread of herpes simplex throughout the eczematous areas (Kaposi varicelliform eruption). In a large series it was found to be closely associated with severe and under-treated atopic dermatitis, and an elevated IgE level, but was not associated with recent systemic steroid usage. Cutaneous dissemination of HSV-1 or -2 may also occur in severe seborrheic dermatitis, scabies, Darier's disease, benign familial pemphigus, pemphigus (foliaceus or vulgaris), pemphigoid, Wiskott-Aldrich syndrome, or burns. In its severest form, hundreds of umbilicated vesicles may be present at the onset, with fever and regional adenopathy. Although the cutaneous eruption is alarming, the disease is often self-limited in healthy individuals. Much milder cases are much more common and probably go unrecognized and untreated. They present as a few superficial erosions or even small papules (Fig. 19-13). Topical immune modulators therapy may be complicated by eczema herpeticum in about 2% of patients. Depending on the severity of the disease, either intravenous or oral acyclovir therapy should be given in all cases of Kaposi varicelliform eruption.

Immunocompromised Patients In patients with immunosuppression of the cell-mediated immune system by cytotoxic agents, corticosteroids, or congenital or acquired immunodeficiency, primary and recurrent cases of herpes simplex are more severe, more persistent, and more symptomatic. In some settings (such as in bone marrow transplant recipients), the risk of severe reactivation is so high that prophylactic systemic antivirals are administered. In immunosuppressed patients, any erosive mucocutaneous lesion should be considered herpes simplex until proved otherwise, especially lesions in the genital and orolabial regions. Atypical morphologies are also seen.

Typically, lesions appear as erosions or crusts (Figs 19-14 to Fig 19-16). The early vesicular lesions may be transient or never seen. The three clinical hallmarks of herpes simplex infection are pain, an active vesicular border, and a scalloped periphery. Untreated erosive lesions may gradually expand, but they may also remain fixed and even become papular or vegetative, mimicking a wart of granulation tissue. In the oral mucosa numerous erosions may be seen, involving all surfaces (as opposed to only the hard, keratinized surfaces usually involved by recurrent oral herpes simplex in the immunocompetent host). The tongue may be affected with geometric fissures on the central dorsal surface. Symptomatic stomatitis associated with cancer chemotherapy is at times caused or exacerbated by HSV infection. Herpetic whitlow presents as a painful paronychia that is initially vesicular and

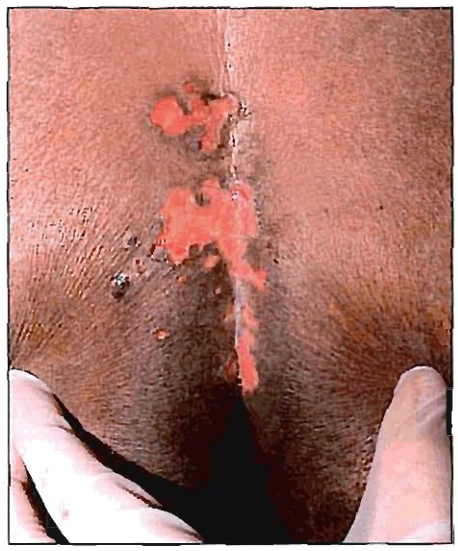

Fig. 19-14 Genital herpes, HSV-2, in a patient on chronic prednisone therapy.

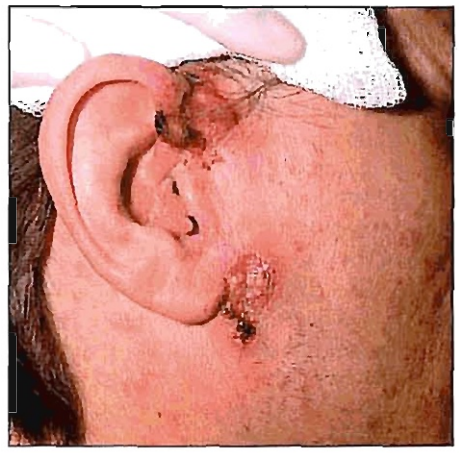

Fig. 19-15 Herpes simplex, HSV-1, in a patient with AIDS.

involves the lateral or proximal nailfolds. Untreated, it may lead to loss of the nail plate and ulceration of a large portion of the digit.

Despite the frequent and severe skin infections caused by HSV in the immunosuppressed, visceral dissemination is unusual. Extension of oral HSV into the esophagus or trachea may develop spontaneously or as a complication of intubation through an infected oropharynx. Ocular involvement can occur from direct inoculation and if lesions are present around the eye, careful ophthalmologic evaluation is required.

In an immunosuppressed host, since most lesions are ulcerative and not vesicular, Tzanck smears are of less value. Viral cultures taken from the ulcer margin are positive. DFA testing is specific and rapid, and is very useful in immunosuppressed hosts in whom therapeutic decisions need to be made expeditiously. At times, these tests are negative, but a skin biopsy will show typical herpetic changes in the epithelium adjacent to the ulceration.

Therapy often can be instituted on clinical grounds pending confirmatory tests. Acyclovir 400 mg orally three times a day, famciclovir 500 mg twice a day, or valacyclovir 1 g twice a day, all for 5 to 10 days. Therapy should continue until lesions are essentially healed. In severe infection, or in the hospitalized patient with moderate disease, intravenous acyclovir (5 mg/kg) can be given initially to control the disease.

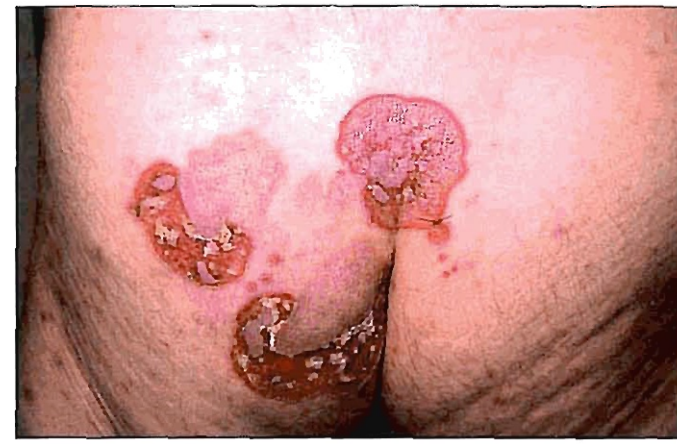

Fig. 19-16 Herpes simplex, HSV-2, infected areas spontaneously heal while new erosions appear.

In patients with acquired immune deficiency syndrome (AIDS) and those with persistent immunosuppression, consideration should be given to chronic suppressive therapy with acyclovir, 400 to 800 mg twice or three times a day, or valacyclovir or famciclovir, both at a dose of 500 mg twice a day.

Long-duration treatment with acyclovir and its analogs, or treatment of large herpetic ulcerations, may be complicated by the development of acyclovir resistance. Antiviral resistance is suspected if maximum oral doses of acyclovir, valacyclovir, or famciclovir do not lead to improvement. Intravenous acyclovir, except if given by constant infusion, will also invariably fail in such cases. Resistance to one drug is associated with resistance to all three of these drugs and is usually due to loss of the viral thymidine kinase. HSV isolates can be tested for sensitivity to acyclovir and some other antivirals. The standard treatment of acyclovir-resistant herpes simplex is intravenous foscarnet. In cases intolerant of or resistant to foscarnet, intravenous cidofovir may be used. Smaller lesions can sometimes be treated with topical trifluorothymidine (Viroptic) with or without topical or intralesional interferon (IFN)-α. Imiquimod may be of benefit in healing these lesions. Destruction of small lesions by desiccation followed by the above therapies may also be of benefit.

Histopathology

The vesicles of herpes simplex are intraepidermal. The affected epidermis and adjacent inflamed dermis are infiltrated with leukocytes and a serous exudate containing dissociated cells collects to form the vesicle. There is ballooning degeneration of the epidermal cells to produce acantholysis. The most characteristic feature is the presence of multinucleated giant cells which tend to mold together forming a crude jigsaw puzzle appearance. The steel-gray color of the nucleus and peripheral condensation of the nucleoplasm may be clues to HSV infection, even if multinucleate cells are not seen. Immunoperoxidase stains can detect herpes simplex infection even in paraffin-fixed tissue, allowing the diagnosis to be absolutely confirmed from histologic material.

Differential Diagnosis

Herpes labialis must most frequently be differentiated from impetigo. Herpetic lesions are composed of groups of tense,

small vesicles, whereas in bullous impetigo the blisters are unilocular, occur at the periphery of a crust and are flaccid. A mixed infection is not unusual and should especially be suspected in immunosuppressed hosts and when lesions are present in the typical herpetic regions around the mouth. Herpes zoster presents with clusters of lesions along a dermatome, but early on, if the number of zoster lesions is limited, it can be relatively indistinguishable from herpes simplex. In general, herpes zoster will be more painful and over 24 h will progress to involve more of the affected dermatome. DFA testing can rapidly make this distinction.

A genital herpes lesion, especially on the glans or corona, is easily mistaken for a syphilitic chancre or chancroid. Darkfield examination, multiplex PCR, and cultures for *Haemophilus ducreyi* on selective media will aid in making the diagnosis, as will diagnostic tests for HSV (Tzanck, culture, or DFA). Combined infections occur in up to 20% of cases, so finding a single pathogen may not complete the diagnostic evaluation.

Herpetic gingivostomatitis is often difficult to differentiate from aphthosis, streptococcal infections, diphtheria, coxsackievirus infections, and oral erythema multiforme. Aphthae have a tendency to occur mostly on the buccal and labial mucosae. They usually form shallow, grayish erosions, generally surrounded by a prominent ring of hyperemia. Aphthae commonly occur on nonattached mucosa while recurrent herpes of the oral cavity primarily affects the attached gingiva and palate.

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Varicella

Varicella, commonly known as *chickenpox*, is the primary infection with the VZV. In temperate regions, 90% of cases occur in children younger than 10 years of age. In tropical countries, however, varicella tends to be a disease of teenagers. The incubation period is 10 to 21 days (usually 14 to 15 days). Transmission is by direct contact with the lesions and by the respiratory route, with initial viral replication in the nasopharynx and conjunctiva. There is an initial viremia between days 4 and 6 seeding the liver, spleen, lungs, and perhaps other organs. A secondary viremia occurs at days 11 to 20, resulting in infection of the epidermis and the appearance of the characteristic skin lesions. Individuals are infectious for at least 4 days before and 5 days after the appearance of the exanthem. Low-grade fever, malaise, and headache are usually present but slight. The severity of the disease is age dependent, with adults having more severe disease and a greater risk of visceral disease. In healthy children the death rate from varicella is 1.4 in 100,000 cases; in adults, 30.9 in 100,000 cases. As with most viral infections, immunosuppression may worsen the course of the disease. Lifelong immunity follows varicella and second episodes of "varicella" indicate either immunosuppression or another viral infection such as coxsackievirus.

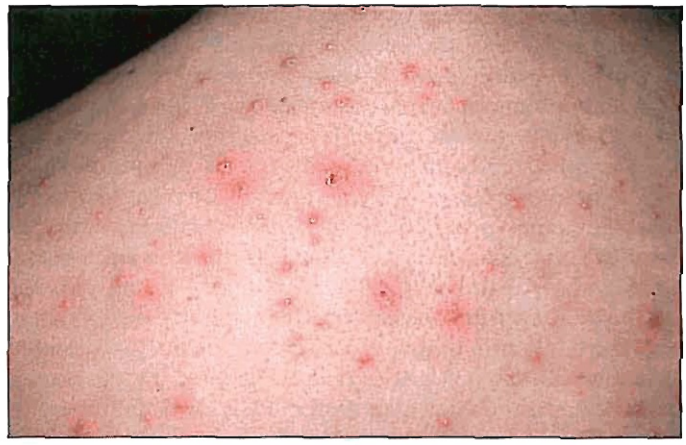

Fig. 19-17 Varicella.

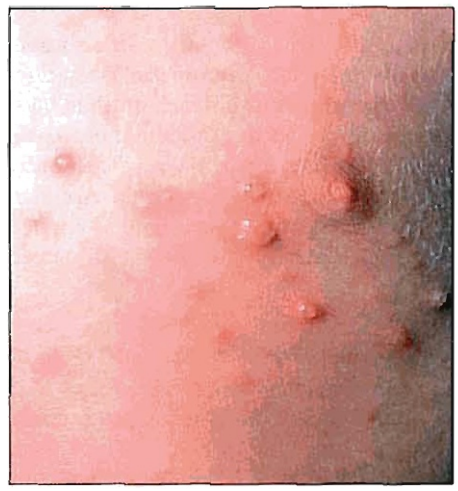

Fig. 19-18 Varicella.

Varicella is characterized by a vesicular eruption consisting of delicate "teardrop" vesicles on an erythematous base (Figs 19-17 and 19-18). The eruption starts with faint macules that develop rapidly into vesicles within 24 h. Successive fresh crops of vesicles appear for a few days, mainly on the trunk, face, and oral mucosa. Initially, the exanthem may be limited to sun-exposed areas, the diaper area of infants, or sites of inflammation. The vesicles quickly become pustular, umbilicated, then crusted. Lesions tend not to scar, but larger lesions and those that become secondarily infected may heal with a characteristic round, depressed scar.

Secondary bacterial infection with *Staphylococcus aureus* or a streptococcal organism is the most common complication of varicella. Rarely, it may be complicated by osteomyelitis, other deep-seated infections or septicemia. Other complications are rare. Pneumonia is uncommon in normal children but is seen in 1 in 400 adults with varicella. It may be bacterial or caused by the varicella, a difficult differential diagnosis. Cerebellar ataxia and encephalitis are the most common neurologic complications. Asymptomatic myocarditis and hepatitis are not uncommon in children with varicella, but these conditions are rarely significant and resolve spontaneously with no treatment. Reye syndrome, a syndrome of hepatitis and acute encephalopathy, is associated with the use of aspirin to treat the symptoms of varicella. Aspirin is absolutely contraindicated in patients with varicella. Any

child with varicella and severe vomiting should be referred immediately to exclude Reye syndrome. Symptomatic thrombocytopenia is a rare manifestation of varicella, which can occur either with the exanthem or several weeks after. Purpura fulminans, a form of disseminated intravascular coagulation associated with low levels of protein C and S, may complicate varicella.

The diagnosis of varicella is easily made clinically. A Tzanck smear from a vesicle will usually show characteristic multinucleate giant cells. If needed, the most useful clinical test is a DFA test, which is rapid and will both confirm the infection and type the virus. Since the VZV grows poorly and slowly in the laboratory, viral culture is rarely indicated.

Treatment

Both immunocompetent children and adults with varicella benefit from acyclovir therapy if started early (within 24 h of the appearance of the eruption). Therapy does not appear to alter the development of adequate immunity to reinfection. Because the complications of varicella are infrequent in children, routine treatment is not recommended; therapeutic decisions are made on a case-by-case basis. Acyclovir therapy seems to benefit most secondary cases within a household, which tend to be more severe than the index case. In this setting, therapy can be instituted earlier. Therapy does not, however, return children to school sooner and the impact on parental work days missed is not known. The dose is 20 mg/kg (maximum 800 mg per dose) four times a day for 5 days. Aspirin and other salicylates should not be used as antipyretics in varicella because their use increases the risk of Reye syndrome. Topical antipruritic lotions, oatmeal baths, dressing the patient in light, cool, clothing, and keeping the environment cool may all relieve some of the symptomatology. Children living in warm homes and kept very warm with clothing have anecdotally been observed to have more numerous skin lesions. Children with atopic dermatitis, Darier's disease, congenital ichthyosiform erythroderma, diabetes, cystic fibrosis, conditions requiring chronic salicylate or steroid therapy, and inborn errors of metabolism should be treated with acyclovir since they may suffer more complications or exacerbations of their underlying illness with varicella.

Because varicella is more severe and complications are more common in adults, treatment is recommended in adolescents and adults (13 and older). The dose is 800 mg four or five times a day for 5 days. Severe, fulminant cutaneous disease and visceral complications are treated with intravenous acyclovir 10 mg/kg every 8 h, adjusted for creatinine clearance. If the patient is hospitalized for therapy, strict isolation is required. Patients with varicella should not be admitted to wards with immunocompromised hosts or onto pediatric wards, but rather are best placed on wards with healthy patients recovering from acute trauma.

Pregnant Women and Neonates Maternal infection with the VZV during the first 20 weeks of gestation may result in a syndrome of congenital malformations (congenital varicella syndrome) as well as severe illness in the mother. In one study, 4 of 31 women with varicella in pregnancy developed varicella pneumonia. The risk for spontaneous abortion by 20 weeks is 3%; in an additional 0.7% of pregnancies, fetal death occurs after 20 weeks. The risk of preterm labor, as reported in various studies, has varied from no increase to a three-fold increase. Severe varicella and varicella pneumonia or disseminated disease in pregnancy should be treated with intravenous acyclovir. The value of oral acyclovir in other patterns of varicella in pregnancy is unknown.

Varicella zoster immune globulin (VZIG) should not be given once the pregnant woman has developed varicella. VZIG should be given for significant exposures (see below) within the first 72 to 96 h to ameliorate maternal varicella and prevent complications. Its use should be limited to seronegative women because of its cost and the high rate of asymptomatic infection in the US. The lack of a history of prior varicella is associated with seronegativity in only 20% or fewer of the US population.

Congenital varicella syndrome is characterized by a series of anomalies, including hypoplastic limbs (usually unilateral and lower extremity), cutaneous scars, and ocular and CNS disease. Female fetuses are affected more commonly than males. The overall risk for this syndrome is between 1% and 2% (the former figure from the largest series). The highest risk is from maternal varicella between weeks 13 and 20 where the risk is 2%. Infection of the fetus in utero may result in zoster occurring postnatally, often in the first 2 years of life. This occurs in about 1% of varicella-complicated pregnancies and the risk for this complication is greatest in varicella occurring in weeks 25 to 36 of gestation. The value of VZIG in preventing or modifying fetal complications of maternal varicella is unknown. In one study, however, of 97 patients with varicella in pregnancy who were treated with VZIG, none had complications of congenital varicella syndrome or infantile zoster, suggesting some efficacy for VZIG. Although apparently safe in pregnancy, acyclovir's efficacy in preventing fetal complications of maternal varicella is unknown.

If the mother develops varicella between 5 days before and 2 days after delivery, neonatal varicella can occur and be severe, as transplacental delivery of antivaricella antibody has been inadequate. These neonates develop varicella at 5 to 10 days of age. In such cases the administration of VZIG is warranted and acyclovir therapy intravenously should be considered.

Varicella Vaccine Live attenuated viral vaccine for varicella is a currently recommended childhood immunization. A single dose is recommended for children aged 1 to 12, and persons aged 13 and older should receive two vaccinations 4 to 8 weeks apart. The vaccine is less protective if given before 15 months of age. Complications are uncommon. A mild skin eruption from which virus can usually not be isolated, occurring locally at the injection site within 2 days or generalized 1 to 3 weeks after immunization, occurs in 6% of children. In healthy children, the vaccine is very efficacious, with 97% efficacy during the first year and 84% efficacy for the next 8 years. Household exposures resulted in a 12% rate of breakthrough varicella, well below the expected 90%. Many of the breakthrough cases were mild and many of the skin lesions were not vesicular (see modified varicella-like syndrome below). Prevention of severe varicella is virtually 100%, even when the vaccine is given within 36 h of exposure. Immunized children with no detectable antibody also have reduced severity of varicella after exposure. Secondary complications of varicella including scarring are virtually eliminated by vaccination. Antibodies appear to

persist for at least between 15 and 20 years. Since adult exposure to children with varicella may stimulate immunity, widespread varicella vaccine usage may result in increased zoster rates in adults.

Household exposure of immunosuppressed children to recently immunized siblings does not appear to pose a great risk. Children whose leukemia is in remission are also protected by the vaccine but may require three doses. Leukemic children still receiving chemotherapy have a complication rate from vaccination (usually a varicella-like eruption) approaching 50%. They may require acyclovir therapy. Unprotected close contacts developed varicella 15% of the time. In leukemic children, adequate immunization results in complete immunity in some and partial immunity in the rest, protecting them from severe varicella. Immunization also reduces the attack rate for zoster in leukemic children.

Modified Varicella-Like Syndrome

Children immunized with live attenuated varicella vaccine may develop varicella of reduced severity on exposure to natural varicella. This has been called *modified varicella-like syndrome* (MVLS). The frequency of MVLS is between 0% and 2.7% per year and children with lower antibody titers are more likely to develop MVLS. The illness occurs an average of 15 days after exposure to varicella and consists primarily of macules and papules with relatively few vesicles. The average number of lesions is about 35 to 50, compared with natural varicella, which usually has about 300 lesions. The majority of patients are afebrile and the illness is mild, lasting fewer than 5 days on average.

Immunocompromised Patients Varicella cases can be extremely severe and even fatal in immunosuppressed patients, especially in individuals with impaired cell-mediated immunity. Before effective antiviral therapy nearly one-third of children with cancer developed complications of varicella and 7% died. In this setting, varicella pneumonia, hepatitis, and encephalitis are frequent. Prior varicella does not always protect the immunosuppressed host from multiple episodes. The skin lesions in the immunosuppressed host are usually identical to varicella in the healthy host; however, the number of lesions may be numerous (Fig. 19-19). In an immunosuppressed patient, the lesions more frequently become necrotic and ulceration may occur. Even if the lesions are few, the size of the lesion may be large (up to several centimeters) and necrosis of the full thickness of the dermis may occur. In HIV infection, varicella may be severe and fatal. Atypical cases of a few scattered lesions without a dermatomal distribution usually represent reactivation disease with dissemination. Chronic varicella may complicate HIV infection, resulting in ulcerative (ecthymatous) or hyperkeratotic (verrucous) lesions. These patterns of infection may be associated with acyclovir resistance.

The degree of immunosuppression likely to result in severe varicella has been a matter of debate. There are case reports of severe and even fatal varicella in otherwise healthy children given short courses of oral steroids or even using only inhaled steroids. In a case-control study, however, corticosteroid use did not appear to be a risk factor for the development of severe varicella. In the UK, any patient receiving or having received systemic steroids in the prior 3 months, regardless of dose, is considered at increased risk for severe varicella. Inhaled steroids are not considered an indication for prophylactic VZIG or antiviral treatment. A "high-risk" or significant exposure had been defined as: 1) household contact, i.e. living in the same house as a case of chickenpox or zoster; 2) face-to-face contact with a case of chickenpox for at least 5 min; 3) contact indoors with a case of chickenpox or herpes zoster for more than 1 h or, within a hospital setting, a case of chickenpox or herpes zoster in an adjacent bed or the same open ward. Immunosuppressed children with no prior history of varicella and a high-risk exposure should be treated with VZIG as soon as possible after exposure (within 96 h). Pre-engraftment bone marrow transplant patients should be treated the same. VZIG treatment does not reduce the frequency of infection, but it does reduce the severity of infection and complications. The value of prophylactic antivirals is unknown. Parents of immunosuppressed children and their doctors should be aware that severe disease can occur and the parents counseled to return immediately after significant exposure or if varicella develops.

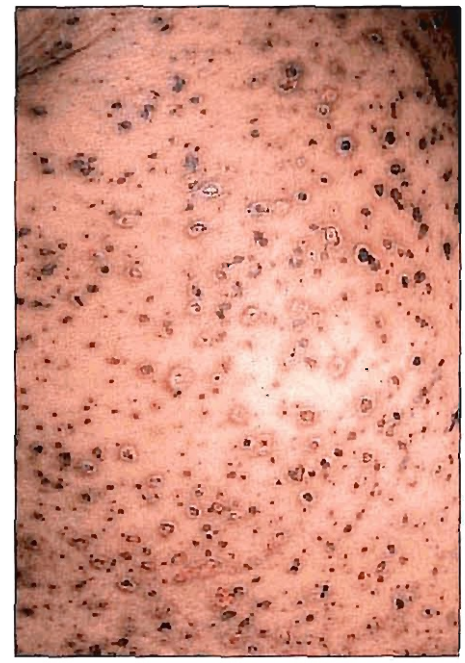

Fig. 19-19 Varicella in a patient with advanced Hodgkin's disease.

An unusual variant of recurrent varicella is seen in elderly patients with a history of varicella in childhood, who have a malignancy of the bone marrow and are on chemotherapy. They develop a mild illness with 10 to 40 widespread lesions and usually no systemic findings. This type of recurrent varicella tends to relapse. It is different from typical varicella as all the lesions are in a single stage of development and for this reason could be easily confused with smallpox.

Ideally, management of varicella in the immunocompromised patient would involve prevention through the use of varicella vaccination before immunosuppression. Vaccination is safe if the person is more than 1 year from induction chemotherapy, chemotherapy is halted around the time of vaccination, and the lymphocyte count is higher than 700/mm^3. Intravenous acyclovir at a dose of 10 mg/kg three times a day (or 500 mg/m^2 in children) is given as soon as the diagnosis of varicella is suspected. Intravenous therapy is continued until 2 days after all new vesicles have stopped.

Oral antivirals are continued for a minimum of 10 days of treatment. VZIG is of no proven benefit once clinical disease has developed, but may be given if the patient has severe life-threatening disease and is not responding to intravenous acyclovir.

In HIV-infected adults, treatment is individualized. Persons with typical varicella should be evaluated for the presence of pneumonia or hepatitis. Valacyclovir, 1 g three times a day; famciclovir, 500 mg three times a day; or acyclovir, 800 mg every 4 h may be used if no visceral complications are present. The former two agents may be preferable to acyclovir because of their enhanced oral bioavailability. Visceral disease mandates intravenous therapy. If the response to oral antiviral agents is not rapid, intravenous acyclovir therapy should be instituted. Antiviral treatment must be continued until all lesions are completely healed. Most cases of chronic or acyclovir-resistant VZV infection are associated with initial inadequate oral doses of acyclovir (either too short in duration, too low a dose, or in patients with gastrointestinal disease, in whom reduced gastrointestinal absorption may be associated with inadequate blood levels of acyclovir). Atypical disseminated cases must be treated aggressively until all lesions resolve. The diagnosis of acyclovir-resistant VZV infection may be difficult. Acyclovir-resistant VZV strains may be hard to culture and sensitivity testing is still not standardized or readily available for VZV. Acyclovir-resistant varicella is treated with foscarnet and in cases failing that agent, cidofovir.

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Zoster (Shingles, Herpes Zoster)

Zoster is caused by reactivation of VZV. Following primary infection or vaccination, VZV remains latent in the sensory dorsal root ganglion cells. The virus begins to replicate at some later time, traveling down the sensory nerve into the skin. Other than immunosuppression and age the factors involved in reactivation are unknown.

The incidence of zoster increases with age. Below the age of 45, the annual incidence is less than 1 in 1000 persons. Among patients older than 75 years of age, the rate is more than four times greater. For white persons older than 80 years of age, the lifetime risk of developing zoster is 10% to 30%. For unknown reasons being nonwhite reduces the risk for herpes zoster, with African Americans being four times less likely to develop zoster. Women may have a slightly greater risk of developing zoster when compared to men. Immunosuppression, especially hematologic malignancy and HIV infection, dramatically increase the risk for zoster. In HIV-infected persons the annual incidence is 30 in 1000 persons, or an annual risk of 3%. With the universal use of varicella vaccination and decrease in pediatric and adolescent varicella cases, older persons will no longer have periodic boosts of the anti-VZV immune activity. This may result in an increase in the incidence of zoster.

Herpes zoster classically occurs unilaterally within the distribution of a cranial or spinal sensory nerve, often with some overflow into the dermatomes above and below. The dermatomes most frequently affected are the thoracic (55%), cranial (20%, with the trigeminal nerve being the most common single nerve involved), lumbar (15%), and sacral (5%). The cutaneous eruption is frequently preceded by one to several days of pain in the affected area, although the pain may appear simultaneously or even following the skin eruption or the eruption may be painless. The eruption initially presents as papules and plaques of erythema in the dermatome. Within hours the plaques develop blisters (Figs 19-20 to 19-22). Lesions continue to appear for several days. The eruption may have few lesions or reach total confluence

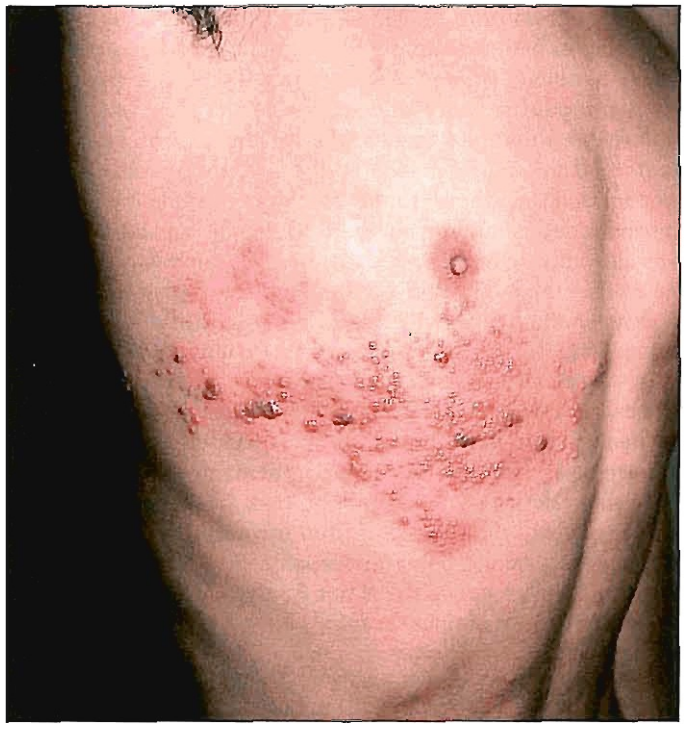

Fig. 19-20 Herpes zoster, classic dermatomal distribution.

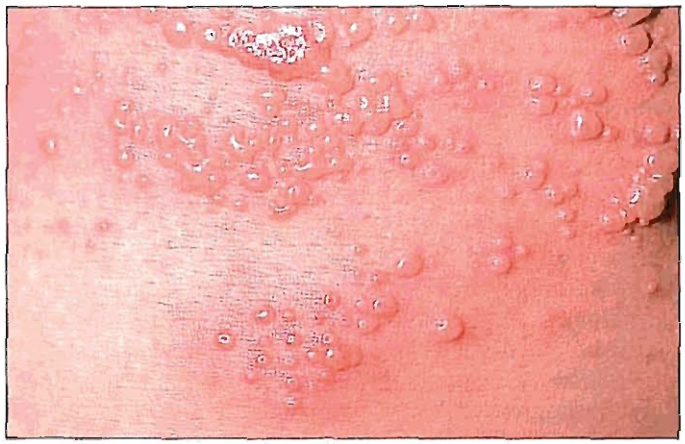

Fig. 19-21 Herpes zoster.

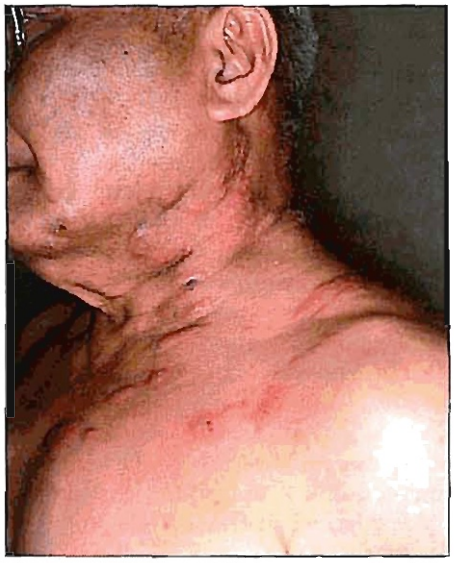

Fig. 19-22 Herpes zoster, early lesions.

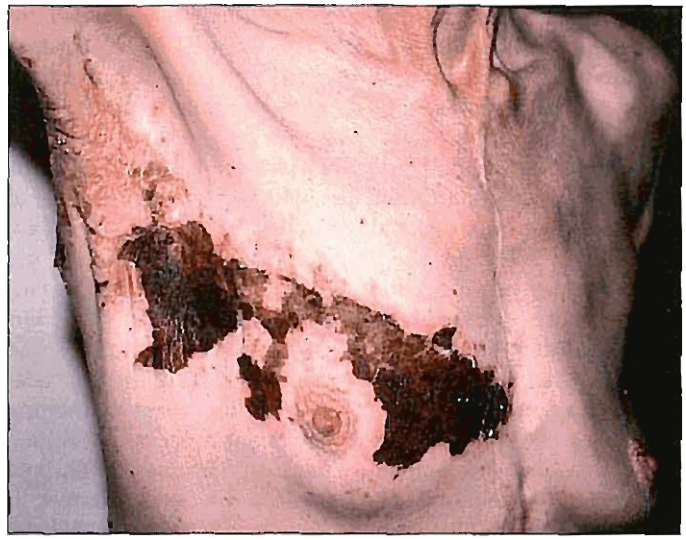

Fig. 19-23 Herpes zoster, necrotic, in an elderly patient.

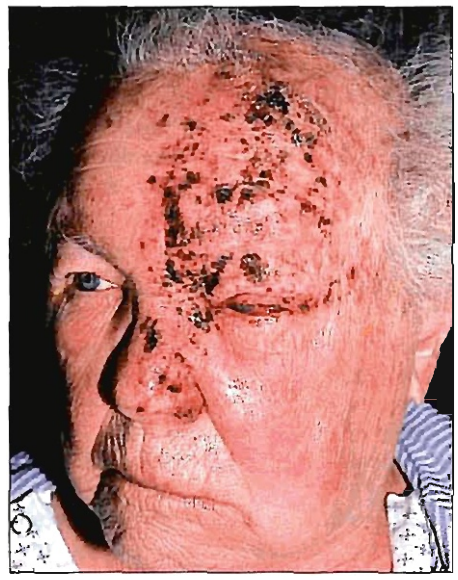

Fig. 19-24 Herpes zoster, involvement of the V1 dermatome.

in the dermatome. Lesions may become hemorrhagic, necrotic, or bullous. Rarely, the patient may have pain, but no skin lesions (zoster sine herpete). There is a correlation with the pain severity and extent of the skin lesions, and elderly persons tend to have more severe pain. In patients under 30 years of age, the pain may be minimal. It is not uncommon for there to be scattered lesions outside the dermatome, usually fewer than 20. In the typical case, new vesicles appear for 1 to 5 days, become pustular, crust, and heal. The total duration of the eruption depends on three factors: patient age, severity of eruption, and presence of underlying immunosuppression. In younger patients, the total duration is 2 to 3 weeks, whereas in elderly patients, the cutaneous lesions of zoster may require 6 weeks or more to heal. Scarring is more common in elderly and immunosuppressed patients (Fig. 19-23). Scarring also correlates with the severity of the initial eruption. Lesions may develop on the mucous membranes within the mouth in zoster of the maxillary or mandibular division of the facial nerve or in the vagina in zoster in the S2 or S3 dermatome. Zoster may appear in recent surgical scars.

Disseminated Herpes Zoster Disseminated herpes zoster is defined as more than 20 lesions outside the affected dermatome. It occurs chiefly in old or debilitated individuals, especially in patients with lymphoreticular malignancy or AIDS. Low levels of serum antibody against VZV are a highly significant risk factor in predicting dissemination of disease. The dermatomal lesions are sometimes hemorrhagic or gangrenous. The outlying vesicles or bullae, which are usually not grouped, resemble varicella and are often umbilicated and may be hemorrhagic. Visceral dissemination to the lungs and CNS may occur in the setting of disseminated zoster. Disseminated zoster requires careful evaluation and systemic antiviral therapy. This would initially be intravenous acyclovir, which may be changed to an oral antiviral agent once visceral involvement has been excluded and the patient has received at least 2 to 3 days of intravenous therapy.

Ophthalmic Zoster In herpes zoster ophthalmicus, the ophthalmic division of the fifth cranial nerve is involved. If the external division of the nasociliary branch is affected, with vesicles on the side and tip of the nose (Hutchinson's sign), the eye is involved 76% of the time, as compared with 34% when it is not involved (Fig. 19-24). Vesicles on the lid margin are virtually always associated with ocular involve-

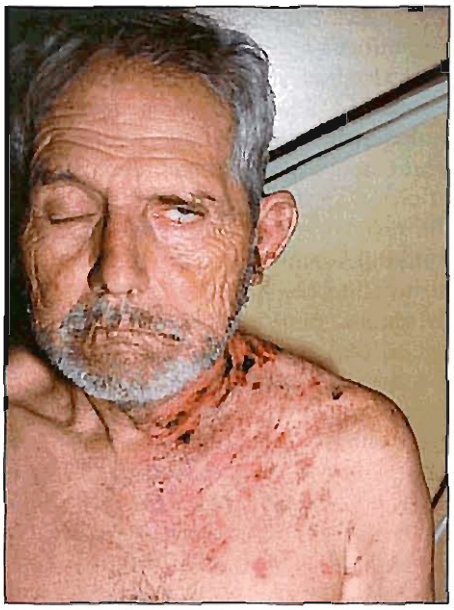

Fig. 19-25 Herpes zoster, motor nerve involvement.

ment. In any case, the patient with ophthalmic zoster should be seen by an ophthalmologist. Systemic antiviral therapy should be started immediately, pending ophthalmologic evaluation. Ocular involvement is most commonly in the form of uveitis (92%) and keratitis (50%). Less common but more severe complications include glaucoma, optic neuritis, encephalitis, hemiplegia, and acute retinal necrosis. These complications are reduced from 50% of patients with herpes zoster ophthalmicus to 20% to 30% with effective antiviral therapy. Unlike the cutaneous lesions, ocular lesions of zoster and their complications tend to recur, sometimes as long as 10 years after the zoster episode.

Other Complications Motor nerve neuropathy occurs in about 3% of patients with zoster and is three times more common if zoster is associated with underlying malignancy (Fig. 19-25). Seventy-five percent of cases slowly recover, leaving 25% with some residual motor deficit. If the sacral dermatome S3 or less often S2 or S4 are involved, urinary hesitancy or actual urinary retention may occur. Hematuria and pyuria may also be present. The prognosis is good for complete recovery. Similarly pseudo-obstruction, colonic spasm, dilation, obstipation, constipation, and reduced anal sphincter tone can occur with thoracic (T6 to T12), lumbar, or sacral zoster. Recovery is complete. Maxillary and mandibular alveolar bone necrosis may occur an average of 30 days after zoster of the maxillary or mandibular branches of the trigeminal nerve. Limited or widespread loss of teeth may result.

Ramsay Hunt syndrome results from involvement of the facial and auditory nerves by VSV. Herpetic inflammation of the geniculate ganglion is felt to be the cause of this syndrome. The presenting features include zoster of the external ear or tympanic membrane; herpes auricularis with ipsilateral facial paralysis; or herpes auricularis, facial paralysis, and auditory symptoms. Auditory symptoms include mild to severe tinnitus, deafness, vertigo, nausea and vomiting, and nystagmus.

Delayed contralateral hemiparesis is a rare but serious complication of herpes zoster that occurs weeks to months (mean 7 weeks) after an episode of zoster affecting the first branch of the trigeminal nerve. By direct extension along the intracranial branches of the trigeminal nerve, VZV gains access to the CNS and infects the cerebral arteries. Patients present with headache and hemiplegia. Arteriography is diagnostic, demonstrating thrombosis of the anterior or middle cerebral artery. Since this is due to viral invasion of the blood vessels, systemic antiviral therapy is beneficial.

Treatment

Middle-aged and elderly patients are urged to restrict their physical activities or even stay home in bed for a few days. Bed rest may be of paramount importance in the prevention of neuralgia. Younger patients may usually continue with their customary activities. Local applications of heat, as with an electric heating pad or a hot-water bottle, are recommended. Simple local application of gentle pressure with the hand or with an abdominal binder often gives great relief.

Antiviral therapy is the cornerstone in the management of herpes zoster. The main benefit of therapy is in reduction of the duration of zoster-associated pain. Therefore, treatment in immunocompetent patients is restricted to those at highest risk for persistent pain—those over 50 years of age. Exceptions are patients with very painful or severe cases of zoster, ophthalmic zoster, Ramsay Hunt syndrome, all immunosuppressed patients, cutaneous or visceral dissemination, and patients with motor nerve involvement. In the most severe cases, especially in ophthalmic zoster and disseminated zoster, initial intravenous therapy may be considered. Therapy should be started as soon as the diagnosis is confirmed, preferably within the first 3 or 4 days. In immunocompetent patients, the efficacy of starting treatment beyond this time is unknown. Treatment leads to more rapid resolution of the skin lesions and, most importantly, substantially decreases the duration of zoster-associated pain. Valacyclovir (1000 mg) and famciclovir (500 mg), may be given three times a day. These agents are as effective as or superior to acyclovir (800 mg five times a day), probably because of better absorption and the fact that higher blood levels are achieved. They are as safe as acyclovir. If not contraindicated they are preferred

In the immunocompetent host 7 days of treatment has been shown to be as effective as 21 days of treatment. Valacyclovir and famciclovir must be dose adjusted in patients with renal impairment. In an elderly patient, if the renal status is unknown, the newer agents may be started at twice a day dosing (which is almost as effective) pending evaluation of renal function, or acyclovir can be used. For patients with renal failure (creatinine clearance of <25 mL/min), acyclovir is preferable.

In the immunosuppressed patient an antiviral agent should always be given because of the increased risk of dissemination and zoster-associated complications. The doses are identical to those used in immunocompetent hosts. In immunosuppressed patients with ophthalmic zoster, disseminated zoster or Ramsay Hunt syndrome, and in patients failing oral therapy, intravenous acyclovir should be used at a dose of 10 mg/kg three times a day, adjusted for renal function.

Zoster-Associated Pain (Postherpetic Neuralgia)

Pain is the most troublesome symptom of zoster. Eighty-four percent of patients over the age of 50 will have pain

preceding the eruption and 89% will have pain with the eruption. Various terminology is used to classify the pain. The simplest approach is to term all pain occurring immediately preceding or after zoster "zoster-associated pain" (ZAP). Another classification system separates acute pain (within the first 30 days), subacute pain (between 30 and 120 days), and chronic pain (lasting >120 days).

Two different mechanisms are proposed to cause ZAP: sensitization and deafferentation. Nociceptors (sensory nerves mediating pain) become sensitized following injury, resulting in ongoing discharge and hyperexcitability (peripheral sensitization). Prolonged discharge of the nociceptor enhances the dorsal horn neurons to afferent stimuli and expands the dorsal horn neuron's receptive field (central sensitization), leading to allodynia and hyperalgesia. In addition, neural destruction causes spontaneous activity in deafferented central neurons, generating constant pain. The spinal terminals of mechanoreceptors may contact receptors formerly occupied by C-fibers, leading to hyperalgesia and allodynia. The loss of function or death of dorsal horn neurons, which have an inhibitory effect on adjacent neurons, contributes to an increase in activity being transmitted up the spinal cord. The central sensitization is initially temporary (self-limited), but may become permanent.

The quality of the pain associated with herpes zoster varies, but three basic types have been described. There is the constant, monotonous, usually burning or deep, aching pain; the shooting, lancinating (neuritic) pain; and triggered pain. The latter is usually allodynia (pain with normal nonpainful stimuli such as light touch) or hyperalgesia (severe pain produced by a stimulus normally producing mild pain). The character and quality of acute zoster pain is identical to the pain that persists after the skin lesions have healed, although they be mediated by different mechanisms.

The rate of resolution of pain following herpes zoster is reported over a wide range. The following data are from a prospective study and do not represent selected patients as are recruited in drug trials for herpes zoster. The tendency to have persistent pain is age dependent, occurring for longer than 1 month in only 2% of persons under 40 years of age. Fifty percent of persons over 60 years of age and 75% of those over 70 years of age continue to have pain beyond 1 month. Although the natural history is for gradual improvement in persons over 70 years, 25% have some pain at 3 months and 10% have pain at 1 year. Severe pain lasting longer than 1 year is uncommon, but 8% of persons over 60 have mild pain and 2% still have moderate pain at 1 year.

ZAP, especially that of long duration, is very difficult to manage. Adequate medication should be provided to control the pain from the first visit. Once established, neuropathic pain is very difficult to control. Every effort should be made to prevent neuronal damage. In addition, chronic pain may lead to depression, complicating management of the pain. Patients with persistent moderate-to-severe pain may benefit from referral to a pain clinic. With this background, the importance of early and adequate antiviral therapy and pain control cannot be overemphasized.

Oral antiviral agents are recommended in all patients over 50 with pain in whom blisters are still present, even if they are not given within the first 96 h of the eruption. Oral analgesia should be maximized using acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and opiate analgesia as required. Capsaicin applied topically every few hours may reduce pain, but the application itself may cause burning and the benefits are modest. Local anesthetics, such as 10% lidocaine in gel form, 5% lidocaine–prilocaine, or lidocaine patches (Lidoderm), may acutely reduce pain. These topical measures may provide some short-term analgesic effect, but do not appear to have any long-term benefit in reducing the severity or prevalence of ZAP. Sublesional anesthesia, epidural blocks, and sympathetic blocks with and without corticosteroids have been reported in large series, but rarely studied in a controlled manner. They provide acute relief of pain. Although the benefit of nerve blocks in preventing or treating persistent ZAP remains to be proven, they are a reasonable consideration in the acute setting if the patient is having very severe pain (unable to eat, sleep) and oral therapy has yet to be effective. They may also be used in patients who have failed the standard therapies listed below. A TENS unit may be beneficial for persistent neuralgia. Botulinum toxin, 20 U, at the site of most significant pain following zoster of the trunk was associated with complete resolution of the pain in one patient.

The value of systemic corticosteroid therapy in the prevention of postherpetic neuralgia is controversial. Most recent studies have failed to show reduction in the duration of ZAP, however, if an antiviral is also given. Corticosteroids reduce the overall severity of acute ZAP, improve quality of life, and return the patient to full daily activity sooner. Therefore, they should be given if there is no contraindication. A tapering 3-week course, starting at 40 to 60 mg/day is recommended. Systemic corticosteroids are contraindicated in immunosuppressed hosts. However, systemic steroids do not increase complications in immunocompetent hosts.

Gabapentin (Neurontin), starting at 100 mg three times a day and increasing up to a target dose of 1800 to 3600 mg/day, is effective as a single agent and may be of additional benefit in patients treated with tricyclic antidepressants. Tricyclics, such as amitriptyline (or nortriptyline) and desipramine, are started at 25 mg/night (or 10 mg for those over the age of 65–70). The dose is increased by the same amount nightly until pain control is achieved or the maximum dose is reached. The ultimate dose is somewhere between 25 and 100 mg in a single nightly dose. The early use of amitriptyline was able to reduce the pain prevalence at 6 months, suggesting that early intervention is optimal. Velafaxine (Effexor) may be used in patients who do not tolerate tricyclics. The starting dose is 25 mg/night and the dose is gradually titrated up as required. The anticonvulsants diphenylhydantoin, carbamazepine, and valproate; neuroleptics, such as chlorprothixene, and phenothiazines; and H_2 blockers, such as cimetidine, cannot be recommended as they have been not been studied critically, many are poorly tolerated by the elderly, and some are associated with significant side effects. If the patient fails to respond to local measures, oral analgesics including opiates, tricyclics, gabapentin, and velafaxine, referral to a pain center is recommended.

Immunosuppressed Patients Patients with malignancy (especially Hodgkin's disease and leukemia) are five times more likely to develop zoster than are their age-matched counterparts. Patients who also have a higher incidence of zoster include those with deficient immune systems, such as individuals who are immunosuppressed for organ transplan-

tation or by connective tissue disease, or by the agents used to treat these conditions (especially corticosteroids, chemotherapeutic agents, cyclosporin, sirolimus and tacrolimus). Although persons who are immunosuppressed have increased rates of zoster, screening for underlying malignancy, beyond a good history and physical examination, is not indicated in patients with zoster. However, since zoster is 30 times more common in HIV-infected persons, the zoster patient under 50 years of age should be questioned about HIV risk factors. In pediatric patients with HIV infection and in other immunosuppressed children, zoster may rapidly follow primary varicella.

The clinical appearance of zoster in the immunosuppressed is usually identical to typical zoster, but the lesions may be more ulcerative and necrotic and may scar more severely. Dermatomal zoster may appear, progress to involve the dermatome, and persist without resolution. Multidermatomal zoster is more common in the immunosuppressed. Visceral dissemination and fatal outcome are extremely rare in immunosuppressed patients (about 0.3%), but cutaneous dissemination is not uncommon, occurring in 12% of cancer patients, especially those with hematologic malignancies. Bone marrow transplant patients with zoster develop disseminated zoster 25% of the time, and visceral dissemination 10% to 15% of the time. Disseminated zoster may be associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and present with hyponatremia, abdominal pain, and ileus. This later presentation has been reported in stem cell transplant patients. Despite treatment with intravenous acyclovir, the SIADH can be fatal. In this setting the number of skin lesions may be small and the lesions resemble "papules" rather than vesicles. Mortality in patients with zoster who have undergone bone marrow transplantation is 5%. Prophylactic antiviral agents are used in this high-risk group. In AIDS patients, ocular and neurologic complications of herpes zoster are increased. Immunosuppressed patients often have recurrences of zoster, up to 25% in patients with AIDS.

Two atypical patterns of zoster have been described in AIDS patients: ecthymatous lesions, which are punched-out ulcerations with a central crust, and verrucous lesions. These patterns were not reported before the AIDS epidemic. Atypical clinical patterns, especially the verrucous pattern, may correlate with acyclovir resistance.

Diagnosis

The same techniques used for the diagnosis of varicella are used to diagnose herpes zoster. The clinical appearance is often adequate to suspect the diagnosis, and an in-office Tzanck smear can rapidly confirm the clinical suspicion. Zosteriform herpes simplex could also produce a positive result to a Tzanck smear, but the number of lesions is usually more limited and degree of pain substantially less. Beyond Tzanck preparation, DFA testing is preferred to a viral culture, since it is rapid, types the virus, and has a higher yield than a culture will produce. When compared in documented VZV infections, Tzanck smear was 75% positive (with up to 10% false-positives and high variability, depending on the skill of the examiner), and culture only 44% positive. PCR testing is 97% positive but is not usually immediately available. In atypical lesions, biopsy may be necessary to demonstrate the typical herpes virus cytopathic effects. Immunoperoxidase stain tests can then be performed on paraffin-fixed tissue to specifically identify the VZV. In cases in which acyclovir fails clinically, viral culture may be attempted, and acyclovir sensitivity testing performed. It is not as standardized for VZV as it is for HSV and its availability is limited.

Histopathology

As in the case of herpes simplex, the vesicles in zoster are intraepidermal. Within and at the sides of the vesicle are found large, swollen cells called *balloon cells*, which are degenerated cells of the spinous layer. Acidophilic inclusion bodies similar to those seen in herpes simplex are present in the nuclei of the cells of the vesicle epithelium. Multinucleated keratinocytes, nuclear moulding, and peripheral condensation of the nucleoplasm are characteristic and confirmatory of an infection with either HSV or VZV. In the vicinity of the vesicle there is marked inter- and intra-cellular edema. In the upper part of the dermis, vascular dilation, edema, and a perivascular infiltration of lymphocytes and polymorphonuclear leukocytes are present. Atypical lymphocytes may be present. An underlying leukocytoclastic vasculitis is suggestive of VZV infection over HSV. Inflammatory and degenerative changes are also noted in the posterior root ganglia and in the dorsal nerve roots of the affected nerve. The lesions correspond to the areas of innervation of the affected nerve ganglion, with necrosis of the nerve cells.

Differential Diagnosis

The distinctive clinical picture permits a diagnosis with little difficulty. A unilateral, painful eruption of grouped vesicles along a dermatome, with hyperesthesia and on occasion regional lymph node enlargement, is typical. Occasionally, segmental cutaneous paresthesias or pain may precede the eruption by 4 or 5 days. In such patients, prodromal symptoms are easily confused with the pain of angina pectoris, duodenal ulcer, biliary or renal colic, appendicitis, pleurodynia, or early glaucoma. The diagnosis becomes obvious once the cutaneous eruption appears. Herpes simplex and herpes zoster are confused if the lesions of HSV are linear (zosteriform HSV) or the number of zoster lesions is small and localized to one site (not involving the whole dermatome). DFA testing or viral culture will distinguish them. DFA is generally preferred because it is rapid and sensitive.

Inflammatory Skin Lesions Following a Zoster Infection (Isotopic Response) Following zoster, inflammatory skin lesions may rarely occur within the affected dermatome, perhaps analogous to the long-standing immunologic ocular and CNS reactions seen in ophthalmic zoster. Lesions usually appear within a month, and rarely, longer than 3 months after the zoster. Clinically, the lesions are usually flat-topped or annular papules in the dermatome. Histologically, such papules most frequently demonstrate various patterns of granulomatous inflammation from typical granuloma annulare, to sarcoidal reactions, or even granulomatous vasculitis (Fig. 19-26). Persistent viral genome has not been detected in these lesions, suggesting that continued antiviral therapy is not indicated. Topical and intralesional therapy with corticosteroid medications is beneficial, but the natural history of these lesions is generally spontaneous resolution. Less commonly other inflammatory skin diseases have been reported in areas of prior zoster, including

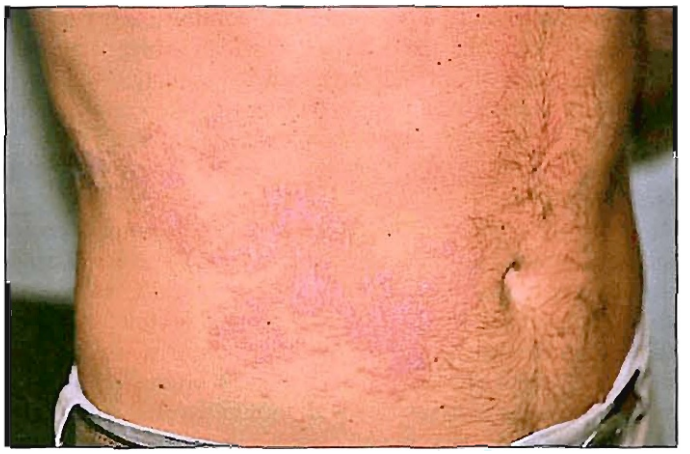

Fig. 19-26 Herpes zoster, dermatome previously affected by zoster developed a granulomatous dermatitis histologically consistent with granuloma annulare.

lichen planus, lichen sclerosus, and benign or even atypical lymphoid infiltrates. Leukemic infiltrates and lymphomas may affect zoster scars, as can metastatic carcinomas (inflammatory oncotaxis) or nonmelanoma skin cancers.

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Epstein-Barr Virus

Epstein-Barr virus (EBV) is a gamma herpesvirus. EBV infects human mucosal epithelial cells and B-lymphocytes, and infection persists for the life of the host. EBV infection may be latent—not producing virions, but simply spread from mother cell to both daughter cells by copying the viral DNA with each host cell replication. Intermittently infection may be productive, resulting in production and release of infectious virions. EBV infection may transit between latent and productive infection many times. The ability of EBV to maintain persistent infection is aided by the expression of the EBV nuclear antigen (EBNA)-1 viral gene product which prevents cytotoxic T-lymphocyte response to the virus.

Initial infection with EBV occurs in childhood or early adulthood, so that by the early 20s, 95% of the population has been infected. The virus is shed into the saliva, so contact with oral secretions is the most common route of transmission. Primary infection may be asymptomatic or produce only a mild, nonspecific febrile illness, especially in younger children. In young adults, primary infection is more likely symptomatic and in 50% of cases produces a syndrome termed infectious mononucleosis. The incubation period is 3 to 7 weeks. Infectious mononucleosis is characterized by a constellation of findings: fever (up to 40° C), headache, lymphadenopathy, splenomegaly, and pharyngitis (sore throat).

Cutaneous and mucous membrane lesions are present in about 10% of patients with infectious mononucleosis; up to 70% of patients require hospitalization. Exanthems occur in 15% to 30% of children with infectious mononucleosis. Edema of the eyelids and a macular or morbilliform eruption are most common. The latter is usually on the trunk and upper extremities. Other less common eruptions are urticarial, vesicular, bullous, petechial and purpuric types. The mucous membrane lesions consist of distinctive pinhead-sized petechiae, 5 to 20 in number, at the junction of the soft and hard palate (Forsheimer spots). Infectious mononucleosis has also been associated with numerous eruptions described as erythema multiforme, erythema nodosum, and acute or cold urticaria. Cold urticaria may be associated with cold agglutinins. Giannoti-Crosti syndrome and the papular-purpuric glove and stocking syndrome are two specific viral exanthem patterns which may occur in the setting of asymptomatic primary EBV infection.

Painful genital ulcerations may precede the symptomatic phase of infectious mononucleosis, especially in premenarcheal girls. The ulcerations are up to 2 cm in diameter, single or multiple, and may be accompanied by marked swelling of the labia. Lesions last several weeks and heal spontaneously, often as the patient is developing symptoms of infectious mononucleosis. Transmission to patients via orogenital sex has been proposed, but the virus may also reach the vulvar mucosa hematogenously. EBV has been recovered by culture from these genital ulcerations. The lesions closely resemble herpetic ulcerations and fixed drug eruption, which must be considered in the differential diagnosis.

Laboratory evaluation in patients with infectious mononucleosis frequently shows an absolute lymphocytosis of greater than 50% and monocytosis with abnormally large lymphocytes. Atypical lymphocytes (Downey cells) usually represent at least 10% of the total leukocyte count. The white blood cell count ranges from 10,000 to 40,000/mm^3. Liver function tests may be elevated. Heterophile antibodies will be present in 95% or more of cases. In acute primary EBV infection the IgM antibodies to early antigen (EA) and viral capsid antigen (VCA) are found in high titer and fall during recovery. Antibodies to VCA and EBNA appear in the recovering phase and persist for years after primary infection. There is no specific therapy and in most cases no treatment is required. Acyclovir is not effective in altering the length or severity of infectious mononucleosis, although it is active against EBV in doses used for VZV. If patients have severe pharyngeal involvement with encroachment on the airway, 4 days of oral corticosteroid therapy (40–60 mg/day prednisone) is useful to induce a prompt reduction in pharyngeal swelling. Most patients recover completely.

Patients with mononucleosis treated with ampicillin, amoxicillin or other semisynthetic penicillins commonly develop a generalized, pruritic, erythematous to copper-colored macular exanthem on the seventh to tenth day of therapy. The eruption starts on the pressure points and extensor surfaces, generalizes, and becomes confluent. The eruption lasts about 1 week and resolves with desquamation. The eruption does not recur when these medications are given after the acute mononucleosis has resolved.

Oral hairy leukoplakia (OHL) is a distinctive condition strongly associated with EBV. It appears as poorly demarcated, corrugated white plaques seen on the lateral aspects of the tongue (Fig. 19-27). Lesions on the other areas of the oral mucosa are simply white plaques without the typical corrugations. OHL can be distinguished from thrush by the fact that OHL cannot be removed by firm scraping with a tongue blade. More than a third of patients with AIDS have OHL, but is not restricted to patients with HIV infection; it also occurs in other immunosuppressed hosts, especially renal and bone marrow transplant recipients. EBV does not establish infection in the basal cell layer of the oral epithelium but is maintained by repeated direct infection of the epithelium by EBV in the oral cavity; it is not reactivation of EBV at the site. Only chronically immunosuppressed patients continuously shed EBV in their oral secretions; hence the restriction of OHL to immunosuppressed hosts. In normal persons a similar morphologic and histologic picture can be seen (pseudo-OHL), but EBV is not found in these patients' lesions. Thus, the finding of OHL warrants HIV testing. If results are negative, special histologic studies searching for

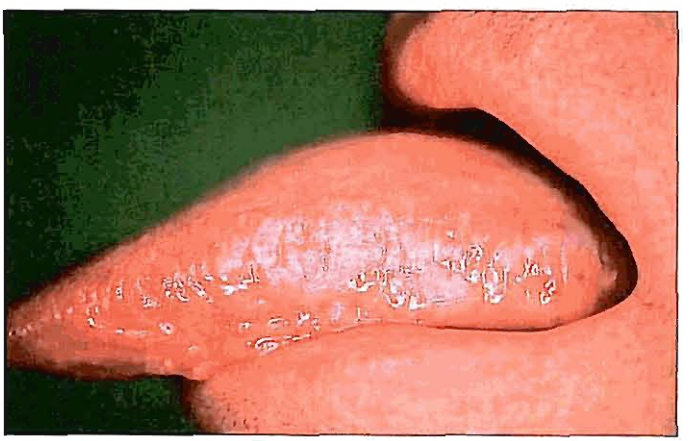

Fig. 19-27 Oral hairy leukoplakia.

EBV in the OHL biopsy should be performed. If EBV is found, a work-up for immunosuppression is recommended.

OHL is usually asymptomatic and requires no treatment. If treatment is requested in immunosuppressed hosts, podophyllin applied for 30 s to 1 min to the lesions once each month is easiest. Tretinoin gel applied topically twice a day or oral acyclovir, 400 mg five times a day, are also effective. Lesions recur when treatment is discontinued.

In immunosuppressed hosts, EBV may be responsible for lymphoproliferative disorders, which can be fatal. These include X-linked lymphoproliferative disease, as well as B-cell proliferations, which may be mono- or poly-clonal. In immunocompetent hosts, EBV is associated with lymphoma. EBV is frequently found in patients with Hodgkin's disease, especially the mixed cellularity type. This may be useful in distinguishing Hodgkin's disease in the skin from lymphomatoid papulosis and anaplastic large cell lymphoma, both of which are negative for EBV.

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Cytomegalic Inclusion Disease

Congenital cytomegalovirus (CMV) infection, as documented by CMV excretion, is found in 1% of newborns. Ninety percent of these babies are asymptomatic. Clinical manifestations in infants may include jaundice, hepatosplenomegaly, cerebral calcifications, chorioretinitis, microcephaly, mental retardation, and deafness. Cutaneous manifestations may result from thrombocytopenia, with resultant petechiae, purpura, and ecchymoses. Purpuric lesions which may be macular, papular, or nodular may show extramedullary hematopoiesis (dermal erythropoiesis), producing the "blueberry muffin baby." A generalized vesicular eruption may very rarely occur. Most symptomatic cases occur within the first 2 months of life. Neonatal disease is more severe and sequelae more frequent in neonates born of mothers with primary rather than recurrent CMV disease in pregnancy.

Fifty to 80% of immunocompetent adults and up to 100% of HIV-infected homosexual men are infected with CMV. Infection in adults may be acquired by exposure to infected children, sexual transmission, and transfusion of CMV-infected blood. Symptomatic primary infection in adults is unusual and is identical to infectious mononucleosis caused by EBV. An urticarial or morbilliform eruption or erythema nodosum may occur in primary CMV infection in immunocompetent adults. Ampicillin and amoxicillin administration will often result in a morbilliform eruption in acute CMV infection, similar to that seen in acute EBV infection.

CMV infection is very common in AIDS patients, most frequently causing retinitis (20% of patients), colitis (15%), cholangitis, encephalitis, polyradiculomyopathy, and adrenalitis. It occurs in the setting of very advanced HIV infection (usually with CD4 counts below 50) and has become much less common in the era of highly active antiretroviral therapy (HAART) therapy.

CMV infection in tissues is usually identified by the histologic finding of a typical CMV cytopathic effect. In a very small percentage of AIDS patients with CMV infection, skin lesions may occur which contain such cytopathic changes. In most cases CMV is found in association with another infectious process and the treatment of that other infection will lead to resolution of the CMV in the skin without treatment of the CMV. This is especially true of perianal HSV ulcerations. CMV may even be found in totally normal skin in CMV-viremic AIDS patients, suggesting that finding the CMV cytopathic effect is alone insufficient to imply a causal relationship of the CMV to any cutaneous lesion. Only in the case of perianal and oral ulcerations has the pathogenic role of CMV been documented. In unusual cases of very painful perianal ulcerations, only CMV infection is found histologically. The CMV cytopathic changes may be noted in the nerves at the base of these ulcerations, suggesting CMV neuritis may be producing the severe pain which characterizes these cases. The diagnosis of CMV ulceration is one of exclusion. CMV cytopathic changes must be seen in the lesion and cultures, and histologic evidence for any other infectious agent must be negative. In these cases, clinically suggested by their location (perianal or oral) and painful nature, specific treatment with ganciclovir, foscarnet, or cidofovir will lead to healing of the ulceration and dramatic resolution of the pain.

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Human Herpesviruses-6 and -7

Infection with HHV-6 is almost universal in adults, with seropositivity in the 80% to 85% range in the US, and seroprevalence almost 100% in children. There are intermittent periods of viral reactivation throughout life; persistent infection occurs in several organs, particularly in the CNS. Acute seroconversion to HHV-6 and HHV-7 each appears to be responsible for about one-third of roseola cases, and in the remaining third neither is found. HHV-6 infection occurs earlier than HHV-7 and second episodes of roseola in HHV-6 seropositive children may be caused by HHV-7. Primary infection with HHV-6 is associated with roseola only 9% of the time and 18% of children with seroconversion have a rash. Primary infection may occur with only fever and no rash or rash without fever. Other common findings include otitis media, diarrhea, and bulging fontanelles, sometimes with findings of meningoencephalitis. Uncommonly, hepatitis, intussusception, and even fatal multisystem disease may occur. In adults, acute HHV-6 infection resembles acute mononucleosis. Viral recovery is reduced in patients receiving acyclovir therapy, but ganciclovir is the recommended agent for treatment of severe disease associated with HHV-6.

HHV-6 and -7 may be the etiologic agents responsible for pityriasis rosea.

As with other herpesviruses, the pattern of disease in HHV-6 may be different in immunosuppressed hosts. Chronic macular or papular generalized exanthems have been reported in two patients, one following bone marrow transplantation for severe combined immunodeficiency and one with acute leukemia who was undergoing chemotherapy. In the latter patient, the eruption cleared with recovery of the bone marrow.

Roseola Infantum (Exanthem Subitum, Sixth Disease) Roseola infantum is a common cause of sudden, unexplained high fever in young children between 6 and 36 months of age. Prodromal fever is usually high and convulsions and lymphadenopathy may accompany it. Suddenly, on about the fourth day, the fever drops. Coincident with the drop in temperature, a morbilliform erythema consisting of rose-colored discrete macules appears on the neck, trunk, and buttocks, and sometimes on the face and extremities. Often there is a blanched halo around the lesions. The eruption may also be papular or, rarely, even vesicular. The mucous membranes are spared. Complete resolution of the eruption occurs in 1 to 2 days.

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Human Herpesvirus-8

HHV-8, a gamma herpesvirus, is most closely related to EBV and *Herpesvirus saimiri*. It has been found in virtually all patients with Kaposi sarcoma, including those who have AIDS, in African cases; in elderly men from the Mediterranean basin, and in transplant patients. In addition, the seropositivity rate (infection rate) for this virus correlates with the prevalence of Kaposi sarcoma in a given population. The background seroprevalence rate in North America and Northern Europe is near zero. Seroprevalence is highest in Kaposi sarcoma endemic areas in sub-Saharan Africa (50–100%). In the general population in Italy, the seroprevalence is 10% to 15%, being 6% to 10% in children under age 16 and 22% after age 50. In south central Italy and Sardinia seroprevalence rates are higher, being in the 20% to 25% range for the general population. In Italy, high rates of HHV-8 seropositivity are also seen in HIV-infected gay men (up to 60%), in female prostitutes (40%), and in heterosexual men who have had sex with prostitutes (40%). Infection with HHV-8 precedes and predicts subsequent development of Kaposi sarcoma in HIV-infected men. In addition to Kaposi sarcoma lesions, HHV-8 can be found in saliva and in circulating blood cells in HHV-8 infected patients. HHV-8 is also found in the semen of up to 20% of patients with Kaposi sarcoma. Heterosexual partners of patients with classic Kaposi sarcoma have high rates of HHV-8 seropositivity (>40%). These epidemiologic features all strongly support sexual transmission as an important mechanism of the spread of HHV-8. The finding of a significant number of infections in prepubertal children, however, suggests nonsexual methods of transmission also exist. HHV-8 seroprevalence rates in heterosexual intravenous drug users and persons with HIV infection acquired via blood transfusion are not increased above the general population, suggesting HHV-8 is poorly transmitted by blood and blood products.

HHV-8 is present in a rare type of B-cell lymphoma called *body cavity-based B-cell lymphoma* or *primary effusion lymphoma* (PEL),which presents with pleural, pericardial, and peritoneal malignant effusions. Rarely, this form of lymphoma may be associated with skin lesions, which histologically are CD30+ anaplastic large cell lymphoma. HHV-8 is also found in all cases of Castleman's disease associated with HIV infection and about half of cases in HIV-negative persons.

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B Virus

B virus (*Herpesvirus simiae*) is endemic in Asiatic Old World monkeys (macaques) and may infect other monkeys housed in close quarters with infected monkeys. In macaques the disease is a recurrent vesicular eruption analogous to HSV in humans, with virus shed from conjunctiva, oral mucosa, and the urogenital area. Humans become infected after being bitten, scratched, or contaminated by an animal shedding B virus. Usually patients are animal handlers or researchers. Rare cases of respiratory or human-to-human contact spread

have been reported. Within a few days after the bite, vesicles, erythema, necrosis, or edema appear at the site of inoculation. Regional lymph nodes are enlarged and tender. Fever is typically present. In a substantial number of human infections rapid progression to neurologic disease occurs. This is initially manifested by peripheral nerve involvement (dysesthesia, paresthesia), progresses to spinal cord involvement (myelitis and ascending paralysis with hyporeflexia), and finally brain disease (decreased consciousness, seizures, and respiratory depression). Fifteen of 22 reported cases have died, and all survivors of encephalitis suffered severe neurologic sequelae. Treatment with acyclovir or ganciclovir has been successful in some cases, but other patients similarly treated have died. Because *H. simiae* infection may recur after a period of latency, lifetime surveillance is required. The Centers for Disease Control (CDC) has issued guidelines to protect workers from B virus infection.

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INFECTIOUS HEPATITIS

Hepatitis B Virus

Hepatitis B virus (HBV) is a double-stranded DNA virus which is spread by blood and blood products, and sexually in Europe and the Western Hemisphere. In Africa and Asia infection often occurs perinatally. HBV is the primary cause of hepatocellular carcinoma and may also cause liver failure and cirrhosis. Acute infection with HBV is associated with anorexia, nausea, right upper quadrant pain, and malaise. Twenty to 30% of persons with acute HBV infection have a serum sickness-like illness with urticaria, arthralgias, and, occasionally, arthritis, glomerulonephritis, or vasculitis. These symptoms appear 1 to 6 weeks before the onset of clinically apparent liver disease. Immune complexes containing hepatitis B surface antigen and hypocomplementemia occur in the serum and in joint fluid. The process spontaneously resolves as antigen is cleared from the blood.

Hepatitis B is also associated with polyarteritis nodosa (PAN) in 7% to 8% of cases. This usually occurs within the first 6 months of infection, even during the acute phase, but may occur as long as 12 years after infection. Unlike the urticarial reaction, which is usually associated eventually with the development of clinical hepatitis, HBV infection associated with PAN may be silent.

A highly effective vaccine is available to prevent HBV infection. It is recommended as a part of standard childhood immunizations and all healthcare workers should be immunized. IFN-α and lamivudine may be used to treat active HBV infection, although following therapy, HBV viremia may recur. Hepatitis B-associated PAN has been treated successfully with systemic steroids, lamivudine, and plasma exchange.

Hepatitis C Virus

Hepatitis C virus (HCV) is a single-stranded RNA virus which causes most cases of non-A, non-B viral hepatitis. Now that a serologic test is available to screen blood products for HCV infection, the vast majority of new cases of HCV infection are parenterally transmitted via intravenous drug usage. Sexual transmission, as compared to HBV, is uncommon (<1% transmission/year of exposure). Maternal-to-infant spread occurs in 5% of cases. Only about one-third of patients are symptomatic during acute infection. Between 55% and 85% of patients will have chronic infections. Although in most cases patients have minimal symptoms for the first one to two decades of infection, cirrhosis and liver failure as well as hepatocellular carcinoma are common sequelae. Chronic HCV infection is associated with various skin disorders, either by direct effect or as a consequence of the associated hepatic damage.

Cutaneous necrotizing vasculitis, which is usually associated with a circulating type II cryoglobulin, occurs in approximately 1% of patients with chronic HCV infection. In 84% of cases of type II cryoglobulinemia, HCV infection is present. The most common clinical presentation is palpable purpura of the lower extremities. Livedo reticularis and urticaria may also occur. Arthropathy, glomerulonephritis, and neuropathy frequently accompany the skin eruption. Histologically, in all cases a leukocytoclastic vasculitis is seen. In some cases the vasculitis may involve small arteries, giving a histologic pattern similar to that seen in PAN. In various studies 5% to 20% of patients with PAN were HCV positive, suggesting that both HBV and HCV can cause PAN. The presence of anti-HCV antibodies should not be used as the sole diagnostic test in persons with PAN, as PAN may cause a false-positive ELISA test for HCV.

Patients with porphyria cutanea tarda (PCT) often have hepatocellular abnormalities. Depending on the prevalence of HCV infection in the population studied, between 10% and 95% of sporadic (not familial) PCT cases are HCV associated. Treatment of the HCV infection with IFN may lead to improvement of the PCT.

HCV infection has been associated with lichen planus. The likelihood of identifying HCV infection in a patient with lichen planus is greatest in geographic regions with high rates of HCV infection. Patients with mucosal ulcerative lichen planus are also more likely to be HCV infected. Serologic testing in a patient should be considered if the patient has HCV risk factors, abnormal liver function tests, or is from a geographic region or population in which HCV infection is common. HCV may also be associated with cutaneous B-cell lymphoma, xerostomia (but not typical Sjögren syndrome), possibly erythema multiforme, and autoimmune thyroid disease. Approximately 15% of patients with HCV infection have pruritus. Pruritus virtually always is associated with advanced liver disease and abnormal liver function tests. Patients with pruritus and normal liver function tests and no history of hepatitis will rarely be found to be infected with HCV.

Necrolytic acral erythema is an uncommon condition uniquely associated with HCV infection. It resembles the "deficiency" dermatoses except it has an acral distribution. The clinical lesions are painful or pruritic, keratotic, well-defined plaques with raised red scaly borders, or diffuse hyperkeratosis. Erosion and flaccid blisters may occur,

contributing to the discomfort. The dorsal feet (less commonly the dorsal hands), as well as the lower extremities, may be involved. Histologically, there is necrosis of the superficial portion of the epidermis along with hyperkeratosis, loss of the granular cell layer, and parakeratosis. Intraepidermal spongiotic foci are present, which may be macroscopic at times, the cleavage plane being between the necrotic and viable epidermis. Zinc, essential fatty acid, and glucagon levels are normal, but the patients may be hypoalbuminemic and have low serum amino acids due to their liver disease. Treatment of the associated HCV infection with IFN and ribavirin, or IFN plus zinc, has resulted in resolution. Hyperalimentation was also partially effective in some patients, as was amino acid supplementation with zinc.

A combination of IFN-α and ribavirin is used to treat patients with chronic HCV infection, with sustained responses (negative HCV in the blood at 12 months) in slightly over 50% of patients. Complications caused by the presence of the virus in the blood, such as vasculitis, improve with such treatment. The response of other associated conditions such as lichen planus and PCT are variable. Combined IFN and ribaviran therapy may be complicated by an eczematous eruption with pruritus in about 8% of patients and severe pruritus in about 1%. Eczema typically affects the distal extremities, dorsal hands, face, neck, and less commonly the trunk, axillae, and buttocks. The eruption may be photodistributed and photoexacerbated. These eczematous eruptions typically begin 2 to 4 months after treatment is begun. In affected patients, prior treatment with IFN alone was usually not associated with an eczematous eruption. Histologically, the eruptions show a spongiotic dermatitis. The eruption resolves completely if treatment is stopped for 2 to 3 weeks, but will recur when treatment is restarted. Aggressive therapy with antihistamines, emollients, and potent topical steroids will usually control the eczema, allowing uninterrupted continuation of treatment. The severity of the pruritus in these cases may relate to the tendency of liver disease to cause itch and the frequent psychiatric side effects of HCV and IFN (depression, anxiety), which may reduce itch threshold.

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Gianotti-Crosti Syndrome (Papular Acrodermatitis of Childhood, Papulovesicular Acrolocated Syndrome)

Gianotti-Crosti syndrome includes cases with or without associated HBV infection. Other implicated infectious agents have included adenovirus, CMV, EBV (initial infection or reactivation), enteroviruses (coxsackie A-16, B4, and B5), vaccinia virus, rotavirus, hepatitis A and C, respiratory syncytial virus, parainfluenza virus, parvovirus B19, rubella virus, HHV-6, HIV-1, streptococcus, and *Mycobacterium avium* infection. Immunizations against poliovirus, diptheria, pertussis, Japanese encephalitis, influenza, and hepatitis B and measles (together) have also caused this syndrome. With widespread immunization against HBV, most cases seen in Europe, India, the US, and Canada are not associated with HBV. The clinical features of Gianotti–Crosti syndrome are identical, independent of the cause:

- The condition typically affects children between 6 months and 14 years of age (median age 2 years), and may rarely be seen in adults. Chuh proposed the following diagnostic criteria: Positive clinical features—1) monomorphous flat-topped, pink-brown, papules or papulovesicles of 1- to 10-mm in diameter (Fig. 19-28); 2) any three or all four sites involved—face, buttocks, forearms, and extensor legs; 3) symmetry; and 4) duration of at least 10 days.
- Negative clinical features—1) extensive truncal lesions; and 2) scaly lesions.

The lesions develop over a few days but last longer than most viral exanthems (2 to 4 weeks). Pruritus is variable and the mucous membranes are spared, except when inflamed by the associated infectious agent.

Depending on the cause, the lymph nodes, mainly inguinal and axillary, are moderately enlarged for 2 to 3 months. Splenomegaly, if present, is slight and rarely lasts long. In cases associated with hepatitis B, acute viral hepatitis occurs, beginning at the same time as or 1 to 2 weeks after onset of the skin eruption. It is generally anicteric, but in some children jaundice may appear about 20 days after onset of the skin eruption. The liver usually remains moderately enlarged, but not tender, for 1 to 2 months. No treatment appears to shorten the course of the disease, which is self-limited.

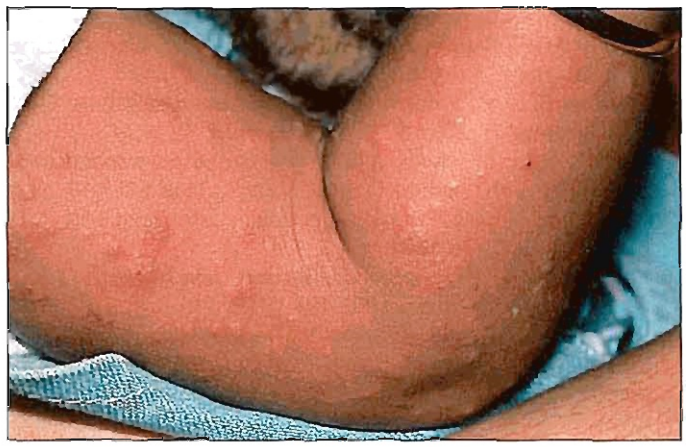

Fig. 19-28 Gianotti-Crosti syndrome.

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POXVIRUS GROUP

The poxviruses are DNA viruses of a high molecular weight. The viruses are 200 to 300 nm in diameter, and hence can be seen in routine histologic material. The orthopoxviruses include variola, vaccinia, monkeypox, cowpox, buffalopox, and Cantagalo and Aracatuba. The parapoxviruses are primarily zoonotic, and include orf, paravaccinia, Bovine papular stomatitis, deerpox, and sealpox. Tanapox is the sole Yatapoxvirus to cause human disease.

Variola Major (Smallpox)

Smallpox was eradicated worldwide in 1977. It continues to be of interest to dermatologists as it is a potential biologic warfare agent. Variola is spread via the respiratory route, with 37% to 88% of unvaccinated contacts becoming infected. The incubation period for smallpox is 7 to 17 days (average 10 to 12 days). The prodromal phase consists of 2 to 3 days of high fever (>40° C), severe headache, and backache. The fever subsides and an enanthem covers the tongue, mouth, and oropharynx. This is followed in one day by the appearance of skin lesions. The skin lesions are distributed in a centrifugal pattern; the face, arms, and legs more heavily involved than the trunk. Lesions appear first on the palms and soles and feel like firm "BBs" under the skin. Beginning as erythematous macules (days 1–2), the lesions all in synchrony become 2- to 3-mm papules (days 2 to 4) and evolve to 2- to 5-mm vesicules (days 4 to 7) and 4- to 6-mm pustules (days 5 to 15). The pustules umbilicate, collapse, and form crusts beginning in the second week. The total evolution averages 2 weeks. Lesions on the palms and soles persist the longest. The crusts separate after about 1 more week, leaving scars, which are permanent in 65% to 80% of the survivors. Patients are infectious from the onset of the enanthema through the first 7 to 10 days of the eruption. A variety of complications occur, including pneumonitis, blindness due to viral keratitis or secondary infection (1% of patients), encephalitis (<1% of patients), arthritis (2% of children), and osteitis. Immunity is lifelong. The mortality rate was 5% to 40% in undeveloped countries (and at a time prior to current intensive care and antiviral management).

Six clinical patterns of smallpox have been described. Variola major, or "ordinary smallpox," had a case fatality rate of 30%. Modified variola represents a small percent of unvaccinated patients and about 25% of vaccinated persons. The lesions are fewer, smaller, and more superficial, and evolve more rapidly. Fatalities were rare. Flat lesions occur in about 7% of persons, and evolve slowly and coalesce. Ninety-seven percent of unvaccinated persons with flat variola died. Hemorrhagic smallpox occurred in a small percent of patients, resembles a purpuric eruption or vasculitis, and was universally fatal within a week. This variant is very hard to diagnose without a biopsy, but is highly infectious. Variola sine eruption describes patients who develop flu-like symptoms but no skin lesions. They do not appear to be infectious. Variola minor appears to be a subtype of variola which is more mild and resulted in death in less than 1% of patients.

Diagnosis is made by electron microscopy, viral culture, and PCR. Special laboratories, usually associated with the City and State Health Departments in the US have the capacity to process these specimens and confirm the diagnosis. The differential diagnosis is primarily varicella, especially of the more severe form seen in adults. In varicella the prodrome lasts for 1 to 2 days; fever begins with the onset of the eruption (not preceding it by 1–3 days as in variola); the eruption is concentrated on the torso (not centrifugally); individual lesions of different stages are present; and individual lesions evolve from vesicles to crust within 24 h. The diagnostic test of choice in this setting would be a Tzanck smear or DFA, which can rapidly confirm the diagnosis of varicella.

Treatment of smallpox includes strict isolation and protection of healthcare workers. Only vaccinated persons should treat the patient and any of those exposed should immediately be vaccinated as this modifies the disease. Cidofovir may be indicated as it modifies infections by other orthopox viruses.

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Vaccinia

The vaccinia virus has been propagated in laboratories for immunization against smallpox. There are multiple strains used in vaccines and the rates of complications vary somewhat depending on the strain used. New vaccines have been developed, but were not used during the mass immunizations which took place between 2002 and 2004, so their adverse reaction profiles are poorly understood.

Vaccination Vaccination is inoculation of live vaccinia virus into the epidermis and upper dermis by the multiple puncture technique. Three to 5 days after inoculation a papule forms, which becomes vesicular at days 5 to 8, then pustular, reaching a maximum size at day 8 to 10. The pustule dries from the center outward and forms a scab that separates 14 to 21 days after vaccination, resulting in a pitted scar. Formation by day 6 to 8 of a papule, vesicle, ulcer or crusted lesion surrounded by a rim of erythema and induration is termed a "major reaction" or "take" (Fig. 19-29). Reactions which do not match this description are considered equivocal and such persons cannot be considered immune. Revaccination should be considered. A large vaccination reaction, or "robust take," is the development of a plaque of erythema and induration of greater than 10 cm at the site of inoculation. This occurs in 10% of initial vaccines. It peaks at days 8 to 10 and resolves without treatment within 72 h. Cellulitis secondary to vaccination occurs in days 1 to 5 after vaccination or after several weeks and progresses without treatment. Management should be expectant, but a bacterial culture may be taken. Since vaccinated patients may have fever at days 8 to 10 following vaccination, this is not helpful in separating cellulitis from a "robust take."

Vaccination involves the inoculation of a live virus. Complications result from an abnormal response to the vaccination by the host or from inadvertent transmission to another person. Persons with defective cutaneous or systemic immunity are at particular risk for adverse outcomes from vaccination. Since some complications may be fatal, extremely careful steps must be taken to avoid complications.

Inadvertent Inoculation and Autoinoculation Inadvertant inoculation of vaccinia may occur by transmission of virus via hands or fomites from the vaccination site to another skin area or the eye, or to another person. Accidental autoinoculation occurs in about 1 in 1000 vaccinees. Autoinoculation most commonly occurs around the eyes and elsewhere on the face. These lesions evolve in parallel with the primary vaccination site and, except for ocular lesions, cause no sequelae except at times scarring. Any evidence of ocular inflammation in a recently vaccinated individual could represent ocular vaccinia infection and requires immediate ophthalmologic evaluation. Transmission to others (secondary transfer) is rare if the vaccination site is kept covered until it heals (7.4 in 100,000 primary vaccinees). It usually occurs within a household or through intimate contact. Serial transmission can occur among male sports partners.

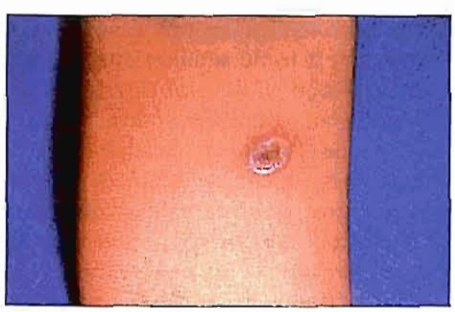

Fig. 19-29 Vaccinia, typical reaction at about 1 week.

Generalized Vaccinia Six to 9 days after vaccination a generalized vaccinia eruption may occur. The lesions are papulovesicles that become pustules and involute in 3 weeks, although successive crops may occur within that time. Generalized vaccinia may be accompanied by fever, but patients do not appear ill. Lesions may be generalized or limited to one anatomic region and can number from a few to hundreds (Fig. 19-30). It can be confused with multiple site autoinoculation as well as erythema multiforme. The diagnosis is confirmed by biopsy, viral culture, or PCR. Generalized vaccinia is self-limited and does not require treatment in the immunocompetent host. In the setting of underlying immunodeficiency, early intervention with vaccinia immune globulin (VIG) may be beneficial.

Eczema Vaccinatum Eczema vaccinatum is analogous to eczema herpeticum, representing vaccinia virus infection superimposed on a chronic dermatitis, especially atopic dermatitis. Patients with Darier's disease, Netherton, and other disorders of cornification may also be at risk. Since patients with atopic dermatitis or any past history of atopic dermatitis should not be vaccinated, most cases of eczema vaccinatum represent secondary transfer to an at-risk individual from a recent vaccinee, usually a family member. The vesicles appear suddenly, mostly in areas of active dermatitis. The lesions are sometimes umbilicated and appear in crops, resembling smallpox or chickenpox. The onset is sudden and fresh vesicles appear for several days. Scarring is common. Often there is cervical adenopathy, fever, and affected persons are systemically ill (as opposed to those with generalized vaccinia). Secondary bacterial infection can complicate eczema vaccinatum. The mortality

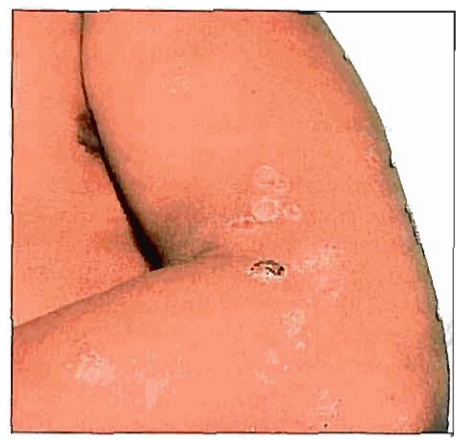

Fig. 19-30 Vaccinia, disseminated.

rate for eczema vaccinatum is 30% to 40% if untreated. VIG reduces mortality to 7%. Multiple doses of VIG and perhaps treatment with cidofovir may be required.

Progressive Vaccinia (Vaccinia Necrosum, Vaccinia Gangrenosum) Progressive vaccinia is a rare, severe and often fatal complication of vaccination that occurs in persons who are immunodeficient. Most cases occur when infants with undiagnosed immunodeficiency are immunized. The initial vaccination site continues to progress and fails to heal after more than 15 days. The vaccination site is characterized by a painless, but progressive necrosis and ulceration, with or without metastatic lesions to distant sites (skin, bones, viscera). No inflammation is present at the sites of infection, even histologically. Inflammation may indicate secondary bacterial infection. Untreated progressive vaccinia is virtually always fatal. Progressive vaccinia is diagnosed by skin biopsy, viral culture, or PCR. VIG should be given, and cidofovir should be considered.

Cutaneous Immunologic Complications A spectrum of erythematous eruptions occurs following vaccination. These eruptions are more common than generalized vaccinia with which they are often confused. Cases of Stevens-Johnson syndrome following vaccination have been seen in the past, primarily in children, but apparently are rare in adult vaccinees (no cases among >30,000 civilian adult vaccinees).

Roseola Vaccinia

Roseola vaccinia occurs primarily in initial adult and child vaccinees with prominent rims of erythema surrounding their vaccination sites. It occurs at the end of the second week after vaccination and as the peak of the local reaction at the vaccination site is resolving. It is characterized by an extensive symmetrical eruption of macules and papules. Lesions blanch with pressure, but may have a tiny central crust or erosion. The eruption may also have a morbilliform character. Individual lesions are discrete and do not coalesce to form a scarlatiniform eruption. The patient is afebrile, feels otherwise well, and no other signs or symptoms are present. Involution takes place in a few days. It is distinguished from generalized vaccinia by a later onset (end of second week as opposed to days 6 to 9 after vaccination), prominent erythema, lack of vesicles and pustules, and negative laboratory testing for vaccinia virus. It is distinguished from erythema multiforme/Stevens-Johnson syndrome by the absence of atypical purpuric or typical targetoid lesions, lack of mucosal involvement, and histologic evaluation.

Post-Vaccination Follicular Eruption

A generalized variant of this eruption occurred in 2.7% of new vaccinees and a localized variant in 7.4% during a trial of Aventis Pasteur Smallpox vaccine. In the second week, 9 to 11 days following vaccination, multiple follicular, erythematous papules appeared, primarily on the face, trunk, and proximal extremities. Lesions were mildly pruritic. Over several days the lesions evolved to pustules which resolved without scarring. Lesions were simultaneously at different stages of development. The number of lesions was usually limited and rarely exceeded 50. Lesions spontaneously resolved over a few days. Histologic evaluation revealed a suppurative folliculitis. No virus was detected in the lesions by PCR or viral culture.

Other Skin Lesions at Vaccination Scars

Melanomas, basal cell carcinomas, and squamous cell carcinomas have all occurred in vaccination scars. Benign lesions with a tendency to occur in scars, such as sarcoidosis and granuloma annulare, also can occur in vaccination scars.

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Human Monkeypox

Human monkeypox is a rare, sporadic zoonosis that occurs in remote areas of the tropical rainforests in central and western Africa. Monkeypox virus is an orthopoxvirus. The main vector for monkeypox is wild African rodents and monkeys. Humans and anteaters are accidental hosts. Direct contact with an infected animal or person appears to be required to acquire the infection. In Africa, more than 90% of cases occur in children under 15 years of age, in whom the fatality rate is 11%. The secondary attack rate in African households is 10%. A recent outbreak of 72 cases of monkeypox occurred in the US. Prairie dogs became infected when housed with infected African rodents. Persons who purchased the prairie dogs become infected, most commonly via bites, scratches, or through areas of damaged skin. The disease is clinically similar to smallpox, with an incubation period of 5 to 21 days. Patients develop headache (100%), fever, sweats, and chills (82%), and lymphadenopathy (55%). The prodrome lasts 2 days, followed by a vesiculopustular eruption. Primary skin lesions appear at the site of inoculation, followed by 1 to 50 satellite and disseminated skin lesions over a period of several days. Lesions began as papules that evolve to vesiculopustules, at times with prominent erythematous flares. The distribution is generalized and the buccal mucosa can be affected. Lesions resolve with hemorrhagic crusts. Patients typically have lesions at all stages of evolution. The disease is self-limited, with lesions crusting by an average of 12 days (range 3–25 days). The disease is less severe in persons previously

vaccinated against smallpox. In animal models, smallpox vaccination protects susceptible animals from severe/fatal monkeypox infection. Early lymphadenopathy is the most important sign in differentiating human monkeypox from smallpox and chickenpox.

Buffalopoxvirus

Buffalopoxvirus is a subspecies of vaccinavirus and is endemic in buffalo herders in India. Lesions occur on the hands and arms of animal handlers and resemble a milder form of cowpox. Family members may be affected and children have developed lesions resembling eczema vaccinatum.

Zoonotic Poxvirus Infections

While these infections are uncommon, increasing numbers are being reported due to the popularity of exotic pets, and travel to endemic areas. They continue to represent, in the case of Orf, an important disease in animal husbandry. The diagnosis of zoonotic poxvirus infection is usually by epidemiologic history, clinical features, and electron microscopy, which can separate the various poxvirus genera. Laboratory culture is slow and PCR analysis of the viral DNA allows for speciation. Rarely is antiviral therapy indicated, as most diseases are self-limited. Cidofovir, and in some cases ribavirin, and adefovir dipivoxil would be anticipated to have activity against this group of viruses.

Cowpox Cowpox is an orthopoxvirus related to smallpox and vaccinia that is geographically restricted to the UK, Europe, Russia, and adjacent states. It is largely a zoonosis that rarely affects cattle. The domestic cat is the usual source of human infection, but the animal reservoirs are apparently small wild rodents (mice and voles) and human infection from contact with such rodents has been confirmed. Most cases occur in the late summer and in autumn.

The incubation period is about 7 days. There is then an abrupt onset of fever, malaise, headache, and muscle pain. Lesions are usually solitary (72%), with co-primaries in 25%. Lesions occur on the hands and fingers in half the cases and the face in another third. Secondary lesions are uncommon and generalized disease is rare, occurring usually in patients with atopic dermatitis. The lesion progresses from a macule through a vesicular stage, then a pustule that becomes blue–purple and hemorrhagic. A hard, painful, 1- to 3-cm indurated eschar develops after 2 to 3 weeks and may resemble cutaneous anthrax. In anthrax, however, the eschar forms by day 6. Lesions are always painful and there is local lymphadenopathy, which is usually tender. The amount of surrounding edema and induration is much more marked than in Orf. Patients are systemically ill until the eschar stage. Healing usually takes 6 to 8 weeks. Scarring is common.

Farmyard Pox Because closely related parapoxviruses of sheep and cattle cause similar disease in humans, orf and milker's nodules have been collectively called *farmyard pox*. The epidemiologic features are discussed separately, but the clinical and histologic features, which are identical, are discussed jointly. The diagnosis of these infections is based on taking an accurate history, and can virtually always be confirmed by routine histologic evaluation. The presence of a homologue gene of vascular endothelial growth factor (VEGF) may explain the vascular nature of lesions produced by parapoxviruses.

Milker's Nodules/Bovine Papular Stomatitis/ Pseudocowpox

These infections cause worldwide occupational disease of milkers or veterinarians, most commonly directly transmitted from the udders (milker's nodules) or muzzles (bovine papular stomatitis) of infected cows. Lesions are usually solitary or only a few in number and are confined to the hands or forearms. Numerous lesions have been reported in healing first- and second-degree burns in milker's nodules. These cases occurred on farms with infected cattle, but the patients had not had direct contact with the cattle, suggesting indirect viral transmission. It is unclear whether milker's nodules and bovine papular stomatitis are caused by one or two species of parapoxvirus.

Orf

Also known as *ecthyma contagiosum*, *contagious pustular dermatosis*, *sheep pox*, and *infectious labial dermatitis*, orf is a common disease in goat- and sheep-farming regions throughout the world (Fig. 19-31). Direct transmission from active lesions on lambs is most common, but infection from fomites is also frequent, since the virus is resistant to heat and dryness. Autoinoculation to the genital area can occur, but human-to-human transmission is rare.

Clinical Features

The incubation period for farmyard pox is about 1 week. Lesions are usually solitary and occur on the hands, fingers, or face. Lesions evolve through six stages: 1) a papule, which then becomes a target lesion with a red center surrounded successively with a white ring and then a red halo; (2) acute stage, in which a red, weeping nodule not unlike pyogenic granuloma appears; (3) in a hairy area, temporary alopecia ensues; (4) regenerative stage, the lesion becomes dry with black dots on the surface; (5) nodule then becomes papillomatous; and (6) nodule finally flattens to form a dry crust, eventually healing. Lesions are usually about 1 cm in diameter, except in immunosuppressed patients, in whom giant lesions may occur. Spontaneous resolution occurs in about 6 weeks, leaving minimal scarring. Mild swelling, fever, pain, and lymphadenitis may accompany the lesions, but these symptoms are milder than those seen in cowpox.

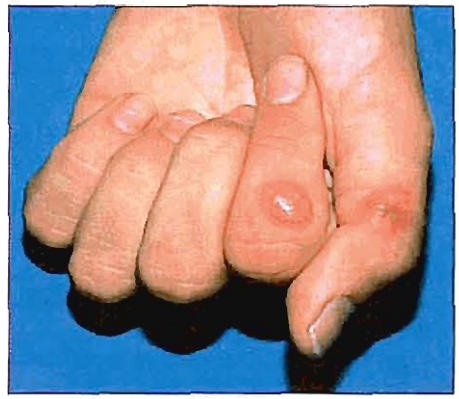

Fig. 19-31 Orf.

Orf may be associated with an erythema multiforme-like eruption in about 5% of cases. Treatment is supportive, although shave excision may accelerate healing.

Histologic Features

Histologic features correlate with the clinical stage. Nodules show a characteristic pseudoepitheliomatous hyperplasia covered by a parakeratotic crust. Keratinocytes always demonstrate viropathic changes of nuclear vacuolization and cytoplasmic 3- to 5-μm eosinophilic inclusions surrounded by a pale halo. The papillary dermis is markedly edematous. The dermal infiltrate, which is dense and extends from the interface to the deep dermis, consists of lymphocytes, histiocytes, neutrophils, and eosinophils. Massive capillary proliferation and dilation are present in the upper dermis.

Sealpox Sealpox, caused by a parapoxvirus, closely resembles orf and has been described in seal handlers who have been bitten by infected harbor or grey seals. Up to 40% of seals in Europe and North America are serologically positive for the virus, suggesting infection is common.

Human Tanapox Tanapox infection is a Yatapoxvirus infection endemic to equatorial Africa. It is spread from its natural hosts, nonhuman primates through minor trauma. Human-to-human transmission is rare. Tanapox infection is manifested by mild fever of abrupt onset lasting 3 to 4 days, followed by the appearance of one or two pock lesions. Lesions are firm and cheesy, resembling cysts. The disease is self-limited and smallpox vaccination would not be expected to be protective. Rare cases have been imported into Europe and the US.

Parapoxvirus Infections from Wildlife Smith et al reported two patients with solitary lesions on the fingers, one following direct inoculation while cleaning a deer and another at the site of a cut sustained on a camping trip in an area with wild deer. Lesions were present for more than 2 months before biopsy. Histologically, there was marked hyperkeratosis, parakeratosis, and pseudoepitheliomatous hyperplasia. The midepidermal cells showed vacuolization with pyknotic nuclei. The dermis had prominent vascular proliferation. Viral particles were identified by electron microscopy in the keratinocytes. These may represent cases of red deer pox, caused by a distinct species of parapoxvirus. Reindeer poxvirus may cause similar disease.

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Molluscum Contagiosum

Molluscum contagiosum is caused by up to four closely related types of poxvirus, MCV-1 to -4, and their variants. Although the proportion of infection caused by the various types varies geographically, throughout the world MCV-1 infections are most common. In small children virtually all infections are caused by MCV-1. There is no difference in the anatomic region of isolation with regard to infecting type (as opposed to HSV, for example). In patients infected with HIV, however, MCV-2 causes the majority of infections (60%), suggesting that HIV infection-associated molluscum does not represent recrudescence of childhood molluscum.

Infection with MCV is worldwide. Three groups are primarily affected: young children, sexually-active adults, and immunosuppressed persons, especially those with HIV infection. Molluscum is most easily transmitted by direct skin-to-skin contact, especially if the skin is wet. Swimming pools have been associated with infection.

In all forms of infection, the lesions are relatively similar. Individual lesions are smooth surfaced, firm, dome-shaped, pearly papules, averaging 3 to 5 mm in diameter. "Giant" lesions may be up to 1.5 cm in diameter. A central umbilication is characteristic. Irritated lesions may become crusted and even pustular, simulating secondary bacterial infection. This may precede spontaneous resolution. Lesions that rupture into the dermis may elicit a marked suppurative inflammatory reaction that resembles an abscess.

The clinical pattern depends on the risk group affected. In young children the lesions are usually generalized and number from a few to more than 100 (Fig. 19-32). Dermatitis surrounding a lesion usually heralds the resolution of that lesion (Fig. 19-33). Lesions tend to be on the face, trunk, and extremities. Genital lesions occurring as part of a wider distribution occur in 10% of childhood cases. When molluscum is restricted to the genital area in a child, the possibility of sexual abuse must be considered.

In adults, molluscum is sexually transmitted and other STDs may coexist. There are usually fewer than 20 lesions;

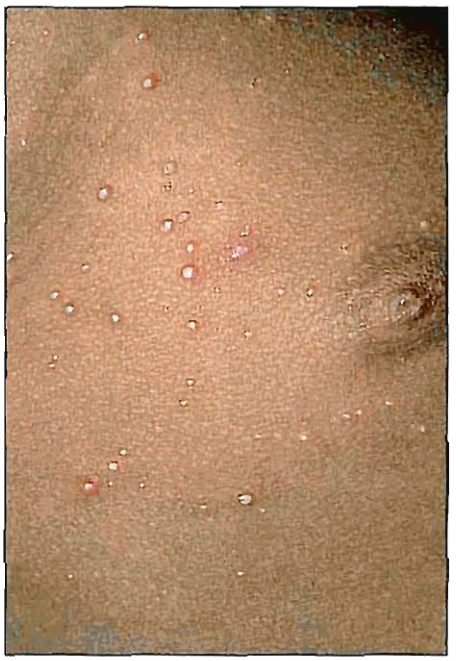

Fig. 19-32 Molluscum contagiosum.

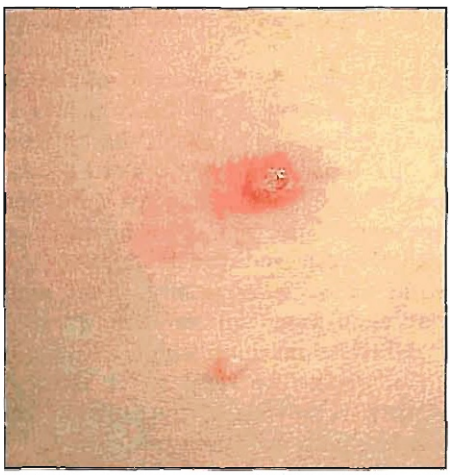

Fig. 19-33 Molluscum contagiosum.

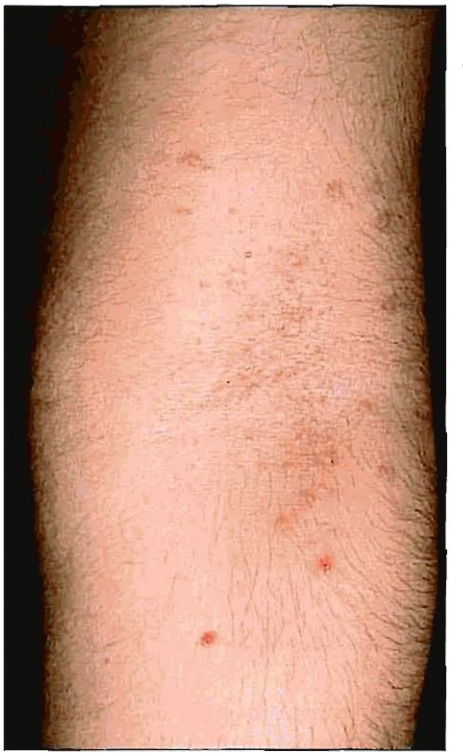

Fig. 19-34 Molluscum contagiosum, child with atopic dermatitis.

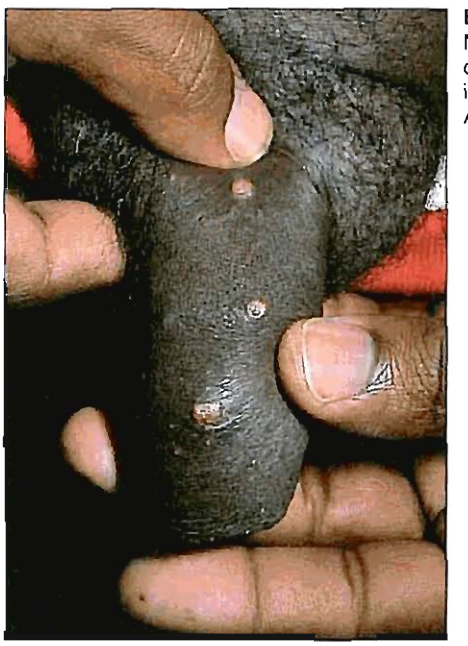

Fig. 19-35 Molluscum contagiosum, genital in a patient with AIDS.

these favor the lower abdomen, upper thighs, and the penile shaft in men. Mucosal involvement is very uncommon.

Immunosuppression, either systemic T-cell immunosuppression (usually HIV, but also sarcoidosis and malignancies) or abnormal cutaneous immunity (as in atopic dermatitis or topical steroid use), predisposes the individual to infection. In atopic dermatitis, lesions tend to be confined to dermatitic skin (Fig. 19-34).

Secondary infection may occur. In addition, in about 10% of lesions, a surrounding eczematous reaction is present (molluscum dermatitis). Rarely, erythema annulare centrifugum may be associated. Lesions on the eyelid margin or conjunctiva may be associated with a conjunctivitis or keratitis. Rarely, the molluscum lesions may present as a cutaneous horn (molluscum contagiosum cornuatum).

Ten to 30% of AIDS patients not receiving antiretroviral therapy have molluscum contagiosum (Figs 19-35 and 19-36). Virtually all HIV-infected patients with molluscum contagiosum already have an AIDS diagnosis and a helper T-cell count of less than 100. In untreated HIV disease, lesions favor the face (especially the cheeks, neck, and eyelids) and genitalia. They may be few or numerous, forming confluent plaques. Giant lesions are not uncommon and may be confused with a basal cell carcinoma. Involvement of the oral and genital mucosa may occur, virtually always indicative of advanced AIDS (helper T-cell count <50). Facial disfigurement with numerous lesions can occur.

Molluscum contagiosum has a characteristic histopathology. Lesions affect primarily the follicular epithelium. The lesion is acanthotic and cup shaped. In the cytoplasm of the prickle cells, numerous small eosinophilic and later basophilic inclusion bodies, called *molluscum bodies* or *Henderson-*

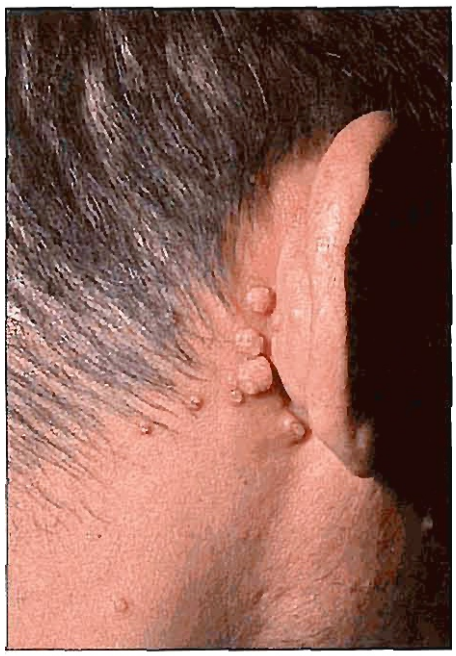

Fig. 19-36 Molluscum contagiosum in a patient with AIDS.

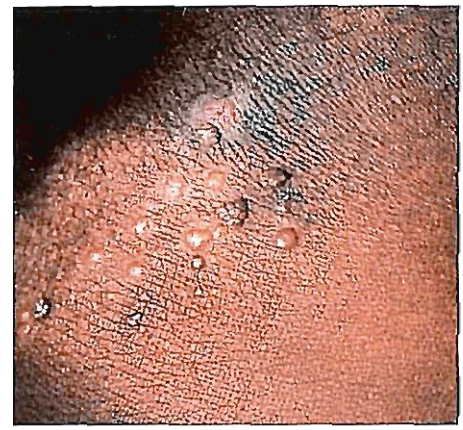

Fig. 19-37 Molluscum contagiosum and *condyloma* accuminata (HPV infection) occurring together.

Paterson bodies, are formed. Eventually, their bulk compresses the nucleus to the side of the cell. In the fully developed lesion each lobule empties into a central crater. Inflammatory changes are slight or absent. Characteristic brick-shaped poxvirus particles are seen on electron microscopy in the epidermis. Latent infection has not been found, except in untreated AIDS patients, in whom even normal-appearing skin may contain viral particles.

The diagnosis is easily established in most instances because of the distinctive central umbilication of the dome-shaped lesion (Fig. 19-37). This may be enhanced by light cryotherapy that leaves the umbilication appearing clear against a white (frozen) background. For confirmation, express the pasty core of a lesion, squash it between two microscope slides (or a slide and a cover glass) and stain it with Wright, Giemsa, or Gram stains. Firm compression between the slides is required.

Treatment is determined by the clinical setting. In young immunocompetent children, especially those with numerous lesions, the most practical course may be to not treat or to use only topical tretinoin. Aggressive treatment may be emotionally traumatic and can cause scarring. Spontaneous resolution is virtually a certainty in this setting, avoiding these sequelae. Individual lesions last 2 to 4 months each; the duration of infection is about 2 years. Continuous application of surgical tape to each lesion daily after bathing for 16 weeks led to cure in 90% of children so treated. Topical cantharidin, applied for 4 to 6 h to approximately 20 lesions per setting led to resolution in 90% of patients and 8% of patients improved. This therapy is well tolerated, has a very high satisfaction rate for patients and their parents, and has rare complications. If lesions are limited and the child is cooperative, nicking the lesions with a blade to express the core (with or without the use of a comedo extractor), light cryotherapy, application of trichloroacetic acid (35–100%), or removal by curettage are all alternatives. The application of EMLA cream for 1 h before any painful treatments has made the treatment of molluscum in children much easier. Topical 5% sodium nitrite with 5% salicylic acid cures about 75% of patients. No controlled trials have confirmed the efficacy of imiquimod in the treatment of molluscum and the above treatments, especially cantharidin, should be considered first line until the efficacy of imiquimod has been demonstrated.

In adults with genital molluscum, removal by cryotherapy or curettage is very effective. Neither imiquimod nor podophyllotoxin has been demonstrated to be effective. In fact, the failure of these agents to improve "genital warts" suggests the diagnosis of genital molluscum contagiosum. Sexual partners should be examined; screening for other coexistent STDs is mandatory.

In patients with atopic dermatitis, application of EMLA followed by curettage or cryotherapy is most practical. Caustic chemicals should not be used on atopic skin. Topical steroid application to the area should be reduced to the minimum strength possible. A brief course of antibiotic therapy should be considered after initial treatment since dermatitic skin is frequently colonized with *S. aureus*.

In immunosuppressed patients, especially those with AIDS, management of molluscum can be very difficult. Aggressive treatment of the HIV infection with HAART, if it leads to improvement of the helper T-cell count, is often associated with a dramatic resolution of the lesions. This response is delayed 6 to 8 months from the institution of the treatment. Molluscum occurs frequently in the beard area, so shaving with a blade razor should be discontinued to prevent its spread. If lesions are few, curettage or core removal with a blade and comedo extractor are most effective. EMLA application may permit treatment without local anesthesia. Cantharone or 100% trichloroacetic acid may be applied to individual lesions. Temporary dyspigmentation and slight surface irregularities may occur. Cryotherapy may be effective but must be used with caution in persons of pigment. Subcutaneous IFN-α has been anecdotally effective. When lesions are numerous or confluent, treatment of the whole affected area may be required because of the possibility of latent infection. Trichloroacetic acid peels above 35% concentration (medium depth) or daily applications of 5-fluorouracil (5-FU) to the point of skin erosion may eradicate lesions, at least temporarily. At times, removal by curette is required. Electron beam has been effective. In patients with HIV infection, continuous application of tretinoin cream once nightly at the highest concentration tolerated seems to reduce the rate of appearance of new lesions. Topical 1% to 3% cidofovir application and systemic infusion of this agent have been reported to lead to dramatic resolution of molluscum in patients with AIDS.

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PICORNAVIRUS GROUP

Picornavirus designates viruses that were originally called *enteroviruses* (polioviruses, coxsackieviruses, and echoviruses), plus the rhinoviruses. The picornaviruses are small, single-stranded RNA, icosahedral viruses varying in size from 24 to 30 nm. Only the coxsackieviruses, echoviruses, and enterovirus types 70 and 71 are significant causes of skin disease.

Enterovirus Infections

Person-to-person transmission occurs by the intestinal–oral route and less commonly the oral–oral or respiratory routes. Enteroviruses are identified by type-specific antigens. The type-specific antibodies appear in the blood about 1 week after infection has occurred and attain their maximum titer in 3 weeks. Viral cultures obtained from the rectum, pharynx, eye, and nose may isolate the infecting agent. Usually the diagnosis is by clinical characteristics, and except in specific clinical settings, the causative virus is not identified. Enteroviral infections particularly occur in children between the ages of 6 months and 6 years.

Many nonspecific exanthems and exanthems that occur during the summer and early fall are caused by coxsackievirus or echovirus (Fig. 19-38). The exanthems are most typically diffuse macular or morbilliform erythemas, which sometimes also contain vesicular lesions, or petechial or purpuric areas. Echovirus 9 has caused an eruption resembling acute meningococcemia. Each type of exanthem has been associated with many subtypes of coxsackievirus or echovirus (one exanthem, many possible viral causes). Echovirus 9, the most prevalent enterovirus, causes a morbilliform exanthem initially on the face and neck, then the trunk and extremities. Only occasionally is there an eruption on the palms and soles. Small red or white lesions on the soft palate may occur. The most common specific eruptions due to enteroviruses are hand-foot-and-mouth disease, herpangina, and roseola-like illnesses. Rare reported presentations of enterovirus infection include a unilateral vesicular eruption simulating herpes zoster, caused by echovirus 6; a fatal dermatomyositis-like illness in a patient with hypogammaglobulinemia, caused by echovirus 24; and a widespread vesicular eruption in atopic dermatitis that simulated Kaposi varicelliform eruption, caused by coxsackievirus A-16. Pleconaril and other future antienteroviral agents may be useful in severe enteroviral infections.

While the cutaneous eruptions due to these viruses are quite benign, infections with enterovirus 71 can be quite severe with the development of brainstem encephalitis and fatal neurogenic pulmonary edema, as well as ascending flaccid paralysis resembling poliomyelitis. Epidemics with severe disease have been reported in Bulgaria, Hungary, Hong Kong, Japan, Australia, Malaysia, Singapore, and

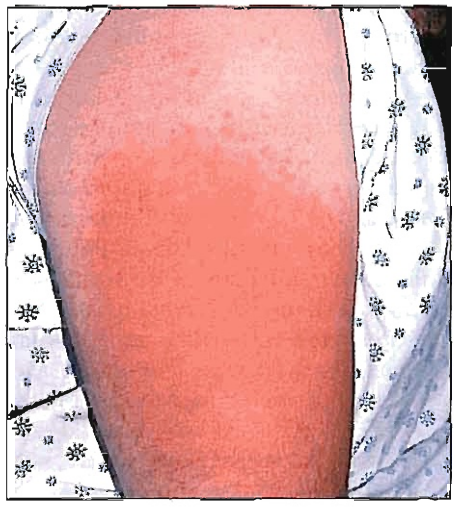

Fig. 19-38 Viral exanthema, photodistributed.

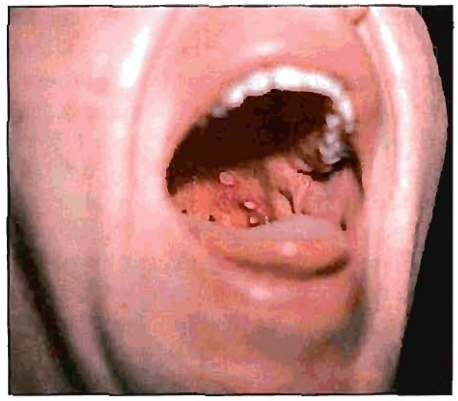

Fig. 19-39 Herpangina.

Taiwan; the latter had the worst epidemic affecting more than 1 million people with 78 deaths in 1998.

Herpangina Herpangina, a disease of children worldwide, is caused by multiple types of coxsackieviruses (most frequently A8, A10, and A16), echoviruses, and enterovirus 71. In the severe outbreaks in Taiwan, 10% of the fatal cases had herpangina. It begins with acute onset of fever, headache, sore throat, dysphagia, anorexia, and sometimes, stiff neck. The most significant finding, which is present in all cases, is of one or more yellowish-white, slightly raised 2-mm vesicles in the throat, usually surrounded by an intense areola (Fig. 19-39). The lesions are found most frequently on the anterior faucial pillars, tonsils, uvula, or soft palate. Only one or two lesions might appear during the course of the illness or the entire visible pharynx may be studded with them. The lesions often occur in small clusters and later coalesce. Usually, the individual or coalescent vesicles ulcerate, leaving a shallow, punched-out, grayish-yellow crater 2 to 4 mm in diameter. The lesions disappear in 5 to 10 days. Treatment is supportive, consisting of topical anesthetics.

Herpangina is differentiated from aphthosis and primary herpetic gingivostomatitis by the location of the lesions in the posterior oropharynx and by isolation of an enterovirus. Coxsackievirus A-10 causes acute lymphonodular pharyngitis, a variant of herpangina, characterized by discrete yellow-white papules in the same distribution as herpangina.

Hand-Foot-and-Mouth Disease Hand-foot-and-mouth disease (HFMD) is usually a mild illness. It primarily affects children from 2 to 10, but exposed adults may also develop disease. Infection begins with a fever and sore mouth. In 90% of cases oral lesions develop; these consist of small (4–8 mm), rapidly ulcerating vesicles surrounded by a red areola on the buccal mucosa, tongue, soft palate, and gingiva. Lesions on the hands and feet are asymptomatic red papules that quickly become small, gray, 3- to 7-mm vesicles surrounded by a red halo. They are often oval, linear, or crescentic and run parallel to the skin lines on the fingers and toes (Fig. 19-40). They are distributed sparsely on the dorsa of the fingers and toes and more frequently on the palms and soles. Especially in children who wear diapers, vesicles and erythematous, edematous papules may occur on the buttocks (Fig. 19-41). The infection is usually mild and seldom lasts more than a week. Treatment is supportive, with the use of oral topical anesthetics.

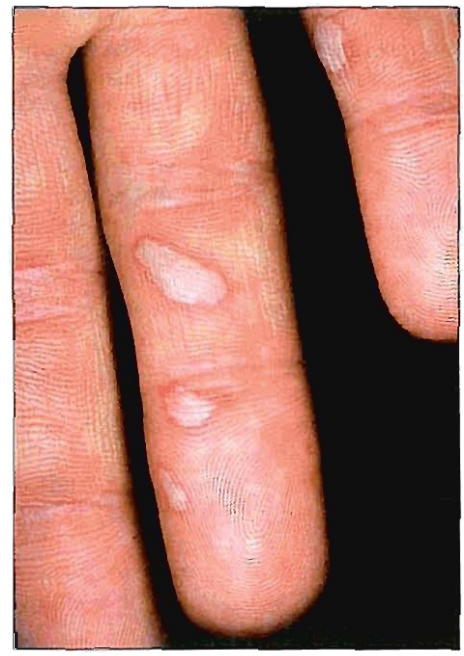

Fig. 19-40 Hand-*foot-and-mouth* disease. (Courtesy of James Fitzpatrick, MD)

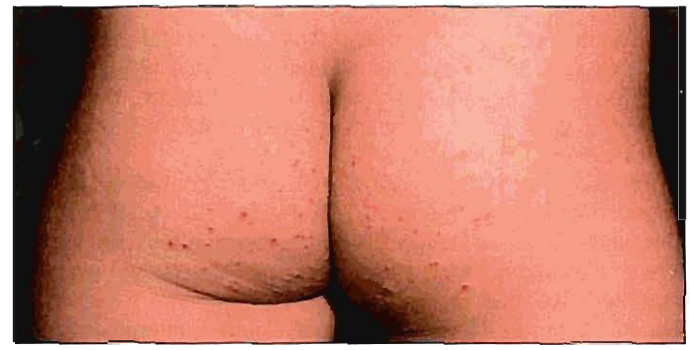

Fig. 19-41 Hand-foot-and-mouth disease.

HFMD is most frequently caused by coxsackievirus A-16 and less commonly by other coxsackie viruses (A5, A7, A 9, A10, B1, B3, and B5) as well as enterovirus 71. In the severe Taiwanese enterovirus 71 outbreak, 80% of cases with CNS disease had HFMD. No cases of HFMD associated with CNS disease were due to coxsackie A16, so the rapid discrimination of viral types may be vital in outbreaks of HFMD. The virus may be recovered from the skin vesicles. Histopathologic findings are those of an intraepidermal blister formed by vacuolar and reticular degeneration of keratinocytes similar to other viral blisters. Inclusion bodies and multinucleated giant cells are absent. HFMD is distinguished from herpangina by the distribution of the oral lesions and the presence of skin lesions. It is differentiated from erythema multiforme minor by the skin lesions, which are oval and gray, as opposed to targetoid, as in erythema multiforme. HFMD usually requires no treatment. Although the coxsackieviruses lack thymidine kinase, acyclovir has anecdotally been reported to hasten resolution of the eruption in two reports.

Boston Exanthem Disease The so-called Boston exanthem disease occurred as an epidemic in Boston and was caused by echovirus 16, a now uncommon cause of viral exanthems. The eruption consisted of sparsely scattered pale red macules and papules. In severe cases, the lesions were

morbilliform and even vesicular. The eruption was chiefly on the face, chest, and back and in some cases on the extremities. On the soft palate and tonsils, small ulcerations like those of herpangina were noted. There was little or no adenopathy. The incubation period was 3 to 8 days.

Eruptive Pseudoangiomatosis Eruptive pseudoangiomatosis describes the sudden appearance of 2- to 4-mm blanchable red papules that resemble angiomas. In children it is usually associated with a viral syndrome, but most affected adults have no viral symptoms. The red papules blanch on pressure and are often surrounded by a 1- to 2-mm pale halo. Lesions often number about 10, but may be much more numerous. Most lesions appear on the face and extremities, but the trunk may also be affected. In children, lesions are short-lived, virtually always resolving within 10 days. Lesions may last slightly longer in adults. Recrudescences may occur. Epidemics have been described in adults and even healthcare workers caring for patients with eruptive pseudoangiomatosis have developed lesions. Histologically, dilated upper dermal vessels, but not increased numbers of blood vessels, with prominent endothelial cells are seen. Echoviruses 25 and 32 have been implicated in the initial reports, and more recently EBV. The occurrence in young children and the presence of miniepidemic outbreaks strongly suggest an infectious trigger.

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PARAMYXOVIRUS GROUP

The paramyxoviruses are RNA viruses that range in size from 100 to 300 nm. In this group, the viral diseases of dermatologic interest are measles (rubeola) and German measles (rubella). Others viruses of this group are mumps virus, parainfluenza virus, Newcastle disease virus, and respiratory syncytial virus.

Measles

Also known as *rubeola* and *morbilli*, measles is a worldwide disease that in developed countries most commonly affects children under 15 months of age. It is spread by respiratory droplets and has an incubation period of 9 to 12 days. Currently, available immunizations are highly effective, with the US being the largest country to have eradicated all endemic cases. Imported cases continue to occur, however, with the highest number coming from China and Japan. In Japan, vaccination is not required and is recommended only after age 2, which are two factors in the failure of that advanced nation to eradicate this viral disease. There is no link between vaccination against measles or rubella and the development of epilepsy.

The prodrome consists of fever, malaise, conjunctivitis, and prominent upper respiratory symptoms (nasal congestion, sneezing, coryza, and cough). After 1 to 7 days, the exanthem appears, usually as macular or morbilliform lesions on the anterior scalp line and behind the ears. Lesions begin as discrete erythematous papules that gradually coalesce. The rash spreads quickly over the face, then by the second or third day (unlike the more rapid spread of rubella) extends down the trunk to the extremities. By the third day, the whole body is involved. Lesions are most prominent and confluent in the initially involved areas and may be more discrete on the extremities. Purpura may be present, especially on the extremities, and should not be confused with "black measles," a rare, disseminated intravascular coagulation-like complication of measles. Koplik spots, which are pathognomonic, appear during the prodrome. They appear first on the buccal mucosa nearest to the lower molars as 1-mm white papules on an erythematous base. They may spread to involve other areas of the buccal mucosa and pharynx. After 6 to 7 days the exanthem clears, with simultaneous subsidence of the fever.

Complications include otitis media, pneumonia, encephalitis, and thrombocytopenic purpura. Infection in pregnant patients is associated with fetal death. Complications and fatalities are more common in children who are undernourished or have T-cell deficiencies. In HIV-infected children the exanthem may be less prominent.

Modified measles occurs in a partially immune host as a result of prior infection, persistent maternal antibodies, or immunization, and is a milder disease. The course is shorter, the exanthem less confluent, and Koplik spots may be absent. It is difficult to differentiate it from other viral exanthems.

Atypical measles was seen in patients who received killed measles vaccine in the early to mid 1960s. The syndrome consists of fever, cough, headache, abdominal pain, myalgia, edema of the extremities, pleural effusion, pneumonia, and hilar adenopathy. Morbilliform lesions occur on the skin, occasionally with intermingled petechiae and/or vesicles, beginning on the hands and feet and spreading centripetally.

The main differential diagnosis is Rocky Mountain spotted fever.

A diagnosis of measles is established by the presence of a high fever, Koplik spots, the characteristic conjunctivitis, upper respiratory symptoms, and typical exanthem. Lymphopenia is common, with a decreased white blood cell count. Biopsies of skin lesions may show syncytial keratinocytic giant cells, similar to those seen in respiratory secretions. Laboratory confirmation is usually with acute and convalescent serologic tests. Rubella, scarlet fever, secondary syphilis, enterovirus infections, and drug eruptions are in the differential diagnosis. Administration of high doses of vitamin A will reduce the morbidity and mortality of hospitalized children with measles. Two doses of retinyl palmitate, 200,000 IU 24 h apart, are recommended for all children 6 months to 24 months of age, immunodeficient children, children with malnutrition or evidence of vitamin A deficiency, and recent immigrants from areas of high measles mortality. Otherwise, treatment is symptomatic, with bed rest, analgesics, and antipyretics.

Live virus vaccination is recommended at 15 months with a booster at 5 years. A faint maculopapular exanthem may occur 7 to 10 days after immunization. When given up to 5 days after exposure, vaccination may prevent infection. Children under 1 year of age who are exposed to measles should be treated with immune serum globulin.

Rubella

Rubella, commonly known as *German measles*, is caused by a togavirus and probably spreads by respiratory secretions. The incubation period is 12 to 23 days (usually 15 to 21). Live virus vaccination is highly effective, providing lifelong immunity. There is no association between measles, mumps, and rubella (MMR) vaccination and autism.

There is a prodrome of 1 to 5 days consisting of fever, malaise, sore throat, eye pain, headache, red eyes, runny nose, and adenopathy. Pain on lateral and upward eye movement is characteristic. The exanthem begins on the face and progresses caudad, covering the entire body in 24 h and resolving by the third day. The lesions are typically pale pink morbilliform macules, smaller than those of rubeola. The eruption may resemble roseola or erythema infectiosum. An exanthem of pinhead-sized red macules or petechiae on the soft palate and uvula (Forscheimer's sign) may be seen. Posterior cervical, suboccipital, and postauricular lymphadenitis occurs in more than half of cases. Rubella is in general a much milder disease than rubeola is. Arthritis and arthralgias are common complications, especially in adult women. These last a month or longer.

Congenital Rubella Syndrome Infants born to mothers who have had rubella during the first trimester of pregnancy may have congenital cataracts, cardiac defects, and deafness. Numerous other manifestations, such as glaucoma, microcephaly, and various visceral abnormalities, may emerge. Among the cutaneous expressions are thrombocytopenic purpura; hyperpigmentation of the navel, forehead, and cheeks; bluish red infiltrated 2- to 8-mm lesions ("blueberry muffin" type), which represent dermal erythropoiesis; chronic urticaria; and reticulated erythema of the face and extremities.

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Asymmetric Periflexural Exanthem of Childhood

This clinical syndrome, also known as *unilateral laterothoracic exanthem*, occurs primarily in the late winter and early spring, and appears to be most common in Europe. It affects girls more often than boys (1.2–2:1). It occurs in children 8 months to 10 years of age, but most cases are between 2 and 3 years of age. Multiple cases have been reported in adults from Europe and China. Its cause is unknown, but a viral origin has been proposed, since it occurs in young children and is seasonal, and secondary cases in families have been reported. No reproducible viral etiology has been implicated, however. Clinically, two-thirds to three-fourths of affected children have symptoms of a mild upper respiratory or gastrointestinal infection, usually preceding the eruption. The lesions are usually discrete 1-mm erythematous papules that coalesce to poorly marginated morbilliform plaques. Pruritus is usually present, but mild. Lesions begin unilaterally close to a flexural area, usually the axilla (75% of cases). Spread is centrifugal with new lesions appearing on the adjacent trunk and extremity. Normal skin may intervene between lesions. The contralateral side is involved in 70% of cases after 5 to 15 days, but the asymmetrical nature is maintained throughout the illness. Lymphadenopathy of the nodes on the initially affected side occurs in about 70% of cases. The syndrome lasts 2 to 6 weeks on average, but may last more than 2 months, and resolves spontaneously. Topical steroids and oral antibiotics are of no benefit, but oral antihistamines may help associated pruritus. Histologically, a mild-to-moderate lymphocytic (CD8+ T-cell) infiltrate surrounds and involves the eccrine ducts but not the secretory coils. There may be an accompanying interface dermatitis of the upper eccrine duct and adjacent epidermis.

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PARVOVIRUS GROUP

Parvovirus B19 is the most common agent in this erythrovirus genus to cause human disease. Infection is worldwide, occurring in 50% of persons by age 15. The vast majority of elderly adults are seropositive. Infections are more common in the spring in temperate climates. Epidemics in communities occur every few years. The virus is spread via the respiratory route and infection rates are very high within households. Most infections are asymptomatic. Erythema infectiosum, papular purpuric gloves and socks syndrome, arthropathy (especially in middle-aged females), aplastic crisis in hereditary spherocytosis and sickle cell disease, and chronic anemia in immunosuppressed patients are clearly related to parvovirus B19 infection. Hydrops fetalis and fetal demise may result if infection occurs during pregnancy, with 30% of fetuses infected and 5% to 9% of affected pregnancies suffering fetal loss.

Erythema Infectiosum (Fifth Disease)

Erythema infectiosum is a worldwide benign infectious exanthem that occurs in epidemics in the late winter and early spring. In normal hosts (but not immunosuppressed or sickle-cell patients in crisis), viral shedding has stopped by the time the exanthem appears, making isolation unnecessary. The incubation period is 4 to 14 days (average 7 days). Uncommonly, a mild prodrome of headache, runny nose, and low-grade fever may precede the rash by 1 or 2 days.

Erythema infectiosum has three phases. It begins abruptly with an asymptomatic erythema of the cheeks, referred to as *slapped cheek* (Fig. 19-42). The erythema is typically diffuse and macular, but tiny translucent papules may be present. It is most intense beneath the eyes and may extend over the cheeks in a butterfly-wing pattern. The perioral area, lids, and chin are usually unaffected. After 1 to 4 days the second phase begins, consisting of discrete erythematous macules and papules on the proximal extremities and later the trunk. This evolves into a reticulate or lacy pattern. These two phases typically last 5 to 9 days. A characteristic third phase is the recurring stage. The eruption is markedly reduced or invisible, only to recur after the patient is exposed to heat (especially when bathing) or sunlight, or in response to crying or exercise. About 7% of children with erythema infectiosum have arthralgias, whereas 80% of adults have joint involvement. Necrotizing lymphadenitis may also occur in the cervical, epitrochlear, supraclavicular, and intra-abdominal lymph nodes. Children with aplastic crisis due to parvovirus B19 usually do not have a rash. However, even healthy children can develop significant bone marrow complications, albeit transient and self-limited (Fig. 19-43).

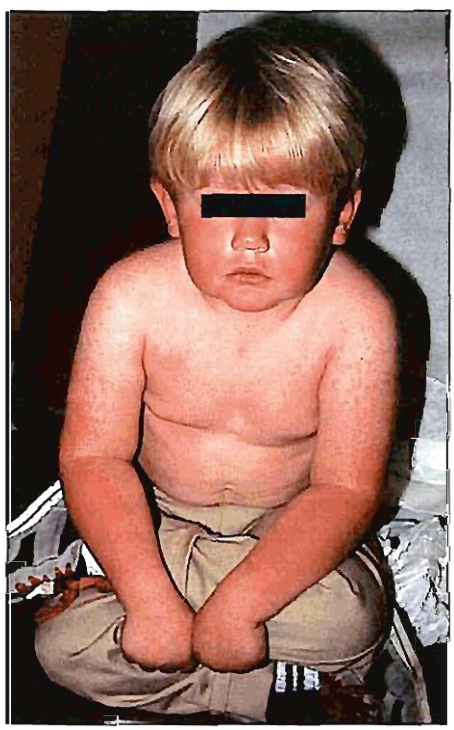

Fig. 19-42 Erythema infectiosum.

Papular Purpuric Gloves and Socks Syndrome

This syndrome, which is less common than erythema infectiosum, occurs primarily in teenagers and young adults. Pruritus, edema, and erythema of the hands and feet appear and a fever is present. The lesions are sharply cut off at the wrists and ankles. Over a few days they become purpuric. There is a mild erythema of the cheeks, elbows, knees, and groin folds. Lesions in the groin may become purpuric. Oral erosions, shallow ulcerations, aphthous ulcers on the labial mucosa, erythema of the pharynx, Koplik spots, or petechial lesions may be seen on the buccal or labial mucosa. The lips may be red and swollen. Vulvar edema and erythema accompanied by dysuria may be seen. An unusual variant is a unilateral petechial and erythematous eruption of the axilla. The acral erythema may rarely move proximally along lymphatics, simulating a lymphangitis. Transient lymphocytopenia, a drop in platelet count, and elevation of liver function tests may be seen. The syndrome resolves within 2 weeks. Evidence of seroconversion for parvovirus B19 has been found in most reported patients. Histologically, there is a dermal infiltrate of CD30+ T-lymphocytes surrounding the upper dermal vessels. There is an interface component and prominent extravasation of red blood cells in petechial lesions. Parvovirus B19 antigen has been found in the endothelial cells, sweat glands and ducts, and epidermis in three

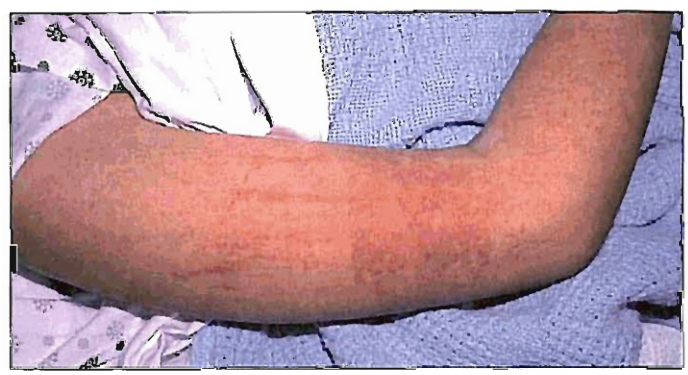

Fig. 19-43 Erythema infectiosum, acral papular eruption and purpura induced by blood pressure cuff and due to the associated thrombocytopenia.

patients. In HIV-infected patients who develop papular purpuric gloves and socks syndrome (PPGSS), the eruption is more persistent (lasting 3 weeks to 4 months) and is associated with anemia.

Not all cases of PPGSS are caused by parvovirus B19. In adults it may be associated with HBV infection. In children the syndrome occurs at an average age of 23 months. The eruption lasts an average of 5 weeks. In children CMV and EBV are the most common documented causes in Taiwan where this syndrome appears to be very common in the last quarter of the year.

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ARBOVIRUS GROUP

The arboviruses comprise the numerous arthropod-borne RNA viruses. These viruses multiply in vertebrates as well as in arthropods. The vertebrates usually act as reservoirs and the arthropods as vectors of the various diseases.

West Nile Fever

West Nile virus (WNV) is a flavavirus which is endemic in East Africa. It first appeared in eastern North America in 1999 and reached California by 2004. It is primarily an infection of the crow family (crows, ravens, magpies and bluejays). It is spread by *Culex* mosquitoes. Approximately 80% of infected persons will have no symptoms. After an incubation period of 3 to 15 days, a febrile illness of sudden onset occurs. The primary complications are neurologic disease, including seizures (10% of symptomatic adults), ascending flaccid paralysis (like poliomyelitis), ataxia, and reduced level of consciousness. A significant percentage of affected persons are left with permanent neurologic sequelae. A morbilliform eruption of the neck, trunk, arms or legs occurs in 20% of patients.

Sandfly Fever

Sandfly fever is also known as *phlebotomus fever* and *pappataci fever*. The vector, *Phlebotomus papatasii*, is found in the Mediterranean area (Sicilian, Naples and Toscana virus), Russia, China, and India. While Sicilian and Naples sandfly fever viral infections disappeared or dramatically decreased with mosquito eradication programs, Toscana virus infection is still common. While most infected persons are asymptomatic, 80% of aseptic meningitis cases in the summer in endemic areas are due to this agent. Small pruritic papules appear on the skin after the sandfly bite and persist for 5 days. After an incubation period of another 5 days, fever, headache, malaise, nausea, conjunctival injection, stiff neck, and abdominal pains suddenly develop. The skin manifestations consist of a scarlatiniform eruption on the face and neck. Recovery is slow, with recurring bouts of fever. No specific treatment is available.

Dengue

Dengue, also known as *break-bone fever*, is a common disease of tropical regions throughout the world, but especially in Southeast Asia. It is spread by the *Aedes aegypti* mosquito. Two to 15 days after the bite of an infected mosquito the disease begins with a sudden high fever, headache, backache, retroorbital pain, bone and joint pain, weakness, depression, and malaise. A scarlatiniform or morbilliform exanthem, especially on the thorax and joint flexors, may accompany these symptoms. The patient may recover completely at this stage. On about the fourth day, after a brief remission of fever, another scarlatiniform exanthem may appear, most vividly over the trunk, face, and extremities. It may be petechial or purpuric (Fig. 19-44). Small spared areas of normal skin (white islands in a sea of red) are characteristic.

In 1% to 7% of cases, dengue hemorrhagic fever (DHF) develops. It usually begins with similar symptoms, but thrombocytopenia and hemoconcentration develop. Spontaneous bleeding may occur in the skin, conjunctiva, and gastrointestinal tract. Up to 30% of patients with DHF may progress to Dengue shock syndrome (DSS) with increased vascular permeability, hypovolemia, and hypotension. Mortality rates are 10% or higher if untreated, but less than 1% if adequate care is provided. The disease is not modified by high doses of systemic corticosteroids.

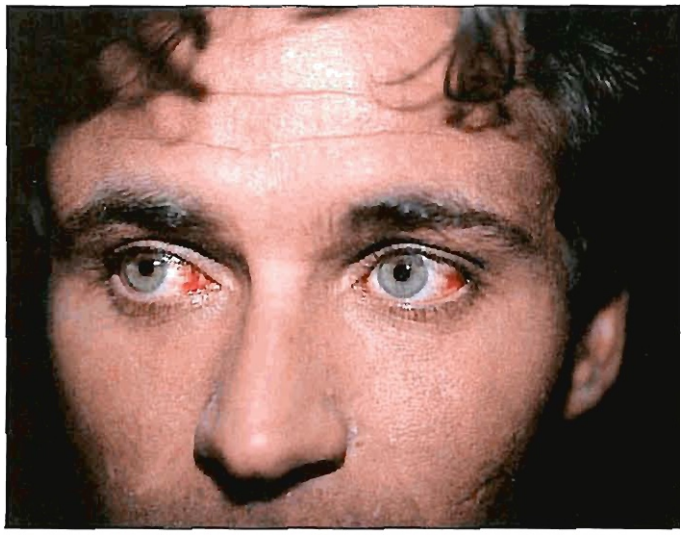

Fig. 19-44 Dengue.

Alphavirus

In Finland, Sindbis virus infection is transmitted by the *Culiseta* mosquito. An eruption of multiple, erythematous, 2- to 4-mm papules with a surrounding halo is associated with fever and prominent arthralgias. The eruption and symptoms resolve over a few weeks. Histologically, the skin lesions show a perivascular lymphocytic infiltrate with large atypical cells, simulating lymphomatoid papulosis. CD30 does not stain the large cells, however, allowing their distinction.

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PAPOVAVIRUS GROUP

Papovaviruses are double-stranded, naked DNA viruses characterized as slow growing. They replicate inside the nucleus. Because they contain no envelope, they are resistant to drying, freezing, and solvents. In addition to the human papillomaviruses (HPVs), which cause warts, papillomaviruses of rabbits and cattle, polyomaviruses of mice, and vacuolating viruses of monkeys are some of the other viruses in this group.

Warts (Verruca)

There are more than 100 types of HPVs. The genome of HPV consists of early genes (E 1, 2, 4, 5, 6, and 7), two late genes (L1 and L2), and in between an upstream regulatory region (URR). L1 and L2 code for the major and minor capsid proteins. A new HPV type is defined when there is less than 90% DNA homology with any other known type in the L1 and E6 genes. Viruses with 90% to 98% homologies are classified as subtypes. The gene sequences from HPVs throughout the world are similar. Most HPV types cause specific types of warts and favor certain anatomic locations, such as plantar warts, common warts, genital warts, and so on. Some wart types, e.g. HPV-27, may be found in several different locations. A large proportion of the HPV types rarely cause warts and appear to be pathogenic only in immunosuppressed patients or those with epidermodysplasia verruciformis. However, many persons may carry or be latently infected with these rare wart types, explaining the uniformity of gene sequence and clinical presentation all over the world. In the setting of immunosuppression, HPV types may cause warty lesions of a different clinical morphology than they would cause in an immunocompetent host.

Infection with HPV may be clinical, subclinical, or latent. Clinical lesions are visible by gross inspection. Subclinical lesions may be seen only by aided examination (e.g. the use of acetic acid soaking). Latent infection describes the presence of HPV virus or viral genome in apparently normal skin. Latent infection is thought to be common, especially in genital warts, and explains in part the failure of destructive methods to eradicate warts.

HPV infection is very common, as most people will experience infection during their lifetime. In school children in Australia, 22% were found to have nongenital cutaneous warts, with 16% having common warts, 6% having plantar warts, and 2% having flat (plane) warts. In the UK, the prevalence has been reported at between 4% and 5%. The peak age for cutaneous warts is in the teenage and early adult years where infection rates reach 25% in some studies. White persons have visible cutaneous warts twice as frequently as other ethnicities. Genital warts begin to appear with sexual activity and infection rates, including latent infection, exceed 50% in sexually-active populations in many parts of the world.

Management of warts is based on their clinical appearance, location, and the immune status of the patient. In general, warts of all types are more common and more difficult to treat in persons with suppressed immune systems. Because warts in some settings are important cofactors in cancer, histologic evaluation of warty lesions in these situations may be important.

Verruca Vulgaris Common warts are a significant cause of concern and frustration on the part of the patient (Figs 19-45 to 19-47). Social activities can be affected, lesions can be uncomfortable or bleed, and treatment is often painful and frustratingly ineffective. HPV-1, -2, -4, -27, -57, and -63 cause common warts. Common warts occur largely between the ages of 5 and 20 and only 15% occur after the age of 35. Frequent immersion of hands in water is a risk factor for common warts. Meat handlers (butchers), fish handlers, and other abattoir workers have a high incidence of common warts of the hands. The prevalence reaches 50% in those persons with direct contact with meat. Warts in butchers are caused by HPV-2 and -4 and up to 27% of hand warts from butchers are due to HPV-7. HPV-7 is very rarely found in warts in the general population (<0.3%), and in butchers it is found only on the hands where there is direct contact with meat. The source of HPV-7 is unknown, but HPV-7 is not bovine papilloma virus and does not come from the slaughtered animals. HPV-57 has been reported to cause dystrophy of all 10 fingernails with marked subungual

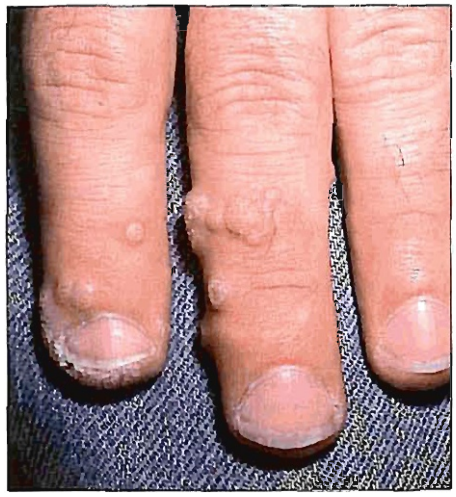

Fig. 19-45 Verruca vulgaris.

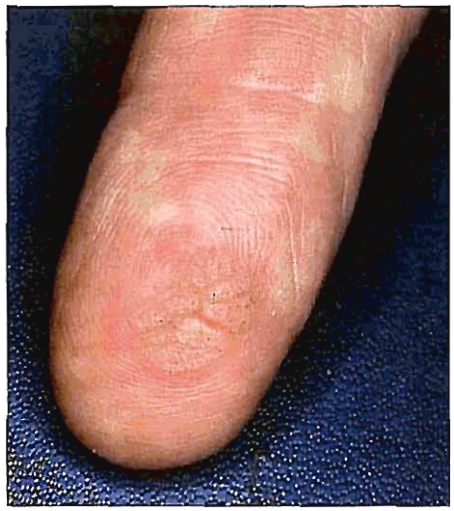

Fig. 19-46 Verruca vulgaris, wart at site of trauma.

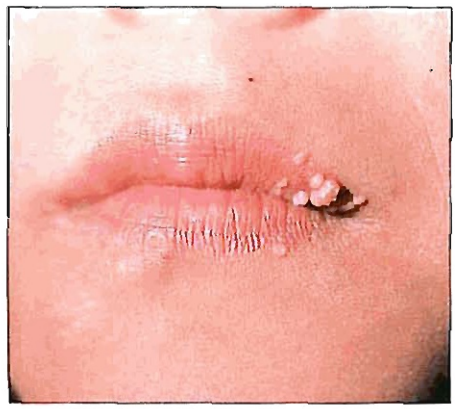

Fig. 19-47 Verruca, nail biter with periungual warts.

hyperkeratosis and destruction of the nail plate without periungual involvement.

The natural history of common warts is for them to spontaneously resolve. Reported clearance rates in children are 23% at 2 months, 30% at 3 months, 65% to 78% at 2 years, and 90% over 5 years. Common warts are usually located on the hands; they favor the fingers and palms. Periungual warts are more common in nail biters and may be confluent, involving the proximal and lateral nailfolds. Fissuring may lead to bleeding and tenderness. Lesions range in size from pinpoint to more than 1 cm, most averaging about 5 mm. They grow in size for weeks to months and usually present as elevated, rounded papules with a rough, grayish surface, which is so characteristic that it has given us the word *verrucous*, used to describe lesions with similar surface character (e.g. seborrheic keratosis). In some instances a single wart (mother wart) appears and grows slowly for a long time and then suddenly many new warts erupt. On the surface of the wart, tiny black dots may be visible, representing thrombosed, dilated capillaries. Trimming the surface keratin makes the capillaries more prominent and may be used as an aid in diagnosis. Warts do not have dermatoglyphics (fingerprint folds), as opposed to calluses, in which these lines are accentuated.

Common warts may occur anywhere on the skin, apparently spreading from the hands by autoinoculation. In nail biters, warts may be seen on the lips and tongue, usually in the middle half, and uncommonly in the commissures. Digitate or filiform warts tend to occur on the face and scalp and present as single or multiple spikes stuck on the surface of the skin.

Pigmented Warts Pigmented warts have been reported commonly in Japan. They appear on the hands or feet and resemble common warts or plantar warts except for their hyperpigmentation. They are caused by HPV-4, -65, and -60. The pigmentation is due to melanocytes in the basal cell layer of the HPV-infected tissue containing large amounts of melanin. This is proposed to be caused by "melanocyte blockade" or the inability of the melanocytes to transfer melanin to the HPV-infected cells.

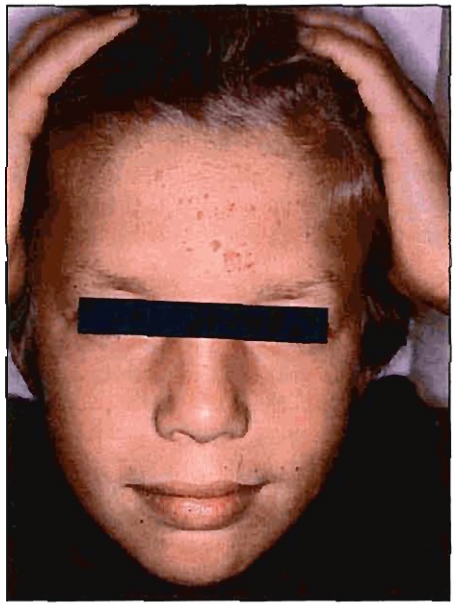

Fig. 19-48 Verruca plana.

Flat Warts (Verruca Plana) HPV-3, -10, -28, and -41 most often cause flat warts. Children and young adults are primarily affected. Flat warts present most typically as 2- to 4-mm flat-topped papules that are slightly erythematous or brown on pale skin and hyperpigmented on darker skin. They are generally multiple and are grouped on the face, neck, dorsa of the hands, wrists, elbows, or knees (Figs 19-48 and 19-49). The forehead, cheeks, and nose, and particularly the area around the mouth and the backs of the hands, are the favorite locations. In men who shave their beards and in women who shave their legs, numerous flat warts may develop as a result of autoinoculation. A useful finding is the tendency for the warts to Koebnerize, forming linear, slightly raised, papular lesions (Fig. 19-50). Hyperpigmented lesions occur and when scarcely elevated, they may be confused with lentigines or ephelides. Plaque-like lesions may be confused with verrucous nevus, lichen planus, and molluscum contagiosum. When lesions occur only on the central face and are erythematous, they can be easily confused with papular acne

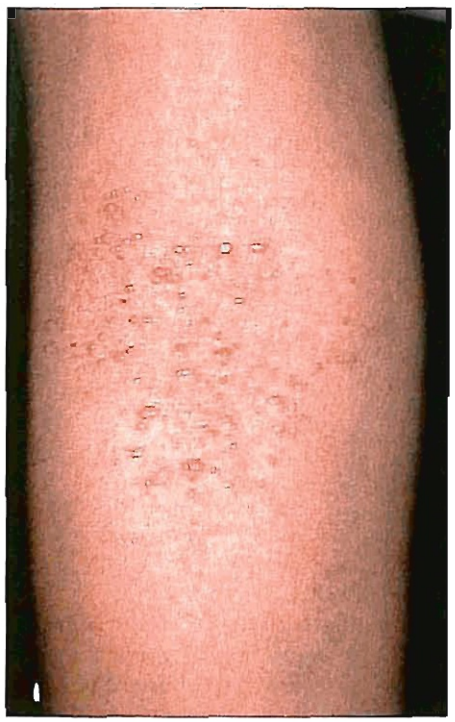

Fig. 19-49 Verruca plana, atopic dermatitis infected with numerous flat warts.

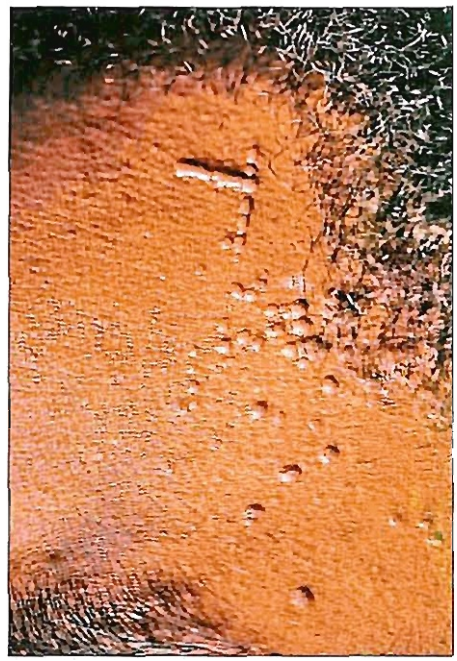

Fig. 19-50 Verruca plana, linear lesions (Koebner).

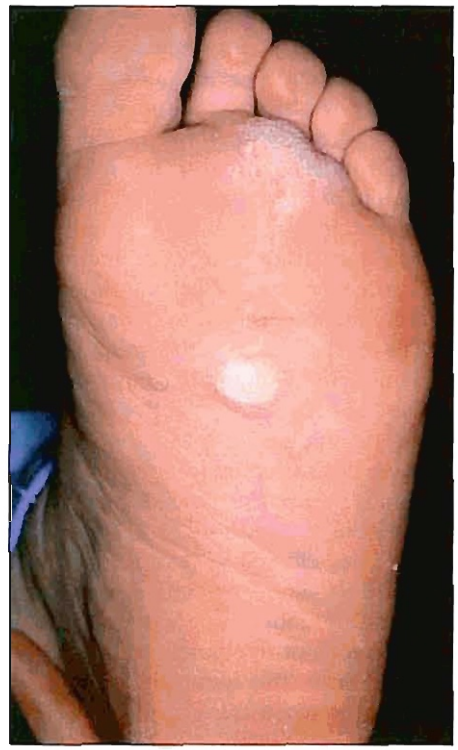

Fig. 19-51 Verruca plantaris.

vulgaris. Of all clinical HPV infections, flat warts have the highest rate of spontaneous remission.

Plantar Warts (Verruca Plantaris) HPV-1, -2, -4, -27 and -57 cause plantar warts. These warts generally appear at pressure points on the ball of the foot, especially over the mid-metatarsal area. They may, however, be anywhere on the sole. Frequently there are several lesions on one foot (Fig. 19-51). Sometimes they are grouped or several contiguous warts fuse so that they appear as one. Such a plaque is known as a *mosaic wart*. The soft, pulpy cores are surrounded by a firm, horny ring. Over the surface of the plantar wart, most clearly if the top is shaved off, multiple small black points may be seen that represent dilated capillary loops within elongated dermal papillae. Plantar warts may be confused with corns or calluses, but have a soft central core and black or bleeding points when pared down, features that calluses do not have.

The myrmecia type of verruca occurs as smooth-surfaced, deep, often inflamed and tender papules or plaques, mostly on the palms or soles, but also beside or beneath the nails, or, less often, on the pulp of the digits. They are distinctively dome-shaped and much bulkier beneath the surface than they appear. Myrmecia are caused by HPV-1. They can be mistaken for a paronychia or digital mucinous cyst.

HPV-60 causes a peculiar type of plantar wart called a *ridged wart* because of the persistence of the dermatoglyphics across the surface of the lesion. Typically, the warts are slightly elevated, skin colored, 3- to 5-mm papules. They occur on non–weight-bearing areas and lack the typical features of plantar warts. HPV-60 also causes plantar verrucous cysts, 1.5- to 2-cm epithelium-lined cysts on the plantar surface. These cysts tend to occur on weight-bearing areas, suggesting that HPV-infected epidermis is implanted into the dermis, forming the cyst. It is common to see ridged warts near plantar verrucous cysts.

Histologic Features

Typical nongenital warts rarely require histologic confirmation. A biopsy may be useful in several settings, however. Histology can be used to distinguish warts from corns and other keratotic lesions that they resemble. This is enhanced by immunoperoxidase staining for HPV capsid antigen. Cytologic atypia and penetration into the dermis suggest the diagnosis of an HPV-induced squamous cell carcinoma. There is a correlation between HPV type and the histologic features of the wart, allowing identification of the HPV types that cause specific lesions, a useful feature in the diagnosis of epidermodysplasia verruciformis, for example.

Treatment

The form of therapy used depends on the type of wart being treated, age of the patient, and previous therapies used and their success or failure. With any treatment modality at least 2 or 3 months of sustained management by that method is considered a reasonable therapeutic trial. Do not abandon any treatment too quickly. Since many nongenital warts will spontaneously regress, the treatment algorithm should allow for nonaggressive options and the patient should be offered the option of no treatment. Indications for treatment are pain, interference with function, social embarrassment, and risk of malignancy. Aims of therapy are 1) to remove the wart; 2) not to produce scarring; and 3) to induce lifelong immunity to prevent recurrence. There are very few controlled studies on the treatment of cutaneous warts, so the evidence for all forms of treatment except cryotherapy is fair to poor.

Flat Warts

Flat warts frequently undergo spontaneous remission, so therapy should be as mild as possible, and potentially scarring therapies should be avoided. If lesions are few, light cryotherapy is a reasonable consideration. Topical salicylic acid products can also be used. Treatment with topical tretinoin once or twice a day in the highest concentration tolerated to produce mild erythema of the warts without frank dermatitis can be effective over several months. Tazarotene cream or gel may also be effective. Imiquimod 5% cream used up to once a day can be effective. If the warts fail to react initially to the imiquimod, tretinoin may be used in conjunction. Should this fail, 5-FU cream 5% applied twice a day may be very effective. Anthralin, although staining, could be similarly used for its irritant effect. For refractory lesions, laser therapy in very low fluences or photodynamic therapy might be considered before electrodesiccation because of the reduced risk of scarring. Ranitidine 300 mg twice a day cleared 56% of refractory flat warts in one study. Cimetidine alone or with levamisole may be considered. Topical immunotherapy with dinitrochlorobenzene (DNCB), squaric acid, or dyphencyprone can be used on limited areas of flat warts. The induced dermatitis requires careful dose monitoring when treating facial lesions.

Common Warts

Treatments for common warts involve two basic approaches: destruction of the wart and induction of local immune reactions (immunotherapy). Destructive methods are most commonly used as initial therapy by most practitioners. Cryotherapy is a reasonable first-line therapy for most common warts. The wart should be frozen adequately to produce a blister after 1 or 2 days. This correlates with a thaw time of 30 to 45 s for most common warts. A sustained 10-s freeze with a spray gun was found more effective than simply freezing to obtain a 2- to 3-mm halo around the wart. Aggressive cryotherapy can produce significant blistering and may be complicated by significant post-procedural pain for several days. Berth-Jones et al found that a single freeze–thaw cycle was as effective as two cycles. The ideal frequency of treatment is every 2 or 3 weeks, just as the old blister peels off. A spray device, while more costly, is quicker, and cannot spread infectious diseases (especially viral hepatitis) from one patient to the next. Children may be frightened by such a device, so a cotton-tipped swab is an option for them. Cryotherapy can be effective for periungual warts. Damage to the matrix is unusual or rare, since periungual warts usually affect the lateral nailfolds, not the proximal one. Complications of cryotherapy include hypopigmentation, uncommonly scarring, and rarely, damage to the digital nerve from freezing too deeply on the side of the digit. Patients with Fanconi anemia, cryoglobulinemia, poor peripheral circulation, and Raynaud may develop severe blisters when cryotherapy is used to treat their warts. Doughnut warts, with central clearing and an annular recurrence, may complicate cryotherapy (Fig. 19-52).

Products containing salicylic acid with or without lactic acid are effective patient-applied treatments; these have an efficacy comparable to that of cryotherapy. After the wart-affected area is soaked in water for 5 to 10 min, the topical medication is applied, allowed to dry, and covered with a strip bandage for 24 h. This is repeated daily. The superficial keratinous debris may be removed by scraping with a table knife, pumice stone, or emery board.

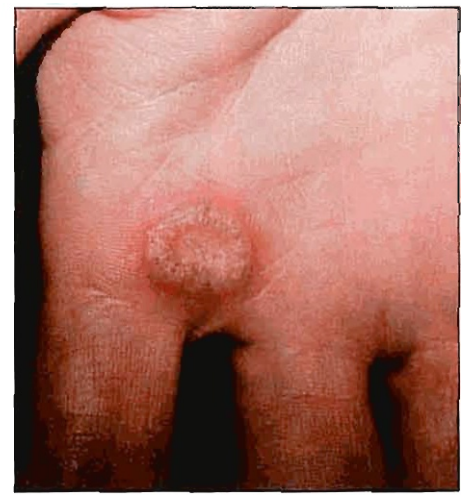

Fig. 19-52 Verruca vulgaris, doughnut wart.

A small amount of cantharone (0.7% cantharidin) is applied to the wart, allowed to dry, and covered for 24 h. A blister, similar to that produced by cryotherapy, develops in 24 to 72 h. These blisters may be as painful as or more painful than those following cryotherapy. Treatment is repeated every 2 to 3 weeks. Perhaps more than any other method, there is a tendency for cantharidin to produce doughnut warts, a round wart with a central clear zone at the site of the original wart (see Fig. 19-52). Nonetheless, this agent is a very useful adjunct in the management of difficult-to-treat verruca.

Simple occlusion with a relatively impermeable tape can be effective in eradicating warts. The key appears to be to keep the wart occluded as much of the time as possible. Duct tape or transparent tapes (Blenderm) are practical options. Fenestrated and semipermeable dressings have not been studied and may not be effective. This is a good initial option for children and others unwilling to have other forms of treatment.

Bleomycin has high efficacy and is an important treatment for recalcitrant common warts. It is used at a concentration of 1 U/mL, which is injected into and immediately beneath the wart until it blanches. The multiple-puncture technique of Shelley—delivering the medication into the wart by multiple punctures of the wart with a needle through a drop of bleomycin—may also be used, as may an airject injector. For small warts (<5 mm), 0.1 mL is used and 0.2 mL for larger warts. The injection is painful enough to require local anesthesia in some patients. Pain for up to 1 week can occur. The wart becomes black and the black eschar separates in 2 to 4 weeks. Treatment may be repeated every 3 weeks, but it is unusual for common warts to require more than one or two treatments. Scarring is rare. Response rates vary by location, but average 90% with two treatments for most common, nonplantar warts, even periungual ones. Treatment of finger warts with bleomycin may uncommonly be complicated by localized Raynaud phenomenon of treated fingers. Bleomycin treatment of digital warts may rarely result in digital necrosis and permanent nail dystrophy, so extreme caution should be used in treating warts around the nailfolds. Lymphangitis/cellulitis is a rare complication. In a patient receiving a total of 14 U for plantar warts, flagellate

urticaria followed by characteristic bleomycin flagellate hyperpigmentation occurred.

Surgical ablation of warts can be effective treatment, but even complete destruction of a wart and the surrounding skin does not guarantee the wart will not recur. Surgical methods should be reserved for warts that are refractory to more conservative approaches. Pulsed dye laser therapy appears to have similar efficacy to cryotherapy. With pulsed dye laser therapy less plume is produced than with CO_2 laser therapy. Depending on the fluences used, the treatment can be performed in two-thirds of patients without anesthesia, although some pain occurs. The energy setting is dependent on the particular device being used. The energy may be as low as 7 J/cm^2 for thinner lesions and up to 15 J/cm^2 for more hyperkeratotic ones. A short pulse duration (0.45 ms) is most effective. A 5- or 7-mm spot size is used and treatment is extended 2 mm beyond the visible wart. Immediately after treatment, the skin has a gray–black discoloration, which evolves to an eschar over 10 to 14 days. Treatment is repeated every 2 to 4 weeks and up to five treatments may be required. In immunocompetent patients, response rates for refractory warts range from 70% to 90%. CO_2 laser destruction requires local anesthesia, causes scarring, and may lead to nail dystrophy. Its efficacy is between 56% and 81% in refractory warts. A potentially infectious plume is produced. Frequency doubled Nd:YAG and 532-nm KTP lasers are also reported to be effective, but there is less evidence for their use. Photodynamic therapy with aminolevulinic acid 20% applied for 5 h prior to irradiation with broad-band sources (400–700 nm, 50 mW/cm^2) produces a clearance rate of 55% to 75% for recalcitrant warts. Several treatments at 3-weekly intervals may be required. Significant pain can occur during treatment and lasts for up to 24 h, which limits its use in children.

Oral cimetidine, 30 to 40 mg/kg/day, has been anecdotally reported to lead to resolution of common warts, perhaps because of its immunomodulatory effects. When used as a single agent, however, in both children and adults, the efficacy is low (30%), comparable with a placebo. It may be beneficial as an adjunct to other methods, however, or for treatment of refractory warts. Heat treatment, either localized to the wart and delivered by radiofrequency or by application to the affected part by soaking it in a hot bath, have been reported to be effective. Treatment for 15 min at 43° C to 50° C (107.6–122° F) to as short as 30 s at higher temperatures has been used. Extreme caution must be exercised to avoid scalding. Oral administration of acitretin or isotretinoin may also be used in refractory cases. Hypnotic suggestion and hypnoanalysis for warts have been reviewed by Shenefelt.

Immunotherapy with topical and intralesional agents has become a mainstay of wart therapy. The hope is that not only will the wart be eradicated, but the immune reaction induced in the wart may also induce widespread and permanent immunity against warts. The commonly used agents are topical dinitrochlorobenzene, squaric acid dibutyl ester, and diphencyprone, as well as intralesional candida or mumps antigen. Patients may be initially sensitized at a distant site (usually the inner upper arm) with the topical agents or the agent may be applied initially to the warts directly. Two treatment approaches are used and their efficacies have not been compared. Some practitioners apply topical agents in the office in higher concentrations (2–5%), but only every 2 weeks or so. Others give their patients take-home prescriptions to use on a daily basis, albeit at lower concentrations to start with (0.2–0.5%). In most cases the agents are dissolved in acetone. The treated wart should be kept covered for 24 h after application. If the reaction is overly severe, the strength of the application may be reduced. Wart tenderness may indicate the need to reduce treatment concentration. Warts may begin to resolve within a week or two, but on average, 2 to 3 months of treatment or more are required. For intralesional candida antigen, treatments are repeated weekly. Overall cure rates for all three topical sensitizers and for intralesional antigen injection is 60% to 80%. Side effects of treatment include local pruritus, local pain, and a mild eczematous dermatitis. Most patients have no limitation of activities or function with topical immunotherapy. Scarring has not been reported.

Imiquimod has been reported to be effective for common warts in small series or single cases. With twice a day treatment for up to 24 weeks (average 19 weeks), 27% of patients cleared their warts. The efficacy of imiquimod for common warts appears to be significantly less than cryotherapy or topical immunotherapy and it is considerably more expensive. The routine use of imiquimod in the treatment of common or plantar warts cannot be recommended. Topical cidofovir has been used in desperate situations.

Plantar Warts

In general, plantar warts are more refractory to any form of treatment than are common warts. Initial treatment usually involves daily application of salicylic acid in liquid, film, or plaster form after soaking. In failures, cryotherapy or cantharidin application may be attempted, alone or in combination. A second freeze–thaw cycle is beneficial when treating plantar warts with cryotherapy. Bleomycin injections, laser therapy, or topical immunotherapy, as discussed above, may be used in refractory cases. Surgical destruction with cautery or blunt dissection should be reserved for failures with nonscarring techniques, since a plantar scar may be persistently painful. CO_2 laser may also result in plantar scars.

Genital Warts Genital warts are the most common STD. Among sexually-active young adults in the US and Europe, infection rates as high as 50% in some cohorts have been found using sensitive PCR techniques. It is estimated that the lifetime risk for infection in sexually-active young adults may be as high as 80%. The number of new cases of genital wart infection diagnosed in the US yearly may approach 1 million. In the vast majority of couples in whom one has evidence of HPV infection, the partner will be found to be concordantly infected. The risk of transmission is not known, however. A large portion of genital HPV infection is either subclinical or latent. Unfortunately, the infectivity of subclinical and latent infection is unknown. Subclinical and latent infection are probably responsible for most "recurrences" following treatment of genital warts. Since the methodology for determining HPV infection in males is less accurate and since women suffer the major complication of HPV infection —cervical cancer, virtually all data on HPV infection rates and epidemiology are derived from studies of women.

Genital HPV infection is closely linked with cancer of the cervix, glans penis, anus, vulvovaginal area, and periungual skin. Cancer occurs when there is integration of the HPV genome into the host DNA. In high-risk genital HPV types, E6 and E7 gene products bind to and inactivate p53 and retinoblastoma protein (pRb), respectively. This is felt to be important in their ability to cause cancer. In most persons, genital HPV infection appears to be transient, lasting about 1 to 2 years, and results in no sequelae. In a small proportion, infection persists and in a small proportion of persons with persistent HPV infection cancer may develop. Certain cofactors, such as the HPV type causing the infection, location of infection, cigarette smoking, uncircumcised status, and immunosuppressed status are associated with progression to cancer. The transition zones of the cervix and anus are at highest risk for the development of cancer.

More than 30 HPV types are associated with genital warts. Patients are commonly infected with multiple HPV types. The HPV types producing genital infection are divided into two broad categories—those that produce benign lesions, or low-risk types (at least 12 types), and those associated with cancer, the so-called high-risk or oncogenic types (at least 15 types). The most common low-risk genital HPV types are HPV-6 and -11, and most HPV-induced genital dysplasias are caused by HPV-16 and -18. There is a strong correlation between the HPV type and the clinical appearance of HPV-induced genital lesions. Virtually all condylomata acuminata are caused by "benign" HPV-6 and -11. High-risk HPV-16 and -18 produce flat or sessile, often hyperpigmented lesions. For this reason, biopsy and HPV typing of external genital warts is rarely necessary.

Genital HPV infection is strongly associated with sexual intercourse. Female virgins rarely harbor HPV (about 1%). For women, insertive vaginal intercourse is strongly associated with acquiring genital HPV infection, with 50% of women testing positive for genital HPV within 5 years of the time of first sexual intercourse. However, sexual contact does not need to be penile–vaginal, as the risk of acquiring genital HPV infection was 10% in women who had nonpenetrative sexual exposure as compared to 1% of women who had no such exposure. Infection may occur at the introitus and then be spread to other sites by self inoculation. Women who have sex with women may have genital HPV infection and still require regular gynecologic evaluations. Condom use may be partly, but not completely, protective for acquisition of genital HPV infection. In men the risk of genital HPV infection is associated with being uncircumcised, having had sex before age 17, having had more than six lifetime sexual partners, and having had sex with professional sex workers.

Condylomata Acuminata

Condylomata on the skin surface appear as lobulated papules that average 2 to 5 mm in size, but they may range from microscopic to several centimeters in diameter and height. Lesions are frequently multifocal. Numerous genital warts may appear during pregnancy. Condylomata acuminata occur in men anywhere on the penis or about the anus. Scrotal condylomata occur in only 1% of immunocompetent male patients with warts (Figs 19-53 and 19-54). Intraurethral condylomata may present with terminal hematuria, altered urinary stream, or urethral bleeding. In women, lesions appear on the mucosal surfaces of the vulva, cervix, on the perineum, or about the anus. Cauliflower-like masses may develop in moist, occluded areas such as the perianal skin, vulva, and inguinal folds. As a result of accumulation of purulent material in the clefts, these may be malodorous. Their color is generally gray, pale yellow, or pink. When perianal lesions occur, a prior history of receptive anal intercourse will usually predict whether intra-anal warts are present and will help to determine the need for anoscopy. Immunosuppressed individuals and those with known high-risk HPV types should have routine anal pap smears to detect malignant change.

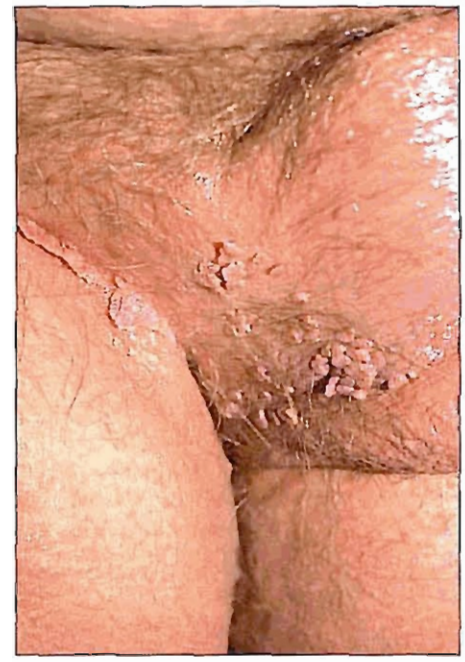

Fig. 19-53 Genital warts, condyloma accuminata.

Fig. 19-54 Genital warts, keratotic type.

Genital warts are sexually transmitted and other STDs may be found in patients with genital warts. A complete history should be taken and the patient screened for other STDs as appropriate. Women with external genital warts should have a routine cervical cytologic screening to detect cervical dysplasia.

Bowenoid Papulosis and HPV-Induced Genital Dysplasias

Bowenoid papulosis is characterized by flat, often hyperpigmented papules a few millimeters to several centimeters

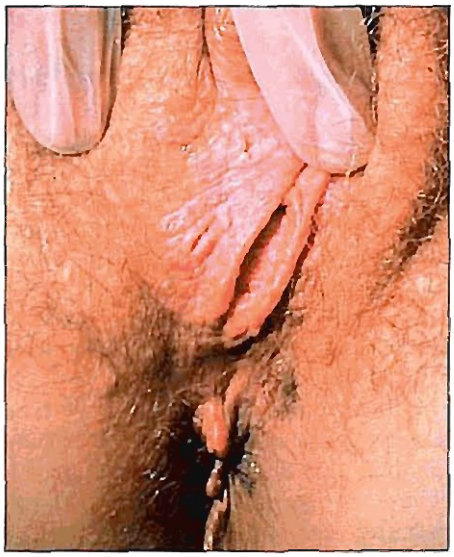

Fig. 19-55 Genital warts, bowenoid papulosis.

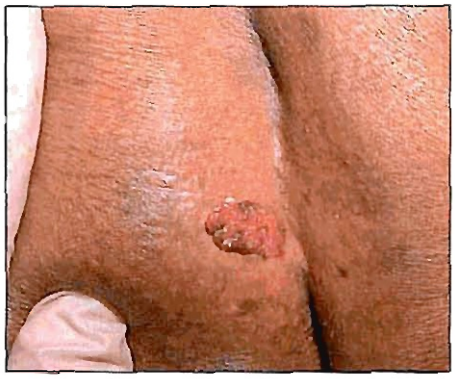

Fig. 19-56 Genital Bowen's disease.

in diameter. These occur singly, or more often, may be found in multiples on the penis, near the vulva, or perianally (Fig. 19-55). At times similar lesions are seen outside the genital area in the absence of genital bowenoid papulosis. They occur most commonly on the neck or face and are more common in men. They contain HPV-16, -18, or other high-risk HPV types. Histologically, bowenoid papulosis demonstrates abnormal epithelial maturation and cellular atypia closely resembling Bowen's disease. It is usually caused by HPV-16. On the glabrous external genitalia, bowenoid papulosis usually behaves similarly to other external genital warts, but may progress to squamous cell carcinoma (SCC). On the glans penis of an uncircumcised male, and on the cervical, vaginal, or rectal mucosa, progression to invasive SCC is more likely (Fig. 19-56). Female partners of men with bowenoid papulosis and women with bowenoid papulosis have an increased risk of cervical dysplasia.

Giant Condyloma Acuminatum (Buschke-Lowenstein Tumor)

Giant condyloma acuminatum is a rare, aggressive, wart-like growth that is a verrucous carcinoma. Unlike other HPV-induced genital carcinomas, this tumor is usually caused by HPV-6. It occurs most often on the glans or prepuce of an uncircumcised male; less often it may occur on perianal skin or the vulva. Despite its bland histologic picture, it may invade deeply and uncommonly it may metastasize to regional lymph nodes. Treatment is by complete surgical excision. Recurrence after radiation therapy may be associated with a more aggressive course.

Diagnosis

Even in women with confirmed cervical HPV infection, serologic tests are positive in only 50%, making serologic diagnosis of HPV infection of no use to the practicing clinician. HPV cannot be cultured. HPV typing via in situ hybridization or PCR is useful in managing HPV infection of the cervix and in some cases of prepubertal HPV infection, but not in the management of most cases of external genital warts. Virtually all condylomata can be diagnosed by inspection. Bright lighting and magnification should be used when examining for genital HPV infection. Flat, sessile and pigmented lesions are suggestive of bowenoid papulosis and may require a biopsy. Subclinical and latent infections are no longer sought or investigated because they are very common and there is no management strategy known to eradicate these forms of HPV infection. Soaking with acetic acid is not generally necessary, but may be helpful to detect early lesions under the foreskin. In patients with multiple recurrences, acetic acid soaking may determine the extent of infection, helping to define the area for application of topical therapies. The procedure is performed by soaking the external genitalia in men and the vagina and cervix in women with 3% to 5% acetic acid for up to 10 min. Genital warts turn white (acetowhitening), making them easily identifiable. Any process that alters the epidermal barrier will be acetowhite, however (dermatitis, for example), so only typical aceto-white lesions should be treated as warts. In atypical cases, a 2-week trial is attempted with a 1% hydrocortisone preparation plus a topical anticandidal imidazole cream. If the acetowhitening persists, a biopsy is performed and histologic evidence of HPV infection sought. Immunoperoxidase or in situ hybridization methods may aid in evaluation. PCR should probably not be performed on such biopsied specimens, except possibly in childhood cases. The high background rate of latent infection (up to 50%) makes interpretation of a positive PCR impossible. In contrast, chromogenic in situ hybridization clearing demonstrates the localization of positive nuclei within the lesion.

Treatment

Because no effective virus-specific agent exists for the treatment of genital warts, their recurrence is frequent. Treatment is not proven to reduce transmission to sexual partners or to prevent progression to dysplasia or cancer. Specifically the treatment of male sexual partners of women with genital warts does not reduce the recurrence rate of warts in these women. Therefore, the goals of treatment must first be discussed with the patient, and perhaps with his/her sexual partner. Observation represents an acceptable option for some patients with typical condylomata acuminata. In some patients, only wart-free periods are achieved. Because genital warts may cause discomfort, genital pruritus, malodor, bleeding, and substantial emotional distress, treatment is indicated if the patient desires it. Bleeding genital warts may increase the sexual transmission of HIV and hepatitis B and C. Bowenoid papulosis may be treated as discussed below when it occurs on the external genitalia. Lesions with atypical histology (squamous intraepithial lesion) on mucosal surfaces and periungually are special cases and treatment

must be associated with histologic confirmation of eradication in cases where topical methods are used.

The treatment chosen is in part dictated by the size of the warts and their location. Podophyllin is more effective in treating warts on occluded or moist surfaces, such as the mucosa or under the prepuce. It is available as a crude extract, usually in 25% concentration in tincture of benzoin. It is applied weekly by the physician and is washed off 4 to 8 h later by the patient, depending on the severity of the reaction. After six consecutive weekly treatments, approximately 40% of patients are free of warts and 17% are free of warts at 3 months after treatment. Purified podophyllotoxin 0.5% solution or gel is applied by the patient twice a day for 3 consecutive days of each week in 4- to 6-week treatment cycles. Efficacy approaches 60% for typical condylomata and side effects are less than with standard, physician-applied podophyllin preparations. Therefore, whenever possible, podophyllotoxin should be used instead of classic podophyllin solutions.

Imiquimod, an immune response modifier which induces IFN locally at the site of application, has an efficacy similar to cryotherapy (about 50%) and yields a low recurrence rate (22%). It is available in a 250 mg sachet containing a 5% cream formulation. One sachet can cover up to 350 cm^2 when applied appropriately, allowing for several treatments with a single sachet if the treatment area is limited. It is more effective than podophyllotoxin in treating women with external genital warts, but it is only equally or slightly less effective in men, especially for warts on the penile shaft. Response is slow, requiring 10 or more weeks in some patients to see a response. It is patient applied, once a day for 3 alternate days per week (usually Monday, Wednesday, and Friday). Treatment results in mild-to-moderate irritation (less than with podophyllin or cryotherapy in men, but with a similar side effect profile in women). Rare complications include flaring of psoriasis and psoriatic arthritis, vitiligo-like hypopigmentation and the production of a local neuropathy. Imiquimod should be used cautiously in persons with psoriasis. Neuropathy is associated with application of excessive amounts, occlusion of the medication, and application to an eroded mucosa.

Imiquimod may be used to treat penile condyloma in circumcised and uncircumcised men, anal and perianal condyloma, and vulvar condyloma. It may be used as the initial treatment or in cases in which recurrence has been frequent after other forms of treatment were attempted. Initial therapy with imiquimod for 16 weeks, followed by surgical removal of residual external genital warts is associated with a reduced risk of recurrence when compared to surgical removal alone (20% vs 65%), suggesting that imiquimod might even be beneficial for patients who do not respond and require other subsequent treatments. Suppositories containing about 5 mg of imiquimod appear to reduce the risk of recurrence of anal condyloma in immunocompetent men after surgical ablation of extensive anal disease. Imiquimod has been effective in the treatment of bowenoid papulosis in scattered case reports.

Bichloroacetic or trichloroacetic acid (TCA) 35% to 85% can be applied to condylomata weekly or biweekly. TCA is safe for use in pregnant patients. When compared with cryotherapy, TCA has the same or lower efficacy and causes more ulcerations and pain. It is not generally recommended for external genital warts as other available treatments are more effective and cause less morbidity.

Cryotherapy with liquid nitrogen is more effective than podophyllin, approaching 80% resolution during treatment and 55% 3 months after treatment. One or two freeze–thaw cycles are applied to each wart every 1 to 3 weeks. A zone of 2 mm beyond the lesion is frozen. Cryotherapy is effective in dry as well as moist areas. Perianal lesions are more difficult to treat than other genital sites and two freeze–thaw cycles are recommended in this location. Cryotherapy is safe to use in pregnant patients. EMLA cream with or without subsequent lidoaine infiltration may be beneficial in reducing the pain of cryotherapy.

Electrofulguration or electrocauterization with or without snip removal of the condyloma is more effective than TCA, cryotherapy, or podophyllin. Wart clearance during therapy is nearly 95% and wart cure at 3 months exceeds 70%. Local anesthesia is required and scarring may occur. Surgical removal is ideal for large exophytic warts that might require multiple treatments with other methods. It has high acceptance in patients who have had recurrences from other methods because results are immediate and cure rates higher.

The use of CO_2 laser in the treatment of genital warts has not been demonstrated to be more effective than simpler surgical methods. Although visible warts are eradicated by the laser, HPV DNA can still be detected at the previous site of the wart. The CO_2 laser has the advantage of being bloodless, but it is costlier and requires more technical skill on the part of the surgeon to avoid complications. It should be reserved for treatment of extensive lesions in which more cost-effective methods have been attempted and failed.

Any surgical method that generates a smoke plume is potentially infectious to the surgeon. HPV DNA is detected in the plumes generated during CO_2 laser or electrocoagulation treatment of genital warts. The laser-generated plume results in longer-duration HPV aerosol contamination and wider spread of detectable HPV DNA. If these methods of wart treatment are used, an approved face mask should be worn, a smoke evacuator should be operated at the surgical site during the procedure to remove the plume and decontamination of the equipment after the surgery should be carried out.

Photodynamic therapy with 20% 5-aminolaevulinic acid (ALA) and irradiation with 70 to 100 J/cm^2 (FORTH-IESL) 6 to 10 h after ALA application lead to clearance of condyloma accuminata in 73% of treated men.

5-FU 5% cream applied twice a day may be effective, especially in the treatment of flat, hyperpigmented lesions, such as those in bowenoid papulosis. Care must be taken to avoid application to the scrotum, as scrotal skin is prone to painful erosions. Twice a day instillation of 5-FU into the urethra can be used to treat intraurethral condylomata. The cone from a tube of xylocaine jelly will fit onto the thread of the 5-FU tube, or the cream may be instilled with a syringe. It is typically left in place for 1 h before the patient voids. Care should be taken that drips of urine containing the medication do not contact the scrotum. 5-FU may also be used to treat intravaginal warts by instillation in the vagina, but is often associated with severe irritation. Intermittent therapy (twice a week for 10 weeks) is better tolerated than daily therapy. 5-FU is not commonly recommended for the treatment of typical external genital warts because other methods of treatment are available.

The efficacy of systemic and intralesional IFN-α therapy has been found to be relatively low in eradicating genital warts. Intralesional therapy eradicates 40% to 60% of warts and systemic IFN treatment will eradicate warts in only about 20% of patients. IFN treatment of genital warts in patients with AIDS has even lower efficacy rates. Response rates to IFN have never reached the levels achieved with electrosurgical methods. Because of the high cost, frequent side effects, and low efficacy associated with IFN therapy, the CDC no longer recommends the use of IFN for the treatment of genital warts.

Human Papillovirus Vaccination

HPV virus-like particles (VLPs) composed of spontaneous assembling L1 molecules have been used as a vaccine against HPV-16. This vaccine was highly effective in preventing HPV-16 infection and the development of HPV-16 associated squamous intraepithelial lesions (dysplasia). The protection was type specific and did not prevent squamous intraepithelial lesions from other HPV types. Since HPV-16 and -18 are the primary HPV types associated with cervical cancer, it is hoped that the rate of cancers induced by high-risk genital HPV types (especially HPV-16 and -18) can be reduced by vaccination.

Genital Warts in Children

Children can acquire genital warts through vertical transmission perinatally, and through digital inoculation or autoinoculation, fomite or social nonsexual contact, and sexual abuse. HPV typing has demonstrated that most warts in the genital area of children are "genital" HPV types and most children with genital warts have family members with a genital HPV infection.

HPV typing can be performed; however, the presence of genital types of HPV does not prove abuse and a finding of a nongenital HPV type does not exclude the possibility of sexual abuse. In children younger than 1 year of age, vertical transmission is possible and is probably the most common means of acquisition. The risk for sexual abuse is highest in children older than 3 years of age. When abuse is suspected, children should be referred to child protection services if the practitioner is not skilled in evaluating children for sexual abuse. Children between 1 and 3 years of age are primarily nonverbal and are difficult to evaluate. Management of such patients is on a case-by-case basis. Other STDs should be screened for in children who have a genital HPV infection. Usually the management of children with anogenital warts requires a multidisciplinary team which should include a pediatrician. Genital warts in children often spontaneously resolve (75%), so nonintervention may be a reasonable consideration. Genital warts in children usually respond quickly to topical therapy, such as podophyllotoxin, imiquimod, or light cryotherapy. In refractory cases, surgical removal or electrocautery may be used. The use of a topical anesthetic is recommended before treatment.

Recurrent Respiratory (Laryngeal) Papillomatosis

HPV-associated papillomas may occur throughout the respiratory tract, from the nose to the lungs. Recurrent respiratory papillomatosis has a bimodal distribution—in children under 5, and after the age of 15. Affected young children are born to mothers with genital condylomata and they present with hoarseness. The HPV types found in these lesions, HPV-6 and -11, are the types seen in genital condylomata. Treatment is with CO_2 laser surgery and IFN. Carcinoma that is often fatal develops in 14% of patients, even in young children. The incidence of carcinoma is higher in those treated with radiation therapy.

Heck's Disease Small white to pinkish papules occur diffusely in the oral cavity in this disease, also known as *focal epithelial hyperplasia*. It occurs most commonly in Native Americans, in Greenland, and in Turkey. HPV-13, -24, and -32 have been associated. Lesions may spontaneously resolve. Treatment options include cryosurgery, CO_2 laser, electrosurgery, and topical (β), intralesional, and systemic IFN.

Epidermodysplasia Verruciformis

Epidermodysplasia verruciformis is a rare, inherited disorder characterized by widespread HPV infection and cutaneous SCCs. Most commonly it is inherited as an autosomal-recessive trait. HPV types associated with this syndrome include those infecting normal hosts, such as HPV-3 and -10, as well as many "unique" HPV types. These HPV types are called *EV HPVs* and include HPV-5, -8, -9, -12, -14, -15, -17, -19 through -25, and -36 through -38. The pathogenesis of this syndrome is unknown, but is felt to be a specific defect of cell-mediated immunity. Patients with epidermodysplasia verruciformis cannot be sensitized to topical immunosensitizers.

The condition presents in childhood and continues throughout life. Skin lesions include flat wart-like lesions of the dorsal hands, extremities, face, and neck. These are flatter than typical flat warts and may be quite abundant, growing to confluence (Fig. 19-57). Typical HPV-3- and -10-induced

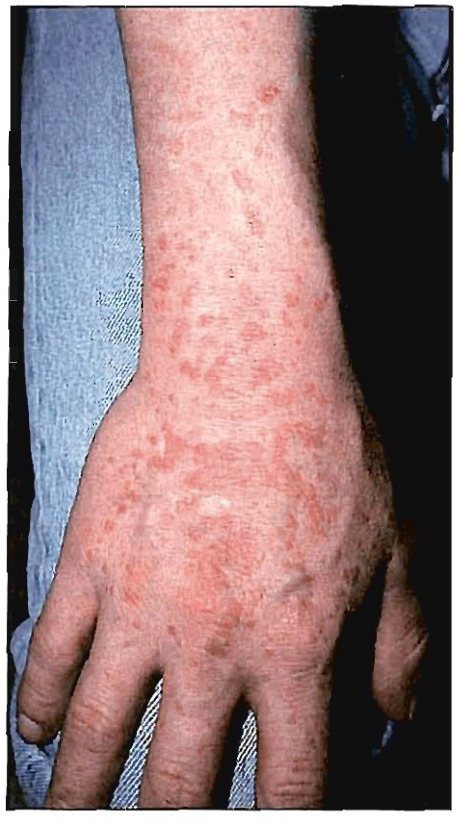

Fig. 19-57 Epidermodysplasia verruciformis.

Fig. 19-58 Epidermodysplasia verruciformis.

flat warts may be admixed. In addition, on the trunk are lesions which are red, tan, or brown patch/plaques or hypopigmented, very slightly scaly plaques resembling tinea versicolor (Fig. 19-58). Plaques on the elbows may resemble psoriasis. Seborrheic keratosis-like lesions may also be seen on the forehead, neck, and trunk.

The histologic features of an epidermodysplasia verruciformis-specific HPV infection are very characteristic. The cells of the upper epidermis have a clear, smoky or light-blue pale cytoplasm and a central pyknotic nucleus.

SCCs develop in 30% to 60% of patients. Most often skin cancers appear on sun-exposed surfaces, but they can appear on any part of the body. They begin to appear at the age of 20 to 40. Skin cancers are less common in African patients, suggesting a protective effect of skin pigmentation. HPV-5, -8, and -47 are found in more than 90% of epidermodysplasia verruciformis skin cancers. The SCCs may appear de novo, but usually appear on the background of numerous actinic keratoses and lesions of Bowen's disease. Surgical treatment is recommended. Radiation therapy is contraindicated. If skin grafting is required, the grafts should be taken from sun-protected skin, such as the buttocks or inner upper arm.

Aside from surgical intervention for skin cancer, treatment for epidermodysplasia verruciformis consists largely of preventive measures. Strict sun avoidance and protection should be started as soon as the syndrome is diagnosed. An approach similar to that for children with xeroderma pigmentosa could be instituted.

The mechanism by which cancer occurs in patients with epidermodysplasia verruciformis is unclear. HPV-5 proteins do not bind to p53 or pRb. The p53 mutations present in the SCCs of patients with epidermodysplasia verruciformis are characteristic of those induced by UVB, confirming the close association of UV exposure and the development of cancer in patients with epidermodysplasia verruciformis. EV HPV DNA has been reported to be found in a large percentage (35%) of the general population in very low copy number. EV HPV DNA is reported to be present on the skin in up to 80% of patients with psoriasis. The genetic loci for epidermodysplasia verruciformis colocalize to two known psoriasis susceptibility loci on chromosomes 17q and 2p, supporting a putative relationship between EV HPV infection and psoriasis.

Immunosuppressed Patients

Patients with defects in their cell-mediated immunity may have an increased frequency of HPV infection. Predisposing conditions include organ transplantation, immunosuppressive medications, congenital immunodeficiency diseases, lymphoma, and HIV infection.

Organ transplant recipients begin to develop warts soon after transplantation and by 5 years up to 90% of transplant patients have warts. Initially these are common and plantar warts, but later numerous flat warts appear, particularly in sun-exposed areas. Depending on the background level of UV radiation, the lifetime risk for cutaneous carcinomas may exceed 40%. Skin cancers begin to appear 5 years or more after transplantation, occur in sun-exposed sites, and are more common in persons with skin types I and II. The duration and intensity of immunosuppression appear more important in causing the skin cancers than are the specific immunosuppressive agents used. Malignant lesions may resemble Bowen's disease, keratoacanthomas, SCCs, or warts. Genital warts are also increased and, especially in women, genital dysplasias are more frequent.

Epidermodysplasia verruciformis types and some unique HPV types are frequently found in the nongenital dysplasias among organ transplant recipients. The skin of organ transplant patients should be examined closely and once skin cancers begin to appear, regular dermatologic examinations should be performed.

In HIV disease, common, plantar, flat, oral and genital warts are all very common. Warty keratoses at the angle of the mouth, often bilateral, are a characteristic, and perhaps unique, manifestation of HPV infection in patients with AIDS (Fig. 19-59). The warts are caused predominantly by HPV-2, -27, and -57. HPV-7 can be found in cutaneous, oral, and perioral warts in non-butchers with HIV infection. HPV-6 may be found in common warts. Genital warts are increased 15-fold among HIV-infected women. Fifty percent or more of HIV-infected homosexual men have evidence of anal HPV infection. Genital neoplasia associated with HPV-16 and -18 occur much more frequently in HIV-infected women and homosexual men. Uncommonly, HIV-infected patients develop HPV-5- and -8-induced epidermodysplasia verruciformis-like lesions. Although nongenital skin cancers are also common in some fair-skinned HIV-infected patients, HPV has not been demonstrated in the nongenital SCCs of these patients. With HAART therapy, warts may disappear. Paradoxically, increased rates of genital and oral warts are seen in HIV-infected persons with adequate control of their HIV infection. The likelihood of clearance of common warts in persons with HIV is related to the nadir of their helper T-cell count. HIV-infected persons whose helper T-cell count never falls below 200 are more likely to have sustained remission of their warts.

The treatment of warts in immunosuppressed hosts is very difficult. Although standard methods are used, their efficacy may be reduced. Imiquimod has low efficacy in this setting, but can be attempted. The addition of a second modality (podophyllin, 5% 5-FU, or surgery) to the imiquimod treatment may lead to improvement. Topical cidofovir (in concentrations from 0.4% to 3%) and systemic cidofovir have been effective in refractory anogenital and common wart cases. Topical cidofovir is very expensive, is irritating, and can cause skin erosion and ulceration. Usually short treatment

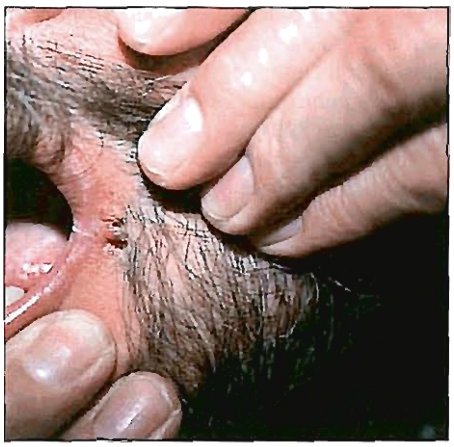

Fig. 19-59 Oral warts.

courses of 5 to 14 days, with 1- to 4-week rest periods to allow healing, have been used. Cidofovir treatment may be combined with destructive methods in refractory cases.

It is especially important in immunosuppressed patients to regularly monitor the genital and anal areas for changing lesions and to have a low threshold for performing a biopsy.

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Viral-Associated Trichodysplasia (Cyclosporin-Induced Folliculodystrophy)

Organ transplant recipients on immunosuppressive regimens rarely develop a characteristic eruption of erythematous 1- to 3-mm facial papules. The midface, glabella, and chin are primarily affected. Lesions are numerous, may reach confluence, and can cause nasal distortion similar to that seen in rosacea and sarcoidosis (Fig. 19-60). Some papules have a central, keratotic white excrescence. Alopecia of the eyebrows and eyelashes may occur, but the scalp is spared. Histology is characteristic, showing massively distended, bulbous follicles with expansion of the inner root sheath cells containing numerous trichohyaline granules. Abrupt inner root sheath-type cornification is present. No hair shafts (or hair cortex) are present in the affected follicles. Electron microscopy demonstrates numerous viral particles about 40 nm in size with features suggestive of a papovavirus. Topical cidofovir 3% cream slowly improved one patient.

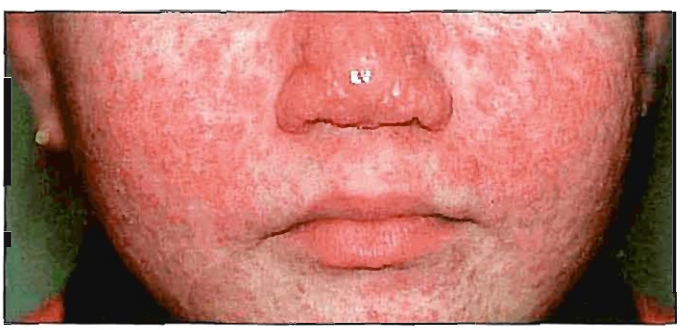

Fig. 19-60 Trichodysplasia. (Courtesy of Len Sperling MD)

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RETROVIRUSES

These oncoviruses are unique in that they contain RNA, which is converted by a virally coded reverse transcriptase to DNA in the host cell. The target cell population is primarily CD4+ lymphocytes (primarily helper T cells), but also, in some cases, macrophages. For this reason they are called human T-lymphotropic viruses (HTLV). Transmission may be by sexual intercourse, blood products/intravenous drug use, and from mother to child during childbirth and breast-feeding. There is often a very long "latent" period from the time of infection until presentation with clinical disease.

Human T-Lymphotropic Virus-1

HTLV-1 is endemic in Japan, the Caribbean, South America (Brazil), sub-Saharan Africa, among Australian Aborigines, and in the southeastern US. In endemic areas infection rates may be quite high, with only a small percentage of infected patients ever developing clinical disease. HTLV-1 is responsible for several clinical syndromes. About 1% of persons who are infected will develop adult T-cell leukemia-lymphoma (ATLL). HTLV-1–associated myelopathy or tropical spastic paraparesis (HAM/TSP) is a less common degenerative neurologic syndrome.

There are four forms of ATLL: smoldering, chronic, acute, and lymphomatous, usually progressing in that order. ATLL is characterized by lymphadenopathy, hepatosplenomegaly, hypercalcemia, and skin lesions. Skin lesions in ATLL include erythematous papules or nodules. Prurigo may be a prodrome to the development of ATLL. Histologically, the cutaneous infiltrates are pleomorphic, atypical lymphocytes with characteristic "flower cells" representing HTLV-1 infected lymphocytes. Epidermotropism may be present, mimicking mycosis fungoides.

HTLV-1 infected patients often have an abnormal skin examination. If they are seropositive but asymptomatic, dermatophytosis (34%), seborrheic dermatitis (6%), xerosis/acquired ichthyosis (7%), are most commonly found. Xerosis occurs in 82% of patients with HAM/TSP, seborrheic dermatitis in 33%, candidiasis and palmar erythema in 15%, and chronic eczema/photosensitivity in up to 20%. Biopsies from the areas of chronic eczema/photosensitivity may show features of ATLL in up to 25% of these patients (smoldering ATLL). Areas of positive biopsies are described as "atrophic."

Scabies is seen in 2% of asymptomatic HTLV-1 infected patients and in 5% of those with HAM/TSP. The scabies may be of the hyperkeratotic (crusted) type and the finding of this pattern of scabies in a person from an HTLV-1 endemic region should trigger serologic testing for HTLV-1. The spectrum of skin disease seen in symptomatic HTLV-1 infected patients is remarkably similar to that seen in HIV-infected patients with CNS disease (xerosis/eczema, seborrheic dermatitis, and scabies).

"Infective dermatitis" occurs in Jamaican children infected with HTLV-1. It is diagnosed by major and minor criteria as delineated by La Grenade et al. Clinically, the children present at an early age (on average, about 7 years) with a chronic eczema of the scalp, axilla, groin, external auditory canal, retroauricular area, eyelid margins, paranasal areas, and neck. There is a chronic nasal discharge. Cultures from the skin and nares are positive for *S. aureus* or beta-hemolytic streptococcus, and the condition responds rapidly to antibiotics. However, the condition is relapsing and recurrent. Skin biopsies show a nonspecific dermatitis.

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Human Immunodeficiency Virus (HTLV-3)

HIV infects human helper T-cells, leading to a progressive immunodeficiency disease. In its end stages it is called *acquired immunodeficiency syndrome* (AIDS). Cutaneous manifestations are prominent, affecting up to 90% of HIV-infected persons. Many patients have multiple skin lesions of different kinds. The skin lesions or combinations of skin conditions are so unique that the diagnosis of HIV infection or AIDS can often be suspected from the skin examination alone. The skin findings can be classified into three broad categories: infections, inflammatory dermatoses, and neoplasms. The skin conditions also tend to appear at a specific stage in the progression of HIV disease, making them useful markers of the stage of HIV disease.

The natural history of HIV infection in the vast majority of patients is a gradual loss of helper T-cells. The rate of this decline is variable, with some patients progressing rapidly and others very slowly or not at all (long-term nonprogressors). Soon after infection there is a seroconversion syndrome called primary HIV infection, or acute infection (group I). Patients recover from this syndrome and enter a relatively long latent period (asymptomatic infection or group II), which averages about 10 years. During this period patients may have persistent generalized lymphadenopathy (group III). When symptoms begin to appear they are often nonspecific and include fever, weight loss, chronic diarrhea, and mucocutaneous disease (group IV A). Helper T-cell counts in group II, III, and IV A patients usually range from 200 to 500. The skin findings at this stage (originally called ARC [AIDS-related complex]) include seborrheic dermatitis, psoriasis, Reiter syndrome, atopic dermatitis, herpes zoster, acne rosacea, oral hairy leukoplakia, onychomycosis, warts, recurrent *S. aureus* folliculitis, and mucocutaneous candidiasis.

Once the helper T-cell count is 200 or less the patient is defined as having AIDS. In this stage of HIV disease the skin lesions are more characteristic of immunodeficiency and include characteristic opportunistic infections: chronic herpes simplex, molluscum contagiosum, bartonellosis (bacillary angiomatosis), systemic fungal infections (cryptococcosis, histoplasmosis, coccidioidomycosis, and penicilliosis), and mycobacterial infection. Paradoxically, patients at this stage also have hyper-reactive skin and, frequently, inflammatory, often pruritic skin diseases. These skin conditions include eosinophilic folliculitis, granuloma annulare, drug reactions, enhanced reactions to insect bites, and photodermatitis.

When the T-cell count falls below 50, the patient is often said to have "advanced AIDS." These patients may have very unusual presentations of their opportunistic infections, including multicentric, refractory molluscum contagiosum; chronic herpes simplex; chronic cutaneous varicella zoster infection; cutaneous acanthamebiasis, cutaneous atypical mycobacterial infections (including *Mycobacterium avium* complex and *Mycobacterium haemophilum*), and crusted scabies. Treatment of their infections is often very difficult because of the significant chronic immunosuppression.

It is now clear that HIV itself is the cause of the loss of helper T-cells and that effective treatment of HIV infection may halt or reverse the natural history of HIV disease. There are numerous antiretroviral agents and they are usually used in combinations called "cocktails." This combination treatment is called *highly active antiretroviral therapy* (HAART). A significant percentage of HIV-infected patients respond to HAART and may show dramatic improvement of their HIV disease. HIV virus disappears from the blood and helper T-cell counts rise. As expected, in patients who respond to HAART, opportunistic infections no longer occur, and subsequently mortality decreases. This is also true of cutaneous infectious conditions. HIV-associated psoriasis usually improves substantially, especially if the patient did not have psoriasis prior to HIV infection.

HAART is typically associated with resolution of all forms of HIV-related cutaneous complications. However, some conditions may initially appear or be exacerbated by the sudden improvement of the immune status that occurs with eradication of HIV viremia. This complex of manifestations has been termed the "*immune reconstitution*" or "*immune restoration*" syndrome. Eosinophilic folliculitis, drug eruptions, at times HPV infections (especially oral and genital), tattoo and foreign body granulomas, and sarcoidosis may exacerbate during this period. The enhancement of T-cell function may activate granulomatous infectious disease, with new lesions of cutaneous tuberculosis and atypical mycobacterial infections appearing after institution of HAART.

Primary HIV Infection (Acute Seroconversion Syndrome) Several weeks after infection with HIV, an acute illness develops in a large proportion of individuals. The clinical syndrome is much like EBV infection, with fever, sore throat, cervical adenopathy, a rash, and oral, genital, and

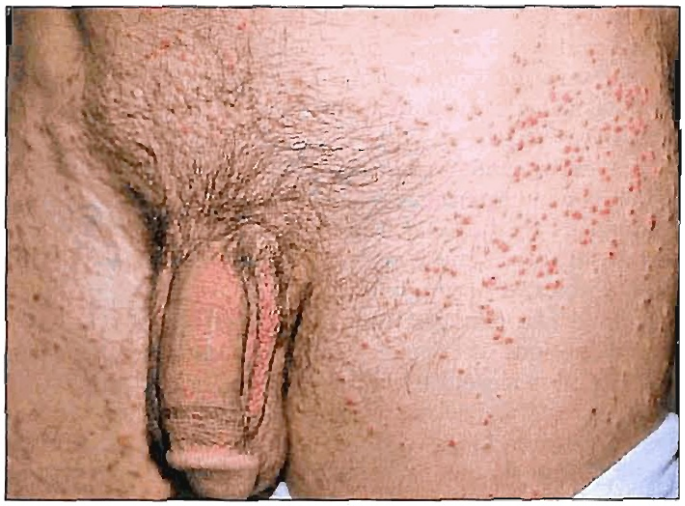

Fig. 19-61 Primary HIV infection.

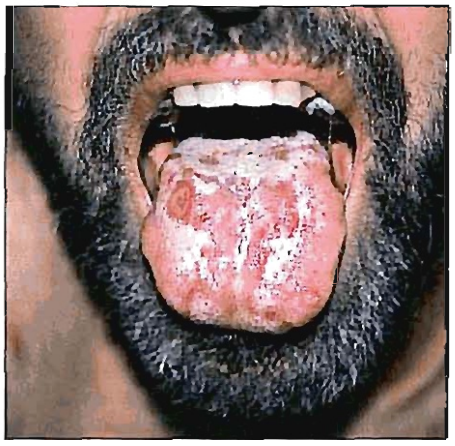

Fig. 19-62 Primary HIV infection. (Courtesy of Ginat Mirowski, MD)

rectal ulceration. The skin eruption can be polymorphous (Figs 19-61 and 19-62). Most characteristic is a papular eruption of discrete, slightly scaly, oval lesions of the upper trunk. The lesions have a superficial resemblance to pityriasis rosea, but the peripheral scale is not prominent, and there is focal hemorrhage in the lesions. A Gianotti-Crosti–like papular eruption may also occur. Purpuric lesions along the margins of the palms and soles, as seen in immune complex disease, have been reported. The mucosal erosions resemble aphthae but are larger and can affect all parts of the mouth, pharynx, esophagus, and anal mucosa. Dysphagia may be prominent. The helper T-cell count falls abruptly during seroconversion. The level of immune impairment may be adequate to allow oral candidiasis or even *Pneumocystis carinii* pneumonia to develop. The diagnosis should be suspected in any at-risk individual with the correct constellation of symptoms. A direct measurement of HIV viral load will confirm the diagnosis. Combination antiviral therapy is instituted immediately in these patients with the hope of improving the natural history of their disease.

HIV-Associated Pruritus From early in the HIV epidemic, it was clear that pruritus was a marker of HIV infection throughout the world, occurring in up to 30% of patients. Pruritus is not caused by HIV disease itself but is related to inflammatory dermatoses associated with the disease. "Papular pruritic eruption" is not a specific disease, but a wastebasket diagnosis used to encompass patients with many forms of HIV-associated pruritus. These pruritic eruptions are best subdivided into follicular and nonfollicular eruptions. The relative prevalence of these two patterns of pruritic eruptions is geographically distinct. In tropical and semi-tropical regions where biting insects are prominent, nonfollicular eruptions are most common, and probably represent insect bite hypersensitivity. In temperate regions, follicular pruritic eruptions are more common.

Eosinophilic folliculitis is the most common pruritic follicular eruption. It is seen in patients with a helper T-cell count of about 200. Clinically, it presents with urticarial follicular papules on the upper trunk, face, scalp, and neck. Pustular lesions are uncommon; pustules are usually smaller than in bacterial folliculitis and represent end-stage lesions. They are uncommonly seen, since the pruritus is so severe that they are excoriated before the lesion evolves to this degree. Ninety percent of lesions occur above the nipple line on the anterior trunk, and lesions typically extend down the midline of the back to the lumbar spine. The disease waxes and wanes in severity and may spontaneously clear, only to flare unpredictably. A peripheral eosinophilia may be present and the serum IgE level may be elevated, suggesting this is a disorder mediated by T-helper 2 cells. Histologically, an infiltrate of mononuclear cells and eosinophils is seen around the upper portion of the hair follicle at the level of the sebaceous gland. As lesions evolve, eosinophils and lymphocytes enter the follicular structure and the sebaceous glands. Pustules are formed late and represent aggregates of eosinophils in the uppermost part of the follicle.

Initial treatment of eosinophilic folliculitis is topical steroids and antihistamines. If the patient fails to respond, phototherapy (UVB or PUVA) or itraconazole 200 mg twice a day may be effective. In some patients repeated applications of permethrin (every other night for up to 6 weeks) may be of benefit. This latter therapy is directed at *Demodex* mites, which may be the antigenic trigger of this condition. Isotretinoin is also effective, often after a few months, in a dose of about 0.5 to 1 mg/kg/day. Staphylococcal folliculitis, which may be severely pruritic in patients with HIV disease, and pityrosporum folliculitis should be included in the differential diagnosis. These are excluded by bacterial culture and skin biopsy, respectively.

The other pruritic dermatoses that are not follicular can be divided into the primarily papular eruptions and the eczematous ones. The papular eruptions include scabies, insect bites, transient acantholytic dermatosis, granuloma annulare, and prurigo nodularis. The eczematous dermatoses include atopic-like dermatitis, seborrheic dermatitis, nummular eczema, xerotic eczema, photodermatitis, and drug eruptions. Patients may have multiple eruptions simultaneously, making differential diagnosis difficult. A skin biopsy from a representative lesion of every morphologic type on the patient may elucidate the true diagnoses. Treatment is determined by the diagnosis and is similar to treatment in persons without HIV infection with these same dermatoses. Special considerations in AIDS patients include the use of topical therapy plus ivermectin for crusted scabies and thalidomide for prurigo nodularis and photodermatitis. Both of these systemic agents are very effective if used appropriately.

HIV-Associated Neoplasia Neoplasia is prominent in HIV infection and in some cases is highly suggestive of HIV infection. Kaposi sarcoma is an example. Other common neoplasms seen in patients with HIV infection include superficial basal cell carcinomas of the trunk, SCCs in sun-exposed areas, genital HPV-induced SCC, and extranodal B- and T-cell lymphomas. Less common neoplasms include lung cancer, leiomyomas and leiomyosarcomas, germ cell tumors, conjunctival cancer, multiple myeloma, and leukaemia. Lipomas and angiolipomas may occur in association with HAART therapy, perhaps more commonly in patients taking protease inhibitors.

Nonmelanoma skin cancers are very common in HIV-infected persons and usually occur as superficial multicentric basal cell carcinomas on the trunk in fair-skinned males in their 20s to 50s. The ratio of basal cell carcinoma to SCC is not reversed in HIV disease, as it is in organ transplant recipients. Basal cell carcinomas behave in the same manner as they do in the immunocompetent host and standard management is usually adequate.

Actinically-induced SCCs are also quite common and present in the standard manner as nodules, keratotic papules, or ulcerations. In most cases their behavior is relatively benign and standard management is adequate. Removal of SCCs in sun-exposed areas by curettage and desiccation in patients with HIV infection is associated with an unacceptably high recurrence rate of about 15%. Complete excision is therefore recommended. The use of imiquimod to treat SCC in situ in the setting of HIV infection should be considered experimental, and if undertaken, very close follow-up is recommended. In a small subset of patients with AIDS, actinic SCCs can be very aggressive—they may double in size over weeks and may metastasize to regional lymph nodes or viscerally, leading to the death of the patient.

Genital SCCs, including cervical, vaginal, anal, penile, and nailbed SCC, all occur in patients with HIV infection. These neoplasms are increased in frequency and the progression from HPV infection to neoplasia appears to be accelerated. This is analogous to the situation in organ transplant and other immunosuppressed patients. It appears that these cancers are associated with primarily "high-risk" HPV types.

For the dermatologist, there are three important manifestations of high-risk genital HPV infection in patients with HIV. Most common is perianal dysplasia, seen most frequently in homosexual men with a history of receptive anal intercourse. Dysplasia in this area may present as velvety white or hyperpigmented plaques involving the whole anal area and extending into the anal canal. These lesions may erode or ulcerate. Histology will demonstrate SCC in situ. The risk of progression of the lesions to anal SCC is unknown but is estimated to be at least 10 times higher than the rate of cervical cancer in women in the general population. The management of such lesions is unclear, but regular follow-up is clearly indicated and any masses in the anal canal should be immediately referred for biopsy. At some centers Pap smear equivalents are performed. Imiquimod has been used as an adjunct in the management of genital warts and HPV-associated genital in situ dysplasias (not genital SCC). While it may be of benefit in patients with reconstituted immune systems on HAART, especially in combination with surgical ablation, the response rate is much lower than in immunocompetent patients. In the only placebo controlled trial, done before standard HAART was available, imiquimod was no more effective than placebo in clearing genital warts in HIV infection (11% of genital warts cleared). Small case series of patients on HAART suggest clearance rates of about 30% to 50%.

The vulvar and penile skin may develop flat white or hyperpigmented macules from a few millimeters to several centimeters in diameter. These show SCC in situ and are analogous to bowenoid papulosis in the immunocompetent host. Rare cases of progression to SCC have occurred. Such lesions are best managed conservatively as warts and watched closely. Lesions of the penis and vulva, not at a transition zone or on mucosal surfaces, have a low risk of progressing to invasive SCC. Lesions of the glans penis that are red and fixed should be biopsied. If the changes of SCC in situ are found, these should be managed aggressively as erythroplasia of Queyrat. Topical 5-FU and superficial radiation therapy are effective. Close clinical follow-up is indicated. Periungual SCC has also been seen in patients with HIV infection. Any persistent keratotic or hyperpigmented lesion in the periungual area must be carefully evaluated. Management is surgical excision.

Extranodal B-cell and, less commonly, T-cell lymphomas are associated with the advanced immunosuppression of AIDS. The B-cell lymphomas and some of the T-cell lymphomas present as violaceous or plum-colored papules, nodules, or tumors. Once the diagnosis is established by biopsy, systemic chemotherapy is required. EBV is found in some cases. HAART therapy is both protective against the development of non-Hodgkin lymphoma (NHL) and Hodgkin's disease in HIV and substantially improves prognosis of HIV-infected patients with NHL. Mycosis fungoides can also be seen in patients with HIV infection, often in patients who have not yet developed AIDS. It presents with pruritic patches or plaques and may progress to tumor stage. EBV in not found in these cases. CD8+ pseudolymphoma is also seen in patients with untreated HIV infection, and may resolve with HAART.

Malignant melanoma is occasionally seen in persons with HIV infection. These patients demonstrate the same risk factors as do other melanoma patients—multiple nevi, fair skin type, and prior intermittent intense sun exposure. HIV-infected patients with melanoma in the era prior to HAART had a significantly shorter disease-free survival and a reduced overall survival. Many fair-skinned patients infected with HIV complain of the new onset of atypical moles (analogous to organ transplant patients). Whether these confer an increased risk of melanoma is unknown.

AIDS and Kaposi Sarcoma Kaposi sarcoma was, along with pneumocystis pneumonia, the harbinger of the AIDS epidemic. Many homosexual and bisexual men presented with this tumor in the early 1980s, with a prevalence of up to 25% in some cohorts. HHV-8, a gamma herpesvirus, has been identified in these lesions and appears to be pathogenically related. The clinical features of Kaposi sarcoma in patients with AIDS are different than those seen in elderly men who do not have AIDS. Patients with AIDS present with symmetrical widespread lesions, often numerous. Lesions begin as macules that may progress to tumors of nodules. Any mucocutaneous surface may be involved, but areas of predilection include the hard palate, trunk, penis, and lower

legs and soles. Visceral disease may be present, and progressive. Edema may accompany lower leg lesions, and if it is significant, it is often associated with lymph node involvement in the inguinal area.

A diagnosis of Kaposi sarcoma is established by skin biopsy, which should be taken from the center of the most infiltrated plaque. Excessive bleeding is not usually a problem. Early macular lesions show atypical, angulated, ectatic vessels in the upper dermis associated with an inflammatory infiltrate containing plasma cells. Plaque lesions show aggregates of small vessels and endothelial cells in the upper dermis, and surrounding adnexal structures. Nodules and tumors show the classic pattern of a spindle cell neoplasm with prominent extravasation of red blood cells.

HAART has reduced the incidence of Kaposi sarcoma in HIV-infected patients by 10-fold. The treatment of AIDS-associated Kaposi sarcoma depends on the extent and aggressiveness of the disease. Effective HAART after about 6 months is associated with involution of Kaposi sarcoma lesions in 50% of patients. This should be the initial management in most patients with mild-to-moderate disease (<50 lesions and <10 new lesions/month) who are not receiving anti-HIV treatment. Intralesional vinblastine 0.2 to 0.4 mg/mL can be infiltrated into lesions (as for a hypertrophic scar) and they will involute over several weeks. Hyperpigmentation usually remains. Cryotherapy is also effective but will leave postinflammatory hypopigmentation in pigmented persons. Persistent individual lesions and lesions of the soles and penis respond well to local irradiation therapy (one single treatment of 80 Gy or fractionated treatments to 150 Gy). For patients with moderate disease (>10 lesions or mucosal or visceral involvement) HAART alone may not be adequate in controlling Kaposi sarcoma, and liposomal doxorubicin may need to be added to their treatment. For patients with symptomatic visceral disease, aggressive skin disease, marked edema, and pulmonary disease, systemic chemotherapy is indicated. Options include IFN-α, vinca alkaloids, bleomycin, and liposomal doxorubicin as first-line therapies and taxol for treatment failures.

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CHAPTER

20 Parasitic Infestations, Stings, and Bites

The major groups of animals responsible for bites, stings and parasitic infections in humans belong to the phyla Arthropoda, Chordata, Cnidaria (formerly Coelenterata), Nemathelminthes, Platyhelminthes, Annelida, and Protozoa. Vector-borne disease continues to be a major worldwide public health threat. Mosquito-borne diseases, such as malaria, West Nile fever, and equine encephalitis present risks for the resident population as well as travelers. Tick-borne diseases include Lyme disease, Rocky Mountain spotted fever, ehrlichiosis, tick-borne relapsing fever, tularemia, babesiosis, and Colorado tick fever. Children and those who work outdoors are at higher risk for contracting arthropod-borne diseases. Protection of children is complicated by the potential toxicity of agents used as repellents. This chapter will review parasitic diseases and the major causes of bites and stings, as well as strategies for prevention.

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PHYLUM PROTOZOA

The protozoa are one-celled organisms, divided into classes according to the nature of their locomotion. Class Sarcodina organisms move by temporary projections of cytoplasm (pseudopods); class Mastigophora by means of one or more flagella; and class Ciliata by short, hairlike projections of cytoplasm (cilia); class Sporozoa have no special organs of locomotion.

CLASS SARCODINA

The amebas are the best known organisms in this class. Of medical significance is *Entamoeba histolytica.*

Amebiasis Cutis

E. hisolytica is an intestinal parasite transmitted by the fecal–oral route or by sexual contact. Cutaneous ulcers usually result from extension of an underlying amebic abscess: the most common sites are the trunk, abdomen, buttocks, or perineum. Those on the abdomen may result from hepatic abscesses. Penile lesions are usually sexually acquired. Most lesions begin as deep abscesses that rupture and form ulcerations with distinct, raised, cordlike edges, and an erythematous halo approximately 2 cm wide. The base is covered with necrotic tissue and hemopurulent, glairy, pus-containing amebae. These lesions are from a few centimeters to 20 cm wide. Without treatment slow progression of the ulcer occurs in an increasingly debilitated patient until death ensues.

The sole manifestation of early amebiasis may be chronic urticaria.

Worldwide, an estimated 10% of the population is infected with *E. histolytica.* An estimated 10 million invasive cases occur annually, most of them in the tropics. Infection may be asymptomatic or bloody diarrhea and hepatic abscesses may be present. In the US, the disease occurs chiefly in institutionalized patients, world travelers, recent immigrants, migrant workers, and male homosexuals.

The histologic findings are those of a necrotic ulceration with many lymphocytes, neutrophils, plasma cells, and eosinophils. *E. histolytica* is found in the tissue, within blood and lymph vessels. The organism measures 50 to 60 μm in diameter, has basophilic cytoplasm, and a single eccentric nucleus with a central karyosome.

The organism is frequently demonstrable in fresh material from the base of the ulcer by direct smear. Culture of the protozoa confirms the diagnosis. Indirect hemagglutination test results remain elevated for years after the initial invasive disease's onset, whereas the results of gel diffusion precipitation tests and counterimmunoelectrophoresis become negative at 6 months; this property can be used to test for recurrent or active disease in persons coming from endemic areas.

When the perianal or perineal areas are involved, granuloma inguinale, lymphogranuloma venereum, deep mycosis, and syphilis must be considered. In chronic urticaria, fresh stool examinations by a trained technician are necessary.

The treatment of choice is metronidazole (Flagyl), 750 mg orally three times a day for 10 days. Abscesses may require surgical drainage, but there is no need for resection of lesions.

Other Ameba

Amebas of the genera *Acanthamoeba* and *Balamuthia* may also cause skin lesions in infected hosts. These organisms are ubiquitous in the environment and are found in soil, water and air. Granulomatous amebic encephalitis is the most common manifestation of infection with these amebas, nearly always in immunocompromised individuals, such as acquired immunodeficiency syndrome (AIDS) or organ transplant patients. Disseminated infection occurs and skin lesions are the most common sign, occurring in 90% of such severely ill individuals. They initially present as pink or violaceous nodules that then enlarge, suppurate, and form ulcers with a necrotic eschar (Fig. 20-1). Other findings include fever, nasal congestion or discharge, epistaxis, cough, headaches, lethargy, altered mental status, and seizures. In patients infected with acanthamoeba who have disease of the central nervous system (CNS), death is nearly universal within days to weeks. The organisms are visible on skin biopsy and culture is definitive. In patients without CNS involvement, the mortality rate is 75%, with successfully treated cases often treated with a combination of 5-flurocyosine and sulfadiazine. In patients infected with *Balamuthia mandrillaris* pentamidine is favored. Chlorhexidine topically and surgical debridement are local adjunctive measures which may prove beneficial.

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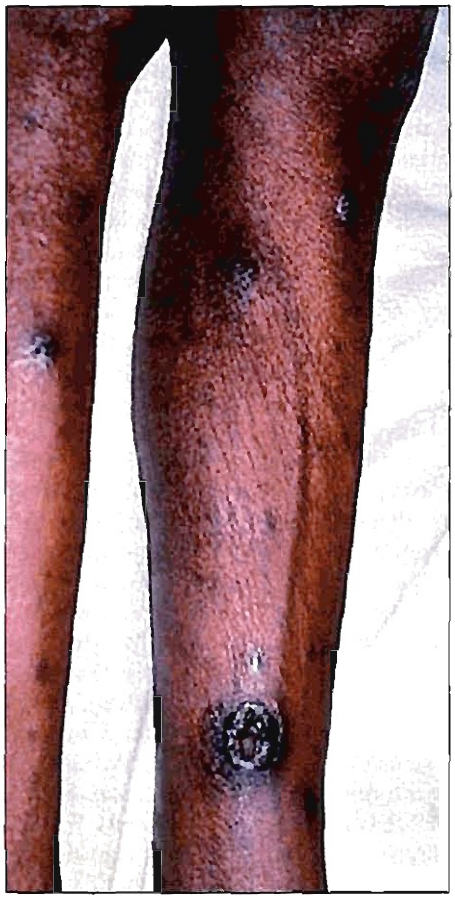

Fig. 20-1
Disseminated acanthomeba in HIV disease.

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CLASS MASTIGOPHORA

Organisms belonging to this class are known as *flagellates*. Many have an undulating membrane with flagella along their crest.

Trichomoniasis

Trichomonas vulvovaginitis is a common cause of vaginal pruritus, with burning and a frothy leukorrhea. The vaginal mucosa appears bright red from inflammation and may be mottled with pseudomembranous patches. The male urethra may also harbor the organism; in the male it causes urethritis and prostatitis. Occasionally, men may develop balanoposthitis. Erosive lesions on the glans and penis or abscesses of the median raphae may occur. Neonates may acquire the infection during passage through the birth canal, but they require treatment only if symptomatic or colonization lasts more than 4 weeks. As this is otherwise nearly exclusively a sexually-transmitted disorder (STD), trichomonas vulvovaginitis in a child should prompt suspicion of sexual abuse.

Trichomoniasis is caused by *Trichomonas vaginalis*, a colorless pyriform flagellate 5 to 15 μm long. *T. vaginalis* is demonstrated in smears from affected areas. Testing by direct immunofluorescence is sensitive and specific.

Metronidazole, 2 g in a single oral dose, is the treatment of choice. Alternatively, 500 mg twice a day for 7 days may be given. Patients should be warned not to drink alcohol for 24 h after the last dose because of the disulfiram type of effects of this medication. Male sex partners should also be treated. The use of metronidazole is contraindicated in pregnant women, and clotrimazole, applied intravaginally, at a dosage of 100 mg a night for 2 weeks may be used in instead.

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Leishmaniasis

Cutaneous leishmaniasis, American mucocutaneous leishmaniasis, and visceral leishmaniasis (kala-azar), which includes infantile leishmaniasis and post–kala-azar dermal leishmaniasis, are all caused by morphologically indistinguishable protozoa of the family Trypanosomidae, called *Leishmania* (pronounced leesh-may-nea). The clinical features of these diseases differ and they have, in general, different geographic distributions. The reason for the variable clinical manifestations may reside with diversity of the organism, the immune status of the patient, and the genetic ability to initiate effective cell-mediated immune response to the specific infecting organism. It is known that the antigen-specific T-cell responses, which lead to the production of interferon (IFN) and

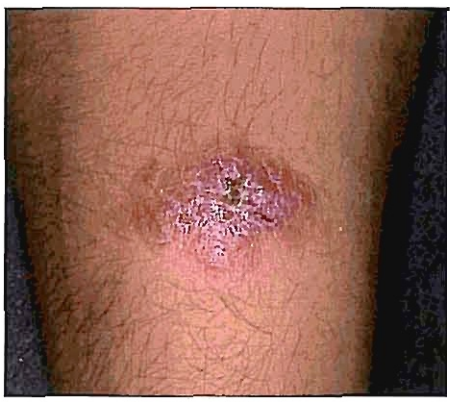


Fig. 20-2 Old World leishmaniasis.

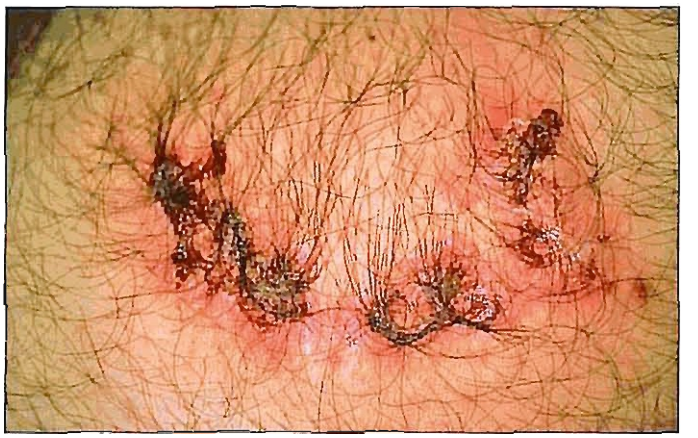


Fig. 20-3 Leishmaniasis recidivans.

interleukin (IL)-12, are important for healing of the lesions and the induction of lifelong, species-specific immunity to reinfection which results after natural infection.

Cutaneous Leishmaniasis There are several types of lesions. All tend to occur on exposed parts as all are transmitted by the sandfly. Old World leishmaniasis manifests mainly in the skin and has also been called *Baghdad boil*, *Oriental sore*, *leishmaniasis tropica*, *Biskra button*, *Delhi boil*, *Aleppo boil*, *Kandahar sore*, and *Lahore sore*. Mild visceral disease may occur. Skin lesions of New World infection have been termed *uta*, *pian bois*, and *bay sore* or *chiclero ulcer*.

Clinical Features

In Old World leishmaniasis lesions may present in two distinct type. One is the moist or rural type, a slowly growing, indurated, livid, indolent papule (Fig. 20-2), which enlarges in a few months to form a nodule that may ulcerate in a few weeks to form an ulcer as large as 5 cm in diameter. Spontaneous healing usually takes place within 6 months, leaving a characteristic scar. This type is contracted from rodent reservoirs such as gerbils via the sandfly vector. The incubation period is relatively short—1 to 4 weeks. The dry or urban type has a longer incubation period (2–8 months or longer), develops much more slowly, and heals more slowly than the rural type.

Rarely, after the initial or "mother" lesion is healed, at the borders of the healed area, a few soft red papules may appear that are covered with whitish scales and have the "apple jelly" characteristics of granulomatous diseases such as lupus vulgaris. These spread peripherally on a common erythematous base and are the lupoid type. This is also known as *leishmaniasis recidivans* (Fig. 20-3) and occurs most commonly with the urban type of disease, caused by *Leishmania tropica*. New World disease may also induce purely cutaneous lesions, of varied morphology. The primary papule may become nodular, verrucous, furuncular, or ulcerated, with an infiltrated red border (Fig. 20-4). Subcutaneous peripheral nodules, which eventually ulcerate, may signal extension of the disease. A linear or radial lymphangitic (sporotrichoid) pattern may occur with lymphadenopathy, and the nodes may rarely yield organisms. Recidivans lesions are unusual in the New World form of disease. In Yucatan and Guatemala, a subtype of New World disease exists: the chiclero ulcer. The most frequent site of infection is the ear (Fig. 20-5). The lesions ulcerate and occur most frequently in workers who harvest chicle for chewing gum in forests, where there is high humidity. This form is a more chronic ulcer that may persist for years, destroying the ear cartilage and leading to deformity. The etiologic agent is *Leishmania mexicana* and the sandfly vector, *Lutzomyia flaviscutellata*.

Uta is a term used by Peruvians for leishmaniasis occurring in mountainous territory at 1200 to 1800 m above sea level. The ulcerating lesions are found on exposed sites and mucosal lesions do not occur.

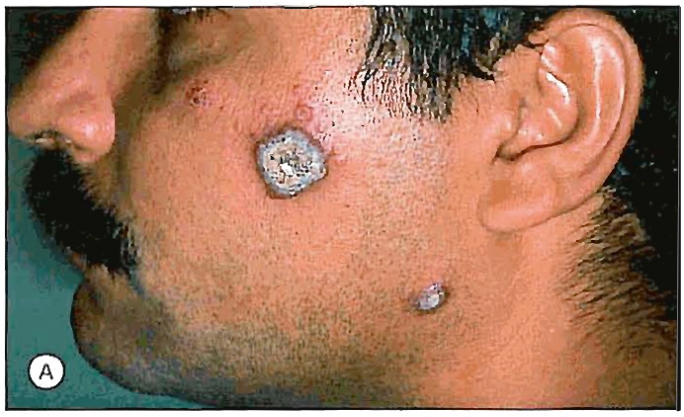
Disseminated cutaneous leishmaniasis may be seen in both New and Old World disease. Multiple nonulcerated papules and plaques, chiefly on exposed surfaces, characterize this type (Fig. 20-6). The disease begins with a single ulcer, nodule, or plaque from which satellite lesions may develop and disseminate to cover the entire body. The disease is progressive and treatment is usually ineffective. It is characterized by anergy to the organism. This type of leishmaniasis must be differentiated from lepromatous leprosy, xanthoma tuberosum, paracoccidioidal granuloma, Lobo's disease, and malignant lymphoma.

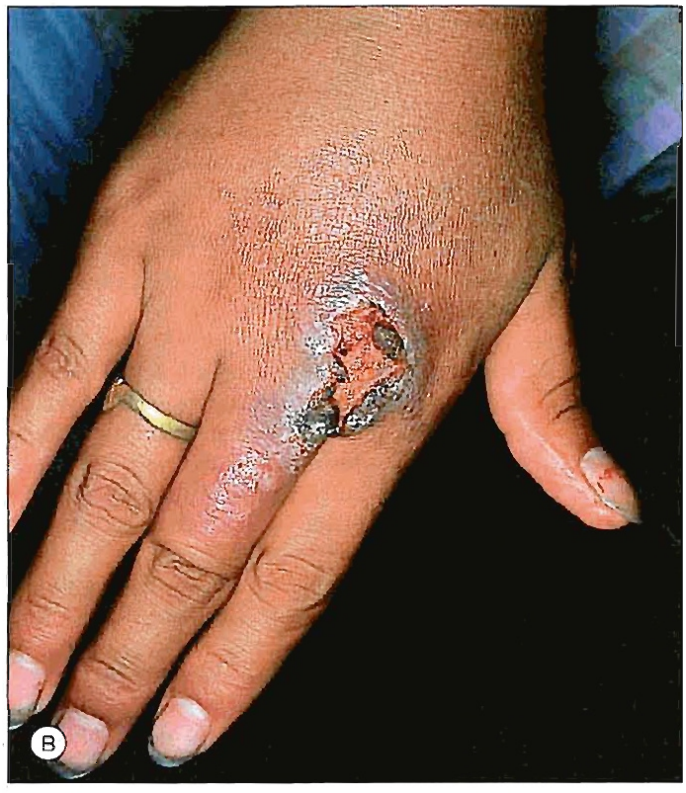
Etiologic Factors

L. tropica, *Leishmania major*, *Leishmania aethiopia*, and *Leishmania infantum*, the cause of Mediterranean visceral leishmaniasis, may cause cutaneous leishmaniasis. Purely cutaneous leishmaniasis is also caused by several species present in the New World. *L. mexicana* does not induce mucosal disease. *Leishmania braziliensis guyanensis* produces cutaneous disease, as does *Leishmania braziliensis braziliensis* and *Leishmania braziliensis panamensis*; however, the latter two may also result in mucocutaneous disease.

Epidemiology

Cutaneous leishmaniasis is endemic in Asia Minor and to a lesser extent in many countries around the Mediterranean. Iran and Saudi Arabia have a high occurrence rate. In endemic areas, deliberate inoculation on the thigh is sometimes practiced so that scarring on the face—a frequent site for Oriental sore—may be avoided. Purely cutaneous lesions may also be found in the Americas. In the US, leishmaniasis is largely restricted to South Texas, although rare reports of human cutaneous disease have occurred as far north as Pennsylvania, and visceral leishmaniasis in immunosuppressed humans is being recognized as an emerging infection in areas not previously thought to be endemic for the disease.





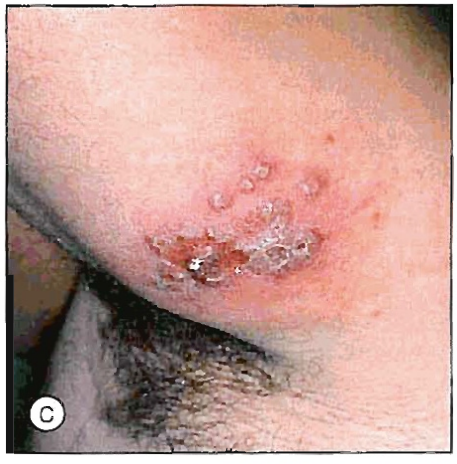


Fig. 20-4 *A–C*, New World leishmaniasis.

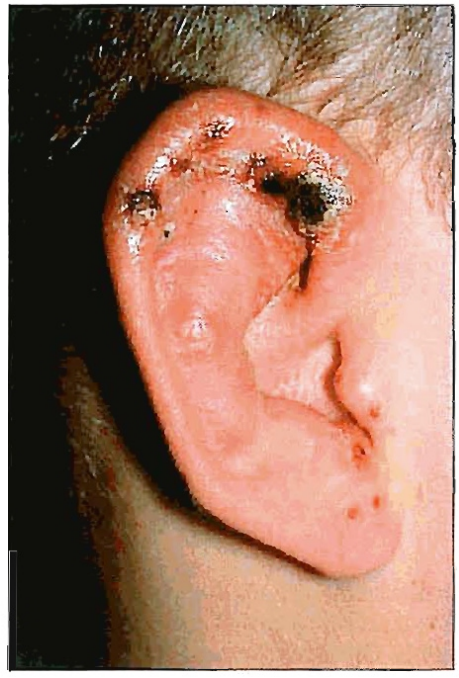


Fig. 20-5 Chiclero ulcer in leishmaniasis.

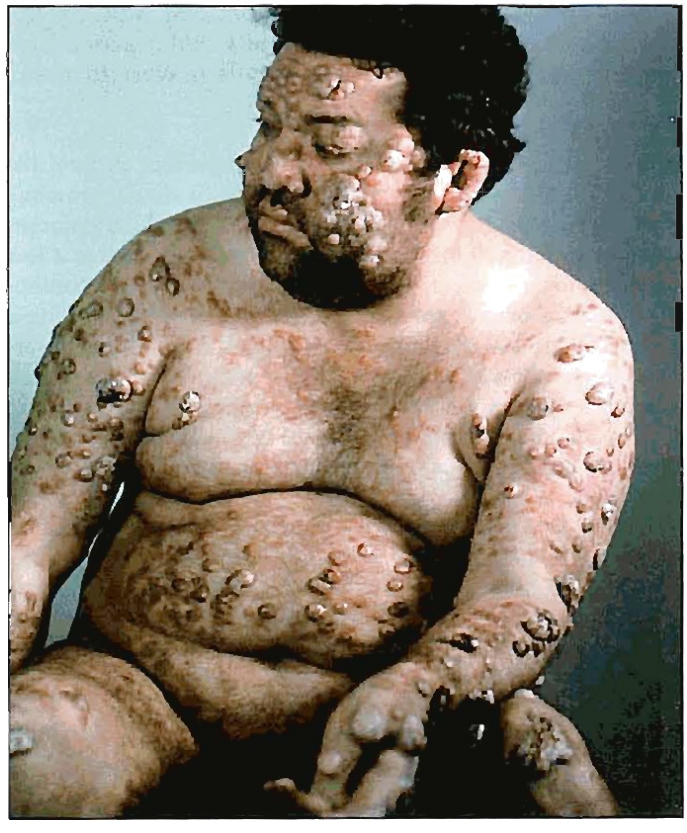


Fig. 20-6 Disseminated cutaneous leishmaniasis.

Pathogenesis

The organism has an alternate life in vertebrates and in insect hosts. Man and other mammals, such as dogs and rodents, are the natural reservoir hosts. The vector hosts are *Phlebotomus* sandflies for the Old World type and *Phlebotomus perniciosus* and *Lutzomyia* sandflies for the New World cutaneous leishmaniasis. After the insect has fed on blood, the flagellates (leptomonad, promastigote) develop in the gut in 8 to 20 days, after which migration occurs into the mouth parts; from here transmission into humans occurs by a bite. In humans, the flagella are lost and a leishmanial form (amastigote) is assumed.

Histopathology

An ulcer with a heavy infiltrate of histiocytes, lymphocytes, plasma cells, and polymorphonuclear leukocytes is seen. The parasitized histiocytes form tuberculoid granulomas in the dermis. Pseudoepitheliomatous hyperplasia may occur in the edges of the ulcer. Numerous organisms are present (mostly in histiocytes), which are nonencapsulated and contain a nucleus and a paranucleus. Wright, Giemsa, and monoclonal antibody staining may be helpful in identifying the organisms. Polymerase chain reaction (PCR) primers are available for a variety of species. The organisms are seen within histiocytes and often line up at the periphery of a vacuole like the bulbs surrounding a movie marquee.

Diagnosis

In endemic areas, the diagnosis is not difficult. In other localities, cutaneous leishmaniasis may be confused with syphilis, yaws, lupus vulgaris, and pyogenic granulomas. The diagnosis is established by demonstration of the organism in smears. A punch biopsy specimen from the active edge of the ulcer is ideal for culture. It can be placed in Nicolle-Novy-MacNeal (NNN) medium and shipped at room temperature. Parasites can also be cultured from tissue fluid. A hypodermic needle is inserted into the normal skin and to the edge of the ulcer base. The needle is rotated to work loose some material and serum, which is then aspirated. A culture on NNN medium at 22° to 35° C (71.6–95° F) is recommended to demonstrate the leptomonads. As expected, PCR is the most sensitive diagnostic test for cutaneous leishmaniasis.

Treatment

Spontaneous healing of primary cutaneous lesions occurs, usually within 12 to 18 months, shorter for Old World disease. The rationale of treating an ordinarily self-limited infection include avoiding disfiguring scars in exposed areas, notably the face; avoiding secondary infection; controlling disease in the population; and failure of spontaneous healing: in the diffuse cutaneous and recidivans types, the disease may persist for 20 to 40 years if not treated.

In areas in which localized cutaneous leishmaniasis is not complicated by recidivans or sporotrichoid forms, or mucocutaneous disease, treatment with such topical modalities as paromycin sulfate 15% plus methylbenzethonium chloride 12%, ketoconazole cream under occlusion, cryotherapy, local heat, and laser ablation, or with intralesional sodium stibogluconate antimony or emetine hydrochloride, may be effective and safe. Perilesional injections of IFN-γ have also been reported to be effective but are expensive.

In patients who are immunosuppressed or who acquire disease in areas where mucocutaneous disease may occur, systemic therapy is recommended. As with topical treatment, many alternatives have been reported effective. Sodium antimony gluconate (sodium stibogluconate) solution is given intramuscularly or intravenously 20 mg/kg/day in two divided doses for 28 days. It can be obtained from the CDC Drug Service (Atlanta, GA 30333). Repeated courses may be given. Antimony *n*-methyl glutamine (Glucantime) is used more often in Central and South America because of its local availability.

Other systemic medications reported to be effective include fluconazole (200 mg per day for six weeks), ketoconazole, dapsone, rifampicin, and allopurinol. Some of these have not been subjected to controlled clinical trials, as is true of most topical treatments. The recidivans and disseminated cutaneous types may require prolonged courses or adjuvant IFN therapy. Amphotericin B may be used in antimony-resistant disease. Lipid formulations of amphotericin B are highly effective in short courses but are expensive.

Control depends chiefly on the success of antifly measures taken by health authorities and personal protection with protective clothing, screening, and repellents. Vaccines are being investigated but are not available.

Mucocutaneous Leishmaniasis (Leishmaniasis Americana, Espundia)

Clinical Features

The initial infection, which occurs at the site of the fly bite, is a cutaneous ulcer. Secondary lesions on the mucosa usually occur at some time during the next 5 years (Fig. 20-7). The earliest mucosal lesion is usually hyperemia of the nasal septum with subsequent ulceration, which progresses to invade the septum and later the paranasal fossae. Perforation of the septum eventually takes place. For some time the nose remains unchanged externally, despite the internal destruction.

At first only a dry crust is observed, or a bright red infiltration or vegetation on the nasal septum, with symptoms of obstruction and small hemorrhages. Despite the mutilating and destructive character of leishmaniasis, it never involves the nasal bones. When the septum is destroyed, the nasal

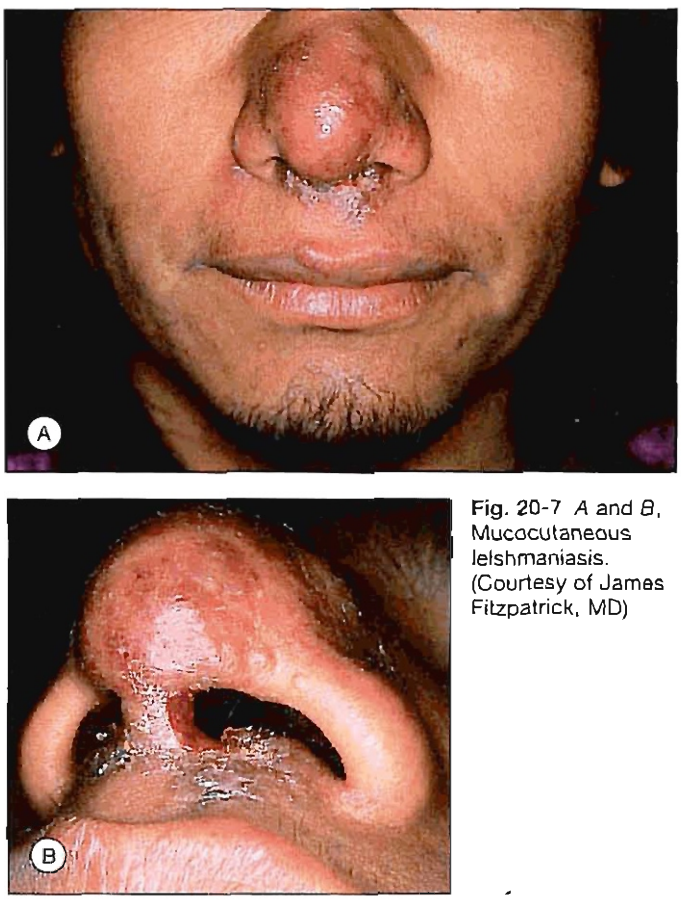


Fig. 20-7 *A* and *B*, Mucocutaneous leishmaniasis. (Courtesy of James Fitzpatrick, MD)

bridge and tip of the nose collapse, giving the appearance of a parrot beak, camel nose, or tapir nose.

It is important to recall that the four great chronic infections (syphilis, tuberculosis, leprosy, and leishmaniasis) have a predilection for the nose. The ulcer may extend to the lips (Fig. 20-8) and continue to advance to the pharynx, attacking the soft palate, uvula, tonsils, gingiva, and tongue. The eventual mutilation is called *espundia*. Two perpendicular grooves at the union of the osseous palate and soft tissues, in the midst of the vegetative infiltration of the entire pharynx, is called the *palate cross of espundia*.

Only in exceptional cases does American leishmaniasis invade the genital or ocular mucous membranes. The frequency of mucous membrane involvement is variable. In Yucatan and Guatemala it is an exception; in other countries, such as Brazil, it may occur in 80% of cases.

Etiologic Factors

Mucocutaneous leishmaniasis is caused by *L. braziliensis braziliensis* and *L. braziliensis panamensis*. Leishmania has two forms, the nonflagellated form or leishmania, which is found in the tissues of humans and animals susceptible to the inoculation of the parasite, and the flagellated form or leptomonad, which is found in the digestive tract of the vector insect (*Lutzomyia* in mucocutaneous disease) and in cultures. The typical morphology of leishmania, as found in vertebrates, is round or oval, usually with one extremity more rounded than the other, measuring 2 to 4 μm × 1.5 to 2.5 μm, with cytoplasm, nucleus, and blepharoplast or kinetoplast.

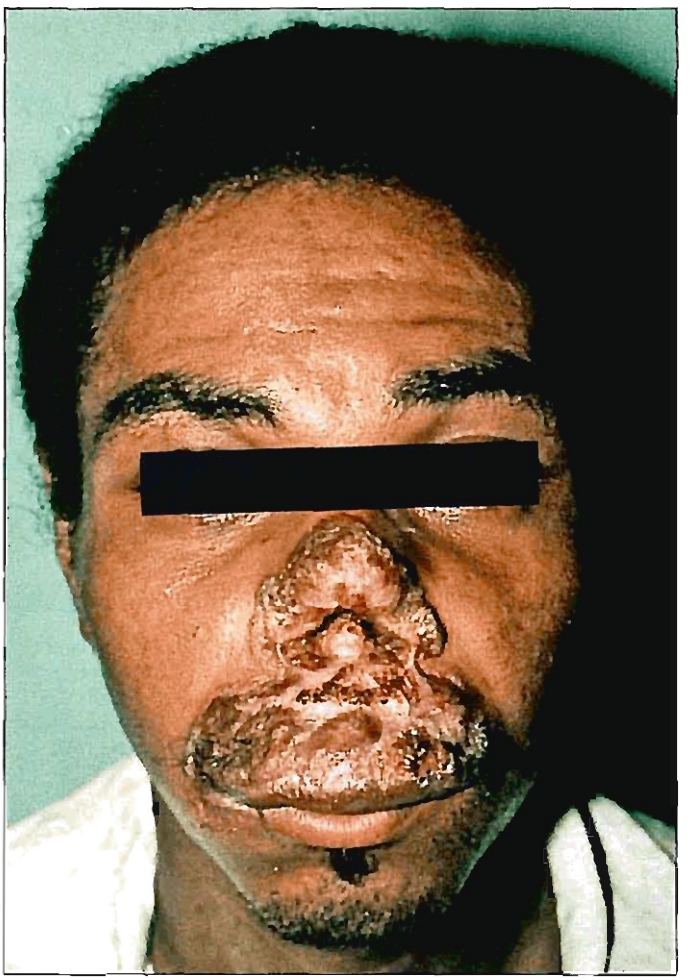


Fig. 20-8 Severe destructive mucocutaneous leishmaniasis. (Courtesy of Debra Kalter, MD)

Epidemiology

Mucocutaneous leishmaniasis is predominantly a rural and jungle disease. It most often occurs in damp and forested regions. The disease can be contracted at any time of the year, but the risk is highest just after the rainy season. All ages and races, and both sexes are equally affected.

Histopathology

In the ulcerous type, marked irregular acanthosis and sometimes pseudoepitheliomatous hyperplasia can be found. The dermis shows a dense infiltration of histiocytes, lymphocytes, and plasma cells. In new lesions some neutrophils are observed. Large Langerhans giant cells or typical tubercles are occasionally seen. Numerous organisms are present (mostly in histiocytes), which are nonencapsulated and contain a nucleus and a paranucleus. Wright, Giemsa, and monoclonal antibody staining may be helpful in identifying the organisms. In patients with granulomatous infiltrates containing intracellular parasites within histiocytes, leishmaniasis is one of several diseases to be considered, including rhinoscleroma, histoplasmosis, granuloma inguinale, Chagas' disease, *Penicillium marneffei* infection, and toxoplasmosis. Touch smears stained with Giemsa are helpful in many cases of cutaneous and mucocutaneous leishmaniasis.

Laboratory Findings

Leishmania is demonstrated in the cutaneous and mucous membrane lesions by direct smears or cultures. In biopsy material stained with Wright stain, intracellular and extracellular organisms are seen with typical morphology of two chromatic structures: nucleus and parabasal body. In later mucosal lesions the scarcity of parasites makes the identification difficult. The culture is done on NNN medium for leptomonads.

Prophylaxis

Although it is impractical to eliminate the insect vector, it is still the only valid measure for the control of this prevalent disease. Effective vaccines are not available.

Treatment

Treatment is the same as described for cutaneous leishmaniasis except that antimony resistance is common in mucocutaneous disease. Combination therapy using antimonials with drugs such as rifampin or azithromycin, or adding immunomodulators such as IFN-γ, IL-2, or imiquimod may result in cure. Amphotericin B treatment may be necessary.

Visceral Leishmaniasis (Kala-Azar, Dumdum Fever)

Clinical Features

The earliest lesion is the cutaneous nodule or leishmanioma, which occurs at the site of the initial sandfly inoculation. *Kala-azar*, meaning "black fever," acquired its name because of the patchy macular darkening of the skin caused by deposits of melanin that develop in the later course of the

disease. These patches are most marked over the forehead and temples, periorally, and on the midabdomen.

The primary target for the parasites is the reticuloendothelial system; the spleen, liver, bone marrow, and lymph nodes are attacked. The incubation period is 1 to 4 months. An intermittent fever, with temperatures ranging from 39° to 40° C (102–104° F) ushers in the disease. There are hepatosplenomegaly, agranulocytosis, anemia, and thrombocytopenia. Chills, fever, emaciation, weight loss, weakness, epistaxis, and purpura develop as the disease progresses. Susceptibility to secondary infection may produce pulmonary and gastrointestinal infection, ulcerations in the mouth (cancrum oris), and noma. Death occurs about 2 years from onset in untreated individuals.

Most infections are subclinical or asymptomatic. In patients with AIDS, papular and nodular skin lesions may occur. Dermatofibroma-type or Kaposi sarcoma-like brown to purple nodules are most commonly reported, although random biopsies of normal skin will reveal organisms; therefore, clinical correlation is necessary to attribute skin findings to leishmania specifically.

Etiologic Factors

L. donovani spp. *donovani, infantum*, and *chagasi*, cause visceral leishmaniasis and are parasites of rodents, canines, and humans. They are nonflagellate oval organisms some 3 μm in diameter, known as *Leishman-Donovan bodies*. In the sandfly it is a leptomonad form with flagella.

Epidemiology

L.d. donovani causes visceral leishmaniasis in India, with the major reservoir being humans and the vector being *Phlebotomus argentipes*. *L.d. infantum* occurs in China, Africa, the Near East and Middle East, and the Mediterranean littoral, where the major reservoirs are dogs, and *Phlebotomus perniciosus* and *Phlebotomus ariasi* are the vectors of the Mediterranean type. American visceral leishmaniasis is caused by *L. donovani chagasi* and is transmitted by the sandfly *Lutzomyia longipalpis*. American visceral leishmaniasis principally affects domestic dogs, although explosive outbreaks of the human infection occur sporadically, when the number of *L. longipalpis* builds up to a high level in the presence of infected dogs. Canine visceral infections with *L. infantum* have been reported in foxhounds in northern states and Canada.

Diagnosis

Leishman-Donovan bodies may be present in the blood in individuals with kala-azar of India. Specimens for examination, in descending order of utility, include spleen pulp, sternal marrow, liver tissue, and exudate from lymph nodes. Culturing on NNN medium may also reveal the organisms.

Treatment

General supportive measures are essential. Pentavalent antimony has long been the drug of choice. In areas of drug resistance, amphotericin B is usually effective, but expensive, toxic and it requires intravenous administration. Miltefosine is an oral alkyl-phosphocholine analog that has proven as effective as amphotericin B in Indian trials, and is being investigated in other regions and other populations.

Post-Kala-Azar Dermal Leishmaniasis In kala-azar, the leishmanoid (amastigote) forms may be widely distributed throughout apparently normal skin. During and after recovery from the disease, a special form of dermal leishmaniasis known as post-kala-azar dermal leishmaniasis appears. This condition appears during or shortly after treatment in the African form, but its appearance may be delayed up to 10 years after treatment in the Indian form. It follows the treatment of visceral leishmaniasis in 50% of Sudanese patients and 5% to 10% of those seen in India. There are two constituents of the eruption: a macular, depigmented eruption found mainly on the face, arms, and upper part of the trunk; and a warty, papular eruption in which amastigotes can be found. Because it may persist for up to 20 years, these patients may act as a chronic reservoir of infection. This condition closely resembles leprosy. High concentrations of IL-10 in the blood of visceral leishmaniasis patients predict those who will be affected by post-kala-azar dermal leishmaniaisis.

Viscerotropic Leishmaniasis Twelve soldiers developed systemic infection with *L. tropica* while fighting in Operation Desert Storm in Saudi Arabia. None had symptoms of kala-azar, but most had fever, fatigue, malaise, cough, diarrhea, or abdominal pain. None had cutaneous disease. Diagnostic tests yielded positive results on bone marrow aspiration; lymph node involvement was also documented. Treatment with sodium stibogluconate led to improvement.

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Human Trypanosomiasis

Three species of trypanosomes are pathogenic to humans: *Trypanosoma gambiense* and *Trypanosoma rhodesiense* in Africa, and *Trypanosoma cruzi* in America. The skin manifestations are usually observed in the earlier stages of the disease as evanescent erythema, erythema *multiforme*, and edema, especially angioedema.

In the early stage of African trypanosomiasis, a trypanosome chancre may occur at the site of a tsetse fly bite. Then erythema with circumscribed swellings of angioedema, enlargement of the lymph nodes, fever, malaise, headache, and joint pains ensue. In the West African (Gambian) form, the illness is chronic, lasting several years, with progressive deterioration, whereas the East African (Rhodesian) form is an acute illness, with a stormy, fatal course of weeks to months. The Rhodesian form is more often associated with cutaneous signs. Annular or deep erythema nodosum-like lesions are frequent manifestations (Fig. 20-9). Lymphadenopathy is generalized, but frequently there is a pronounced enlargement of the posterior cervical group (Winterbottom's sign).

In American trypanosomiasis (Chagas' disease), similar changes take place in the skin. The reduviid bug *(kissing bug, assassin bug)* (Fig. 20-10) usually bites at night, frequently at mucocutaneous junctions, where the bug's infected feces are deposited when it feeds. The unsuspecting sleeping person rubs the feces into the bite and becomes infected. If the bite of the infected bug occurs near the eye, Romana's sign develops; this consists of unilateral conjunctivitis and edema of the eyelids, with an ulceration or chagoma in the area. The bite of a "kissing bug" becomes markedly swollen and red, whether trypanosomes are involved or not. Acute Chagas' disease is usually a mild illness consisting of fever, malaise, edema of the face and lower extremities, and generalized lymphadenopathy. Skin lesions occurring in this phase include nodules at the site of inoculation, disseminated nodules or morbilliform and urticarial lesions. In chronic Chagas' disease, which occurs in 10% to 30% of infected persons years to decades later, the heart (myocarditis, arrhythmias, thromboembolism, and cardiac failure) and the gastrointestinal system (megaesophagus and megacolon) are the most commonly involved organs. During the remaining infected but asymptomatic indeterminate phase patients may transmit the disease through transfusion. When such patients become immunosuppressed (with AIDS or organ transplantation) reactivation skin lesions may occur.

Rhodesian trypanosomiasis is endemic among the cattle-raising tribes of East Africa, with the savannah habitat of the vectors determining its geographic distribution. Wild game and livestock are reservoir hosts, in addition to humans. The tsetse fly, *Glossina morsitans*, is the principal vector.

For Gambian trypanosomiasis, humans are the only vertebrate host and the palpalis group of tsetse flies is the invertebrate host. These flies are found close to the water, and their fastidious biologic requirements restrict their dis-

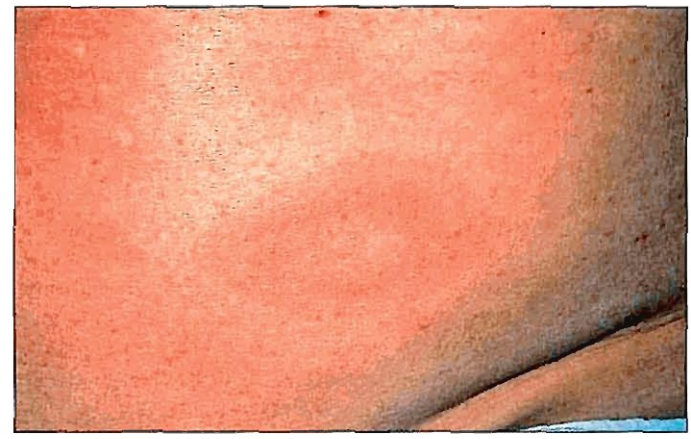

Fig. 20-9 African trypanosomiasis. (Courtesy of James Fitzpatrick, MD)

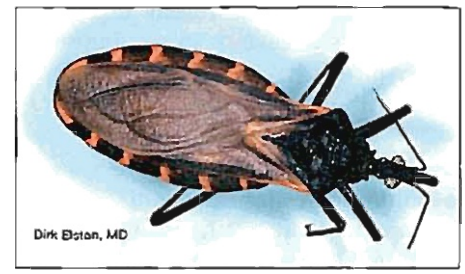

Fig. 20-10 Triatome reduviid bug.

tribution, and thus that of the disease. Incidence is seasonal, with humidity and temperature being determining factors. The highest incidence is in males aged 20 to 40 years in tropical areas of West and Central Africa.

Chagas' disease is prevalent in Central and South America from the US to Argentina and Chile; the highest incidence is in Venezuela, Brazil, Uruguay, Paraguay, and Argentina. Approximately 29% of all male deaths in the 29- to 44-year-old age group in Brazil are ascribed to Chagas' disease.

Before CNS involvement has occurred in the Rhodesian form, suramin, a complex, non–metal-containing, organic compound, is the treatment of choice. When the CNS is involved, melarsoprol is the drug of choice. Pentamidine isethionate is the drug of choice for the Gambian disease. For American trypanosomiasis, treatment is of limited efficacy. Nifurtimox and benzimidazole clear the parasitemia and reduce the severity of the acute illness. There is a high incidence of adverse effects, however. Conservative treatment is most appropriate for the patient with congestive heart failure from Chagas myocarditis. Gastrointestinal complications may be treated surgically.

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CLASS SPOROZOA

Toxoplasmosis

Toxoplasmosis is a zoonosis caused by a parasitic protozoan, *Toxoplasma gondii*. Infection may be either congenital or acquired. Congenital infection occurs from placental transmission. Abortion or stillbirth may result. However, a full-term child delivered to an infected mother may have a triad of hydrocephalus, chorioretinitis, and cerebral calcification. In addition, there may be hepatosplenomegaly and jaundice. Skin changes in toxoplasmosis are rare and clinically nonspecific.

In congenital toxoplasmosis, macular and hemorrhagic eruptions predominate. Blueberry muffin lesions, reflecting dermatoerythropoesis, may be seen. Occasionally, abnormal hair growth and exfoliative dermatitis have also been observed. The differential diagnosis of congenital toxoplasmosis is the TORCH syndrome (toxoplasmosis, rubella, cytomegalovirus, and herpes simplex). In acquired toxoplasmosis, early skin manifestations consist of cutaneous and subcutaneous nodules, and macular, papular, and hemorrhagic eruptions. These may be followed by scarlatiniform desquamation, eruptions mimicking roseola, erythema multiforme, dermatomyositis or lichen planus, as well as exfoliative dermatitis. As a rule, the exanthem is accompanied by high fever and general malaise.

Diagnosis of acquired toxoplasmosis is of special importance to three groups of adults: healthy pregnant women concerned about recent exposure; adults with lymphadenopathy, fever, and myalgia, who might have some other serious disease, such as lymphoma; and immunocompromised persons, such as patients with AIDS, in whom toxoplasmosis might be fatal. It is the most common cause of focal encephalitis in patients with AIDS and this may be accompanied by a widespread papular eruption.

Toxoplasma gondii is a crescent-shaped, oval, or round protozoan that can infect any mammalian or avian cell. The disease is often acquired through contact with animals, particularly cats. Reservoirs of infection have been reported in dogs, cats, cattle, sheep, pigs, rabbits, rats, pigeons, and chickens. The two major routes of transmission of *T. gondii* in humans are oral and congenital. Meats consumed by humans may contain tissue cysts, thus serving as a source of infection when eaten raw or undercooked. There is no evidence of direct human-to-human transmission, other than from mother to fetus.

The diagnosis cannot be made on clinical grounds alone. It may be established by isolation of *T. gondii*, demonstration of the protozoa in tissue sections, smears, or body fluids by Wright or Giemsa stain; characteristic lymph node histology; and serologic methods.

A combination of pyrimethamine (Daraprim) and sulfadiazine act synergistically and form an effective treatment. Dosages and total treatment time vary according to the age and immunologic competence of the infected patient.

Baggett K, et al: Tender nodules on the legs of a cardiac transplant recipient. Arch Dermatol 2000;136:791.

Fine JD, et al: The TORCH syndrome. J Am Acad Dermatol 1985;12:697.

Hirschmann JV, et al: Skin lesions with disseminated toxoplasmosis in a patient with AIDS. Arch Dermatol 1988; 124:1446.

PHYLUM CNIDARIA

The cnidarians include the jellyfish, hydroids, Portuguese man-of-war, corals, and sea anemones. These are all radial marine animals, living mostly in ocean water. When a swimmer's skin contacts these organisms, they release a toxin through small spicules.

Portuguese Man-of-War Dermatitis

Stings by the Portuguese man-of-war (*Physalia physalis* in the Atlantic, or the much smaller *Physalia utriculus* or "bluebottle" in the Pacific) are characterized by linear lesions that are erythematous, urticarial, and even hemorrhagic. The forearms, sides of the trunk, thighs, and feet are common sites of involvement. The usual local manifestation is sharp, stinging, and intense pain. Internally there may be severe dyspnea, prostration, nausea, abdominal cramps, lacrimation, and muscular pains. Death may occur if the areas stung are large in relation to the patient's size.

The fluid of the nematocysts contains toxin that is carried into the victim through barbs along the tentacle. The venom is a neurotoxic poison that can produce marked cardiac changes.

Each Portuguese man-of-war is a colony of symbiotic organisms consisting of a blue to red float or pneumatophore with a gas gland, several gastrozooids measuring 1 to 20 mm, reproductive polyps, and the fishing tentacles bearing the

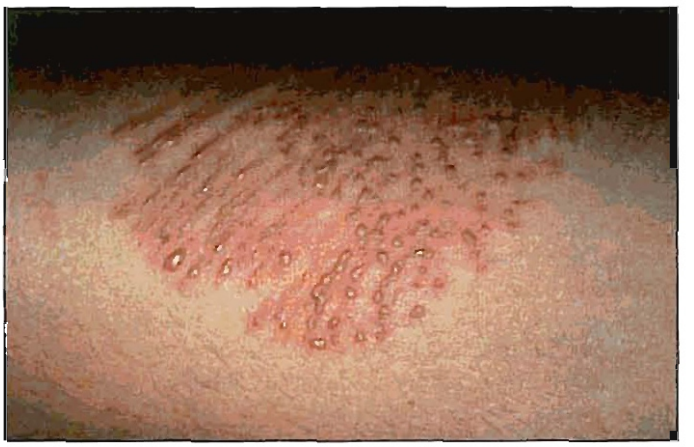


Fig. 20-11 Jellyfish sting. (Courtesy of Anthony Slagel, MD)

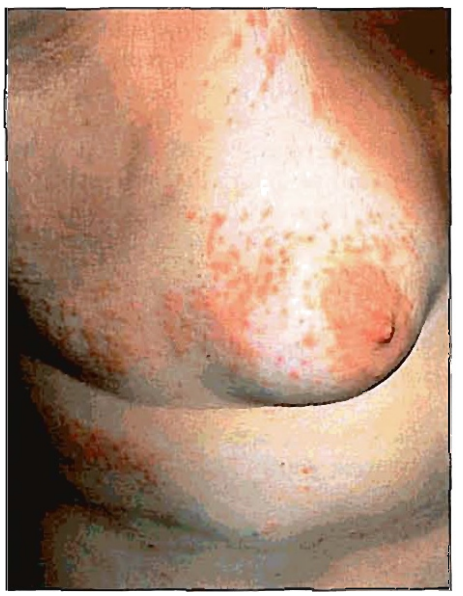


Fig. 20-12 Seabather's eruption.

Fig. 20-13 Sea anemone.

nematocysts from which the barbs are ejected. The hydroid is found most frequently along the southeastern Florida coastline and in the Gulf of Mexico, and on windward coasts throughout the mid-Pacific and South Pacific.

Jellyfish Dermatitis

This produces lesions similar to those of the Portuguese man-of-war, except that the lesions are not so linear (Fig. 20-11). Immediate allergic reactions occur infrequently as urticaria, angioedema or anaphylaxis. Delayed and persistent lesions also rarely occur.

The Australian sea wasp, *Chironex fleckeri*, which is colorless and transparent, is the most dangerous of all, with a sting that is often fatal. Another sea wasp, *Carybdea marsupialis*, much less dangerous, occurs in the Caribbean.

Seabather's eruption is an acute dermatitis that begins a few hours after bathing in the waters along the coast of the Atlantic. It affects covered areas of the body as Cnidarian larvae become entrapped under the bathing suit and the nematocyst releases its toxin because of external pressure. Thus, the buttocks and waist are affected primarily, with the breast also involved in women (Fig. 20-12). Erythematous macules and papules appear and may develop into pustules or vesicles. Urticarial plaques are also present in a smaller number of patients. Crops of new lesions may occur for up to 72 h, and the eruption persists for 10 to 14 days on average. It is quite pruritic.

Outbreaks in Florida are usually caused by larvae of the thimble jellyfish *Linuche unguiculata* which patients report as "black dots" in the water or their bathing suits. The larvae of the sea anemone *Edwardstella lineata* caused one epidemic of seabather's eruption in Long Island, New York. This organism also has nematocysts; thus, the mechanism of the eruption is the same as with the jellyfish-induced eruption. It is likely that different cnidarian envenomations in different waters produce a similar clinical picture. Other reports focus on spring plants, dinoflagellates, protozoans, or crustaceans as potential causes. Since trapping of cnidarian larvae with their nematocysts or other toxic or irritant substances under the bathing suit accounts for this eruption, seabathers who take off their bathing suit and shower soon after leaving the water may limit it.

Hydroid, Sea Anemone, and Coral Dermatitis

Patients contacting the small marine hydroid *Halecium* may develop a dermatitis. The organism grows as a centimeter-thick coat of moss on the submerged portions of vessels or pilings. Sea anemones (Fig. 20-13) produce reactions similar to those from jellyfish and hydroids. Coral cuts (Fig. 20-14) are injuries caused by the exoskeleton of the corals, Milleporina. They have a reputation for becoming inflamed and infected, and for delayed healing. The combination of implantation of fragments of coral skeleton and infection (since the cuts occur most commonly on the feet) probably accounts almost entirely for these symptoms. Detoxification as soon as possible after the injury is advisable for all these types of stings or cuts.

Treatment of Stings and Cuts

Hot water immersion may be an effective remedy for many stings, but scald injuries must be avoided. Undischarged nematocytes may be removed with sea water, but never with fresh water, as this may cause them to discharge. Pacific *Chironex* (box jellyfish) nematocytes should always be inactivated with 5% acetic acid (vinegar) when it is available, but pacific *Physalia* (blue bottle) nematocytes may discharge

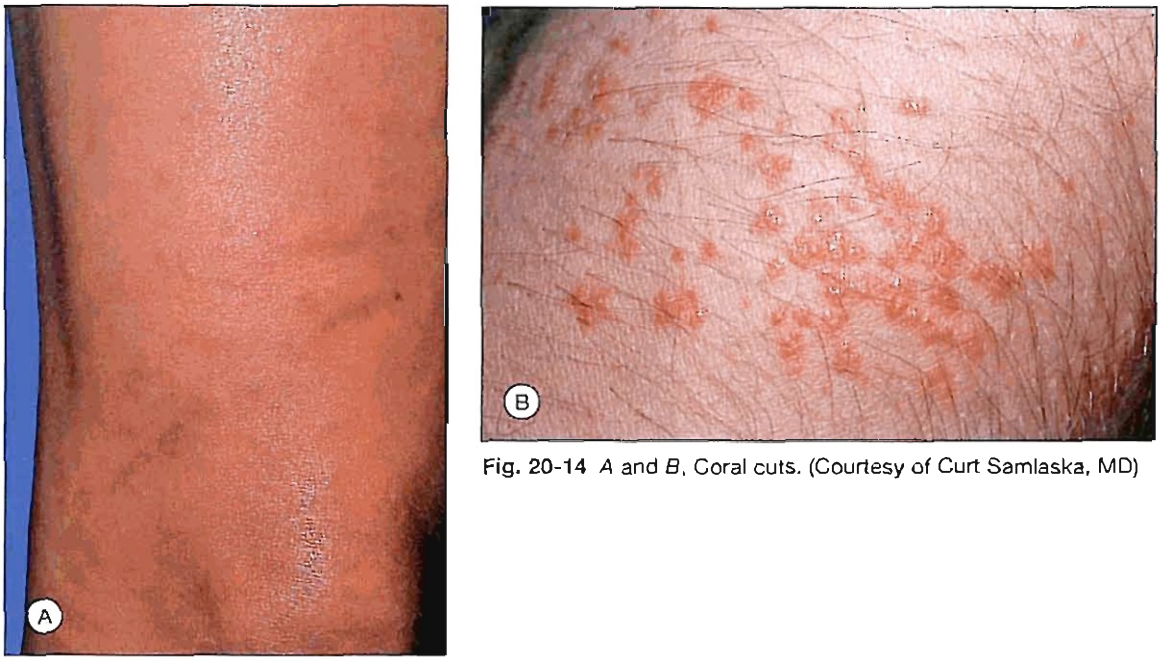


Fig. 20-14 *A* and *B*, Coral cuts. (Courtesy of Curt Samlaska, MD)

on contact with vinegar. Large visible tentacles may be removed with forceps in a double-gloved hand. Remaining nematocysts may be removed by applying a layer of shaving cream and shaving the area gently. Meat tenderizer may cause tissue damage and has been shown to be no better than placebo in some studies.

Pressure dressings and abrasion will worsen the envenomation. Topical anesthetics or steroids may be applied after decontamination. Systemic reactions may occur either through large amounts of venom or a previously sensitizing exposure from which anaphylaxis may result, and systemic treatment with epinephrine, antihistamines, or corticosteroids may be needed. Specific antivenin is available for the box jellyfish, *Chironex fleckeri*. This should be administered intravenously to limit myonecrosis. $MgSO_4$ may also be of value in the setting of box jellyfish envenomation.

Sponges and Bristleworms

Sponges have horny spicules of silicon dioxide and calcium carbonate. Some sponges produce dermal irritants, such as halitoxin and okadaic acid, and others may be colonized by cnidaria. Allergic or irritant reactions may result. Bristleworms may also produce stinging. All of these may be treated by first using adhesive tape to remove the spicules, then applying vinegar soaks, as described above, and finally, applying topical corticosteroid agents.

Sea Urchin Injuries

Puncture wounds inflicted by the brittle, fragile spines of sea urchins, mainly of genus *Diadema* or *Echinothrix*, are stained blue–black by the black spines and may contain fragments of the spines. The spines consist of calcium carbonate crystals which most commonly induce an irritant reaction with pain and inflammation of several days' duration. Foreign-body or sarcoid-like granulomas may develop, as may a vesicular hypersensitivity reaction 10 days after exposure. Injuries by spines of the genus *Tripneustes* have been reported to cause fatal envenomation, but this genus is not found on US coasts.

Starfish also have thorny spines that can sting and burn if they are stepped on or handled. Several different types of stinging fish also produce puncture wounds. Stingrays, scorpionfish, stonefish, catfish, and weaverfish may cause such envenomations.

These wounds should be immersed in nonscalding water (45° C [113° F]) for 30 to 90 min or until the pain subsides. Calcified fragments may be visible on x-ray evaluation, with fluoroscopy guiding extraction of spines, especially on the hands and feet. Sea urchin spines have been effectively removed using the erbium:YAG laser. Debridement and possibly antibiotic therapy for deep puncture wounds of the hands and feet are recommended. There is a specific antivenin for stonefish stings.

Seaweed Dermatitis

Although this is caused by a marine alga and not by an animal, it deserves mention with other problems associated with swimming or wading. The dermatitis occurs 3 to 8 h after the individual emerges from the ocean. The distribution is in parts covered by a bathing suit: scrotum, penis, perineum, and perianal area. The dermatitis is caused by a marine plant, *Lyngbya majuscula Gomont*. It has been observed only in bathers swimming off the windward shore of Oahu, Hawaii. Seabather's eruption, clamdigger's itch, and swimmer's itch must be differentiated from seaweed dermatitis caused by marine algae. Prophylaxis is achieved by refraining from swimming in waters that are turbid with such algae. Swimmers should shower within 5 min after swimming. Active treatment in severe cases is the same as for acute burns.

Dogger Bank Itch

Dogger Bank itch is an eczematous dermatitis caused by the sea chervil, *Alcyondium hirsutum*, a seaweed-like animal colony. These sea mosses or sea mats are found on the Dogger Bank, an immense shelflike elevation under the North Sea between Scotland and Denmark.

Auerbach PS: Marine envenomations. N Engl J Med 1991; 325:486.
Boer A, et al: Effective removal of sea-urchin spines by erbium:YAG laser ablation. Br J Dermatol 2001;145:169.
Bowers PW, et al: Dogger Bank itch and cyclosporin. J Dermatol Treat 2001;12:23.
De La Torre C, et al: Sea-urchin granuloma. J Cutan Pathol 2001; 28:223.
Freudenthal AR, et al: Seabather's eruption. N Engl J Med 1993;329:542.
Freudentahl AR, et al: Ghost anemone dermatitis. J Am Acad Dermatol 2002;47:722.
Haddad V Jr, et al: Seabather's eruption. Rev Inst Med Trop Sao Paulo 2001;43:171.
Miracco C, et al: Delayed skin reaction to Red Sea coral injury showing superficial granuloma and atypical CD30+ lymphocytes. Br J Dermatol 2001;145:849.
Nomura JT, et al. A randomized paired comparison trial of cutaneous treatments for acute jellyfish (Carybdea alata) stings. Am J Emerg Med 2002;20:624.
Reed KM, et al: Delayed and persistent cutaneous reactions to coelenterates. J Am Acad Dermatol 1984;10:462.
Segura-Puertas L, et al: One Linuche mystery solved. J Am Acad Dermatol 2001;44:624.
Smith S, et al: Chronic cutaneous *Mycobacterium haemophilum* infection acquired from coral injury. Clin Infect Dis 2003;37:e100.
Tamanaha RH, et al: Persistent cutaneous hypersensitivity reaction after a Hawaiian box jellyfish sting (Carybdea alata). J Am Acad Dermatol 1996;35:991.
Tomchick RS, et al: Clinical perspectives on seabather's eruption, also known as "sea lice." JAMA 1993;269:1669.
Wong DE, et al: Seabather's eruption. J Am Acad Dermatol 1994;30:399.

PHYLUM PLATYHELMINTHES

Phylum Platyhelminthes includes the flatworms, of which two classes, trematodes and cestodes, are parasitic to humans. The trematodes, or blood flukes, parasitize human skin or internal organs. The cestodes are segmented, ribbon-shaped flatworms that inhabit the intestinal tract as adults and involve the subcutaneous tissue, heart, muscle, and eye in the larval form. This is encased in a sac that eventually becomes calcified.

CLASS TREMATODA

Schistosome Cercarial Dermatitis

Cercarial dermatitis is a severely pruritic, widespread, papular dermatitis caused by cercariae of schistosomes for which humans are not hosts (the usual animal hosts are waterfowl and rodents, such as muskrats).

The eggs in the excreta of these animals, when deposited in water, hatch into swimming miracidia. These enter a snail, where further development occurs. From the snail, the free-swimming cercariae emerge to invade human skin on accidental contact. The swimming, colorless, multicellular organisms are a little less than a millimeter long. Exposure to cercariae occurs when a person swims or, more often, wades in water containing them. They attack by burrowing into the skin, where they die. The species that causes this eruption cannot enter the bloodstream or deeper tissues.

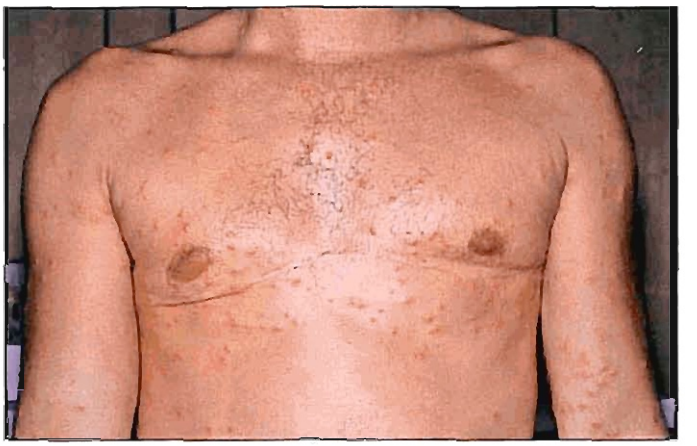


Fig. 20-15 Swimmer's itch.

After coming out of the water, the bather begins to itch and a transient erythematous eruption appears, but after a few hours, the eruption subsides, together with the itching. Then, after a quiescent period of 10 to 15 h, the symptoms recur, and erythematous macules and papules develop throughout the exposed parts that were in the water (Fig. 20-15). After several days the dermatitis heals spontaneously. There are two types: the freshwater swimmer's itch, and the saltwater marine dermatitis or clam digger's itch. It is not communicable.

Various genera and species of organisms have been reported from various locations worldwide. An outbreak of cercarial dermatitis was reported from Delaware in 1991 in which the avian schistosome *Microbilharzia variglandis* was implicated as the causative organism. *Schistosoma spindale* cercaria caused a recent epidemic in southern Thailand.

Thoroughly washing, then drying with a towel after exposure can prevent the disease. Rubbing with alcohol is an additional preventive measure advocated by some. Snail populations can be controlled or waterfowl may be treated with medicated feedcorn to destroy the adult schistosomes and prevent outbreaks of swimmer's itch.

Visceral Schistosomiasis (Bilharziasis)

The cutaneous manifestation of bilharziasis may begin with mild itching and a papular dermatitis of the feet and other parts after swimming in polluted streams containing cercariae. The types of schistosomes causing this disease can penetrate into the bloodstream and eventually inhabit the venous system draining the urinary bladder (*Schistosoma haematobium*) or the intestines (*Schistosoma mansoni* or *Schistosoma japonicum*). After an asymptomatic incubation period, there may be a sudden illness with fever and chills, pneumonitis, and eosinophilia. Petechial hemorrhages may occur.

Cutaneous schistosomal granulomas most frequently involve the genitalia, perineum, and buttocks. The eggs of *S. haematobium* or *S. mansoni* usually cause these bilharziomas. Vegetating, soft, cauliflower-shaped masses, fistulous tracts and extensive hard masses occur; these are riddled by sinuses that exude a seropurulent discharge with a characteristic odor. Phagedenic ulcerations and pseudoelephantiasis of the scrotum, penis, or labia are sometimes encountered. Histologically, the nodules contain bilharzial ova undergoing

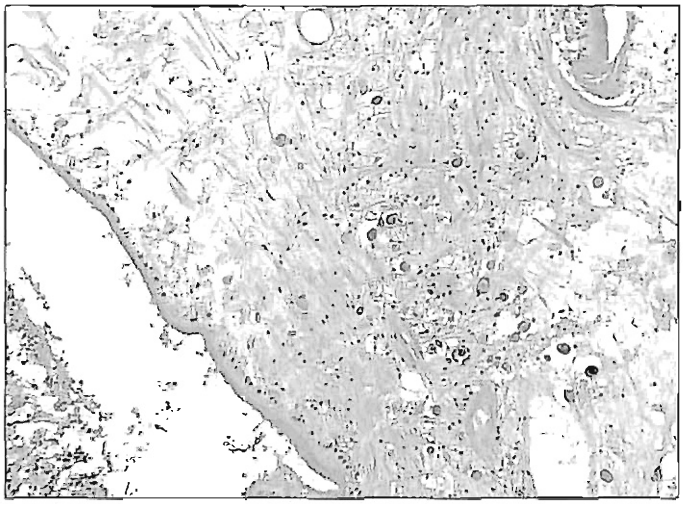


Fig. 20-16 Sparganosis is characterized histologically by a secretory tegument and loose stroma with smooth mucle and calcareous bodies.

degeneration, with calcification and a surrounding cellular reaction of histiocytes, eosinophils, and occasional giant cells. In some cases, eventual malignant changes have been noted in chronic lesions.

Infrequently, ectopic or extragenital lesions may occur, mainly on the trunk. This is a papular eruption tending to group in plaques and become darkly pigmented and scaly (Fig. 20-16).

A severe urticarial eruption known as *urticarial fever* or *Katayama fever* is frequently present along with a *S. japonicum* infection; it occurs with the beginning of oviposition, 4 to 8 weeks after infection. This condition occurs mainly in China, Japan, and the Philippines. In addition to the urticaria, fever, malaise, abdominal cramps, arthritis, and liver and spleen involvement are seen. This is felt to be a serum sickness-like reaction.

Preventive measures include reducing infection sources, preventing contamination by human excreta of snail-bearing waters, control of snail hosts, and avoiding exposure to cercaria-infested waters. Prophylactic measures are constantly sought to control one of the world's worst parasitic diseases, but as yet none has been found to be practical.

For both *S. haematobium* and *S. mansoni*, praziquantel (Biltricide) 40 mg/kg orally for each of two treatments in 1 day is the treatment of choice. *S. japonicum* treatment requires 60 mg/kg in three doses in 1 day.

Schistosomicides exhibit toxicity for the host as well as for the parasite, and the risk of undesirable side effects may be enhanced by concomitant cardiac, renal, or hepatosplenic disease.

Amer M: Cercaria dermatitis outbreak at a state park-Delaware, 1991. Arch Dermatol 1992;128:945.

Amer M: Cutaneous schistosomiasis. Dermatol Clin 1994; 12:713.

Elston DM: Schistosoma japonicum. Cutis 2004;73:299.

Farrell AM, et al: Ectopic cutaneous schistosomiasis: extragenital involvement with progressive upward spread. Br J Dermatol 1996;135:110.

Kolarova L, et al: Schistosome cercariae as the causative agent of swimmer's itch in Iceland. J Helminthol 1999;73:215.

Cysticercosis Cutis

The natural intermediate host of the pork tapeworm, *Taenia solium*, is the pig, but under some circumstances humans act in this role. The larval stage of *T. solium* is *Cysticercus cellulosae*. Infection takes place by the ingestion of food contaminated with the eggs, or by reverse peristalsis of eggs or proglottides from the intestine to the stomach. Here the eggs hatch, freeing the oncospheres. These enter the general circulation and form cysts in various parts of the body, such as striated muscles, brain, eye, heart, and lung.

In the subcutaneous tissues the lesions are usually painless nodules that contain cysticerci. They are more or less stationary, usually numerous, and often calcified, and are therefore demonstrable radiographically. Pain and ulceration may accompany the lesions. The disease is most prevalent in countries in which pigs feed on human feces. It may be confused with gumma, lipoma, and epithelioma. A positive diagnosis is established solely by incision and examination of the interior of the calcified tumor, where the parasite will be found.

Albendazole or praziquantel are effective; however, the status of the CNS, spinal and ocular involvement, needs to be thoroughly assessed prior to treatment. The length of therapy and use of concominant corticosteroids depends upon the location of the cysts. None of the regimens clear the calcified parasites, however, which need to be surgically removed.

Garcia HH, et al: *Taenia solium* cysticercosis. Infect Dis Clin North Am 2000;14:97.

Schmidt DK, et al: Cerebral and subcutaneous cysticercosis treated with albendazole. Int J Dermatol 1995;34:574.

Uthida-Tanaka AM, et al: Subcutaneous and cerebral cysticercosis. J Am Acad Dermatol 2004;50:S14.

Wortman PD: Subcutaneous cysticercosis. J Am Acad Dermatol 1991;25:409.

Sparganosis

Sparganosis is caused by the larva of the tapeworm of the species *Spirometra*. The adult tapeworm lives in the intestines of dogs and cats. This is a rare tissue infection occurring in two forms. *Application sparganosis* occurs when an ulcer or infected eye is poulticed with the flesh of an infected intermediate host (such poultices are frequently used in the Orient). The larvae become encased in small nodules in the infected tissue. *Ingestion sparganosis* occurs when humans ingest inadequately cooked meat, such as snake or frog, or when a person drinks water that is contaminated with *Cyclops*, which are infected with plerocercoid larvae. One or two slightly pruritic or painful nodules may form in the subcutaneous tissue or on the trunk and legs.

Humans are the accidental intermediate host of the Sparganum, which is the alternative name for the plerocercoid larva. Treatment is surgical removal or ethanol injection of the infected nodules (Fig. 20-17). This may be difficult because of the swelling and extensive vascularity.

Kim SH, et al: Three cases of cutaneous sparganosis. Int J Dermatol 2001;40:656.

Kimura S, et al: A case of subcutaneous sparganosis. Br J Dermatol 2003;148:369.

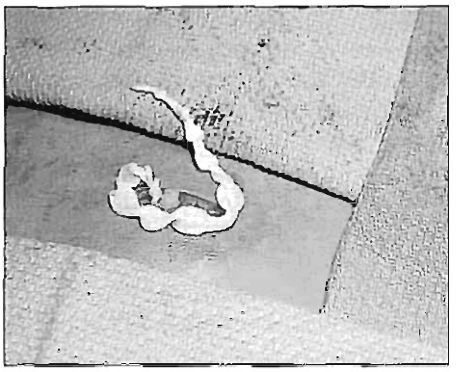


Fig. 20-17
Sparangosis. (Courtesy of James Fitzpatrick, MD)

Pampiglione S, et al: Human sparganosis in Italy. APMIS 2003; 111:349.

Echinococcosis

Echinococcosis is also known as *hydatid disease*. In humans, infection is produced by the ova reaching the mouth from the hands, in food, or from containers soiled by ova-contaminated feces from an infected dog. This leads to *Echinococcus granulosus* infestation of the liver and the lungs. Soft, fluctuating, semitranslucent, cystic tumors may occur in the skin, sometimes in the supraumbilical area as fistulas from underlying liver involvement. These tumors become fibrotic or calcified after the death of the larva. The treatment is excision, with care being taken to avoid rupturing the cyst. Albendazole combined with percutaneous drainage may also be used

Eosinophilia, intractable urticaria and pruritus, and even acute generalized exanthematous pustulosis may be present. Such reactive findings may be present as skin manifestations of many of the helminthic infections, including other types of tapeworms. *Hymenolepis nana* is a cosmopolitan dwarf tapeworm endemic in the tropics which may cause a treatment-resistant pruritic papular eruption associated with eosinophilia. Stool specimens for ova and parasites are definitive and praziquantel is curative.

Baldi A, et al: Echinococcal cysts with primary cutaneous localization. Br J Dermatol 2002;147:807.

Bresson-Hadni S, et al: Skin localization of alveolar echinococcosis of the liver. J Am Acad Dermatol 1996;34:873.

Cannistraci C, et al: Acute generalized exanthematous pustulosis in cystic echinococcosis. Br J Dermatol 2003;148:1245.

Di Lernia V, et al: Skin eruption associated with *Hymenolepis nana* infection. Int J Dermatol 2004;43:357.

PHYLUM ANNELIDA

LEECHES

Leeches, of the class Hirudinea, are of marine, freshwater, or terrestrial types. After attaching to the skin, they secrete an anticoagulant, *hirudin*, and then engorge themselves with blood. Local symptoms at the site of the bite may include bullae, hemorrhage, pruritus, whealing, necrosis, or ulceration. Allergic reactions, including anaphylaxis, may result. Leeches may be removed by applying salt, alcohol, or vinegar, or by use of a match flame. Bleeding may then be stopped by direct pressure or by applying a styptic pencil to the site.

Leeches may be used medicinally to salvage tissue flaps that are threatened by venous congestion. However, aeromonas infection, anetoderma, and pseudolymphoma may be complications of their attachment.

Abdelgabar AM, et al: The return of the leech. Int J Clin Pract 2003;57:103.

Haycox CL, et al: Indications and complications of medicinal leech therapy. J Am Acad Dermatol 1995;33:1053.

Ouderkirk JP, et al: Aeromonas meningitis complicating medicinal leech therapy. Clin Infect Dis 2004;38:e36.

Smolle J, et al: Multiple pseudolymphomas caused by Hirudo *medicinalis* therapy. J Am Acad Dermatol 2000;43:867.

PHYLUM NEMATHELMINTHES

Phylum Nemathelminthes includes the roundworms, both free-living and parasitic forms. Multiplication is usually outside the host. Both the larval and adult stages may infect humans.

CLASS NEMATODA

Enterobiasis (Pinworm Infection, Seatworm Infection, Oxyuriasis)

The chief symptom of pinworm infestation, which occurs most frequently in children, is nocturnal pruritus ani. There is intense itching accompanied by excoriations of the anus, perineum, and pubic area. The vagina may become infested with the gravid pinworms. A pruritic papular dermatosis of the trunk and extremities may be observed infrequently. Restlessness, insomnia, enuresis, and irritability are but a few of the many symptoms ascribed to this exceedingly common infestation.

Oxyuriasis is caused by the roundworm *Enterobius vermicularis*, which may infest the small intestines, cecum, and large intestine of humans. The worms, especially gravid ones, migrate toward the rectum and at night emerge to the perianal and perineal regions to deposit thousands of ova; then the worm dries and dies outside the intestine. These ova are then carried back to the mouth of the host on the hands. The larvae hatch in the duodenum and migrate into the jejunum and ileum, where they reach maturity. Fertilization occurs in the cecum, thus completing the life cycle.

Humans are the only known host of the pinworm, which probably has the widest distribution of all the helminths. Infection occurs from hand-to-mouth transmission, often from handling soiled clothes, bedsheets, and other household articles. Ova under the fingernails are a common source of autoinfection. Ova may also be airborne and collect in dust that may be on furniture and the floor. Investigation may show that all members of the family of an affected person also harbor the infection. It is common in orphanages and mental institutions and among people living in communal groups.

Rarely is it feasible to identify a dead pinworm in the stool. Diagnosis is best made by demonstration of ova in smears taken from the anal region early in the morning before the patient bathes or defecates. Such smears may obtained with a small eye curette and placed on a glass slide with a drop of saline solution. It is also possible to use Scotch tape, looping

the tape sticky-side out over a tongue depressor and then pressing it several times against the perianal region. The tape is then smoothed out on a glass slide. A drop of a solution containing iodine in xylol may be placed on the slide before the tape is applied to facilitate detection of any ova. These tests should be repeated on 3 consecutive days to rule out infection. Ova may be detected under the fingernails of the infected person.

Albendazole, 400 mg, mebendazole, 100 mg, or pyrantel pamoate, 11 mg/kg (maximum 1 g) given once and repeated in 2 weeks, is effective. Personal hygiene and cleanliness at home are important. Fingernails should be cut short and scrubbed frequently; they should be thoroughly cleaned on arising, before each meal, and after using the toilet. Sheets, underwear, towels, pajamas, and other clothing of the affected person should be laundered thoroughly and separately.

Elston DM: *Enterobius vermicularis* (pinworms, threadworms). Cutis 2003;71:268.

Pack SC, et al: Pruritus vulvae in prepubertal children. J Am Acad Dermatol 2001;44:795.

Hookworm Disease (Ground Itch, Uncinariasis, Ancylostomiasis, Necatoriasis)

The earliest skin lesions (ground itch) are erythematous macules and papules, which in a few hours become vesicles. These itchy lesions usually occur on the soles, toe webs, and ankles; they may be scattered or in groups. The content of the vesicles rapidly becomes purulent. These lesions are produced by invasion of the skin by the *Ancylostoma* or *Necator* larvae, and precede the generalized symptoms of the disease by 2 or 3 months. The cutaneous lesions last less than 2 weeks before the larvae continue their human life cycle. There may be as high as 40% eosinophilia around the fifth day of infection.

The onset of the constitutional disease is insidious and is accompanied by progressive iron-deficiency anemia and debility. During the course of the disease urticaria often occurs. The skin ultimately becomes dry and pale or yellowish.

Hookworm is a specific communicable disease caused by *Ancylostoma duodenale* or *Necator americanus*. In the soil, under propitious circumstances, they attain the stage of infective larvae in 5 to 7 days. These tiny larvae (which can scarcely be seen with a small pocket lens), when they come into accidental contact with bare feet, penetrate the skin and reach the capillaries. They are carried in the circulation to the lungs, where they pass through the capillary walls into the bronchi. They move up the trachea to the pharynx and, after being swallowed, eventually reach their habitat in the small intestine. Here they bury their heads in the mucosa and begin their sexual life.

Hookworm is prevalent in most tropical and subtropical countries and is often endemic in swampy and sandy localities in temperate zones. In these latter regions the larvae are killed off each winter, but the soil is again contaminated from human sources the following summer. *Necator americanus* prevails in the western hemisphere, Central and South Africa, South Asia, Australia, and the Pacific islands.

The defecation habits of infected individuals in endemic areas are largely responsible for its widespread distribution, as is the use of human feces for fertilization in many parts of the world. In addition, the climate is usually such that people go barefoot because of the heat or because they cannot afford shoes. Infection is thereby facilitated, especially through the toes.

Finding the eggs in the feces of a suspected individual establishes the diagnosis. The ova appear in the feces about 5 weeks after the onset of infection. The eggs may be found in direct fecal films if the infection is heavy, but in light infections it may be necessary to resort to zinc sulfate centrifugal flotation or other concentration methods. Mixed infections frequently occur.

Albendazole, 400 mg once, or mebendazole, 100 mg twice a day for 3 days or 500 mg once, or pyrantel pamoate 11 mg/kg (maximum 1 g) each day for 3 days is effective. Prophylaxis is largely a community problem and depends on preventing fecal contamination of the soil. This is best attained by proper sanitary disposal of feces, protecting individuals from exposure by educating them about sanitary procedures, and mass treatment through public health methods.

Nematode Dermatitis

Miller et al described a patient who developed a persistent widespread folliculitis caused by *Ancyclosforma caninum*. It was apparently acquired by his lying in grass contaminated by the droppings of his pet dogs and cats. A biopsy revealed hookworm larvae within the hair follicle. Oral thiabendazole was curative.

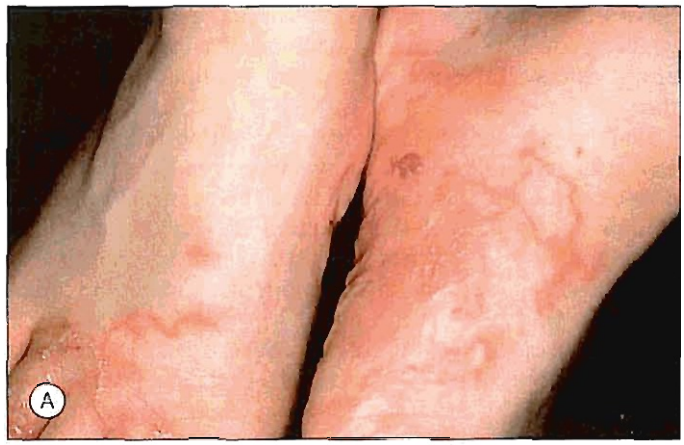
Creeping Eruption (Larva Migrans)

Creeping eruption is a term applied to twisting, winding linear skin lesions produced by the burrowing of larvae. People who go barefoot on the beach, children playing in sandboxes, carpenters and plumbers working under homes, and gardeners are often victims. The most common areas involved are the feet, buttocks, genitals, and hands.

Slight local itching and the appearance of papules at the sites of infection characterize the onset. Intermittent stinging pain occurs, and thin, red, tortuous lines are formed in the skin. The larval migrations begin 4 days after inoculation and progress at the rate of about 2 cm/day. However, they may remain quiescent for several days or even months before beginning to migrate. The linear lesions are often interrupted by papules that mark the sites of resting larvae (Fig. 20-18). As the eruption advances, the old parts tend to fade, but sometimes there are purulent manifestations caused by secondary infection; erosions and excoriations caused by scratching frequently occur. If the progress of the disease is not interrupted by treatment, the larvae usually die in 2 to 8 weeks, with resolution of the eruption, although rarely it has been reported to persist for up to 1 year. At times the larvae are removed from the skin by the fingernails in scratching. Eosinophilia may be present.

Loeffler syndrome, consisting of a patchy infiltrate of the lungs and eosinophilia as high as 50% in the blood and 90% in the sputum, may complicate creeping eruption.

The majority of cases in the US occur along the southeast coast and are caused by penetration by the larvae of a cat and dog hookworm, *Ancylostoma braziliense*. It is acquired from body contact with damp sand or earth that has been contaminated by the excreta of dogs and cats. The larvae of *Ancylostoma caninum*, which also infests the dog and the cat, rarely produce a similar dermatitis.



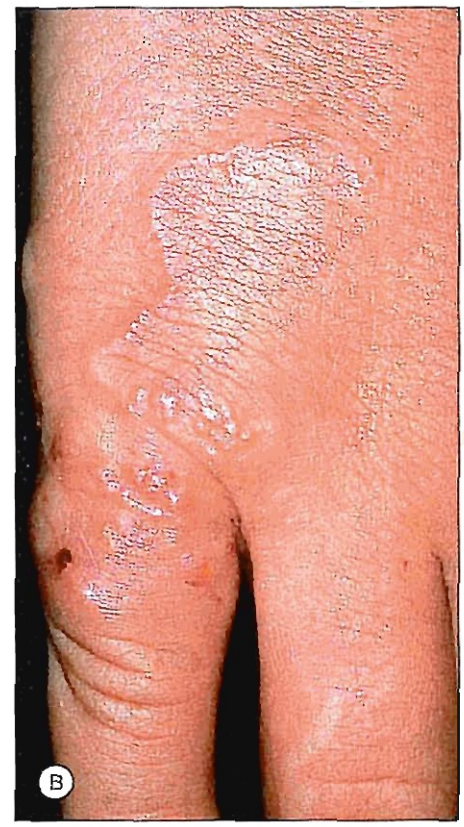


Fig. 20-18 A and B, Cutaneous larva migrans.

Ivermectin 200 µg/kg, generally given as a single 12-mg dose and repeated the next day, or albendazole, 400 mg/day for 3 days, are effective treatments. Criteria for successful therapy are relief of symptoms and cessation of tract extension, which usually occurs within a week. Topical thiabendazole compounded as a 10% suspension or a 15% cream used four times a day will result in marked relief from pruritus in 3 days, and the tracts become inactive in 1 week. Topical metronidazole has also been reported to be effective.

Another condition, not to be confused with this helminthic disease, which also is called *creeping eruption* (or *sandworm*, as it is known in South Africa, particularly in Natal and Zululand), is caused by a small mite about 300 µm long that tunnels into the superficial layers of the epidermis.

Gnathostomiasis

Migratory, intermittent, erythematous, urticarial plaques characterize human gnathostomiasis. Each episode of painless swelling lasts from 7 to 10 days and recurs every 2 to 6 weeks. Movement of the underlying parasite may be as much as 1 cm/h. The total duration of the illness may be 10 years. Histopathologic examination of the skin swelling will demonstrate eosinophilic panniculitis. The clinical manifestation has been called *larva migrans profundus*.

The nematode *Gnathostoma dolorosi* or *spinigerum* is the cause; most cases occur in Asia or South America. Eating raw flesh from the second intermediate host, most commonly freshwater fish, in such preparations as sashimi and ceviche, allows humans to become the definitive host. Eating raw squid or snake are other less common exposures. As the larval cyst in the flesh is digested, it becomes motile and penetrates the gastric mucosa, usually within 24 to 48 h of ingestion. Symptoms then occur as migration of the parasite continues. Surgical removal is the treatment of choice, if the parasite can be located. This may be combined with albendazole 400 mg/day or twice a day for 21 days, or ivermectin 200 µg/kg/day for 2 days.

Creeping eruption in several reports from Japan has been found to be caused by a newly recognized causative parasite of the nematode superfamily Spiruroidea. Eating raw squid was associated with the onset of long, narrow lesions that were pruritic, linear, and migratory. Surgical removal is necessary; chemotherapy has been unsuccessful.

Larva Currens

Intestinal infections with *Strongyloides stercoralis* may be associated with a perianal larva migrans syndrome, called *larva currens*, because of the rapidity of larval migration (*currens* means "running" or "racing"). Larva currens is an autoinfection caused by penetration of the perianal skin by infectious larvae as they are excreted in the feces. An urticarial band is the prominent primary lesion of cutaneous strongyloidiasis. Strongyloidiasis, and the creeping eruption secondary to it, is often a chronic disease; infections may persist for more than 40 years. Approximately one-third of patients infected are asymptomatic.

Signs and symptoms of systemic strongyloidiasis include abdominal pain, diarrhea, constipation, nausea, vomiting, pneumonitis, urticaria, eosinophilic folliculitis, and a peripheral eosinophilia. The skin lesions originate within

30 cm of the anus and characteristically extend as much as 10 cm/day.

Fatal cases of hyperinfection occur in immunocompromised patients. In such patients the parasite load increases dramatically and can produce a fulminant illness. Widespread petechiae and purpura are helpful diagnostic signs of disseminated infection and chronic urticaria is a possible presenting sign. Periumbilical ecchymoses may appear as if they were caused by a thumbprint.

Administration of ivermectin, 200 µg/kg/day for 2 days, or thiabendazole 50 mg/kg/day in two doses (maximum 3 g/day) for 2 days, is the treatment of choice. Immunosuppressed hosts may be treated with thiabendazole 25 mg/kg twice a day for 7 to 10 days.

There are free-living strongyloides known as *Pelodera* that can produce a creeping eruption also. Jones et al reported a case of widespread follicular, erythematous, dome-shaped papules and pustules that began within 24 h of working under a house. This eruption persisted for 1 month before presentation. Scraping the lesions revealed live and dead larvae of the free-living soil nematode *Pelodera strongyloides*. Treatment with oral thiabendazole led to resolution.

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Dracunculiasis (Guinea Worm Disease, Dracontiasis, Medina Worm)

Guinea worm disease is now limited to remote villages in several sub-Saharan African countries. It is caused by *Dracunculus medinensis* and is contracted through drinking water that has been contaminated with infected water fleas in which *Dracunculus* is parasitic. In the stomach, the larvae penetrate into the mesentery, where they mature sexually in 10 weeks. Then the female worm burrows to the cutaneous surface to deposit her larvae and thus causes the specific skin manifestations. As the worm approaches the surface, it may be felt as a cordlike thickening and forms an indurated cutaneous papule. The papule may vesiculate and a painful ulcer develops, usually on the leg. The worm is often visible (Fig. 20-19). When the parasite comes in contact with water, the worm rapidly discharges its larvae, which are ingested by water fleas (*Cyclops*), contaminating the water.

The cutaneous lesion is usually on the lower leg, but it may occur on the genitalia, buttocks, or arms (Fig. 20-20). In addition to the ulcers on the skin, there may be urticaria, gastrointestinal upsets, eosinophilia, and fever.

The disease may be prevented by boiling drinking water, providing safe drinking water through boreholes, or filtering the water through mesh fibers. Native treatment consists of gradually extracting the worm a little each day, with care not to rupture it; in the event of such an accident, the larvae escape into the tissues and produce fulminating inflammation. Surgical removal is the treatment of choice. Metronidazole 500 mg/day resolves the local inflammation and permits

Fig. 20-19 Dracunculosis.

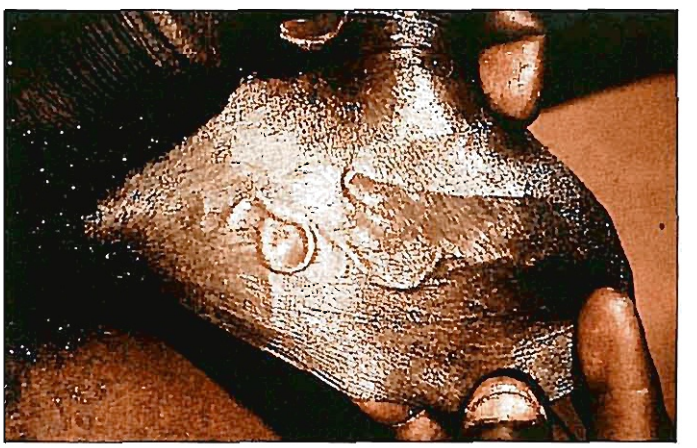

Fig. 20-20 Dracunculosis.

easier removal of the worm. Immersion in warm water promotes emergence of the worm.

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Filariasis

Elephantiasis Tropica (Elephantiasis Arabum)

Filariasis is a widespread tropical disorder caused by infestation with filarial worms of *Wuchereria bancrofti*, *Brugia malayi*, or *Brugia timori*. It is characterized by lymphedema, with resulting hypertrophy of the skin and subcutaneous tissues, and by enlargement and deformity of the affected parts, usually the legs, scrotum, or labia majora. The disease occurs more frequently in young men than in women.

The onset of elephantiasis is characterized by recurrent attacks of acute lymphangitis in the affected part, associated with chills and fever (elephantoid fever) that lasts for several days to several weeks. These episodes recur over several months to years. After each attack the swelling subsides only partially, and as recrudescences supervene, thickening and hypertrophy become increasingly pronounced. The overlying epidermis becomes stretched, thin, and shiny, and in the course of years, leathery, insensitive, and verrucous or papillomatous from secondary pyogenic infection. There may be a dozen or more attacks in a year.

In addition to involvement of the legs and scrotum, the scalp, vulva, penis, female breasts, and arms are at times affected, either alone or in association with the other regions. The manifestations vary according to the part involved. When the legs are attacked, both are usually affected in a somewhat symmetrical manner, the principal changes occurring on the posterior aspects above the ankles and on the dorsa of the feet. At first, the thickening may be slight and associated with edema that pits on pressure (Fig. 20-21). Later, the parts become massive and pachydermatous, the thickened integument hanging in apposing folds, between which there is a fetid exudate (Fig. 20-22).

When the scrotum is affected, it gradually reaches an enormous size and the penis becomes hidden in it. The skin, which at first is glazed, later is coarse and verrucous, or, in far-advanced cases, ulcerated or gangrenous. Resistant urticaria may occur. Filarial orchitis and hydrocele are common. A testicle may enlarge rapidly to the size of an apple and be extremely painful. The swelling may subside within a few days, or the enlargement may be permanent. As a result of obstruction and dilation of the thoracic duct or some of its lower abdominal tributaries into the urinary tract, chyle appears in the urine, which assumes a milky appearance. Lobulated swellings of the inguinal and axillary glands, called *varicose glands*, are caused by obstructive varix and dilation of the lymphatic vessels.

Filaria are transmitted person-to-person by the bites of a variety of mosquitoes of the *Culex*, *Aedes*, and *Anopheles* species. The adult worms are threadlike, cylindrical, and creamy white. The females are 4 to 10 cm long. Microfilarial embryos may be seen coiled each in its own membrane near the posterior tip. Fully grown, sheathed microfilariae are 130 to 320 μm long. The adult worms live in the lymphatic system, where they produce microfilariae. These either

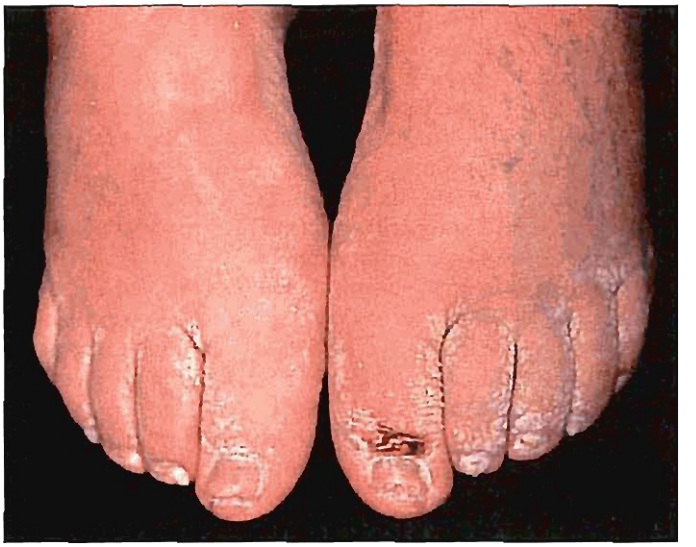

Fig. 20-21 Filarial elephantiasis.

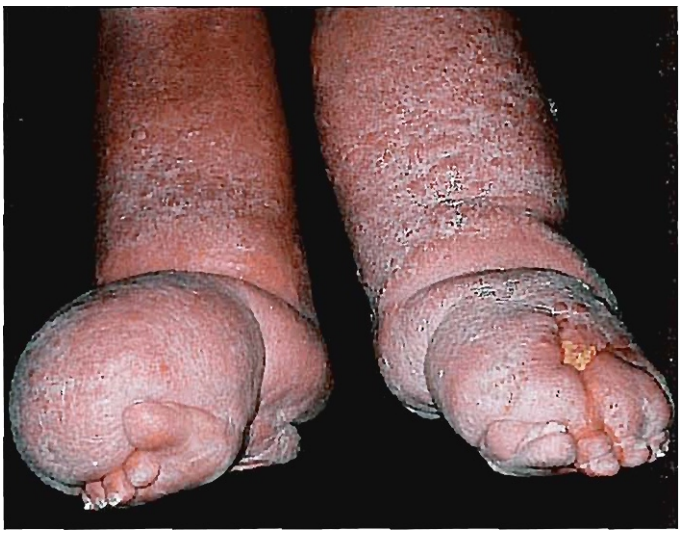

Fig. 20-22 Filarial elephantiasis. (Courtesy of James Fitzpatrick, MD)

remain in the lymphatic vessels or enter the peripheral bloodstream. An intermediate host is necessary for the further development of the parasite.

It is important to realize that infestation by the filaria is often asymptomatic, and elephantiasis usually occurs only if hundreds of thousands of mosquito bites are suffered over a period of years, with episodes of intercurrent streptococcal lymphangitis. Filariasis was endemic in the considerable Samoan population of Hawaii for half a century, and only one case of elephantiasis has occurred among this group.

Search for the microfilariae should be made on fresh coverslip films of blood (collected at night), urine, or other body fluid and examined with a low-power objective lens. Calcified adult worms may be demonstrated on x-ray examination and ultrasound can detect adult worms. At times adult filariae are found in abscesses or in material taken for pathologic examination. Specific serologic tests and a simple card tests for filarial antigen are available. The prognosis in regard to life is good, but living becomes burdensome unless the condition is alleviated.

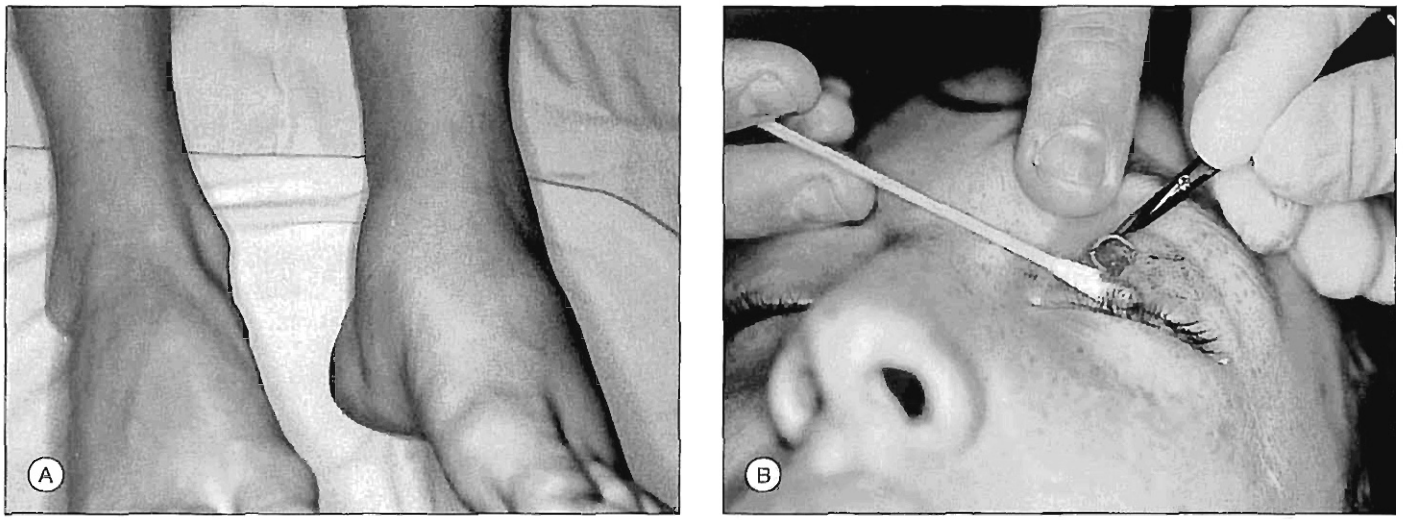

Fig. 20-23 *A* and *B*, Lolasis. (Courtesy of Curt Samlaska, MD)

Dithylcarbamazine in increasing doses over a 14-day period is the treatment of choice. This regimen clears microfilariae but not adult worms. A single dose of ivermectin may also be effective. Doxycycline kills the intracellular symbiotic bacteria *Wolbachia*. This leads to long-term sterility of adult female worms. It is being studied to determine its place in the treatment of both bancroftian filariasis and onchercerciasis. A worldwide effort to eliminate these diseases is underway. Surgical operations have been devised to remove the edematous subcutaneous tissue from the scrotum and breast. Prophylactic measures consist of appropriate mosquito control. Diethylcarbamazine has been effective in mass prophylaxis and if a trip of over 1 month is planned to areas with endemic *W. bancrofti* and extensive exposures to mosquitoes is likely, taking 500 mg/day for 2 days each month is recommended.

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Loaiasis (*Loa loa*, Calabar Swelling, Tropical Swelling, Fugitive Swelling)

Infection with *Loa loa* is often asymptomatic. In infected persons, the parasite develops slowly and there may even be an interval of as much as 3 years between infection and the appearance of symptoms, although the usual interval is 1 year. The first sign is often painful localized subcutaneous nonpitting edema called *calabar or fugitive swelling* (Fig. 20-23A). These are one or more slightly inflamed, edematous, transient swellings, usually about the size of a hen's egg. They usually last a few days and then subside, although recurrent swellings at the same site may eventually lead to a permanent cystlike protuberance. These swellings may result from hypersensitivity to the adult worm or to materials elaborated by it. Eosinophilia may be as high as 90% and often is between 60% and 80%.

The filariae may be noticed subcutaneously in the fingers, breasts, eyelids, or submucosally under the conjunctivae. The worm may be in the anterior chamber of the eye, the myocardium, or other sites. It has a predilection for loose tissues such as the eye region, the frenum of the tongue, and the genitalia. The wanderings of the adult parasite may be noticed by a tingling and creeping sensation. The death of the filaria in the skin may lead to the formation of fluctuant cystic lesions.

Loaiasis is a form of filariasis caused by *Loa loa*, widely distributed in west and central Africa. It is transmitted by the mango fly, *Chrysops dimidia* or *Chrysops silacea*. This fly bites only in the daytime. Humans are the only important reservoir for the parasite.

The observation of the worm under the conjunctiva, calabar swellings, and eosinophilia establish the diagnosis. Demonstration of the characteristic microfilariae in the blood during the day is possible in only some 20% of patients. Specific serologic tests are available.

Removal of the adult parasite whenever it comes to the surface of the skin is mandatory (Fig. 20-23B). This must be done quickly by seizing the worm with forceps and placing a suture under it before cutting down to it. Worms that are not securely and rapidly grasped quickly escape into the deeper tissues.

Diethylcarbamazine kills both adults and microfilariae and is given in increasing doses for 21 days.

In regions in which onchocerciasis and loaiasis are both endemic and ivermectin is used in a community-based elimination strategy for onchocerciasis, simultaneously infected patients with a high *Loa loa* load have a high risk of serious side effects. If ivermectin treatment of these patients is undertaken, proper monitoring and appropriate supportive treatment should be available in anticipation of this risk. Diethylcarbamazine is an effective chemopreventive, using 300 mg/week in temporary residents of regions of Africa where *Loa loa* is endemic.

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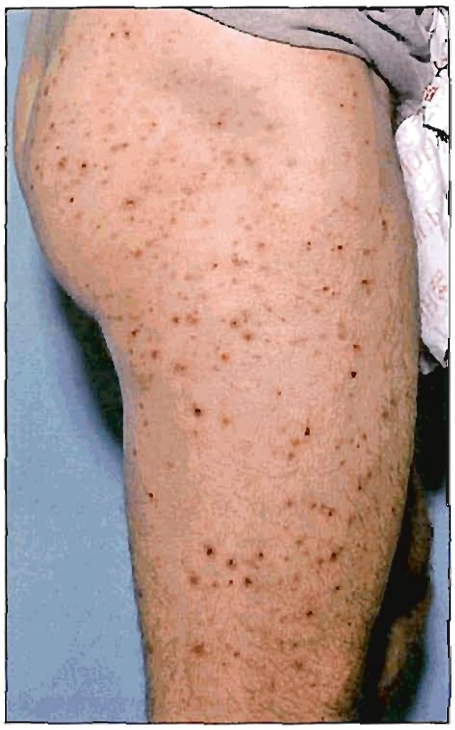

Fig. 20-24 Early onchocerciasis.

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Onchocerciasis

The skin lesions are characterized by pruritus, dermatitis, and onchocercomata. The dermatitis is variable in its appearance and probably relates to chronicity of infection, age of the patients, geographic area in which it was acquired, and relative immune responsiveness. Early in the course of the infection an itchy papular dermatitis may occur, and in visitors who acquire the infection this may be localized to one extremity (Fig. 20-24). In Central America, papules may appear only on the head and neck area. This unusual localization of insect bite-appearing papules with excoriations may lead to the diagnosis in travelers returning to their home countries. In Central America, another manifestation of the acute phase is acute swelling of the face with erythema and itching, known as *erisipela de la costa*. In Zaire and Central America, an acute urticarial eruption is seen. The inflammation, which is accompanied by hyperpigmentation, is known as *mal morado*.

As time passes, the dermatitis becomes chronic and remains papular; however, thickening, lichenification, and depigmentation occur (Fig. 20-25). Later, atrophy may supervene. When the depigmentation is spotted, it is known as *leopard skin*; when the skin is thickened, it is called *elephant skin*. When local edema and thickened, wrinkled, dry dermatitic changes predominate, it is sometimes called *lizard skin*.

In Saudi Arabia, Yemen, and East Africa, a localized type of onchocerciasis exists called *sowda*, which is Arabic for "black." It is characterized by localized, pruritic, asymmetrical, usually darkly pigmented, chronic lichenified dermatitis of one leg or one body region. It is also known as the chronic hyperreactive type, and an association with anti-

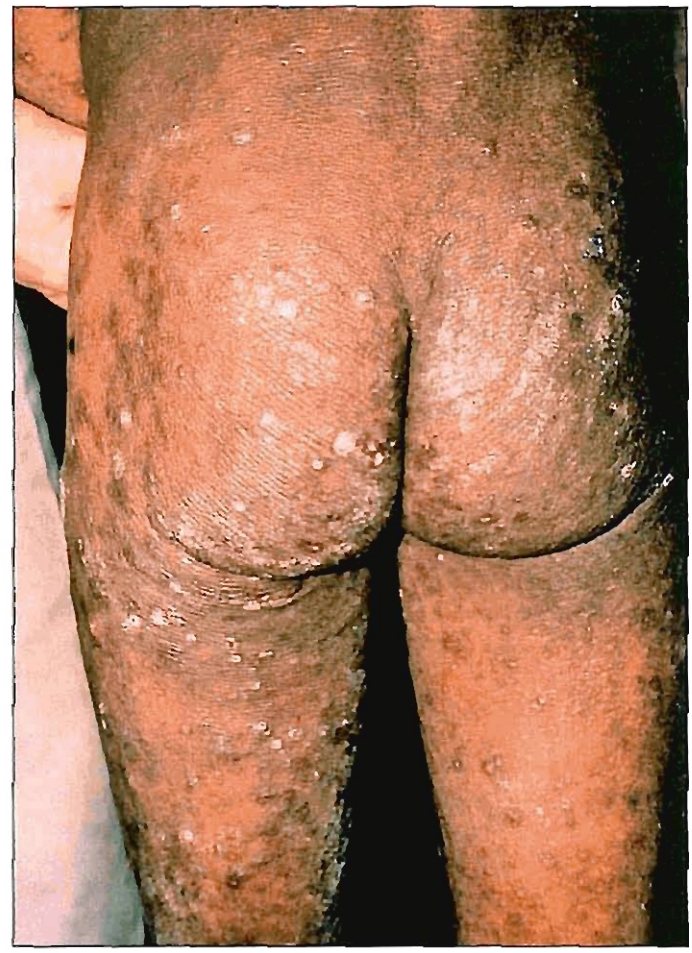

Fig. 20-25 Onchocerciasis. (Courtesy of Debra Kalter, MD)

definsin antibodies suggests a reason for this enhanced reactivity against the parasite.

After a time, firm subcutaneous nodules, pea-sized or larger, develop on various sites of the body. These nodules are onchocercomas containing myriad microfilariae. These occur in crops, are frequently painful, and their site varies. In parts of Africa, where natives are wholly or nearly unclothed, the lesions occur on the trunk, axillae, groin, and perineum. In Central and South America, the head, especially the scalp, is the usual site of involvement.

Firm, nontender lymphadenopathy is a common finding in patients with chronically infected onchocerciasis. "Hanging groin" describes the loose, atrophic skin sack that contains these large inguinal nodes (Fig. 20-26).

In about 5% of affected persons, serious eye lesions arise late in the disease, gradually leading to blindness.

Onchocerciasis is caused by *Onchocerca volvulus*, which is transmitted to humans by the bite of the black fly of the genus *Simulium*. It breeds in fast-flowing streams. When the black fly bites, it introduces larvae into the wound. The larvae reach adulthood in the subdermal connective tissue in about 1 year. Then millions of the progeny migrate back into the dermis and the aqueous humor of the eye.

Onchocerciasis occurs in Africa on the west coast, in the Sahara, Sudan, and the Victoria Nile division, where this disease is known as *river blindness*. In Central and South America, it is to be found in Guatemala, Brazil, Venezuela, and southern Mexico.

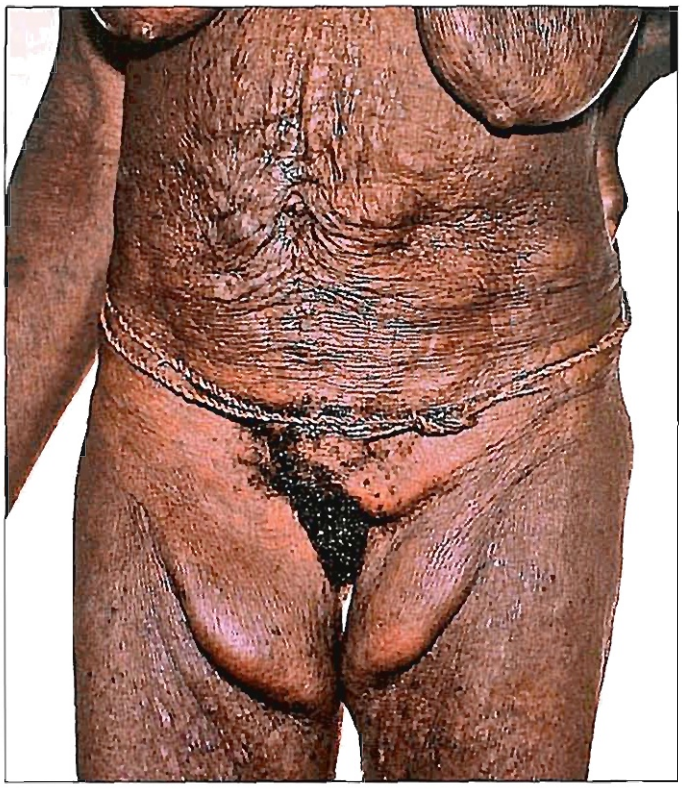

Fig. 20-26 Onchocerciasis.

The presence of eosinophilia, skin lesions, and onchocercomas with ocular lesions is highly suggestive in endemic areas. Frequently the microfilariae may be found in skin shavings or dermal lymph, even when no nodules are detectable. The scapular area is the favorite site for procuring specimens for examination by means of a skin snip. This is performed in the field or office by lifting the skin with an inserted needle and then clipping off a small, superficial portion of the skin with a sharp knife or scissors. The specimen is laid in a drop of normal saline solution on a slide, covered with a coverslip, and examined under the microscope. The filariae wriggle out at the edges of the skin slice.

Specific serologic and polymerase chain reaction-based diagnostic tests from blood and skin biopsies are available. Other filarial parasites can be detected in similar systems. When patients suspected of having onchocerciasis were given a single oral dose of 50 mg of diethylcarbamazine, a reaction consisting of edema, itching, fever, arthralgias, and an exacerbation of pruritus was described as a positive Mazzotti test reaction, which supported the diagnosis of onchocerciasis. The reaction may be related to *Wolbachia* organisms within the worms.

Onchocercomas may be surgically excised whenever feasible. Ivermectin as a single oral dose of 150 µg/kg is the drug of choice. Skin microfilaria counts remain low at the end of 6 months' observation. Ivermectin should be repeated every 6 months to suppress the dermal and ocular microfilarial counts. Doxycycline kills the intracellular symbiotic bacteria *Wolbachia* which leads to nematode sterility, and inhibits larval development and adult worm viability. It is being tested for long-term effects and determination of its place in the treatment of onchocerciasis and bancroftian filariariasis. If there is eye involvement, prednisone 1 mg/kg should be started several days before treatment with ivermectin.

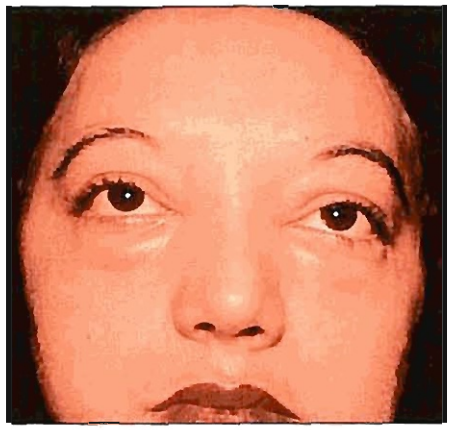

Fig. 20-27 Trichinosis.

There are community-based treatment protocols that have the objective of eliminating onchocerciasis from endemic areas. Severe reactions may occur in patients simultaneously infected with *Loa loa*.

Gallin MY, et al: Human autoantibody to defensin: disease association with hyperreactive onchocerciasis (sowda). J Exp Med 1995;182:41.

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Murdoch ME, et al: Onchocerciasis: the clinical and epidemiological burden of skin disease in Africa. Ann Trop Med Parasitol 2002;96:283.

Nguyen JC, et al: Cutaneous onchocerciasis in an American traveller. Int J Dermatol 2005;44:125.

Siddiqui MA, et al: The black disease of Arabia, sowda-onchocerciasis. Int J Dermatol 1991;30:130.

Trichinosis

Ingestion of *Trichinella spiralis* larva-containing cysts in inadequately cooked pork, bear, or walrus meat may cause trichinosis. It usually causes a puffy edema of the eyelids (Fig. 20-27), redness of the conjunctivae, and sometimes urticaria associated with hyperpyrexia, headache, erythema, gastrointestinal symptoms, muscle pains, and neurologic signs and symptoms. Ten percent of patients develop a bilateral, asymptomatic hand swelling that is especially prominent over the digits, and erythema along the perimeters of the palms and volar surfaces of the digits, which progresses to desquamation. In 20% of cases a nonspecific macular or petechial eruption occurs and splinter hemorrhages are occasionally present. Eosinophilia is not constant, but may be as high as 80%. In the average patient, eosinophilia begins about 1 week after infection and attains its height by the fourth week.

The immunofluorescence antibody test has the greatest value in establishing early diagnosis. The bentonite flocculation test, an enzyme-linked immunosorbent assay (ELISA) test, and other serologic tests are limited by their inability to detect infection until the third or fourth week.

Diagnosis is confirmed by a muscle biopsy that demonstrates larvae of *Trichinella spiralis* in striated muscle. Unfortunately, trichinae cannot usually be demonstrated unless

the infection is very heavy, of over a month's duration, and the biopsy specimen is very large. A 2-mm thick slice of the muscle biopsy may be compressed between two glass slides to demonstrate the cysts.

The condition is treated with albendazole 400 mg twice a day for 14 days. Corticosteroidal agents are effective as a means of controlling the often severe symptoms and should be given at doses of 40 to 60 mg/day.

Chaudhry AZ, et al: Cutaneous manifestations of intestinal helminthic infections. Dermatol Clin 1989;7:275.

Herrera R, et al: Dermatomyositis-like syndrome caused by trichinae. J Rheumatol 1985;12:782.

Walsh DS, et al: Hand rash in trichinosis. Clin Exp Dermatol 2001;26:2001.

PNEUMOCYSTOSIS

Pneumocystis carinii has features characteristic of both protozoa and fungi. It is an opportunistic infection, occurring primarily as a pulmonary infection in AIDS patients. Extrapulmonary involvement is uncommon and usually occurs in the reticuloendothelial system. Skin findings are uncommon. At least half of reported cases are of nodular growths in the auditory canal with the remainder having nonspecific pink-to-skin colored papules and nodules which may ulcerate. On biopsy the dermis contains foamy material within which Giemsa-positive organisms are identified. A 3-week course of trimethoprim–sulfamethoxazole combination is the treatment of choice.

Bundow DL, et al: Skin involvement with *Pneumocystis* despite dapsone prophylasix. Am J Med Sci 1997;313:182.

Sandler B, et al: Cutaneous *Pneumocystis carinii* and *Cryptococcus neoformans* in AIDS. Br J Dermatol 1996;134:159.

PHYLUM ARTHROPODA

This phylum contains more species than all the other phyla put together. The following classes are of dermatologic significance: Myriapoda, Insecta, and Arachnida. Mosquitoes, flies, ticks, and fleas transmit diseases throughout the world.

Prevention of Arthropod-Related Disease

Mosquitoes remain the most important vectors of arthropod-borne disease, and mosquito control programs are an essential component of the public health efforts of many states. Insect repellents are effective in preventing disease transmission and are especially important during travel to areas endemic for vector-borne disease. Most are based on DEET (*N*,*N*-diethyl-3-methylbenzamide, previously called *N*,*N*-diethyl-*m*-toluamide). DEET has been tested against a wide range of arthropods, including mosquitoes, sandflies, ticks, and chiggers. The American Academy of Pediatrics recommends concentrations of 30% or less in products intended for use in children. As this represents a major market share for these products, many formulations that comply with the recommendation are available. Some evidence suggests that children do not have a higher incidence of adverse reactions when compared to adults, but even in adults there have been occasional reports of neurotoxicity. High concentrations of DEET can also produce erythema and irritation or bullous eruptions. Extended-release products reduce the need for repeated application, and appear to minimize the risk of complications. Overall, DEET has a good safety record in widespread use. Picaridin (KBR 3023) is a piperidine-derived repellent ingredient that is also effective against a range of arthropods. In some studies, it has been shown to be less irritating than DEET while providing comparable efficacy. The best studies for the evaluation of repellents are field trials that involve a range of arthropods. Arm box studies are still performed, but must be interpreted with caution. In a well designed arm box study, soybean oil (Bite Blocker for Kids) performed reasonably well, and was second only to DEET in efficacy. Citronella did not perform well. Citronella candles have little documented efficacy. Neem oil is an effective mosquito repellent that is used in many areas of the world that are endemic for malaria.

Travelers to malaria-endemic areas should follow Centers for Disease Control (CDC) guidelines for malaria prophylaxis. They should also avoid night-time outdoor exposure and use protective measures such as repellents and bed netting. The anopheline mosquitoes that carry malaria tend to bite at night, so bed nets and screens are important measures. Mosquitoes that carry Dengue mostly bite during the day. Repellents play a greater role in protection against Dengue as it is more difficult to limit daytime outdoor activity. Mosquito control programs depend largely on drainage of stagnant water and spraying of breeding areas. In developing countries, water barrels may be stocked with fish or turtles to consume mosquito larvae. Both can soil the water and the relative risks must be evaluated. In some studies, the risk has clearly favored stocking the barrel. Mosquito traps, including the Mosquito Magnet, have been shown to be effective for the control of mosquitoes in limited areas. Generally, mosquitoes fly upwind to bite, and downwind to return to their resting area. Mosquito traps must be positioned between the breeding and resting areas, and the area to be protected. Mosquito traps commonly use CO_2, heat, and chemical attractants. Some Culex mosquitoes are repelled by octenol, and the manufacturer may provide guidelines for areas where the attractant should not be used.

Prevention of Disease from Ticks and Chiggers

Tick-borne diseases include rickettsial fevers, ehrlichiosis, Lyme disease, babesiosis, relapsing fever, and tularemia. Most require a sustained tick attachment of more than 24 h for effective transmission, and frequent tick checks with prompt removal of ticks is an important strategy for the prevention of tick-borne illness. Unfortunately, tick inspections frequently fail to identify the tick in time for prompt removal. Some data suggest that adult ticks are found and removed only 60% of the time within 36 h of attachment. Nymphal ticks are even more difficult to detect, and may be removed in as few as 10% of patients within the first 24 h. Because of this, repellents and acaricides remain critical to prevent tick-borne illness. Permethrin has cidal activity against a wide range of arthropods. Some North African *Hyalomma* ticks are resistant to permethrin, and may exhibit a paradoxical pheromone-like attachment response when exposed to the agent, but permethrin performs very well with other species of ticks, as well as mosquitoes and chiggers. It can be used to treat clothing, sleeping bags, mosquito netting, and tents. Permethrin-treated clothing, used in conjunction with a

repellent, provides exceptional protection against bites in most areas of the world. Permethrin has a good record of safety, although there is a single case report of congenital leukemia with 11q23/MLL rearrangement in a preterm female infant whose mother had abused permethrin because of a pathologic fear of spiders. Permethrin can induce cleavage of the MLL gene in cell culture, providing a plausible link between the agent and the leukemia. It should be emphasized that permethrin in this case was not used according to the manufacturer's instructions, and the theoretical risk of carcinogenicity should be weighed against the very real risk of death from arthropod-borne disease. Cardiac glycosides have also been used topically as acaricides and have performed well in limited studies.

Ixodes scapularis is the major North American vector for Lyme disease, human granulocytic ehrlichiosis, and human babesiosis. An effective Lyme vaccine was marketed in the US, but proved to be a commercial failure and was voluntarily withdrawn from the market. Prevention of Lyme disease now centers on prevention of tick attachments, and prompt tick removal. Back yards and recreational areas adjacent to wooded areas have higher rates of tick infestation. Tick numbers can be reduced by deer fencing, removal of leaf debris, application of an acaricide, and by creating border beds with wood chip mulch or gravel. Bait boxes and deer feeding stations have been devised that are capable of delivering a topical acaricide while the animal feeds. Parasitic wasps control tick numbers in nature, but wasp populations may fluctuate, and investment in wasp-control may be a risky venture compared with other forms of tick control. Other natural forms of tick control have been investigated, as they have the potential to become self-sustaining in the environment, at least for a period of time. Fungi and nematodes show some promise. In southern states, fire ants control tick populations by eating tick eggs.

Prevention of Flea-Borne Illness

Fleas are important vectors of plague, endemic typhus, and *Rickettsia felis* (a spotted fever organism). They may also be vectors of cat scratch disease. Lufenuron is a maturation inhibitor that prevents fleas from breeding. It is commonly used in oral and injectable forms for the prevention of flea infestation in cats and dogs. Fipronil is used topically for the prevention of flea and tick infestation. Other agents in use include imidacloprid, selamectin, and nitenpyram. House sprays often include pyrethroids or pyriproxyfen. Powdered boric acid may be helpful for the treatment of infested carpets or floor boards. A knowledgeable veterinarian and an exterminator should be consulted.

Anon: Picardin – a new insect repellent. Med Lett Drugs Ther 2005;47:46.

Borkhardt A, et al: Congenital leukaemia after heavy abuse of permethrin during pregnancy. Arch Dis Child Fetal Neonatal Ed 2003;88:F436.

Corazza M, et al: Allergic contact dermatitis due to an insect repellent: double sensitization to picaridin and methyl glucose dioleate. Acta Derm Venereol 2005;85:264.

Fradin MS, et al: Comparative efficacy of insect repellents against mosquito bites. N Engl J Med 2002;347:13.

Hayes EB, et al: How can we prevent Lyme disease? N Engl J Med 2003;348:2424.

Jennings KA, et al: Human exposure to fipronil from dogs treated with frontline. Vet Hum Toxicol 2002;44:301.

Piesman J, et al: Protection against Lyme disease spirochete transmission provided by prompt removal of nymphal *Ixodes scapularis* (Acari: *Ixodidae*). Med Entomol 2002;39:509.

Ritzhaupt LK, et al: Evaluation of the comparative efficacy of selamectin against flea (*Ctenocephalides felis felis*) infestations on dogs and cats in simulated home environments. Vet Parasitol 2002;106:165.

Rueda LM, et al: Composition and adult activity of salt-marsh mosquitoes attracted to 1-octen-3-ol, carbon dioxide, and light in Topsail Island, North Carolina. J Am Mosq Control Assoc 2003;19:166.

Rust MK, et al. Efficacy and longevity of nitenpyram against adult cat fleas (Siphonaptera: Pulicidae). J Med Entomol 2003; 40:678.

Samish M: Biocontrol of ticks. Ann N Y Acad Sci 2000;916:172.

Solberg VB, et al: Control of *Ixodes scapularis* (Acari: Ixodidae) with topical self-application of permethrin by white-tailed deer inhabiting NASA, Beltsville, Maryland. J Vector Ecol 2003; 28:117.

Trongtokit Y, et al: Comparative repellency of 38 essential oils against mosquito bites. Phytother Res 2005;19:303.

CLASS MYRIAPODA

Morphologically, and genetically, the class Myriapoda is distinct from other groups of arthropods. This group contains the centipedes and millipedes. Both are capable of producing significant skin manifestations.

Centipede Bites (Chilopoda)

Centipede bites are manifested by paired hemorrhagic marks that form a chevron shape caused by the large paired mouthparts (Fig. 20-28). The bite is surrounded by an erythematous swelling (Fig. 20-29) that may progress into a brawny edema

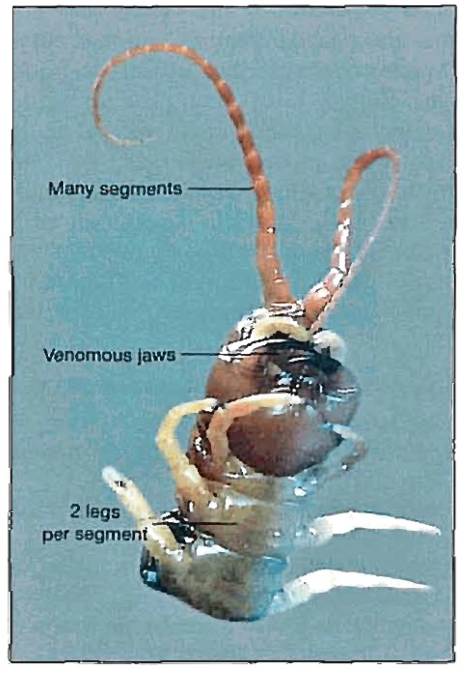

Fig. 20-28 Centipede.

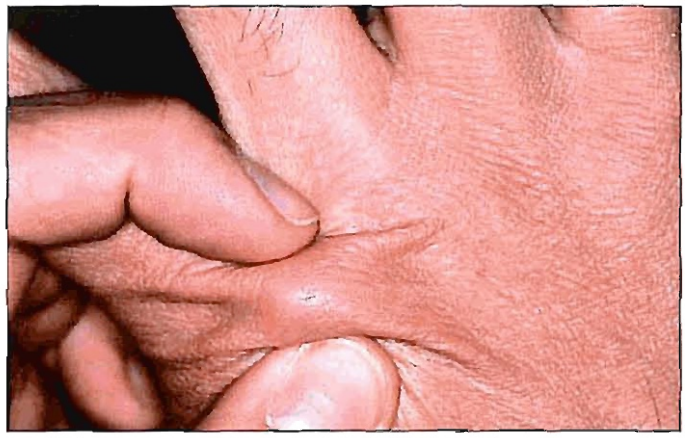

Fig. 20-29 Centipede bite.

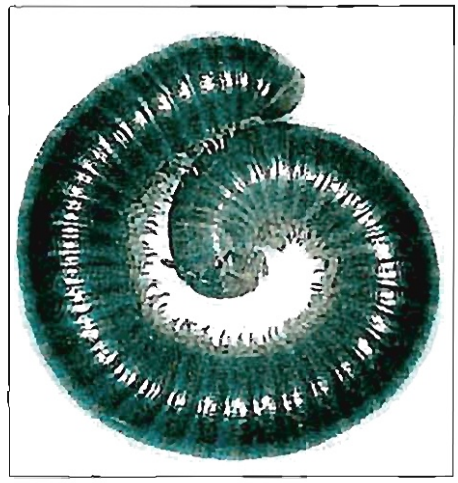

Fig. 20-30 Millipede.

or lymphangitis. Locally there may be intense itching and pain, often associated with toxic constitutional symptoms. Most centipede bites run a benign self-limited course, and treatment is only supportive. Children are often bitten when they try to handle centipedes. As some species of *Scolopendra in the* western US will attain a length of 15 to 20 cm, the child may describe it as a snake. Recognition of the characteristic chevron shape is important to avoid inappropriate treatment with snake antivenin. In the eastern US, the common house centipede, *Scutigera coleopterata*, does not bite humans. *Scolopendra subspinipes*, in Hawaii, inflicts a painful bite. As exotic species appear more commonly at pet stores and swap meets, envenomation by them will become more common.

In some tropical and subtropical areas, centipede bites account for about 17% of all envenomations (compared to the 45% caused by snakes and 20% by scorpions). Most bites occur at home and involve an upper extremity. Local pain and edema occur in up to 96% of patients, depending on the species involved. Treatment is largely symptomatic. Rest, ice, and elevation may be sufficient, but topical or intralesional anesthetics may be required in some cases. Tetanus immunization should be considered if the patient has not been immunized within the past 10 years. Centipede bites can result in Wells syndrome, requiring topical or intralesional corticosteroids. Rarely, bites may produce more serious toxic responses, including rhabdomyolysis and acute renal failure. These have been reported following the bite of *Scolopendra heros*, the giant desert centipede. Although centipedes have sometimes been found in association with corpses, injuries from the centipede tend to be postmortem and are rarely the cause of death. Ingestion of centipedes by children is usually associated with transient, self-limited toxic manifestations.

Barroso E, et al: Centipede stings notified by the "Centro de Informacoes Toxicologicas de Belem", over a 2-year period. Rev Soc Bras Med Trop 2001;34:527.

Bush SP, et al: Centipede envenomation. Wilderness Environ Med 2001;12:93.

Harada K, et al: Centipede inflicted postmortem injury. J Forensic Sci 1999;44:849.

McFee RB, et al: Envenomation by the Vietnamese centipede in a Long Island pet store. J Toxicol Clin Toxicol 2002;40:573.

Millipede Burns (Diplopoda)

Some millipedes secrete a toxic liquid that causes a brownish pigmentation or burn when it comes into contact with skin. Burns may progress to intense erythema and vesiculation. Millipedes may be found in laundry hung out to dry, and millipede burns in children have been misinterpreted as signs of child abuse. Recognition of the characteristic curved shape of the burn can be helpful in preventing misdiagnosis. Some millipedes can squirt their venom and ocular burns are reported. Washing off the toxin as soon as possible will limit the toxic effects. Other treatment is largely symptomatic.

Diplipods (Fig. 20-30) have evolved a complex array of chemicals for self-defense. Some primates take advantage of these chemicals. Two millipede compounds, 2-methyl-1,4-benzoquinone and 2-methoxy-3-methyl-1,4-benzoquinone, demonstrate a repellent effect against *Aedes aegypti* mosquitoes. Tufted and white-faced capuchin monkeys anoint themselves with the secretions to ward off mosquitoes. Effective commercial repellents are available for human use and millipede juice is not recommended.

Hudson BJ, et al: Giant millipede "burns" and the eye. Trans R Soc Trop Med Hyg 1997;91:183.

Weldon PJ, et al: Benzoquinones from millipedes deter mosquitoes and elicit self-anointing in capuchin monkeys (Cebus spp.). Naturwissenschaften 2003;90:301.

CLASS INSECTA

Order Lepidoptera

Order Lepidoptera includes butterflies and moths and their larval forms, caterpillars. Severe systemic reactions have occurred as the result of ingestion of some caterpillars, and with some species the sting alone can produce severe toxicity. *Lonomia achelous*, found in Latin America, can cause a fatal bleeding diathesis. The Spanish pine caterpillar, *Thaumetopoea pityocampa*, causes both dermatitis and anaphylactoid symptoms. Pine caterpillars are also an important cause of systemic reactions in China and Israel. The tussock moth, *Orgyia pseudotsugata*, causes respiratory symptoms in forestry workers in Oregon.

Caterpillar Dermatitis Irritation is produced by the hairs coming in contact with the skin. Toxins in the hairs can

Fig. 20-31 Puss caterpillar.

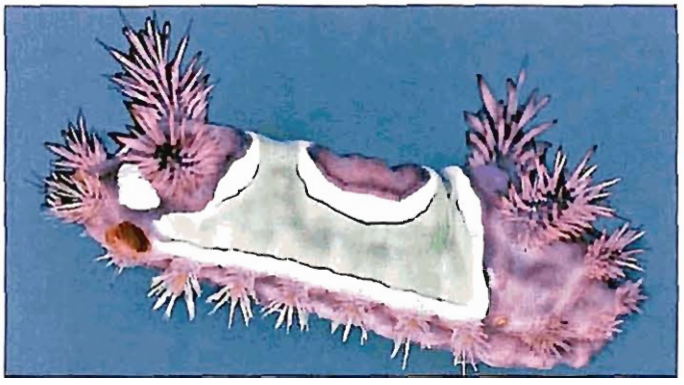

Fig. 20-33 Saddleback caterpillar.

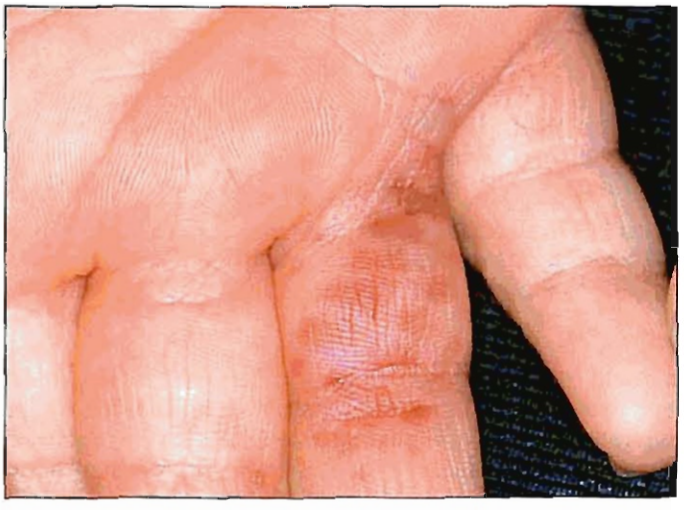

Fig. 20-32 Characteristic railroad track purpura of a puss caterpillar sting.

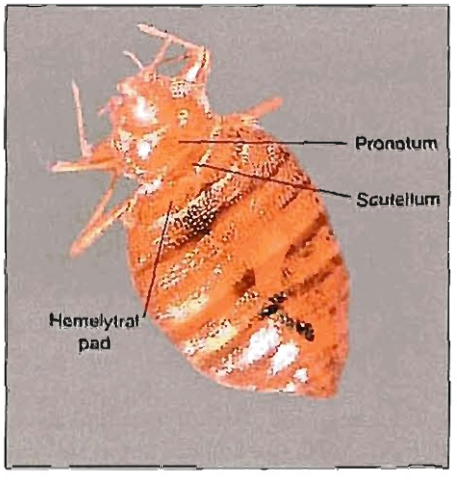

Fig. 20-34 Bedbug.

produce severe pain, local pruritic erythematous macules, and wheals, depending on the species. If the hairs get into the clothing, widespread persistent dermatitis may result. Not only the caterpillars, but their egg covers and cocoons also commonly contain stinging hairs. In the US the most common caterpillars of medical importance are the brown-tail moth caterpillar (*Nygmia phoeorrhoea*), puss caterpillar (*Megalopyge opercularis*) (Figs 20-31 and 20-32), saddleback caterpillar (*Sibine stimulae*) (Fig. 20-33), io moth caterpillar (*Automeris io*), crinkled flannel moth caterpillar (*Megalopyge crispata*), Oklahoma puss caterpillar (*Lagoa crispate*), buck moth caterpillar (*Hemileuca maia*), and flannel moth caterpillar (*Norape cretata*). The hairs of the European processionary caterpillar (*Thaumetopoea processionea*) are especially dangerous to the eyes, but ophthalmia nodosa (a papular reaction to embedded hairs) can be seen with a wide variety of caterpillars and moths.

Moth Dermatitis Moth dermatitis may be initiated by the hairs of the brown-tail moth (*Euproctis chrysorrhoea*), goat moth (*Cossus cossus*), puss moth (*Dicranura vinula*), gypsy moth (*Lymantria dispar*), and Douglas fir tussock moth (*Hemerocampa pseudotsugata*). In Latin America, the moths of the genus *Hylesia* are most frequently the cause of moth dermatitis. Severe conjunctivitis and pruritus are the first signs, and may persist for weeks aboard ships that have docked in ports where the moth is common. Caripito itch is named after Caripito, Venezuela, a port city where the moth is found. Korean yellow moth dermatitis is caused by *Euproctis flava* Bremer.

Topical applications of various analgesics, antibiotics, and oral antihistaminics are of little help. Topical or oral corticosteroids are sometimes helpful, as is scrubbing and tape stripping of skin. Contaminated clothing may need to be discarded if dermatitis persists after the clothing is washed.

Lee D, et al: Oropharyngeal manifestations of lepidopterism. Arch Otolaryngol Head Neck Surg 1999;125:50.

Maier H, et al: The oak processionary caterpillar as the cause of an epidemic airborne disease: survey and analysis. Br J Dermatol 2003;149:990.

Natsuaki M: Immediate and delayed-type reactions in caterpillar dermatitis. J Dermatol 2002;29:471.

Order Hemiptera

The true bugs belong to the order Hemiptera. The order includes bedbugs, water bugs, chinch bugs, stink bugs, squash bugs, and reduviid bugs (kissing bugs, assassin bugs). The latter are vectors of South American trypanosomiasis. In most true bugs, the wings are half sclerotic and half membranous, and typically overlap. In bedbugs, the wings are vestigial.

Cimicosis (Bedbug Bites) Bedbugs have flat oval bodies and retroverted mouthparts used for taking blood meals (Fig. 20-34). *Cimex lectularius* is the most common

Fig. 20-35 Tropical bedbug.

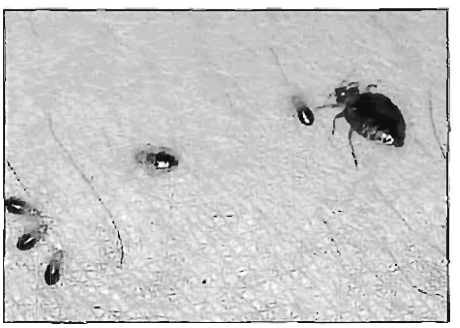

Fig. 20-36 Bedbug.

species in temperate climates, and *Cimex hemipterus* in tropical climates. Both are reddish brown, and about the size of a tick. *C. hemipterus* (Fig. 20-35) is somewhat longer than *C. lectularius* (Fig. 20-36). They breed through a process referred to as traumatic insemination, where the male punctures the female and deposits sperm into her body cavity. Bedbugs hide in cracks and crevices, then descend to feed while the victim sleeps. It is common for bedbugs to inflict a series of bites in a row ("breakfast, lunch and dinner"). Bullous and urticarial reactions occur. In some refugee camps, almost 90% of residents suffer from bedbug bites. Bedbugs are suspected vectors for Chagas' disease and hepatitis B.

Bedbugs often infest bats and birds, and these hosts may be responsible for infestation in houses. Management of the infestation may require elimination of bird nests and bat roosts. Cracks and crevices should be eliminated, and the area treated with an insecticide such as dichlorvos or permethrin. As most insecticides have poor residual effect on mud bricks, wood, and fabric, frequent retreatment may be necessary. Microencapsulation of insecticides enhances persistence. Permethrin-impregnated bednets have been shown to be effective against bedbugs in tropical climates.

Fletcher CL, et al: Widespread bullous eruption due to multiple bed bug bites. Clin Exp Dermatol 2002;27:74.

Gbakima AA, et al: High prevalence of bedbugs *Cimex hemipterus* and *Cimex lectularis* in camps for internally displaced persons in Freetown, Sierra Leone: a pilot humanitarian investigation. West Afr J Med 2002;21:268.

Liebold K, et al: Disseminated bullous eruption with systemic reaction caused by Cimex lectularius. J Eur Acad Dermatol Venereol 2003;17:461.

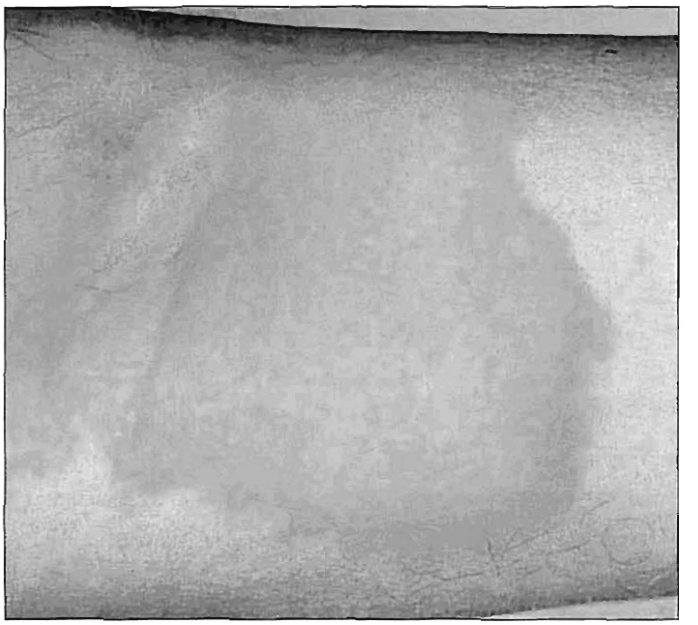

Fig. 20-37 Triatome bite.

Myamba J, et al: Pyrethroid resistance in tropical bedbugs, *Cimex hemipterus*, associated with use of treated bednets. Med Vet Entomol 2002;16:448.

Reduviid Bites Triatome reduviid bugs (kissing bugs, assassin bugs, conenose bugs) descend on their victims while they sleep, and feed on an exposed area of skin. The bite is typically painless, although they are capable of producing a more painful defensive bite. Swelling and itching occur within hours after the bite (Fig. 20-37). Many Latin American species have a pronounced gastrocolic reflex and defecate when they feed. Romana's sign is unilateral eye swelling after a night-time encounter with a triatome bug. *Trypanosoma cruzi* is transmitted by the feces and rubbed into the bite. American trypanosomiasis can produce heart failure and megacolon. Triatome bugs infest thatch, cracks and crevices, and infestation is associated with poor housing conditions. In nonendemic areas, bites are sporadic, and are often followed by a red swelling suggestive of cellulitis. Anaphylaxis has also occurred. *Arilus cristatus*, the wheal bug, is widely distributed and has an extremely painful defensive bite. It is not known to carry disease.

Elston DM: What's eating you? Wheel bug (Reduviidae: Arilus cristatus). Cutis 1998;61:189.

Elston DM, et al: What's eating you? Triatome reduviids Cutis 1999;63:63.

Order Anoplura

Pediculosis Three varieties of these flattened, wingless insects infest humans, *Pediculus humanus* var. *capitis* (the head louse), *P. humanus* var. *corporis* (the body louse), and *Phthirus pubis* (the pubic or crab louse) (Fig. 20-38). Rarely, zoonotic lice or louse-like psocids will cause infestation.

Pediculosis Capitis

Pediculosis capitis is more common in children, but occurs in adults also. Patients present with intense pruritus of the

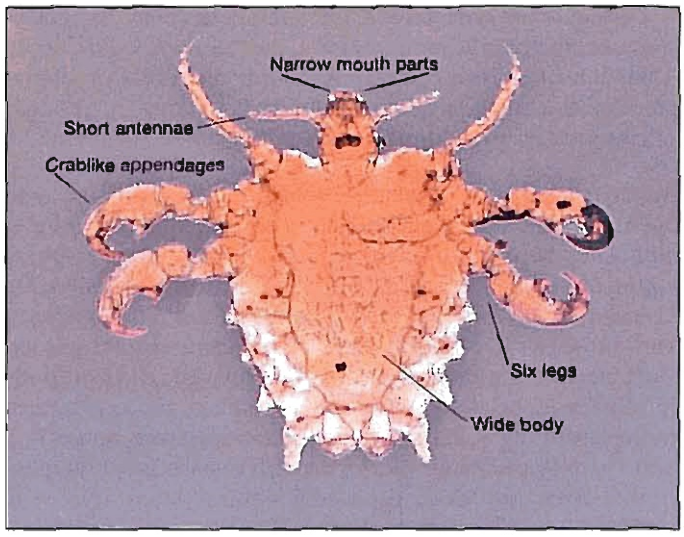

Fig. 20-38 Crab louse.

scalp, and often have posterior cervical lymphadenopathy. Excoriations and small specks of louse dung are noted on the scalp, and secondary impetigo is common. Lice may be identified, especially when combing the hair. Nits may be present throughout the scalp, but are most common in the retroauricular region. Generally, only those ova close to the scalp are viable, and nits noted along the distal hair shaft are empty egg cases. In very humid climates, however, viable ova may be present along the entire length of the hair shaft. Peripilar keratin (hair) casts are remnants of the inner root sheath that encircle hair shafts. They may be mistaken for nits. While nits are firmly cemented to the hair, casts move freely along the hair shaft.

Effective therapeutic agents must kill or remove both lice and ova. Permethrin is the most widely used pediculicide in the US. It is available as an over-the-counter 1% cream rinse (Nix) and a 5% prescription cream (Elimite) that is marketed for the treatment of scabies. The 1% cream rinse must be applied after shampooing and drying the hair completely. Applying to dry hair lessens dilution of the medication. Product labeling states the medication should be applied for 10 min, then rinsed off, but longer applications may be required. Shampooing should not take place for 24 h afterward. Permethrin has a favorable safety profile, although as noted above congenital leukemia has been reported in a preterm infant whose mother had heavily abused aerosolized permethrin.

Pyrethrins, combined with piperonyl butoxide (RID, A-200, R+C Shampoo), are sold over the counter. Malathion 0.5% lotion (Ovide) is marketed as a prescription product in the US. The efficacy is partly dependent upon the vehicle, and the product is flammable and can be irritating to the eyes. As it has not been widely used in the US, resistance has not emerged. Lindane is also marketed as a prescription product. The efficacy is somewhat lower, and the product has potential neurotoxicity if abused. Carbaryl is used in many parts of the world, but not in the US. Various "natural" remedies are marketed that contain coconut oil, anise oil, and ylang ylang oil, but these agents are potential contact allergens, and there are few data regarding their safety and efficacy. Aliphatic alcohols show promise as pediculicides, and crotamiton (Eurax), an antiscabetic agent, has some efficacy in the treatment of pediculosis. As no treatment is reliably ovidical, retreatment in a week is reasonable for all patients. Combing with a metal or plastic nit comb is an important adjunctive measure. The hair should be wet, and nit removal is facilitated by a conditioner, 8% formic acid solution (Step 2), or an enzymatic nit removal system (Clear and others).

Resistance to pediculicides is an emerging problem in many parts of the world. The emergence of resistance to an agent is related to the frequency with which that agent is used. Knockdown resistance (KDR) is a common mechanism of resistance that manifests as lack of immobilization of the lice. Responsible gene mutations (T929I and L932F) have been identified and can be used to screen for KDR. In countries like the US, where permethrin is used commonly, permethrin-resistant lice have emerged. Cross-resistance among pyrethroids is typical. In the UK, resistance to malathion has been reported, and multidrug-resistant lice have been identified.

KDR results in slower killing of lice, but may be overcome to some degree by longer applications. Monooxygenase-based resistance to pyrethrins may be overcome by synergism with piperonyl butoxide. Sequential use of pediculicides may be useful in overcoming resistance, and systemic agents may play some role. Trimethoprim–sulfamethoxazole has been shown to be effective as an off-label oral agent, although data regarding efficacy are mixed. For practical purposes, physical modalities are useful only as adjunctive measures. Shaving the head will cure head lice, but has poor patient acceptance in most cultures. Wet combing produces a cure rate of only 38% when used alone. Occlusive agents that asphyxiate the louse have great appeal because of their lack of toxicity. Those currently available are best used as adjunctive therapy, together with a pediculicide. Simple public health measures are also of value when epidemics of louse infestation occur in schools. Hats, scarves, and jackets should be stored separately under each child's desk. Louse education and inspections by the school nurse facilitate targeted treatment of infested individuals.

Pediculosis Corporis

Pediculosis corporis (pediculosis vestimenti, "vagabond's disease") is caused by body lice that lay their eggs in the seams of clothing. The parasite obtains its nourishment by descending to the skin and taking a blood meal. Generalized itching is accompanied by erythematous and copper-colored macules, wheals, and lichenification. Secondary impetigo and furunculosis are common.

Body louse infestation is differentiated from scabies by the lack of involvement of the hands and feet. Infestation by both lice and scabies is common, and a given patient may suffer from lice, scabies and flea infestation.

Lice may live in clothing for 1 month without a blood meal. If discarding the clothing is feasible, this is best. Destruction of body lice can also be accomplished by laundering the clothing and bedding. Clothing placed in a dryer for 30 min at 65° C (149° F) is reliably disinfected. Pressing clothing with an iron, especially the seams, is also effective. Permethrin spray or 1% malathion powder can be used to treat clothing and reduce the risk of reinfestation.

Body lice are vectors for relapsing fever, trench fever, and epidemic typhus. These diseases are most prevalent among

refugee populations. The trench fever organism is also an important cause of endocarditis among the homeless.

Pediculosis Pubis (Crabs)

Pthirius pubis, the crab louse, is found in the pubic region, as well as hairy areas of the legs, abdomen, chest, axillae, and arms. Pubic lice may also infest the eyelashes and scalp. The lice spread through close physical contact, and are commonly transmitted sexually. A diagnosis of pediculosis pubis should initiate a search for other STDs, including HIV disease. Contaminated bedding is also a source of infestation. Pubic louse nits are attached to the hairs at an acute angle. Other than the presence of lice and nits in the hair, the signs and symptoms are similar to those of body louse infestation.

Occasionally, blue or slate-colored macules occur in association with pediculosis pubis. These macules, called *maculae cerulae*, are located chiefly on the sides of the trunk and on the inner aspects of the thighs. They are probably caused by altered blood pigments.

Treatment of pediculosis pubis is similar to that for head lice. The affected person's sexual contacts should be treated simultaneously. For eyelash involvement, a thick coating of petrolatum can be applied twice daily for 8 days, followed by mechanical removal of any remaining nits. Fluorescein is also effective. Clothing and fomites should be washed and dried by machine or laundered and ironed.

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Order Diptera

Order Diptera includes the two-winged biting flies and mosquitoes. Adult dipterids bite and spread disease, while larvae parasitize humans in the form of myiasis. Medically important families of flies include the *Tabanidae* (horsefly, deerfly, gadfly), which inflict extremely painful bites, and the *Muscidae* (housefly, stablefly, and tsetse fly). Tsetse fly bites transmit African trypanosomiasis. *Simulidae* include the black fly (buffalo gnat, turkey gnat), the vector of onchocerciasis. These flies are dark colored and "hunchbacked." They may produce extremely painful bites that may be associated with fever, chills, and lymphadenitis. Black flies are seasonal annoyances in the northern US and Canada.

Psychodidae sandflies (*Diptera: Phlebotominae*) are small, hairy-winged flies that transmit leishmaniasis, sandfly fever, and verruga peruana. Sandfly fever viruses are a problem in Africa, the Mediterranean basin, and Central Asia, and are carried by *Phlebotomus* flies. *Lutzomyia* flies are common in Latin America and South Texas.

Culicidae, or mosquitoes, are vectors of many important diseases, such as filariasis, malaria, dengue, and yellow fever. Their bites may cause severe urticarial reactions. *Ceratopogonidae*, the biting midges or gnats, fly in swarms and produce erythematous, edematous lesions at the site of their bite.

Mosquito Bites Moisture, warmth, CO_2, estrogens, and lactic acid in sweat attract mosquitoes. Drinking alcohol also stimulates mosquito attraction. Mosquito bites are a common cause of papular urticaria. More severe local reactions are seen in young children, individuals with immunodeficiency, and those with new exposure to indigenous mosquitoes. Both necrotizing fascitis and the hemophagocytic syndrome have been reported following mosquito bites, and exaggerated hypersensitivity reactions to mosquito bites are noted in a wide variety of Epstein-Barr virus (EBV)-associated lymphoproliferative disorders, especially natural killer (NK) cell proliferations. Mosquito bites may play a key role in reactivation of latent EBV infection.

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Ked Itch The sheep ked (*Melophagus ovinus*) feeds by thrusting its sharp mouth parts into the skin and sucking blood. Occasionally, it attacks woolsorters and sheepherders, causing pruritic, often hemorrhagic papules, nearly always with a central punctum. Deer keds attack humans in a similar way. The papules are very persistent and may last for up to 12 months. Favorite locations are the hips and the abdomen.

Myiasis Myiasis is the infestation of human tissue by fly larvae. Forms of infestation include wound myiasis, furuncular myiasis, plaque myiasis, creeping dermal myiasis and body cavity myiasis. Wound myiasis occurs when flies lay their eggs in an open wound. Furuncular myiasis often involves a mosquito vector that carries the fly egg. Plaque myiasis typically involves many maggots and occurs after flies lay their eggs on clothing. Creeping myiasis develops when the larvae of the *Gasterophilus* fly wander intradermally. The most common species are *Gasterophilus nasalis* and *Gasterophilus intestinalis*. An itching pink papule develops, followed by a tortuous line that extends by 1 to 30 cm a day. Body cavity myiais may involve the orbit, nasal cavity, gastrointestinal tract, or urogenital system.

The human botfly, *Dermatobia hominis*, is a common cause of furuncular myiasis (Fig. 20-39) in the neotropical regions of the New World. The female glues its eggs to the body of a mosquito, stablefly, or tick. When the unwitting vector punctures the skin by biting, the larva emerges from the egg and enters the skin through the puncture wound. Over a period of several days a painful furuncle develops in which the larva is present. Other larvae that frequently cause furuncular lesions in North America are the common

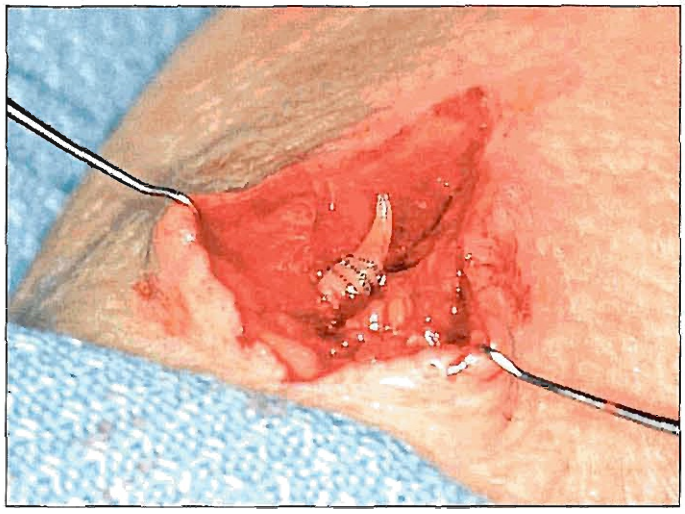

Fig. 20-39 Myiasis.

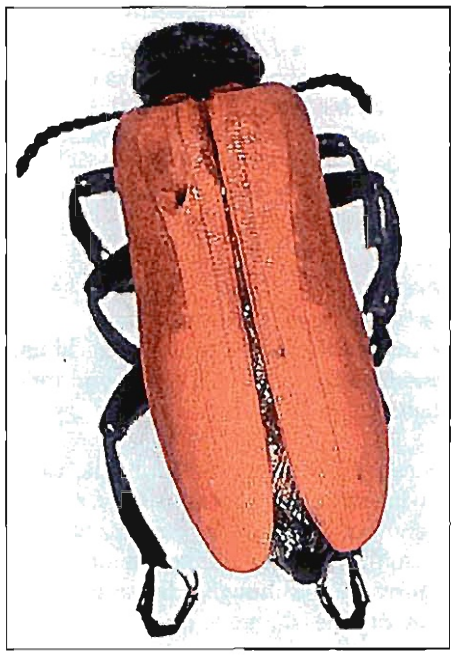

Fig. 20-40 Blister beetle.

cattle grub (*Hypoderma lineatum*), rabbit botfly (*Cuterebra cuniculi*), and *Wohlfahrtia vigil*. This last fly can penetrate infant skin, but not adult skin. Thus, nearly all reported cases have occurred in infants. The New World screw worm, *Cochliomyia hominivorax*, often involves the head and neck region. Larvae of Calliphoridae flies, especially *Phaenicia sericata*, the green blowfly, cause wound myiasis. Other blowflies, flesh flies (Sarcophagidae), and humpbacked flies (Phoridae) are less common causes of wound myiasis. In tropical Africa the Tumbu fly (*Cordylobia anthropophaga*) deposits her eggs on the ground or on clothing. The young maggots penetrate the skin and often form a plaque with many furuncular-appearing lesions. *Cordylobia ruandae* and *Cordylobia rodhaini* are less frequent causes of plaque myiasis.

Removal of the maggots of furuncular myiasis can be accomplished by injection of a local anesthetic into the skin, which causes the larva to bulge outward. The opening of the furuncle can also be occluded with hair gel, surgical lubricant, lard, petrolatum, or bacon, causing the larva to migrate outward.

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Safdar N, et al: Autochthonous furuncular myiasis in the United States: case report and literature review. Clin Infect Dis 2003; 36:e73.

Tamir J, et al: Myiasis with Lund's fly (*Cordylobia rodhaini*) in travelers. J Travel Med 2003;10:293.

Order Coleoptera

Blister Beetle Dermatitis Blister beetle (Fig. 20-40) dermatitis occurs after contact with several groups of beetles. The *Meloidae* and *Oedemeridae* families produce injury to the skin by releasing a vesicating agent, cantharidin. Members of the family *Staphylinidae* (genus *Paederus*) contain a different vesicant, pederin. None of the beetles bites or stings; rather, they exude their blistering fluid if they are brushed against, pressed, or crushed on the skin. Many blister beetles are attracted at night by fluorescent lighting.

Slight burning and tingling of the skin occur within minutes, followed by the formation of bullae, often arranged in a linear fashion. "Kissing lesions" are observed when the blister beetle's excretion is deposited in the flexures of the elbows or other folds. Ingestion of beetles or cantharidin results in poisoning, presenting with hematuria and abdominal pain. In many tropical and subtropical habitats, rove beetles (genus *Paederus*) produce a patchy or linear erythematous vesicular eruption. In parts of South America, it is known as *podo*. It occurs frequently during the rainy season and appears predominantly on the neck and exposed parts. In the American southwest, outbreaks of rove beetle dermatitis have followed unusually rainy periods. In southeastern Australia, corneal erosions are caused by small Corylophidae beetles (*Orthoperus spp*).

Treatment consists of drainage of the bullae and application of cold wet compresses and topical antibiotic preparations. Early cleansing with acetone, ether, soap, or alcohol may be helpful to remove cantharidin.

Other Beetles Papulovesicular and urticarial dermatitis is caused by the common carpet beetle (Dermestidae: *Anthrenus scrophulariae*). The eruption involves the chest, neck, and forearms. The larvae inhabit warm houses throughout the winter months. They are reddish brown, fusiform, about 6 mm long, and covered by hairs. A generalized pruritic eruption has been attributed to the larvae of the carpet beetle *Anthrenus verbasci*. Bombardier beetles of the family Carabidae (subfamily Brachininae) can cause skin burns with a deep yellow-brown color. Chemicals released when these beetles are crushed include acids, phenols, hydrocarbons, and quinines. When the beetle is threatened, chemical reactions produce an explosive spray of boiling hot benzoquinones from the tip of the abdomen. Dermestidae (skin beetles) and Cleridae (bone beetles) infest exposed human remains and are useful in estimating the postmortem interval.

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Order Hymenoptera

Hymenopterids include bees, wasps, hornets, and ants. Stings by any of these may manifest the characteristic clinical and histologic features of eosinophilic cellulitis (Wells syndrome) complete with flame figures.

Bees and Wasps Yellowjackets are the principal cause of allergic reaction to insect stings, because they nest in the ground or in walls and are disturbed by outdoor activity, such as gardening or lawn mowing. Bees are generally docile and sting only when provoked, although Africanized bees display aggressive behavior. The allergens in vespid venom are phospholipase, hyaluronidase, and a protein known as *antigen 5*. Bee venom contains histamine, mellitin, hyaluronidase, a high molecular weight substance with acid phosphatase activity, and phospholipase A. The barbed ovipositor of the honeybee is torn out of the bee and remains in the skin after stinging. The bumble bee, wasp, and hornet are able to withdraw their stinger.

The reaction to these stings ranges from pain and mild local edema to exaggerated reactions that may last for days. Serum sickness, characterized by fever, urticaria, and joint pain may occur 7 to 10 days after the sting. Severe anaphylactic shock and death may occur within minutes of the sting. Most hypersensitivity reactions have been shown to be mediated by specific IgE antibodies. Anaphylaxis to vespids may also be the presenting symptom of mastocytosis, with no demonstrable specific IgE against wasp venom.

Treatment of local reactions consists of immediate application of ice packs or topical anesthetics. Chronic reaction sites may be injected with triamcinolone suspension diluted to 5 mg/mL with 2% lidocaine. Oral prednisone may be required for severe local reactions.

For severe systemic reactions, 0.3 mL of epinephrine (1:1000 aqueous solution) is injected intramuscularly. This may need to be repeated after 10 min. Susceptible persons should carry a source of injectable epinephrine. Corticosteroids and epinephrine may be required for several days following severe reactions. Hyposensitization by means of venom immunotherapy can reduce the risk of anaphylaxis in people at risk. Those at risk should be evaluated by an allergist.

Ants The sting of most ants is painful, but that of the fire ants (*Solenopsis invicta*, *Solenopsis geminata*, or *Solenopsis richteri*) is especially painful. Fire ants are vicious and will produce many burning, painful stings within seconds if their mound is disturbed. The sting causes intense pain and whealing. Later, an intensely pruritic sterile pustule develops at the site (Fig. 20-41). Anaphylaxis, seizures, and mononeuropathy have been reported. The sting of harvester ants and soldier ants may produce similar reactions. Treatment options are similar to those for vespid stings.

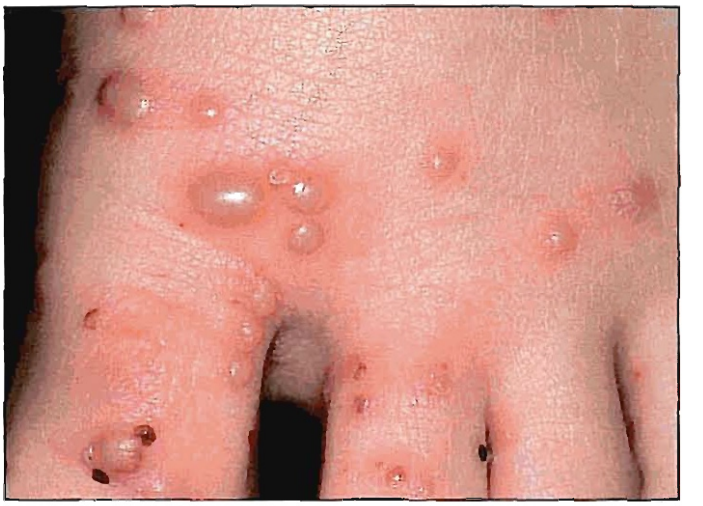

Fig. 20-41 Sterile pustules at the site of fire ant stings.

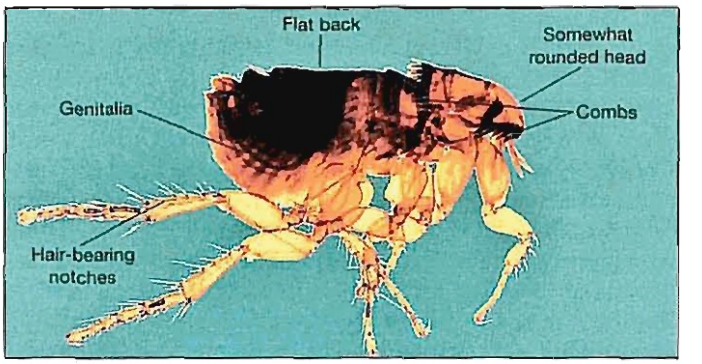

Fig. 20-42 Cat flea.

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Order Siphonaptera

Fleas are wingless, with highly developed legs for jumping. They are blood-sucking parasites, infesting most warm-blooded animals. Fleas are important vectors of plague, endemic typhus, brucellosis, melioidosis, and erysipeloid.

Pulicosis (Flea Bites) The species of fleas that most commonly attack humans are the cat flea (*Ctenocephalides felis*) (Fig. 20-42), human flea (*Pulex irritans*) (Fig. 20-43), dog flea (*Ctenocephalides canis*), and oriental rat flea (*Xenopsylla cheopis*) (Fig. 20-44). The stick tight flea (*Echidnophaga gallinacea*) (Fig. 20-45), mouse flea, (*Leptopsylla segnis*), and chicken flea (*Ceratophyllus gallinae*) are sometimes implicated.

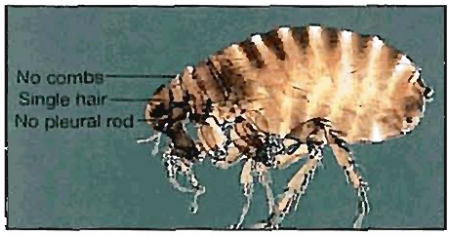

Fig. 20-43 Human flea.

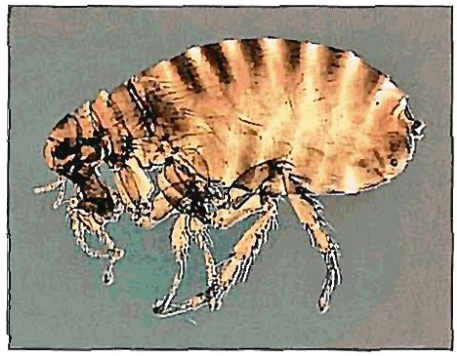

Fig. 20-44 Oriental rat flea.

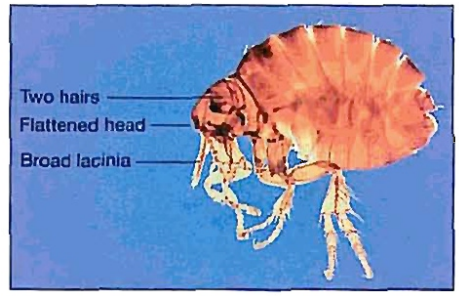

Fig. 20-45 Stick-tight flea.

Fleas are small, brown insects about a 16th of an inch long, flat from side to side, with long hind legs. They slip into clothing or jump actively when disturbed. They bite about the legs and waist and may be troublesome in houses where there are dogs or cats. The lesions are often grouped and may be arranged in zigzag lines. Hypersensitivity reactions may appear as papular urticaria, nodules or bullae. Camphor and menthol preparations, topical corticosteroids, and topical anesthetics can be of benefit.

Vectors of Disease *Xenopsylla cheopis* and *Xenopsylla braziliensis* are vectors of plague and endemic typhus. The cat flea (*Ctenocephalides felis*) is the vector for *R. felis*. Plague and tularemia are transmitted by the squirrel flea, *Diamanus montanus*. Several species of flea are intermediate hosts of the dog tapeworm and rat tapeworm, which may be an incidental parasite of humans.

Tungiasis Tunga penetrans is also known as *nigua, the chigoe, sand flea*, or *jigger*. It is a reddish-brown flea about 1 mm long. It resides in the Caribbean, equatorial Africa, Central and South America, India, and Pakistan. It was first reported in crewmen who sailed with Christopher Columbus.

The impregnated female chigoe burrows into the skin, often adjacent to a toenail. The eggs develop and drop to the ground. These eggs develop into larvae, which form cocoons from which the insects emerge in about 10 days. Skin lesions are pruritic swellings the size of a small pea. These may occur on the ankles, feet, soles, as well as the anogenital areas. The lesions become extremely painful and secondarily infected.

Curettage or excision of the burrows is recommended. Topical ivermectin, metrifonate or thiabendazole can be used, and oral thiabendazole, 25 mg/kg/day, has been effective in heavily infested patients. Antibiotics should be used for the secondary infection and tetanus prophylaxis given. These lesions can be prevented by the wearing of shoes. Infested ground and buildings may be disinfected by the use of insecticides and growth inhibitors.

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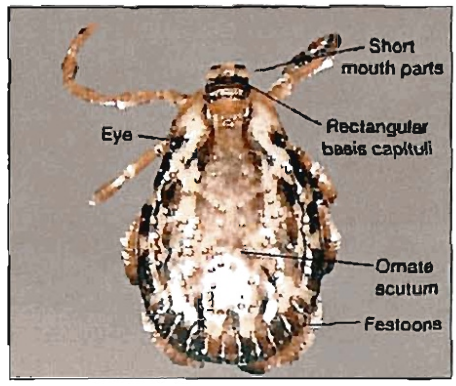

Fig. 20-46 Dermacentor variabilis.

CLASS ARACHNIDA

Arachnida includes the ticks, mites, spiders, and scorpions. Adult and nymph stages of arachnids have four pairs of legs, while larval forms have six legs. Their bodies consist of cephalothorax and abdomen, in contrast to insects which have three body segments.

Order Acarina

Tick Bite Several varieties of the family *Ixodidae* (hard ticks) and *Argasidae* (soft ticks) will attack human skin, but only hard ticks remain attached. In the US, the wood tick (*Dermacentor andersoni*) is an important disease vector in western states. It carries Rocky Mountain spotted fever, tularemia, ehrlichiosis, and Colorado tick fever. The dog tick (*Dermacentor variabilis*) (Fig. 20-46) is prevalent in the eastern states, and is the most common vector of Rocky Mountain spotted fever. It also carries tularemia. The brown dog tick (*Rhipephalus sanguineus*) (Fig. 20-47) is a vector of Rocky Mountain spotted fever, tularemia, and Boutonneuse fever. The lone star tick (*Amblyomma americanum*) (Fig. 20-48) carries Rocky Mountain spotted fever, tularemia, and human monocytic ehrlichiosis. *Ixodes ricinus* in Europe and *Ixodes scapularis* and *Ixodes pacificus* in the US transmit *Borrelia burgdorferi*, the cause of Lyme disease. Ixodes ticks also transmit human granulocytic ehrlichiosis and babesiosis.

The female hard tick attaches itself to the skin by sticking its proboscis into the flesh to suck blood from the superficial vessels. The insertion of the hypostome is generally unnoticed by the subject. The attached tick may be mistaken by the patient as a new mole. The parasite slowly becomes engorged and then falls off. During this time, which may last

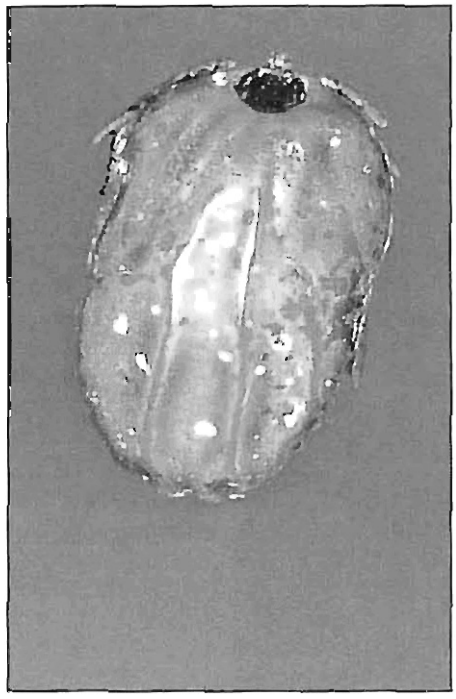

Fig. 20-47 Rhipicephalus tick, engorged female.

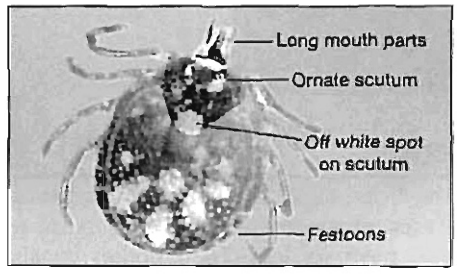

Fig. 20-48 Lone star tick.

for 7 to 12 days, the patient may suffer from fever, chills, headache, abdominal pain, and vomiting. This is called *tick bite pyrexia*. Removal of the engorged tick causes a subsidence of the general symptoms in 12 to 36 h.

The bites may be followed by small, severely pruritic, fibrous nodules (tick bite granulomas) that persist for months, or by pruritic circinate and arciform localized erythemas that may continue for months.

Tick Paralysis Tick paralysis most commonly affects children, and carries a mortality rate of about 10%. Flaccid paralysis begins in the legs, then the arms, and finally the neck, resembling Landry-Guillain-Barré syndrome. Bulbar paralysis, dysarthria, dysphagia, and death from respiratory failure may occur. Prompt recovery occurs if the tick is found and removed before the terminal stage. *Dermacentor* ticks in North America and *Ixodes* ticks in Australia are the most important causes of tick paralysis. As *Dermacentor* ticks commonly attach to the scalp, the tick may go unnoticed.

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Mites

Scabies

Sarcoptes scabiei, the itch mite, is an oval, ventrally flattened mite with dorsal spines. The fertilized female burrows into the stratum corneum and deposits her eggs. Scabies is characterized by pruritic papular lesions, excoriations, and burrows. Sites of predilection include the finger webs, wrists, axillae, areolae, umbilicus, lower abdomen, genitals, and buttocks. An imaginary circle intersecting the main sites of involvement—axillae, elbow flexures, wrists and hands, and crotch—has long been called the *circle of Hebra*. In adults, the scalp and face are usually spared, but in infants lesions are commonly present over the entire cutaneous surface. The burrows appear as slightly elevated, grayish, tortuous lines in the skin. A vesicle or pustule containing the mite may be noted at the end of the burrow, especially in infants and children. To identify burrows quickly, a drop of India ink or gentian violet can be applied to the infested area, then removed with alcohol. Thin threadlike burrows retain the ink.

The eruption varies considerably, depending on the length of infestation, previous sensitization, and previous treatment. It also varies with climate and the host's immunologic status. Lichenification, impetigo, and furunculosis may be present. Bullous lesions may contain many eosinophils, resembling bullous pemphigoid. Positive immunofluorescent findings may also be noted. Scabies may also resemble Langerhans cell histiocytosis clinically and histologically. Misdiagnosis has lead to systemic treatment with toxic agents.

Dull red nodules may appear during active scabies; these are 3 to 5 mm in diameter, may or may not itch, and persist on the scrotum, penis, and vulva. Intralesional steroids, tar, or excision are methods of treatment for this troublesome condition, termed *nodular scabies*. Histologically, the lesions may suggest lymphoma.

Crusted scabies (Norwegian, or hyperkeratotic, scabies) is found in immunocompromised or debilitated patients, including those with neurologic disorders, Down syndrome, organ transplants, graft-versus-host disease, adult T-cell leukemia, leprosy, or AIDS. In these patients, the infestation assumes a heavily scaling and crusted appearance. Crusts and scales teem with mites, and there is involvement of the face and especially the scalp. Itching may be slight. Psoriasis-like scaling is noted around and under the nails. The tips of the fingers are swollen and crusted; the nails are distorted. Severe fissuring and scaling of the genitalia and buttocks may be present. Pressure-bearing areas are the sites of predilection for the heavy keratotic lesions, in which the mites may abound.

Scabies is usually contracted by close personal contact, although it may also be transmitted by contaminated linens and clothing. Screening for other STDs is appropriate. Sensitization begins about 2 to 4 weeks after onset of infection. During this time the parasites may be on the skin and may burrow into it without causing pruritus or discomfort. Severe itching begins with sensitization of the host. In reinfections, itching begins within days and the reaction may be clinically more intense. The itching is most intense at night, whereas during the daytime the pruritus is tolerable but persistent. The eruption does not involve the face or scalp in adults. In

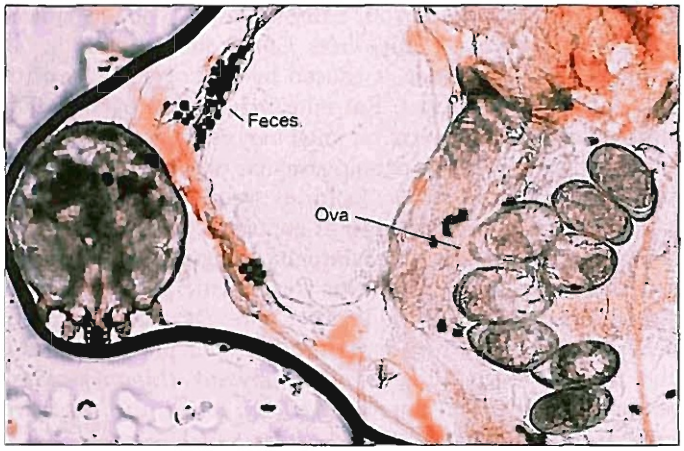

Fig. 20-49 Scabies mite, ova, and feces.

women, itching of the nipples associated with a generalized pruritic papular eruption is characteristic; in men, itchy papules on the scrotum and penis are equally typical. When more than one member of the family has pruritus, a suspicion of scabies should be aroused. Whenever possible, though, it is advisable to identify the mite, as a diagnosis of scabies usually requires treatment of close physical contacts in addition to the patient. Because scabies cannot always be excluded by examination, treatment on presumption of scabies is sometimes necessary.

Positive diagnosis is made only by the demonstration of the mite under the microscope (Fig. 20-49). A burrow is sought and the position of the mite is determined. A surgical blade or sterile needle is used to remove the parasite. A drop of mineral or immersion oil can be placed on a lesion and gently scraped away with the epidermis beneath it. The majority of mites are found on the hands and wrists, less frequently (in decreasing order) at the elbows, genitalia, buttocks, and axillae. Children have often gathered mites and ova under the nails when scratching. A blunt curette can be used to gather material from under the nails for examination.

Permethrin 5% cream (Elimite) is the most widely used medication for scabies. It is a synthetic pyrethroid that is lethal to mites and has low toxicity for humans. Lindane (γ-benzene hexachloride) is also effective, with a low incidence of adverse effects when used properly. Because of the availability of less toxic agents, lindane is rarely used as a first-line agent. In much of the world, benzyl benzoate and 10% precipitated sulfur in white petrolatum are used to treat scabies. The scabicide should be thoroughly rubbed into the skin from the neck to the feet, with particular attention given to the creases, perianal areas, umbilicus, and free nail edge and folds. It is washed off 8 to 10 h later. Clothing and bed linen are changed and laundered thoroughly. Crotamiton (Eurax) has a lower cure rate than other available agents. When used, it should be applied on 5 successive nights and washed off 24 h after the last use.

Ivermectin has been used to control onchocerciasis since 1987, and is marketed in the US for the treatment of strongyloides. Numerous publications attest to its efficacy in treating scabies. It is supplied as 3- and 6-mg pills, and is usually given at a dose of 200 μg/kg. Although an oral treatment is very convenient, it may not be any more effective than topical therapy. In the crusted type, it should be used in conjunction with a topical agent. It may need to be repeated two or three times at intervals of 1 to 2 weeks. The drug appears to have a good margin of safety, although neurotoxicity may be possible.

Individuals in close contact with the patient should be treated. Scabies in long-term healthcare institutions is an increasing problem. Other residents, staff, and visitors may be affected, and delays in treating close contacts may result in large numbers requiring treatment.

Animal Scabies. Zoonotic scabies and scab mites may affect humans who come in close contact with the animal. The reaction resembles scabies, but runs a self-limited course. Burrows are usually absent.

Other Mite Diseases

Demodex Mites. *Demodex folliculorum* is a vermiform mite that inhabits the pilosebaceous units of the nose, forehead, chin, and scalp. The mite has a flattened head, four pairs of short, peglike legs, and an elongated abdomen. *Demodex brevis* is shorter, and is more commonly found on the trunk.

In dogs, the lesions of demodectic mange contain numerous mites. In humans, numerous mites have been found in skin lesions, and yet demodectic disease has not been as well accepted. There are convincing reports of demodectic blepharitis, demodectic folliculitis, demodectic abscess, and demodectic alopecia that respond to eradication of the mites. Some rosacea-like lesions may also be caused by *Demodex*. Treatment of the eruptions in which *Demodex* has been implicated consists of applying permethrin, sulfur, lindane, benzyl benzoate, or benzoyl peroxide. Oral ivermectin and metronidazole have also been used.

Cheyletiella Dermatitis. *Cheyletiella yasguri*, *Cheyletiella blakei* (Fig. 20-50), and *Cheyletiella parasitovorax* are three species of nonburrowing mites that are parasitic on dogs, cats, and rabbits, respectively, where they present as "walking dandruff." They may bite humans when there is close contact with the animals, producing an itchy dermatitis resembling scabies or immunobullous disease. The mites are similar in diameter to *Sarcoptes scabiei*, but are elongated and have prominent anterior hooked palps. They may be found by brushing the animal's hair over a dark piece of paper. The brushings can be placed in alcohol, where the scales and hair sink while the mites float. The pet should by treated by a qualified veterinarian.

Chigger Bite. The trombiculid mites are known as *chiggers*, *mower's mites*, or *red bugs*. In North America *Eutrombicula alfreddugesi* attacks humans and animals. In Europe, the harvest mite, *Neotrombicula autumnalis*, is a common nuisance. Attacks occur chiefly during the summer

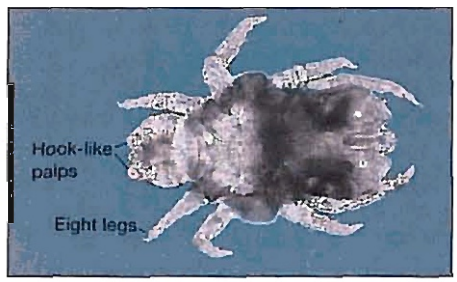

Fig. 20-50
Cheyletiella blakei.

and fall, when individuals have more frequent contact with mite-infested grass and bushes. The lesions occur chiefly on the legs, and at the belt line and other sites at which clothing causes constriction. Penile lesions are common in males. Lesions generally consist of severely pruritic hemorrhagic puncta surrounded by red swellings. On the ankles, intensely pruritic grouped excoriated papules are noted. Several varieties of trombiculid mites in East Asia and the South Pacific are vectors of scrub typhus (tsutsugamushi fever).

Gamasoidosis. Persons in contact with canaries, pigeons, and poultry are prone to develop gamasoidosis. The dermatosis occurs chiefly on the hands and arms, where the bite produces inflammatory, itchy papules. Any area on the body may be attacked and common additional sites are the groin, areolae, umbilicus, face, and scalp. The mites may wander from birds' nests as soon as the young birds begin to fly, and they may infest terrace cushions and furniture. In large metropolitan areas, especially where pigeons tend to gather, it is not unusual to see pigeons roosting on window ledges. Through the open windows or even through air conditioners the pigeon mites attack humans and cause urticarial and papular eruptions. The tropical fowl mite (*Ornithonyssus bursa*), widely prevalent in wild birds in both continental US and Hawaii, may do this as well.

Two genera of mites, *Ornithonyssus* and *Dermanyssus*, commonly infest birds. *Ornithonyssus bursa* and *Ornithonyssus sylvarium* are the two common species of feather mites. *Dermanyssus gallinae*, the red or chicken mite, is also a common parasite of birds. *Dermanyssus* mites may carry *Erysipelothrix rhusiopathiae*. *Dermanyssus gallinae* tends to leave the bird during the day and hide in cracks and crevices, and therefore can be killed without direct treatment of the bird. Thorough spraying of the surroundings with an agent such as malathion is effective. Mites of the *Ornithonyssus* group require treatment of the birds themselves.

Grocer's Itch. This is a pruritic dermatitis of the forearms, with occasional inflammatory and urticarial papules on the trunk. It results from the handling of figs, dates, and prunes when it is caused by *Carpoglyphus passularum*, or from exposure to the cheese mite (*Glyciphagus domesticus*). This must be distinguished from grocer's eczema caused by sensitization to flour, sugar, cinnamon, chocolate, and similar items.

Grain Itch. Grain itch is also known as *straw itch*, *barley itch*, *mattress itch*, and *prairie itch*. Causative mites include *Pyemotes tritici*, *Pyemotes ventricosus*, *Cheyletus malaccensis*, and *Tyrophagus putrescentiae* (the copra itch mite). Those chiefly affected are harvesters of wheat, hay, barley, oats, and other cereals, or farm hands and packers who have contact with straw. Grain itch has a typical lesion consisting of an urticarial papule on which is a small vesicle. There is intense pruritus, with lesions occurring predominantly on the trunk. Frequently, there is a central hemorrhagic punctum in the beginning that rapidly turns into an ecchymosis with hemosiderin pigmentation.

Other Mite-Related Dermatitis. *Lepidoglyphus destructor* is the hay mite. There have been outbreaks of *Pyemotes boylei* bites in homes fumigated for termites. Although mites do not appear capable of survival when forced to share an environment with termites, they thrive in locations in which there are termite carcasses. Vanillism is a dermatitis caused by *Acarus siro* and occurs in workers handling vanilla pods. Copra itch occurs on persons handling copra who are subject to *Tyrophagus longior* mite bites. Coolie itch is found in tea plantations in India and is caused by *Rhizoglyphus parasiticus*. It causes sore feet. Rat mite itch caused by *Ornithonyssus bacoti*, the tropical rat mite, may result in an intensely pruritic dermatitis. This papulovesicular urticarial eruption is seen in workers in stores, factories, warehouse, and stockyards. The rat mite may transmit endemic typhus, Rickettsial pox, equine encephalitis, tularemia, plague, and relapsing fever. Feather pillow dermatitis is a pruritic papular dermatitis traced to the Psoroptid carpet mite, *Dermatophagoides scheremetewskyi*, which may infest feather pillows. Finally, the house mouse mite, *Allodermanyssus (Liponyssoides) sanguineus*, is the vector of *Rickettsia akari*, the causative organism of rickettsialpox.

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Order Scorpionidae

Scorpion Sting Scorpions (Fig. 20-51) are different from other arachnids in that they have an elongated abdomen

Fig. 20-51 Common *Centruroides* scorpion.

ending in a stinger. They also have a cephalothorax, four pairs of legs, pincers, and mouth pincers. Two poison glands in the back of the abdomen empty into the stinger. Scorpions are found all over the world, especially in the tropics. They are nocturnal and hide during the daytime under table tops, in closets, shoes, and folded blankets. Ground scorpions may burrow into gravel and children's sandboxes. The most venomous species include *Tityus serrulatus*, found in Brazil, *Buthotus tamulus*, found in India, *Leiurus quinquestriatus* and *Androctonus crassicauda*, found in North Africa and southwest Asia, and *Centruroides suffussus*, found in Mexico. *Centruroides exilicauda* and *sculpturatus* are the most toxic scorpion in the United States.

Scorpions sting only by accident or in self-defense. The venom causes pain, paresthesia, and variable swelling at the site of the sting. The sting of the Egyptian scorpion (*Leiurus quinquestriatus*) has a mortality rate of 50% in children. The neurotoxic venom may produce numbness at the sting site, laryngeal edema, profuse sweating and salivation, cyanosis, nausea, and paresthesia of the tongue. There is little or no visible change at the site of the sting. Death may occur from cardiac or respiratory failure, especially in children.

Treatment depends on the species and toxic symptoms. Antiarrhythmics, antiadrenegic agents, vasodilators, and calcium-channel blockers may be required. Antivenin is available for many species of scorpion.

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Order Arachnidae

Arachnidism Spiders are prevalent throughout the world. Most are beneficial to humans, as they trap many insects, but a few species are dangerous to humans. Many spider venoms are not well characterized, and in most cases of envenomation, the responsible spider is never identified. The Brazilian armed spider (*Phoneutria nigriventer*) is well characterized. Its venom contains neurotoxins that may be fatal in children.

Latrodectism The various species of *Latrodectus* have similar toxins and cause similar reactions in humans. The black widow spider, *Latrodectus mactans*, is of chief concern in the continental US. It may also be found in the Caribbean. Black widows are web-building spiders, and are commonly found in woodpiles and under outhouse seats. Their venom is more potent than that of related brown widow spiders. *Latrodectus curacavienis* is native to South America, and Australia and New Zealand have related red-black spiders (*Latrodectus mactans* hasselti). *Latrodectus indistinctus* is found in Africa, and the brown widow, *Latrodectus geometricus* is native to southern Africa and Madagascar.

The female *Latrodectus mactans* (Fig. 20-52) spider is 13 mm long, shiny black, with a red hourglass-shaped marking on its abdomen. The legs are long, with a spread of up to 4 cm. The black widow spider is not aggressive, and bites only when disturbed. Severe pain usually develops within a few minutes and spreads throughout the extremities and trunk. Within a few hours there may be chills, vomiting, violent cramps, delirium or partial paralysis, spasms, and abdominal rigidity. The abdominal pains are frequently most severe and may be mistaken for appendicitis, colic, or food poisoning. Toxic morbilliform erythema may occur.

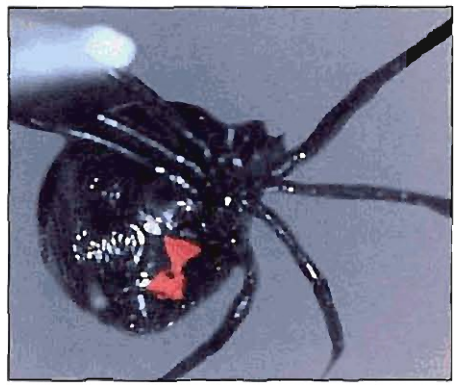

Fig. 20-52 Black widow.

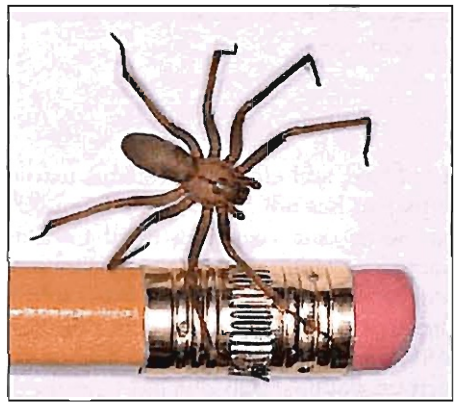

Fig. 20-53 Brown recluse spider.

Antivenin is indicated for severe symptoms of envenomation. Benzodiazepines reduce the associated tetany.

Loxoscelism The brown recluse spider (*Loxosceles reclusa*) (Fig. 20-53) is the major cause of necrotic arachnidism in the US. It is most common in the lower Midwest and Southwest. This reclusive spider may be identified by a dark, violin-shaped marking over the cephalothorax and three sets of eyes, rather than the usual four. It is light brown, about 1 cm long, with a small body and long delicate legs. It is found in storage closets, basements, cupboards, and among clothing. Outdoors it has been found in woodpiles, grass, on rocky bluffs, and in barns. It stings in self-defense. *Loxosceles rufescens*, *Loxosceles desert*, and *Loxosceles arizonica* cause lesser degrees of skin necrosis. *Loxosceles laeta* occurs throughout Latin America and produces changes similar to those of *Loxosceles reclusa*. The venom contains a phospholipase enzyme, sphingomyelinase D, which is the major toxin. Hyaluronidase contributes to a gravity-dependent spread of the necrotic lesions.

In the localized type of reaction, known as *necrotic cutaneous loxoscelism*, extensive local necrosis develops (Fig. 20-54). A painful severe edematous reaction occurs within the first 8 h, with development of a bulla with surrounding zones of erythema and ischemia. In about a week the central portion becomes dark, demarcated, and gangrenous. Systemic loxoscelism is rare, but may be associated with minor appearing bite reactions. Systemic toxic symptoms are associated with disseminated intravascular coagulation.

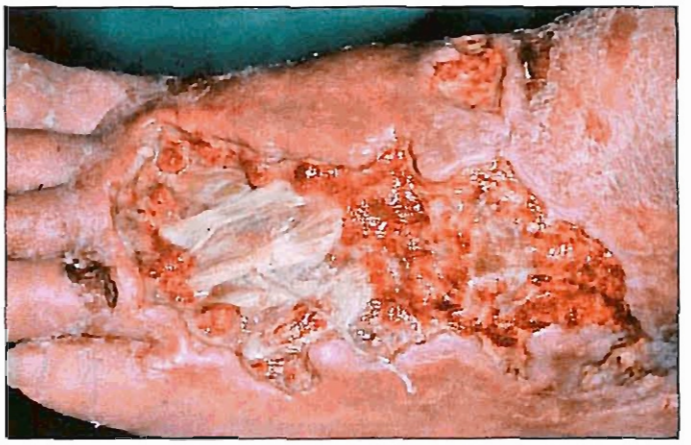

Fig. 20-54 Brown recluse spider bite.

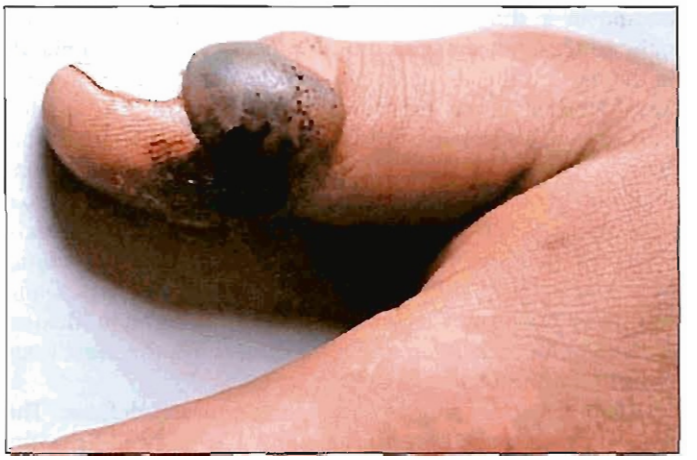

Fig 20-55 Snake bite.

Treatment

Treatment consists of rest, ice, and elevation. Tetanus toxoid should be given if the patient has not received the immunization within 10 years. Some data suggest a trend towards better outcome with injections of intralesional triamcinolone, and there are anecdotal reports of sparing of necrosis in the injected site, while the area above and below the injection site show necrosis. Antibiotics and conservative debridement may be needed for necrotic wounds. Dapsone has been used, but some studies show that it is no better than placebo, and it may be toxic, especially in the setting of venom-induced hemolysis.

Funnel web spiders Funnel web spiders include *Tegenaria agrestis* (the hobo spider or aggressive house spider of the Pacific Northwest) and *Atrax robustus* (the Sydney funnel web spider of Australia). Australian funnel web spiders are dangerous, but antivenin is available.

Tarantulas (Lycosoidae: Theraphosidae) Tarantulas are large hairy hunting spiders. American species have urticating hairs that produce cutaneous wheal and flare reactions and embed in the cornea causing ophthalmia nodosa.

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PHYLUM CHORDATA

Stingray Injury

The two stingray families (*Dasyatidae* and *Myliobatidae*) are among the most venomous fish known to man. Attacks generally occur as a result of an unwary victim stepping on a partially buried stingray. A puncture-type wound that later ulcerates occurs about the ankles or feet. Sharp, shooting pain develops immediately, with edema and cyanosis. Symptoms of shock may occur.

Persons wading in shallow, muddy waters where stingrays may be found should shuffle their feet through the mud to frighten the fish away. Successful treatment is usually attained by immersing the injured part in hot water for 30 to 60 min. The water should be as hot as can be tolerated, since the venom is detoxified by heat. Meperidine hydrochloride administered intravenously or intramuscularly may be necessary. If the ulcer remains unhealed after 8 weeks, excision is indicated.

Snake Bite

Venomous snake bites are a serious problem in some parts of the world. In the US the rattlesnake, cotton-mouth moccasin, copperhead and coral snake are the venomous snakes most frequently encountered. Patients are usually young men, with 98% of bites on the extremities, most often the hands or arms (Fig. 20-55). Nearly 30 enzymes are found in snake venom, most of which are hydrolases. Snake venom has effects on the cardiovascular, hematologic, respiratory, and nervous systems. Local effects at the bite site include the rapid onset of swelling, erythema, and ecchymosis. In more severe reactions bullae and lymphangitis may appear. Fang marks are often visible and pain is common, except with Mojave rattlesnake bites. Antivenin is of great value. In addition antibiotics and antitetanus measures are often needed.

Lizard Bite

Heloderma suspectum (the Gila monster) is found chiefly in Arizona and New Mexico. Another venomous lizard is the beaded lizard of southwestern Mexico (*Heloderma*

horridum). Bites from these poisonous lizards may cause paralysis, dyspnea, and convulsions. Systemic toxicity usually resolves spontaneously with supportive care within 1 or 2 days. Death is rare. There is no antivenom.

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CHAPTER

21 Chronic Blistering Dermatoses

In the noninherited chronic blistering (vesicular or bullous) dermatoses, the cause of blistering is an autoimmune reaction, and the pattern of immunofluorescence is critical in establishing the diagnosis. Usually, antibodies are bound in perilesional skin and at the site of the earliest lesions. Lesional skin often fails to demonstrate deposits, and lower extremity skin may be prone to false-negative reactions. Salt-split skin preparations are useful in determining the site of deposition of the autoantibodies. A 1 M solution of NaCl predictably splits skin at the level of the lamina lucida. Localization of immune deposits to the roof or floor of this split is diagnostically useful. Immunoprecipitation and immunoblotting have helped to define the molecular targets of the autoantibodies.

Transient acantholytic dermatosis (Grover's disease) is an idiopathic nonimmune vesiculobullous disease that may mimic the histologic patterns of immunobullous disease, but shows no specific findings on direct immunofluorescence (DIF). Specific dermatoses of pregnancy are discussed under the differential diagnosis of herpes gestationis.

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PEMPHIGUS VULGARIS

Clinical Features

Pemphigus vulgaris (PV) is characterized by mucosal erosions, and thin-walled, relatively flaccid, easily ruptured bullae that appear on apparently normal skin and mucous membranes or on erythematous bases. The fluid in the bulla is clear at first but may become hemorrhagic or even seropurulent. The bullae rupture to form erosions. The denuded areas soon become partially or totally covered with crusts that have little or no tendency to heal (Fig. 21-1). When they finally heal, lesions often leave hyperpigmented patches with no scarring.

PV usually appears first in the mouth (60% of cases) or at the site of a burn or other skin injury. Other common sites include the groin, scalp, face, neck, axillae, and genitals. The Nikolsky sign is present (intact epidermis shearing away from the underlying dermis leaving a moist surface). The sign is elicited by slight pressure, twisting or rubbing. The "bulla-spread phenomenon" (Asboe-Hansen sign) is elicited by pressure on an intact bulla, gently forcing the fluid to spread under the adjacent skin.

Short-lived bullae quickly rupture to involve most of the mucosa with painful erosions. The lesions extend onto the lips and form heavy, fissured crusts on the vermilion. Involvement of the throat produces hoarseness and difficulty in swallowing. The mouth odor is offensive. The esophagus may be involved, and sloughing of its entire lining in the form of a cast (esophagitis dissecans superficialis) may occur, even when the cutaneous disease appears to be well controlled. The conjunctiva, nasal mucosa, vagina, penis, and anus may also be involved. Chronic lesions may involve the face, scalp or flexures (Fig. 21-2). Widespread cutaneous

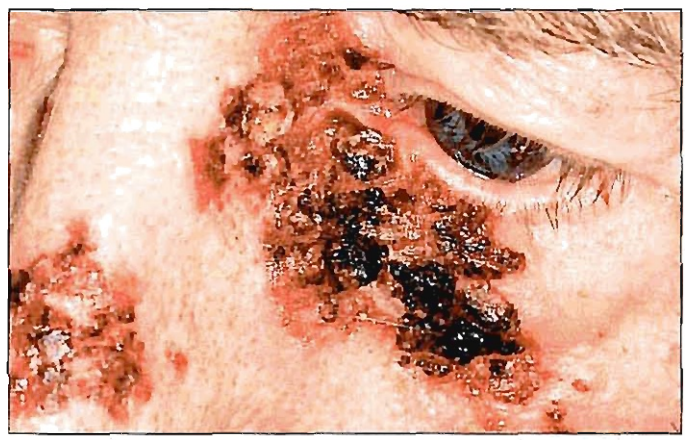

Fig. 21-1 Nonhealing crusted lesions of pemphigus vulgaris.

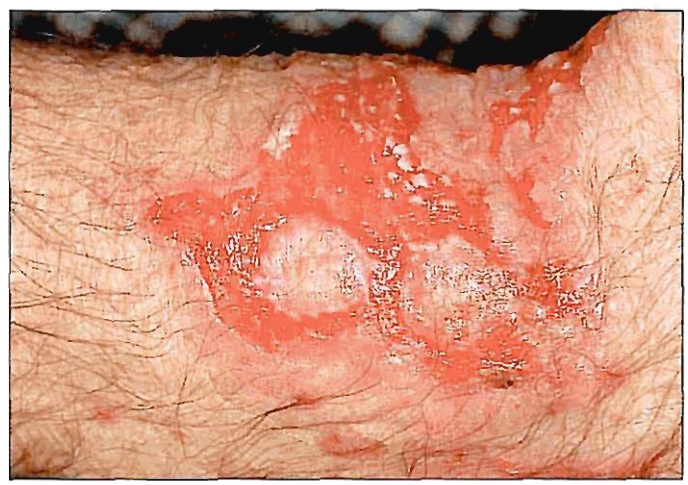

Fig. 21-2 Nonhealing erosions of pemphigus vulgaris.

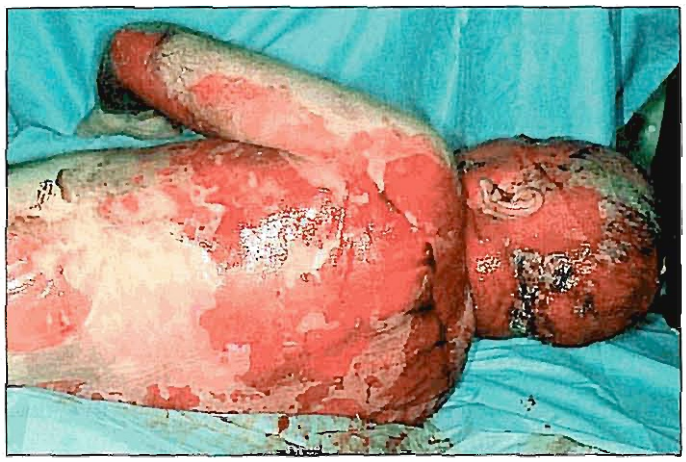

Fig. 21-3 Pemphigus vulgaris.

disease (Fig. 21-3) may cause death through sepsis or fluid and electrolyte imbalance.

The diagnosis is made by histology, immunofluorescence pattern of perilesional skin or plucked hairs, indirect immunofluorescence (IIF) testing of serum, or enzyme-linked immunosorbent assay (ELISA) testing for anti-desmoglein (Dsg)1 and -Dsg3 autoantibodies. As in other autoimmune diseases, specific antibodies may be present in relatives of patients with pemphigus who do not manifest any signs of disease.

Epidemiology

PV occurs with equal frequency in men and women, usually in their fifth and sixth decades. It is rare in young persons. The condition occurs more often in Jewish people and those of Mediterranean descent.

Etiologic Factors

Antibodies in PV are most commonly directed against Dsg3. The presence of antibodies to both Dsg1 and Dsg3 correlates with mucocutaneous disease. If autoantibodies are only directed against Dsg3, mucosal lesions predominate. Both humoral and cellular autoimmunity are important in the pathogenesis of skin lesions. Antibody alone can produce acantholysis, without complement or inflammatory cells. Both IgG1 and IgG4 autoantibodies to Dsg3 occur in patients with pemphigus, but some data suggest that the IgG4 antibodies are pathogenic. Plasminogen activator is associated with antibody-mediated acantholysis. Involved T-cells are usually CD4 α/β cells that secrete a T-helper 2 (Th2)-like cytokine profile, although Th1 cells may also be involved in antibody production in chronic disease. IgG is found in both involved and clinically normal skin. C3 deposits are heavier in acantholytic areas. DIF may remain positive for years after clinical remission, and conversion to negative predicts sustained remission after withdrawal of therapy. Pemphigus may be associated with myasthenia gravis and thymoma.

The PV antigen (130-kD transmembrane desmosomal glycoprotein) shows homology with the cadherin family of calcium-dependent cell-adhesion molecules. With IIF, circulating antibodies can be demonstrated in 80% to 90% of patients. Circulating intercellular antibodies may also be present in patients with thermal or actinic burns, and in patients with drug eruptions. These antibodies are not directed against Dsg3. They do not bind to the epidermis in vivo and may be directed against ABO blood-group antigens.

Penicillamine treatment of rheumatoid arthritis has induced pemphigus, most often of the foliaceous type. Nearly all the reported cases have had a positive DIF and more than half have had a positive IIF. Penicillamine and captopril may induce acantholysis in organ explant cultures in the absence of autoantibody. The doses responsible for induction of disease have ranged from 250 to 1500 mg/day, and were taken for an average of 13 months before the onset of pemphigus. A long list of drugs, including captopril, enalapril, penicillin, thiopronine, interleukin (IL)-2, nifedipine, piroxicam, and rifampicin, have also been reported to induce pemphigus. Many drugs implicated in inducing pemphigus contain either a sulfhydryl or an amide group. Only 10% to 15% of patients with drug-induced pemphigus have had oral lesions. Most disease resolves when the medication is discontinued, but some have persisted for many months.

Many studies have indicated a genetic predisposition to pemphigus. Statistical analysis shows a skewed distribution of various HLA antigens. Most patients are of HLA phenotype DR4 or DR6. In addition, a HLA-DQ β restriction fragment has been identified in many patients with pemphigus. HLA-G is associated with pemphigus in Jewish patients. Thus, there may be a genetically inherited susceptibility to the disease. Additionally, a predisposition to develop other autoimmune diseases may occur in relatives of pemphigus patients.

Histopathology

The characteristic findings consist of suprabasilar acantholysis with intraepidermal blister formation. Acantholytic cells are round and show no intercellular bridges. Regeneration of the epidermis occurs, and may cause the split to appear to be higher as cells regenerate beneath the cleft. At least some areas generally still demonstrate the characteristic tombstone row of basal keratinocytes underneath the bulla. An early intact bulla shows the most characteristic histology. Asboe–Hansen modification of the Nikolsky test may be used to extend the bulla beyond its original margin to where secondary regenerative changes have not taken place.

In early disease, spongiosis with eosinophils may be noted in the epidermis, in the absence of acantholysis. In the setting of immunobullous disease, spongiosis with eosinophils is more likely to represent pemphigoid than pemphigus, and immunofluorescent findings readily distinguish the two.

DIF demonstrates a "chicken wire" pattern of intercellular IgG in perilesional skin or plucked hairs. C3 may also be present. The staining is uniform, not granular. IIF shows a similar pattern of staining. Prozone reactions occur, so the serum should be tested at a wide range of dilutions. Positive tests may be confirmed with ELISA assays for the antibody.

Treatment

Large-scale, prospective, double-blinded studies are lacking, and the management of PV is based largely on smaller open trials and clinical experience. A survey of 24 very experienced clinicians showed that half used prednisone in doses of 1 mg/kg/day, while half used higher doses. Adjuvant steroid-sparing agents were commonly used, with almost half of the respondents reporting the use of azathioprine. Because of its

tolerability and simpler dosing schedule, mycophenolate mofetil is now used very commonly in place of azathioprine. Other agents used less commonly include cyclophosphamide and methotrexate. Almost 40% of the clinicians aimed to replace prednisone with a steroid-sparing agent, while others were content to continue a low dose of prednisone. The survey suggests that even among the world's experts, there is significant variation in how this difficult disease is managed.

Most agents used are immunosuppressive, although the mechanism of action may not merely be suppression of T-cells and antibody production. Methylprednisolone can directly block pemphigus antibody-induced acantholysis. It also upregulates expression of the genes encoding Dsg3 and periplakin, increases measurable levels of E-cadherin, Dsg1 and Dsg3, and interferes with phosphorylation of these adhesion molecules. Many of these effects antagonize those of pemphigus antibodies.

Topical Treatment

The skin lesions are extremely painful in advanced cases. When there are extensive raw surfaces, prolonged daily baths are helpful in removing the thickened crusts and reducing the foul odor. Silver sulfadiazine (Silvadene) 1%, widely used for local therapy of burns, is an effective topical antimicrobial agent, suitable for treatment of limited disease. Silver nitrate-impregnated cotton batting, manufactured for burn units, can be used in more extensive disease. Very localized areas can be treated with silver nitrate-impregnated dressings such as Acticoat 7 or Aquacell Ag. Painful ulcerations of the lips and mouth may benefit from topical application of a mixture of equal parts of Maalox and elixir of diphenhydramine hydrochloride (Benadryl) or viscous xylocaine, especially before meals. The various commercial antiseptic mouthwashes are helpful in alleviating discomfort and malodor. Potent topical corticosteroids and topical tacrolimus have been successful in some patients with limited disease.

Systemic Therapy

A common method of treatment for severe disease would be to begin with doses of prednisone adequate to control the disease. High doses of prednisone (100–150 mg) are sometimes needed, but prolonged high doses are associated with significant morbidity and mortality, so adjuvant therapy should be started early. During the early phase of therapy, if a prednisone dose of 1 mg/kg/day proves inadequate, the dose is commonly increased to a split dose of 1 mg/kg twice a day. Mycophenolate mofetil is commonly chosen as a steroid-sparing agent at a dose of 1 to 1.5 g twice a day. Gastrointestinal intolerance is the most common side effect, and blood counts must be monitored. If the disease does not respond, either plasmapheresis or intravenous immunoglobulin (IVIG) is added to the regimen. Azathioprine is less expensive than mycophenolate mofetil, and is commonly used as an alternative when cost is an overriding issue. It is best dosed based on measurement of the patient's thiopurine methyltransferase (TPMT) level. The majority of patients metabolizes the drug quickly, and may be underdosed if TPMT is not measured. Patients with high levels of the enzyme may require 2.5 to 5 mg/kg/day. Patients with mid-range levels are treated with 1 to 3 mg/kg/day. Patients who are deficient in the enzyme may be treated with very low doses, or with a different agent. Allopurinol interferes with metabolism of the drug and increased serum levels may lead to toxicity. Patients with refractory disease may be treated with cyclophosphamide, either alone or in conjunction with plasmapheresis. Plasmapheresis alone is followed by rebound of antibody production, but the rebounding clone of plasma cells is sensitized to the effects of cytotoxic agents. Both daily cyclophosphamide dosing and pulse dosing schedules can be used. Pulse dosing is usually given with MESNA rescue and is associated with less bladder toxicity. Both dosing schedules should be planned early in the day with vigorous hydration to minimize the risk of bladder toxicity. Blood counts must be monitored closely. Other risks of therapy with high doses of corticosteroids and immunosuppressants include diabetes, infection, hypertension, and cardiorespiratory disease. All of these risks must be monitored, and all patients must receive gentle wound care and fluid and electrolyte management. In patients who cannot tolerate cyclophosphamide, chlorambucil has been used, but is associated with a greater risk of hematologic malignancy. In addition to the use of IVIG as an adjuvant to conventional therapy, it has also been used as monotherapy. Onset of action is fairly rapid, and may be seen within 1 to 2 weeks.

The sooner the diagnosis is established and the sooner treatment is given, the more favorable the prognosis. The therapeutic effects are estimated by the number of new lesions per day and the rate of healing of the new lesions. In patients with and Dsg3 antibodies, mucosal disease may still be active when cutaneous disease appears to be in remission. Pemphigus antibody titers can be performed on esophageal substrate, watching for a fall in titer. If after 4 to 8 weeks of treatment new blister formation is not suppressed, prednisone dosage may be increased to 150 mg/day. Dosage adjustments are, of course, made more frequently and aggressively in severe, progressive disease. Dividing the daily dose will usually result in greater efficacy, but will also result in greater adrenal suppression. Additionally, intravenous pulse therapy with megadose corticosteroids (Solu-medrol) at a dose of 1 g/day over a period of 2 to 3 h, repeated daily for 5 days, may be employed for cases that are unresponsive to oral doses. Untreated disease is commonly fatal, but the clinician should remember that in treated patients, side effects of therapy are the most common cause of death. Adjuvant therapy to decrease steroid dependence has reduced mortality.

Medication is continued until clinical disease is suppressed and pemphigus antibody disappears from the serum. Once the antibody is no longer present, a DIF test is repeated. A negative DIF is predictive of sustained remission after withdrawal of therapy.

Immunosuppressant therapy alone has been reported as a successful treatment of early stable PV. If a contraindication to the use of corticosteroids exists or only limited disease is present, these may be used as single agents. In general, however, combined treatment with corticosteroids is superior in gaining early control of the disease.

Dexamethasone–cyclophosphamide therapy was studied in 32 patients with PV. Monthly pulses consisted of intravenous dexamethasone (136 mg) for 3 consecutive days monthly with intravenous cyclophosphamide (500 mg) on the second day. Daily oral cyclophosphamide (50 mg) and oral tapered courses of oral corticosteroids were given in the intervals between the pulses. All patients responded. Partial

remissions were noted after two to eight pulses. From 8 to 32 pulses were required to achieve complete remission. The duration of pulsed therapy correlated with both the disease severity and the time to achieve remission.

Oral cyclophosphamide was successful in 17 of 20 patients who had failed therapy with prednisone and an antimetabolite. The median time to achieve complete remission was 8.5 months, and the median duration of treatment was 17 months. Plasmapheresis was used in nine patients. Hematuria developed in five patients and in six infections were noted. One patient developed bladder cancer 15 years after therapy.

Intramuscular or oral gold are no longer commonly used. Gold is less effective than immunosuppressive therapy, but its advantages include lack of carcinogenicity and infertility. A minimum of 6 months is required to judge the effectiveness of gold therapy. Infliximab or rituximab, an anti-CD20 monoclonal antibody, have been used successfully in several with refractory disease, but may be associated with serious infections. Extracorporeal photochemotherapy has been used in a few patients, and dapsone may have some value as a steroid-sparing agent. Nicotinamide and tetracycline can be tried in patients with milder disease. In one study, it was successful in two of six patients. In another study, it was only successful in 1 of 10 patients. Data on the effectiveness of cyclosporin have been mixed. Etanercept has also been used.

PEMPHIGUS VEGETANS

Pemphigus vegetans may present as localized plaques in the scalp, or in two classic forms, the Neumann type (which generally begins and ends as typical pemphigus) and Hallopeau type (which usually remains localized). Both types show pseudoepitheliomatous hyperplasia, and the Hallopeau type is characterized by eosinophil microabscesses within the epidermis.

Pemphigus vegetans may begin with flaccid bullae that become erosions and form fungating vegetations or papillomatous proliferations, especially in body folds or on the scalp. The tongue often shows cerebriform morphologic features early in the course. At times there is a tendency for the lesions to coalesce to form large patches or to arrange themselves into groups or figurate patterns.

The laboratory findings, etiologic factors, epidemiology, pathogenesis, and treatment of pemphigus vegetans are the same as those for PV. Captopril-induced pemphigus vegetans has been reported.

Pemphigus vegetans must be differentiated from other conditions characterized by pseudoepitheliomatous hyperplasia and microabscesses, including halogenoderma, chromoblastomycosis, blastomycosis, granuloma inguinale, blastomycosis-like pyoderma, conyloma lata, and amebic granulomas. The Hallopeau type is distinguished by the presence of eosinophils, and both types by immunofluorescent findings.

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PEMPHIGUS FOLIACEUS

Pemphigus foliaceus (PF) is characterized by flaccid bullae and localized or generalized exfoliation. Antibodies target Dsg1. Lesions start as small, flaccid bullae that rupture almost as they evolve to form crusting, below which is a moist surface with a tendency to bleed. A Nikolsky sign may be easily elicited by rubbing the skin (Fig. 21-4). After a time, the exfoliative characteristics predominate, with few bullae (Fig. 21-5). Adherent scale crusts may resemble corn flakes.

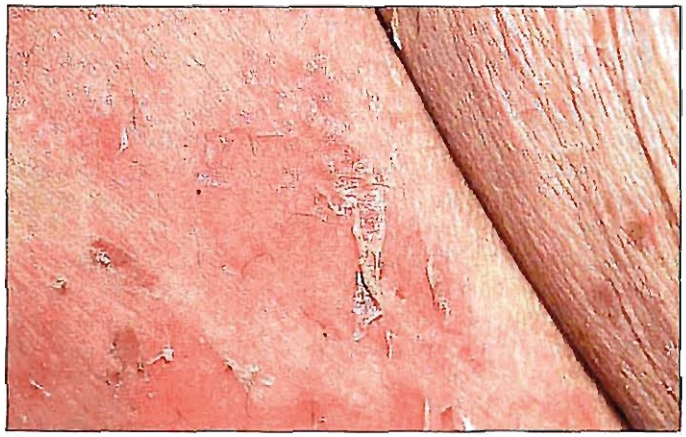

Fig. 21-4 Pemphigus foliaceus.

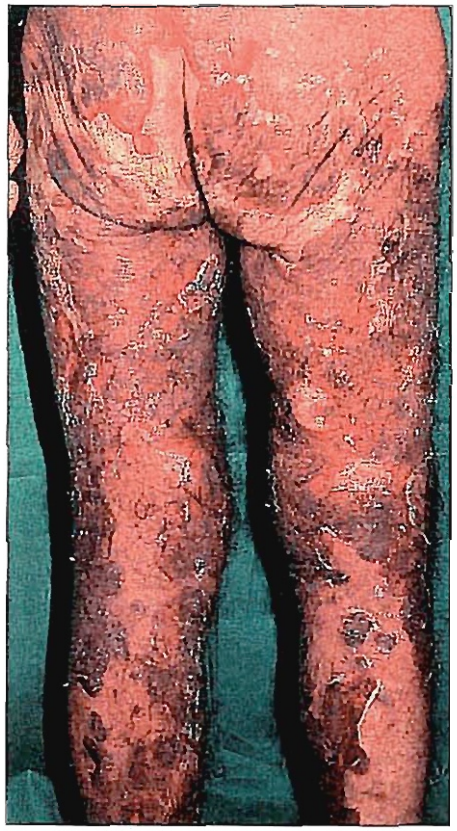

Fig. 21-5 Pemphigus foliaceus.

A variant of pemphigus that has clinical features suggestive of dermatitis herpetiformis but has immunologic features of pemphigus has been called *herpetiform pemphigus*. Most of these patients represent a clinical variant of PF, with the remainder being PV patients. A few have also demonstrated desmocollin antibodies.

The Nikolsky sign is present in PF. Oral lesions are rarely seen, and then only as superficial erosive stomatitis. This may be because Dsg3, present throughout the epithelium, is unaltered in PF and provides enough adherence to maintain clinical integrity. Several patients have been described whose clinical picture shifted from PF to PV or vice versa, with an accompanying change in antibody profile.

Most patients with PF are not severely ill. They complain of burning, pain, and pruritus. The lesions may persist for many years without affecting general health. PF occurs mostly in adults between 40 and 50 years of age, but has also been reported in children. The sexes are affected equally. Prevalence of PF in people of Jewish heritage is much less than with PV. The drugs listed under PV more commonly induce PF.

The principal histologic finding consists of acantholysis in the upper epidermis, usually in the granular layer. The stratum corneum may be missing entirely, or separated from the underlying epidermis. Individual elongated acantholytic cells are noted above the epidermis or clinging to the underside of the stratum corneum.

DIF demonstrates intercellular IgG throughout the epidermis, although the deposits may be somewhat more prominent in the upper epidermis. IIF is positive in most patients, although prozone reactions occur and a wide range of dilutions should be tested. A sensitive and specific ELISA for detecting antibodies to Dsg1 is now available to confirm positive IIF results. Patients with a distinct clinical picture of PF or PV may have a mix of antibodies. Western blot has shown Dsg1 in roughly 86% of PF patients and 25% of PV patients. ELISA has shown anti-Dsg1 antibodies in up to 71% of PF patients and in 62% of PV patients. In one study, antibodies to Dsg3 were detected in 19 of 276 patients with PF and fogo selvagem who had only cutaneous disease. The antibody was capable of producing disease in laboratory animals, suggesting they were pathogenic in the PF patients. Therefore, ELISA studies must always be interpreted in the context of clinical, histologic, and immunofluorescence findings. In PV, Dsg3 mediates mucosal disease and cutaneous disease is associated with antibodies to Dsg1. A shift to predominantly Dsg1 antibodies has accompanied a clinical shift from PV to PF.

Dsg1, the antigen in PF, was first identified by immunoprecipitation consisting of polypeptides of molecular weight 260, 160, and 85 kD. The 260-kD molecule is a complex of the 160- and 85-kD polypeptides. The PF antibody binds to a 160-kD glycoprotein extracted from normal epidermis. This glycoprotein is identical to Dsg1. The 85-kD glycoprotein is plakoglobulin, a desmosomal and adherens junction-associated molecule.

Desmogleins are cadherin-type adhesion molecules found in desmosomes. The N-terminal extracellular domain of Dsg1 contains the dominant autoimmune epitopes in both PF and PV. Antibodies include both IgG1 and IgG4 subclasses. IgG4 antibodies appear to be pathogenic in most patients. In a subset of patients, IgG1 autoantibodies are pathogenic.

Treatment

Treatment is similar to that for PV. In fact, many clinical trials include patients with both diseases. PF patients are generally less ill, and may not need oral corticosteroid therapy. Dapsone and hydroxychloroquine may be useful, either alone in mild cases or to reduce the steroid dose level. Nicotinamide and tetracycline may be more effective than in PV. Azathioprine, mycophenolate mofetil, or cyclophosphamide may be needed, just as in PV. Rituximab, IVIG, and immunoablative high-dose cyclophosphamide without stem cell rescue have been used for refractory disease. Immunoadsorption with tryptophan-linked polyvinylalcohol adsorbers or adsorption with plant lectins, such as wheat germ agglutinin, have been effective in animal models and hold promise as adjuvant therapy.

ENDEMIC PEMPHIGUS (FOGO SELVAGEM)

Endemic pemphigus is found in tropical regions, mostly in certain interior areas of Brazil. Fifteen percent of cases are familial. The disease is common in children, adolescents, and young adults, with about one-third of cases occurring before the age of 20 and two-thirds by the age of 40. The initial lesions may be flaccid bullae, but later lesions are eczematoid, psoriasiform, impetiginous, or seborrheic in appearance. The mid-facial areas may be involved. Melanoderma and verrucous vegetative lesions are not unusual, and exfoliative dermatitis may occur. The mucous membranes are not often involved. The Nikolsky sign is present. The disease is often seen in those with arthropod exposure, and may be initiated by an infectious agent, possibly carried by mosquitoes or black flies. Histologically and immunohistologically, fogo selvagem is identical to PF. Peripheral blood mononuclear cells from patients produce more IL-1β than those from healthy controls. A strong Th2 bias is also observed.

A distinct subset has been described in a rural area in north-eastern Colombia. This subset differs from previously described forms of endemic pemphigus, and shares some immunoreactivity with paraneoplastic pemphigus. It is not, however, associated with malignant tumors. Clinically, the disease resembles Senear-Usher syndrome. A systemic form may affect internal organs and has a poorer prognosis. All patients appear to have antibodies to Dsg1. In addition, many sera react with desmoplakin I, envoplakin, and periplakin. A few Brazilian sera also react with plakins. None of the Colombian patients' sera reacted with Dsg3, but about half of Brazilian patients' sera react with Dsg3. This area of Colombia is a mining region and the population is exposed to high environmental levels of mercuric sulfides and selenides; these compounds have been found in the skin of patients with the disease.

PEMPHIGUS ERYTHEMATOSUS (SENEAR-USHER SYNDROME)

In Senear-Usher syndrome, the early lesions are circumscribed patches of erythema and crusting that clinically resemble lupus erythematosus and are immunopathologically positive for the lupus band in 80% of patients. The lesions are erythematous and thickly crusted, bullous, or even hyperkeratotic. These are usually localized on the nose, cheeks, and ears, sites frequently affected by lupus erythematosus. In addition, crusting and impetiginous lesions appear amid bullae on the scalp, chest, and extremities. In most patients, the disease runs an indolent course.

The histopathology is that of pemphigus foliaceus. DIF shows IgG and complement localized in both intercellular and basement membrane sites. At the dermoepidermal junction, the deposits are continuous and granular, as in lupus. In the epidermis, they resemble those of pemphigus. The antinuclear antibody is present in low titer in 30% of patients. Patients have demonstrated anti-Dsg1 but not anti-Dsg3 autoantibodies. Additional autoantibodies may be directed against bullous pemphigoid antigen 1 (BP230) and periplakin.

Patients often respond to low doses of prednisone, and may respond well to topical steroids and sunscreens. Immunosuppressants may be needed in severe cases.

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PARANEOPLASTIC PEMPHIGUS

In 1990, Anhalt et al described five patients with underlying neoplasms who presented with painful mucosal ulcerations and polymorphous skin lesions, which progressed to blistering eruptions on their trunk and extremities. Most patients described since then have has associated neoplasms or Castleman's disease. The mucosal lesions pf paraneoplastic pemphigus (PNP) may appear lichenoid or more commonly Stevens-Johnson–like with crusting of the lips. The skin lesions may appear as erythematous macules, lichenoid lesions, erythema multiforme-like lesions, flaccid bullae, and erosions typical of pemphigus, or tense, more deep-set bullae.

Histologically, the lesions demonstrate epidermal acantholysis, suprabasal cleft formation, dyskeratotic keratinocytes, and vacuolar change of the basalar epidermis. Biopsies that demonstrate both acantholysis and lichenoid change or individual cell necrosis should raise the suspicion of PNP.

DIF reveals IgG and C3 deposition in the intercellular spaces of the epithelium. IIF shows a similar pattern in a wide range of stratified squamous epithelium and transitional epithelium (such as rat bladder). About 25% of cases will be negative and some erythema multiforme may be falsely positive. Immunoprecipitation is the definitive test. It reveals a complex immune response with autoantibodies directed against four high molecular weight keratinocyte proteins. Antibody targets include desmoplakin 1 (250 kD), envoplakin (210 kD), the major plaque protein of hemidesmosomes BPAg1 (230 kD), and periplakin (190 KD). Many cases also recognize an additional antigen at 170 kD. Finally, by ELISA testing, antibodies to Dsg3 and Dsg1 are frequently present. On DIF, some cases also demonstrate a linear or granular IgG and/or C3 at the basement membrane zone.

Whereas the dominant epitopes in PV reside in N-terminal regions of Dsg3, epitopes on Dsg3 in PNP are distributed more broadly through the extracellular domain. The N-terminal domains are still recognized more frequently than the C-terminal domains. IgG subclasses in PNP are IgG1 and IgG2 dominant, contrasting with the IgG4 dominance in PV. There is a significant association in PNP with HLA-DRB1*03 allele (61.5% of those studied). In one study, eight of nine fatal PNP cases had distinctive cell surface antibodies detected in a beaded pattern by complement indirect immunofluorescent (CIIF) tests on monkey esophagus. Three long-term survivors with PNP lacked this pattern, suggesting the test may have prognostic value.

A wide variety of both benign and malignant tumors are seen in these patients, and some have no identifiable neoplasm. The most common associations are non-Hodgkin lymphoma, chronic lymphocytic leukemia, Castleman tumor, sarcoma, and thymoma. Most reported patients die from their tumor. Others have died from bronchiolitis obliterans.

Therapy for the bullous dermatoses with prednisone and/or immunosuppressive agents should be balanced with treatment of the tumor. Immunoablative high-dose cyclophosphamide without stem cell rescue, cyclosporin A, plasmapheresis, immunoapheresis, and rituximab have been successful in some cases.

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INTRAEPIDERMAL NEUTROPHILIC IgA DERMATOSIS

In 1985, Huff et al reported the case of an elderly man with a chronic bullous dermatosis with unique histologic and immunopathologic findings. Clinically, there were generalized flaccid bullae, which rapidly ruptured and crusted. There was no scarring when the dermatosis healed. No mucosal lesions were present, and the distal extremities, face, and neck were spared. Neither grouping nor symmetry were present. Histologic findings consisted of neutrophilic exocytosis and in some areas neutrophils arranged in a linear fashion at the dermoepidermal junction. Later, intraepidermal abscesses were formed; no acantholysis was present. DIF repeatedly showed an intercellular deposition of IgA within the epidermis, with minimal staining of the basal layer. No circulating antibodies were found.

Since this report, many additional patients with intraepidermal IgA deposition have been described. They have been classified as belonging in two subsets, one closely mimicking pemphigus and the second simulating subcorneal pustular dermatosis (SPD). The former starts with vesicles that become pustular within a few days, enlarge peripherally, rupture in the center, then form a crust. Continued peripheral vesiculation may lead to a flower-like appearance. The head, neck, and trunk are frequent sites of involvement. In some patients, the condition is induced by ultraviolet (UV)A light. The second subset presents much like Sneddon-Wilkinson disease, with serpiginous and annular pustules. Some cases have been induced by granulocyte–macrophage colony-stimulating factor.

Histologically, intraepidermal bullae with neutrophils, some eosinophils, and acantholysis are seen. DIF shows intraepidermal IgA deposition, usually throughout the epidermis and IIF may reveal circulating autoantibody that binds to the same location. There is evidence that the IgA specificity in individual cases may be directed at either Dsg1 or Dsg3. Some patients have concurrent IgG intercellular antibodies directed at Dsg1, and some have a monoclonal IgA gammopathy. The antigen in SPD-type IgA pemphigus is

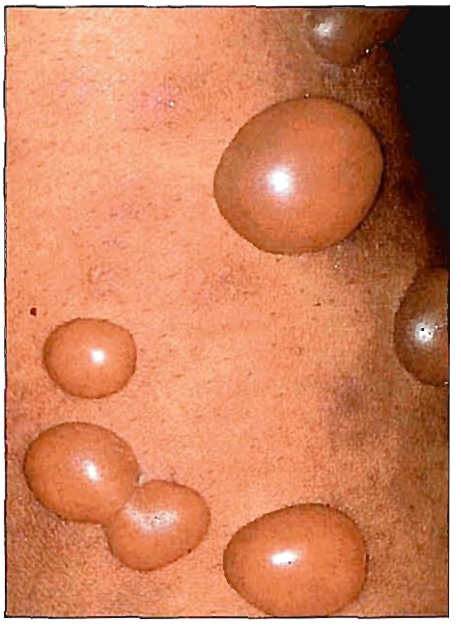

Fig. 21-6 Bullous pemphigoid.

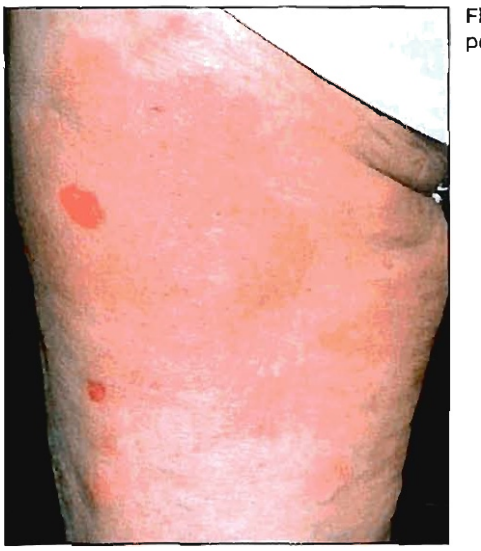

Fig. 21-7 Urticarial pemphigoid.

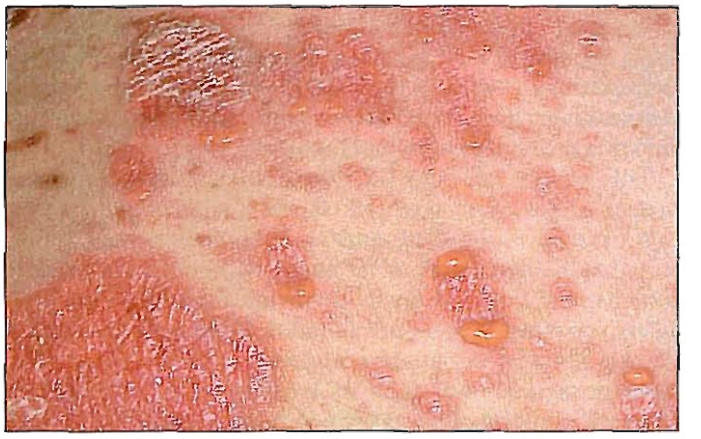

Fig. 21-8 Pemphigoid in psoriatic plaques (psoriasis pemphigoides).

desmocollin, a type of desmosomal cadherin. Some patients have a circulating IgA monoclonal gammopathy.

Therapy with topical corticosteroids may be effective in mild cases. Dapsone is often effective, and may be so even at doses as low as 25 mg/day. Oral corticosteroids may be necessary, and some resistant cases have required immunosuppressive agents and plasmapheresis. Colchicine, acitretin, adalimumab, mycophenolate mofetil, and isotretinoin have been effective in some patients.

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BULLOUS PEMPHIGOID

Clinical Features

Bullous pemphigoid (BP) was described by Lever in 1953. Clinically, it is characterized by large, tense, subepidermal bullae with a predilection for the groin, axillae, trunk, thighs (Fig. 21-6) and flexor surfaces of the forearms. Key features distinguishing BP from other immunobullous diseases include subepidermal separation at the dermoepidermal junction, an inflammatory cell infiltrate that tends to be rich in eosinophils, and antibodies directed against two hemidesmosomal antigens, BP230 and BP180.

After the bullae rupture, large denuded areas are seen, but the bullae and denuded areas do not tend to increase in size as they do in PV. Instead, the denuded areas show a tendency to heal spontaneously. In addition to the bullae, there often are erythematous patches and urticarial plaques (Fig. 21-7), with a tendency to central clearing. These patches and plaques may be present without bullae early in the course of the disease. Later, bullae often occur on an urticarial base. Sometimes, targetoid lesions are present.

BP may begin at a localized site, frequently on the shins. The disease may also be limited to areas of radiation therapy, burns or plaques of psoriasis (Fig. 21-8). It may remain localized throughout the course of the disease or eventuate in generalized pemphigoid. Cases of the localized disease in which a vesicular eruption is limited to the palms or soles (dyshidrosiform pemphigoid) are occasionally observed. Young girls may present with localized vulvar erosions and ulcers that resemble the signs of child abuse (Fig. 21-9). These localized varieties have been shown to have circulating IgG antibody, which immunoprecipitates the 230-kD BP antigen.

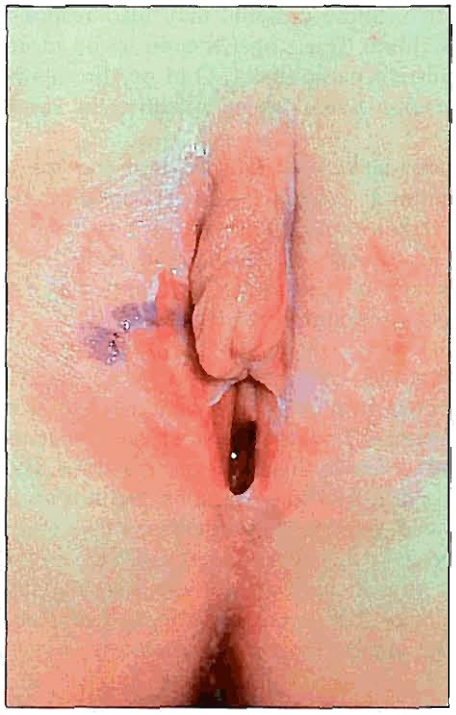

Fig. 21-9 Vulvar pemphigoid.

Many other variants of BP have been described. A vesicular variant manifested by tense, small, occasionally grouped blisters is termed vesicular pemphigoid. Other patients, mostly women, have papules and nodules of the scalp and extremities, with sparing of the mucous membranes, in a pattern resembling prurigo nodularis (pemphigoid nodularis). Cases resembling pemphigus vegetans, but with IgG and C3 at the basement membrane zone, are occasionally observed (pemphigoid vegetans). Erythroderma may be present (erythrodermic pemphigoid) or there may be no bullae at all (nonbullous variant). The latter type may present as generalized pruritus, pruritic eczema or urticarial eruptions with peripheral eosinophilia. Overall, incidence of oral involvement is about 20%, but involvement of the pharynx, larynx, nasal mucosa, vulva, urethra, and eye is rare.

BP occurs most frequently in the elderly. The age of onset averages 65 to 75 years. It also occurs, however, in young children with clinical and pathologic findings similar to those in adults. Many of these cases begin with hand and foot bullae. Facial involvement may be somewhat more common in children. In children, the course of disease is usually under 1 year, with most cases lasting 5 months or less.

In patients with lichen planus, a bullous eruption similar to BP may develop. This condition, called lichen planus pemphigoides, is sometimes related to the 230-kD antigen, the 180-kD antigen, or a unique 200-kD subepidermal antigen. A nonscarring eruption with acute onset, widespread erosions and severe mucous membrane involvement resembling toxic epidermal necrolysis or PV has been referred to as anti-p105 pemphigoid. Linear IgG and C3 are noted at the basement membrane zone. The 105-kD antigen is found in the lower portion of the lamina lucida.

Etiologic Factors

Circulating basement membrane zone antibodies of the IgG class are present in approximately 70% of patients with BP. In most instances the antibodies fix complement in vitro, in contrast to pemphigus antibodies, which fail to do so. Complement is activated by both the classic and alternate pathways. No close correlation exists between the titer of antibodies and clinical disease activity.

Passive transfer mouse models suggest that subepidermal blistering is initiated by anti-BP180 antibodies. Blister formation involves complement activation, mast cells, and neutrophils. Basement membrane zone damage is caused by proteinases and reactive oxygen species released by the infiltrating neutrophils.

The site of IgG binding has been localized to the lamina lucida, with accentuation near hemidesmosomes. BP antigen 1 (BPAg1) is synthesized by the keratinocyte and is an intracytoplasmic hemidesmosomal plaque protein of molecular weight 230 kD with disulfide-linked chains. The second BP antigen (the 180-kD BPAg2) is a transmembrane protein with a long C-terminal collagenous domain that projects into the extracellular region below the hemidesmosome. The antibody to BPAg2 is the primary pathogenic factor. The noncollagenous (NC) 16A domain harbors the major epitopes of autoantibodies in BP. A predominance of the IgG4 subclass has been observed in several studies. In addition to this humoral response, infiltrating T-helper lymphocytes with a mixed Th1/Th2 cytokine profile may play a role in blister formation. Peripheral blood eosinophilia is present in 50% of pemphigoid patients.

BP has occasionally been reported to be associated with other diseases, such as diabetes mellitus, rheumatoid arthritis, PF, dermatomyositis, ulcerative colitis, myasthenia gravis and thymoma. Drugs have been reported to induce BP; these include penicillamine, furosemide, captopril, penicillin, sulfasalazine, nalidixic acid, and enalapril.

Histopathology

The histologic changes are characterized by subepidermal bullae, by the absence of acantholysis, and by a superficial dermal infiltrate containing many eosinophils. The amount of inflammatory infiltrate varies, and individual bullae may be "infiltrate poor" or "infiltrate rich." Often the infiltrate contains many eosinophils, although neutrophil-predominant cases exist. Spongiosis with eosinophils occurs more frequently than in pemphigus. Urticarial lesions often demonstrate eosinophils lined up along the dermoepidermal junction.

Atypical presentations are fairly common. In one study of 23 new cases of BP, only 7 of 22 biopsy specimens showed subepidermal blister formation, and only 12 of these had a predominance of eosinophils in the blister cavity. In 23% of patients, the biopsy was not particularly suggestive of BP. DIF, IIF, immunoblot analysis and ELISA are critical in establishing the diagnosis in such cases.

DIF is a more sensitive test than IIF, just as in pemphigus. In a positive test, continuous linear (tubular or toothpaste pattern) IF is seen along the basement membrane zone. IgG and/or C3 are best found in perilesional skin. False-negative tests are somewhat more common on the lower extremities. A positive DIF test is found in nearly 100% of patients, with C3 most commonly present and IgG present in about 80% of cases. IgA and IgM are occasionally present.

About 20% of patients have negative staining for IgG on DIF, even though C3 is present. In some of these patients, IgG may be present at subthreshold levels which cannot

be detected. Also, the major subclass, IgG4, shows limited reactivity with most commercial antihuman IgG conjugates. Double sandwich antibody immunofluorescence methods have been developed that offer greater sensitivity for IgG4 antibodies.

All histologic features present in BP may also be seen in epidermolysis bullosa acquisita (EBA); therefore, immunofluorescence testing on salt-split skin is required to differentiate EBA from BP. C3 deposition is nearly always present in BP, whereas it may be absent in EBA. Type IV collagen mapping in BP localizes to the base of the blister. In EBA it stains the roof.

Bullous scabies can also mimic both the histology and DIF findings of BP.

Treatment

Relatively few controlled trials have been performed, and many recommendations are based on experience and consensus of opinion. A Cochrane Library search strategy identified seven randomized controlled trials through 2003. A total of 634 patients were enrolled in the trials. One comparing prednisolone, 0.75 mg/kg/day, with prednisolone, 1.25 mg/kg/ day, found no statistical difference between the two. The same was true of a trial comparing methylprednisolone with prednisolone. Higher doses of prednisolone were associated with more severe side effects in these studies. Two trials confirmed that adjuvant therapy with azathioprine or plasma exchange could reduce the required steroid dose. Another trial failed to confirm the superiority of combination treatment (with either azathioprine or plasma exchange) over steroid alone, and one trial found no statistically significant difference between prednisone and a combination of tetracycline and niacinamide. The steroid-treated group had more side effects.

Another study compared ultrapotent topical corticosteroid treatment (clobetasol propionate cream 40 g/day) with oral prednisone (0.5–1 mg/kg/day). In those with severe disease, the 1-year survival rate was better in the topical corticosteroid group (76% vs 58%). Disease control at 3 weeks was also better in the topical steroid group (99% vs 91%). Side effects were common in both groups, but more common in the prednisone group (29% vs 54%). Among those with moderate disease, there were no significant differences between the two groups.

Even is those with extensive disease, topical corticosteroid treatment should be attempted. Prednisone has long been the standard approach, but the complication rate must be weighed carefully, especially in those with severe disease. Oral therapy with tetracycline (500 mg four times a day) combined with niacinamide (500 mg three times a day) is effective in some cases. It should be noted that occasional patients with BP may respond to tetracycline alone or nicotinamide alone. Dapsone is also effective in some patients. Immunosuppressive therapy may still be necessary in resistant cases, either in combination with systemic or topical steroids, or as sole therapy. Azathioprine has been used most commonly, but mycophenolate mofetil is being used more commonly. Methotrexate, cyclophosphamide, chlorambucil, IVIG, and cyclosporin have also proved effective in some patients. In exceptionally severe cases, pulse therapy with methylprednisolone (15 mg/kg in 16 mL of bacteriostatic water over a period of 30–60 min/day for three doses) can be rapidly effective. Some patients may also respond to dapsone or sulfapyridine. These agents tend to be more effective in neutrophil-rich pemphigoid. Oral erythromycin and topical macrolactams have proved effective in some patients.

Double-filtration plasmapheresis (DFPP) may be more effective than conventional plasma exchange, possibly by removing pathogenic cytokines. DFPF reduces a variety of cytokines, including IL-8, MIP-1α, TNF-α and IL-2. IVIG produces faster clearance of antibody titers, and may be helpful in inducing and maintaining remission.

Course and Prognosis

BP is usually self-limited over a 5- to 6-year period. This period is generally a year or less in children. Relapse occurs in 10% to 15% of patients once therapy is discontinued. The presence of circulating anti-BP180 antibodies, but not anti-BP230, is associated with a statistically increased chance of death in the first year after diagnosis. Other risk factors for death during the first year include greater age, higher daily steroid dosage at discharge, low serum albumin, and erythrocyte sedimentation rate greater than 30 mm/h.

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Fig. 21-10 Targetoid lesions of pemphigoid gestationis.

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PEMPHIGOID GESTATIONIS (HERPES GESTATIONIS)

Clinical Features

Pemphigoid gestationis (PG) is an autoimmune inflammatory, bullous disease with onset during pregnancy or during the postpartum period. It occurs in approximately 1 in 50,000 pregnancies. The onset is usually during the second trimester, with urticarial plaques and papules developing around the umbilicus and extremities. Targetoid lesions may be present (Fig. 21-10). As the disease progresses, lesions may spread over the abdomen, back, chest, and extremities, including the palms and soles. The face, scalp, and oral mucosa are usually spared. Within the infiltrated erythematous plaques, tense vesicles and bullae erupt (Fig. 21-11), often in an annular or polycyclic configuration. Pruritus is severe and may be paroxysmal. The disease will often flare shortly after delivery and then remit spontaneously, usually within 3 months. There is no scarring, except that caused by excoriations or secondary infections. Recurrences with subsequent pregnancies are common, and the disease may be provoked by subsequent menstrual periods or oral contraceptives. A number of cases of persistent disease have been reported.

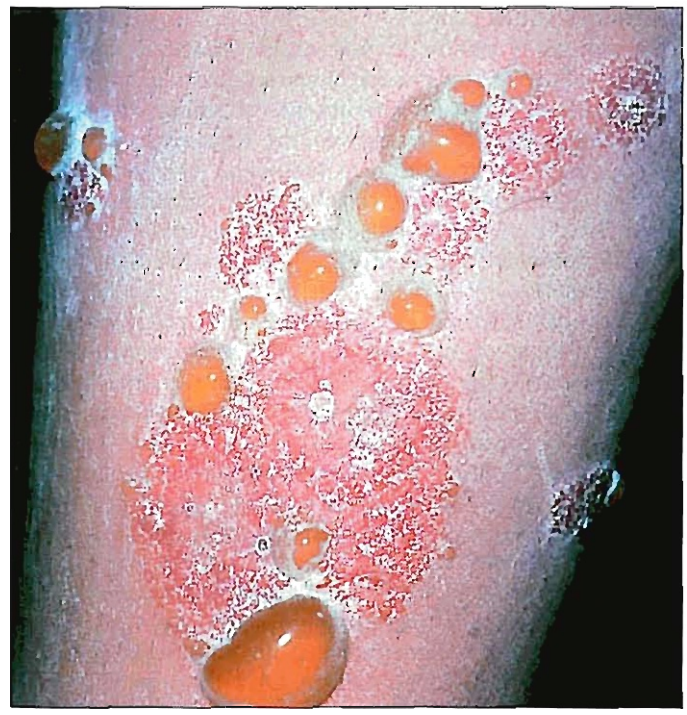

Fig. 21-11 Bullous lesions of pemphigoid gestationis. (Courtesy of Martha McCollough, MD)

Most studies data suggest that fetal loss is not statistically increased, although infants are often born prematurely and are small for gestational age. In fewer than 5% of cases, infants manifest the disease in the form of urticarial lesions or bullae. The lesions are usually limited and clear spontaneously without the need for therapy.

Etiologic Factors

PG is an autoimmune, antibody-mediated disease. A complement-fixing IgG antibody is present in the serum, and is deposited in the lamina lucida. The antigenic epitopes are usually restricted to the N-terminal portion of the extracellular domain of BP180 (BPAg2). The antigenic N-terminal portion of MCW-1 is located in the noncollagenous domain (NC16A) of BP180. Other antigens are located nearby, and four major PG epitopes are clustered within a 22 amino acid region of the BP180 ectodomain. Both IgG1 and IgG3 subtypes are noted.

Studies have documented an increased frequency of HLA-DR3, DR4, and C4 null alleles in patients with PG. A woman may have antibodies directed against her husband's HLA antigens. Black women rarely manifest PG, possibly related to the low incidence of HLA-DR4 in American black persons. There is an increased frequency of Graves' disease in PG patients.

Pathogenesis

Pathogenesis is similar to that of BP. However, hormonal factors influence the disease manifestation. In addition to being seen in pregnant patients, menstruating women, and those taking oral contraceptives, the disease may occur in association with hydatidiform mole and choriocarcinoma. The IgG antibodies bind to the lamina lucida and fix complement. Activated eosinophils, neutrophils, and T-cells with a predominant Th2 phenotype are involved in blister formation.

Patients with chronic PG tend to be older and multigravid, with a history of PG during previous pregnancies. They often have widespread cutaneous and mucosal involvement. The IgG1 subclass is commonly present. Antibodies to a C-terminal portion of BP180 have been noted in a patient with chronic PG. This same region is targeted in patients with cicatricial pemphigoid and some with BP.

Histopathology

A subepidermal bulla with eosinophils and some neutrophils is usually present. In the urticarial stage, eosinophils may line up along the dermoepidermal junction, as in urticarial BP. Civatte bodies may be present. On DIF, all patients have C3 deposited in a linear pattern at the dermoepidermal junction. Approximately 25% to 40% also have detectable IgG. By conventional IIF testing, approximately 25% of patients have a circulating IgG anti-basement zone antibody, but in nearly 75% the PG factor, a complement-fixing IgG antibody, can be demonstrated by complement-enhanced IF. Immunoelectron microscopy has demonstrated that the blister occurs at the level of the lamina lucida, with deposition of C3 and IgG at this site, exactly as in BP.

Differential Diagnosis

The main diagnosis to be considered is pruritic urticarial papules and plaques of pregnancy (PUPPP). The differential diagnosis also includes erythema multiforme, drug reactions, and bullous scabies. Acrodermatitis enteropathica has also been reported to flare as a bullous eruption with each pregnancy. Biopsy, immunofluorescence findings, and clinical course establish the diagnosis.

Treatment

The use of potent topical steroids may be adequate in some milder cases of PG. Prednisone in an oral dose of about 40 mg/day is usually effective in the remainder of cases. The dose is tapered to the lowest effective dose given on alternate days. Pyridoxine has been reported to be effective in some cases. Persistent PG after delivery has been treated with various tetracyclines, together with nicotinamide. A few severe cases have required treatment with cyclophosphamide, dapsone, methotrexate, IVIG, or plasmapheresis.

OTHER PREGNANCY-RELATED DERMATOSES

Intrahepatic Cholestasis of Pregnancy (Prurigo Gravidarum)

This pregnancy-related disease has no primary skin lesions, and is usually manifested only by severe generalized pruritus and jaundice. Secondary excoriations may be present. It is caused by cholestasis, occurs late in pregnancy, resolves after delivery, and recurs with subsequent pregnancies. There is an increased incidence of fetal complications. It has been estimated to occur in 0.5% of 3192 pregnancies. Both ursodeoxycholic acid and *S*-adenosyl-L-methionine improve pruritus, but the former is more effective in regard to improving liver function.

Polymorphic Eruption of Pregnancy

Some investigators have proposed grouping all the pruritic inflammatory dermatoses of pregnancy into the designation *polymorphic eruption of pregnancy*. This argument has some merit, as many of the pruritic eruptions of pregnancy are nonspecific or variable manifestations of pruritic urticarial papules and plaques of pregnancy, and there are no consistent hormonal or immunopathogenetic factors that reliably separate them. These eruptions occur in approximately 1 in 120 to 240 pregnancies.

Pruritic Urticarial Papules and Plaques of Pregnancy Lawley et al first reported seven patients under the name *pruritic urticarial papules and plaques of pregnancy* (PUPPP) in 1979. This eruption is characterized by erythematous papules and plaques that begin as 1- or 2-mm lesions within the abdominal striae. They then spread over the course of a few days to involve the abdomen, buttocks, thighs, and in some cases the arms and legs. The upper chest, face, and mucous membranes are generally spared. The lesions coalesce to form urticarial plaques, sometimes in figurate patterns, and occasionally spongiotic vesicles are present. Intense pruritus is characteristic. In contrast to PG, postpartum onset or exacerbation is uncommon. Fetal and maternal outcomes are not affected by this eruption, and only rarely do newborns manifest transient lesions of PUPPP.

This eruption occurs in primigravidas 75% of the time, and rarely recurs with subsequent pregnancies. It begins late in the third trimester and resolves with delivery. Many studies have investigated the relationship of maternal weight gain to the development of this dermatosis. Patients with PUPPP average more weight gain and greater abdominal distension than those without the disease. It is more common in those carrying twins or triplets.

Histologic findings consist of a perivascular lymphohistiocytic infiltrate in the upper and mid-dermis, with a variable number of eosinophils and dermal edema. The epidermis is usually normal, although focal spongiosis, parakeratosis, or scales or crust may be present. The results of a direct immunofluorescence test are negative or nonspecific.

Usually, potent topical steroids are required to control the eruption. A few patients require prednisone. The disease remits after delivery.

Papular Dermatitis of Pregnancy Papular dermatitis of pregnancy is a controversial entity. It is defined as a pruritic, generalized eruption of 3- to 5-mm erythematous papules, each surmounted by a small, firm, central crust. The lesions may erupt at any time during pregnancy and usually resolve with delivery. Marked elevation of the 24-h urinary chorionic gonadotropin has been cited as a marker for the condition.

Administration of systemic corticosteroids is reportedly effective in controlling the eruption. The condition may recur in subsequent pregnancies. The high incidence of fetal deaths reported by Spangler is now felt to have been overstated.

Prurigo Gestationis (Besnier) This eruption consists of pruritic, excoriated papules of the proximal limbs and upper trunk; these occur most often between the 20th and 34th week of gestation. It clears in the postpartum period and usually does not recur.

Therapy with potent topical steroidal agents is recommended. No adverse effects on maternal or fetal health are seen. This eruption may simply be an expression of atopic dermatitis in pregnancy.

Pruritic Folliculitis of Pregnancy Several authors have reported on pruritic folliculitis in gravid women, with small follicular pustules scattered widely over the trunk appearing during the second or third trimester and resolving by 2 or 3 weeks after delivery. Acute folliculitis and focal spongiosis with exocytosis of polymorphonuclear leukocytes are present on biopsy, and DIF results are negative. This condition may be a type of hormonally-induced acne.

Linear IgM Dermatosis of Pregnancy In 1988, Alcalay et al described a woman who developed small, red, follicular papules and pustules that on immunofluoresence testing showed linear deposits of IgM. This finding is common in a wide variety of dermatoses, and is nonspecific.

Impetigo Herpetiformis Impetigo herpetiformis is a form of severe pustular psoriasis occurring in pregnancy. It consists of an acute, usually febrile onset of grouped pustules on an erythematous base, which begins in the groin, axillae, and neck. There is a high peripheral white blood cell count, and hypocalcemia may be present. The histopathology is that of pustular psoriasis. The condition resolves with delivery, but recurrences with subsequent pregnancies may be expected. Fetal death is not uncommon, and results from placental insufficiency. Treatment is with systemic corticosteroids, in the range of 40 to 60 mg/day of oral prednisone. The condition is discussed in more detail in Chapter 10.

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CICATRICIAL PEMPHIGOID (BENIGN MUCOSAL PEMPHIGOID)

In 1953, Lever suggested the designation *benign mucosal pemphigoid* for what had previously been called *ocular pemphigus, cicatricial pemphigoid*, or *essential shrinkage of the conjunctiva*. Because of its scarring nature, the designation cicatricial pemphigoid (CP) has gained predominance. The term encompasses a group of immunologically distinct immunobullous diseases with scarring.

Clinical Features

CP usually occurs in older women, with a female-to-male ratio of approximately 2:1. The condition is characterized by evanescent vesicles that rupture quickly, leaving behind erosions and ulcers. In most patients, they primarily occur on the mucous membranes, especially the conjunctiva (Fig. 21-12) and oral mucosa. Oral lesions occur in approximately 90% of cases and conjunctival lesions in 66%. The oral mucosa may be the only affected site for years.

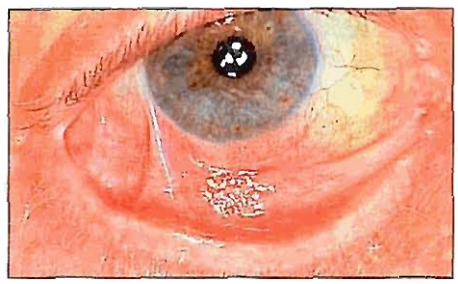

Fig. 21-12 Cicatricial pemphigoid.

Desquamative gingivitis, diffuse erythema of the marginal and attached mucosa associated with mucosal desquamation and pain, is often the presenting sign. The mucosa readily peels away in response to pressure from a cotton-tipped applicator or stream of air from a dental air hose. The gingivae are almost always involved, and the lingual surfaces less regularly. The palate, tongue, and tonsillar pillars may be involved.

The disorder is chronic. In ocular cases, it leads to scarring and progressive shrinkage of the ocular mucous membranes. Blindness may result. It is usually bilateral and associated with redness and flaccid vesicles on the conjunctiva, xerosis, and fibrous adhesions (symblepharon). Entropion, trichiasis, and corneal opacities develop and ultimately, the adhesions attach both lids to the eyeball and narrow the palpebral fissure. Scarring may also develop in the pharynx, esophagus, larynx, and anogenital mucosa. Esophageal stricture may occur, and deafness has been reported.

Cutaneous lesions are seen in approximately 25% of patients. These begin as tense bullae, similar to those in BP. The bullae may occur on the face, scalp, neck, and the inguinal region or extremities. Generalized lesions may also occur. Some of these patients will have circulating antibodies targeted against the classic BP antigens, and should be classified as mucosal predominate BP. Some have secondary antibodies against other antigens. Some patients have EBA, as the IgG autoantibody was found to target type VII collagen. In Brunsting-Perry pemphigoid there are no mucosal lesions, but one or several circumscribed erythematous patches develop on which recurrent crops of blisters appear. Ultimately, atrophic scarring results. Generally, the areas of involvement are confined to the head and neck. The average age at onset is 58 with a 2:1 male-to-female ratio. In contrast to BP, cicatricial pemphigoid shows little tendency for remission. Although the disease is chronic, and produces significant morbidity, the patient's general health is usually not jeopardized.

Etiologic Factors

Circulating autoantibodies target the hemidesmosomal protein BP180, but the target epitopes differ from those usually targeted in BP. While most BP patients react with the noncollagenous domain (NC16a) on the extracellular N-terminal portion of BP180, most cicatricial pemphigoid antibodies target C-terminal domains. Fluorescence typically is found on the epidermal side of 1 M NaCl split skin.

Although patients share a similar phenotype, CP is a heterogeneous group of autoimmune subepidermal blistering diseases. Although most patients' autoantibodies target BP180, others target laminin 5 (antiepiligrin cicatricial pemphigoid), or the β4 subunit of α6β4 integrin. Some patients with a CP phenotype have antibodies to multiple epitopes, including the β4 subunit of α6β4 integrin, BP180 and BP230. Other subsets of patients targeting unique basement membrane zone antigens will likely be identified.

Among patients whose antibodies target laminin 5, most exhibit antibodies to the α subunit, especially the G domains of the α3 subunit. Antibodies may also target the β3 and γ2 subunits. Other patients have been found to have autoantibodies that react with both laminin 6 as well as laminin 5, prompting the proposed designation of *antilaminin cicatricial pemphigoid*. In antilaminin cicatricial pemphigoid IgG anti-basement membrane zone autoantibodies bind to the dermal side of 1 M NaCl split skin. There is an increased relative risk for solid cancers (mostly adenocarcinomas) in these patients. Tumors are commonly found during the first year of the disease. Like other forms of CP, the disease rarely remits spontaneously.

Histopathology

The histologic findings are identical to those of bullous pemphigoid, with the exception that fibrosis and scarring may be present in the upper dermis. Basement membrane separation occurs in the lamina lucida or below the lamina densa, depending on the targeted antibody. The inflammatory infiltrate is variable.

DIF testing of perilesional skin or mucosa reveals C3 and IgG at the lamina lucida in 80% to 95% of patients. The basement membrane zone of mucosal glands stains as well. IgA may be found occasionally. A circulating antibody to the basement membrane zone is found by IIF in about 20% of cases. Immunoelectron microscopy shows that lamina lucida antibodies bind at a deeper level than with BP. Most IIF-positive cases show IgG binding to the epidermal side of salt-split skin, although combined staining and dermal staining may be present in different subtypes, as noted above. Laser scanning confocal microscopy using fluorescein isothiocyanate-conjugated anti-human IgG antibody has been used to determine the localization of IgG at the basement membrane zone, and may be of value in patients with negative IIF. "Knockout" skin substrates and fluorescent overlay antigen mapping have also been used to differentiate between anti-epiligrin CP and EBA.

Treatment

A review of studies using the Cochrane criteria found two small randomized controlled trials, both in patients with severe eye involvement. In one, 6 months of cyclophosphamide was superior to prednisone. In the second trial, 20 of 20 patients responded well to 3 months of cyclophosphamide, while only 14 of 20 responded to dapsone. Based on these limited data, and other uncontrolled trials, the reviewers concluded that severe ocular CP responds best to cyclophosphamide combined with corticosteroids, and that mild-to-moderate disease may respond to dapsone.

In mild cases, oral hygiene, topical steroids, intralesional triamcinolone, or topical steroids occluded under vinyl inserts may be effective for desquamative gingivitis and other oral, genital or cutaneous disease. Cream and gel formulations may be used, or the steroid may be compounded in orabase. Topical sucralfate suspension may decrease the pain and healing time of the oral and genital ulcers. Cyclosporin washes have some efficacy but are too expensive for general use. Other topical calcineurin inhibitors have been used effectively. There have been reports of efficacy of thalidomide, tetracycline combined with niacinamide, dapsone, IVIG, systemic corticosterois, and immunosuppressive drugs.

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EPIDERMOLYSIS BULLOSA ACQUISITA

Criteria for epidermolysis bullosa acquisita (EBA) were proposed in 1971 by Roenigk, and included 1) clinical lesions of dystrophic epidermoylsis bullosa, including increased skin fragility, trauma-induced blistering with erosions, atrophic scarring, milia over extensor surfaces, and nail dystrophy; 2) adult onset; 3) lack of a family history of epidermoylsis bullosa; and 4) exclusion of all other bullous diseases such as porphyria cutanea tarda, pemphigoid, pemphigus, dermatitis herpetiformis, and bullous drug eruption. In 1981, Roenigk et al extended these criteria to include 5) IgG at the basement membrane zone by DIF; 6) the demonstration of blister formation beneath the basal lamina; and (7) deposition of IgG beneath the basal lamina. Since then, the clinical spectrum of this disease has expanded, with evidence that some patients have histologic findings identical to BP, but show positive immunofluorescence on the floor of salt-split skin. The antibodies have been found to target type VII collagen, a major component of anchoring fibrils. The target is the same as that in bullous lupus erythematosus. In some patients, it has been shown that autoantibodies bind to the NC-1 domain of collagen VII within the lamina densa. IIF studies reveal circulating antibasement membrane zone antibodies in approximately half of cases. The antibodies are directed against multiple epitopes on the N-terminal noncollagenous domain of type VII collagen.

The noninflammatory clinical presentation of EBA is the most commonly recognized type. The association of EBA with many systemic diseases, such as myeloma, granulomatous colitis, diabetes, lymphoma, leukemia, amyloidosis, and carcinoma is well established. In rare instances, cases of this noninflammatory subset may mimic either BP or CP. When the onset is in childhood, hereditary dystrophic epidermoylsis bullosa may be considered.

In 1982, Gammon described patients with generalized inflammatory bullous disease that resembled BP clinically, but with immunologic and ultrastructural features of EBA. Many of these patients have associated diabetes mellitus, are HLA-DR2 positive, and progress to the trauma-induced scarring type of EBA in the long-term. Approximately 5% to 10% of patients referred to medical centers as having BP may actually have EBA.

EBA patients usually have a predominance of neutrophils over eosinophils, although this is variable. On IIF, EBA patients are more likely to have linear IgG without concomitant C3 deposition than are patients with BP. Immunofluorescence on salt-split skin allows differentiation of the majority of cases without needing to resort to immunoblot techniques or immunoelectron microscopy. By DIF testing of the patient's salt-split skin biopsy, EBA will manifest IgG deposition only on the dermal side of the split, whereas the majority of BP patients will have IgG bound only to the epidermal side or to both sides. As demonstrated by IIF, the same results apply in the majority of cases. As noted above, some patients with BP have antibodies that target sub-lamina densa antigen. Absolute differentiation of these diseases is obtained by immunoelectron microscopy or immunoblot findings. In EBA, immunoblotting identifies 290-kD and 145-kD proteins, corresponding to type VII collagen.

Because bullous systemic lupus erythematosus (SLE) and EBA share antibasement membrane zone antibodies of identical specificity, and there is clinical and histologic overlap as well, this differential diagnosis may be difficult. The following features help to identify EBA: skin fragility, predilection for traumatized areas, and healing with scars and milia. In SLE, sun-exposed skin is involved by preference, the patient has a diagnosis of SLE established by ACR criteria, and in bullous SLE there is usually a dramatic response to dapsone. In addition to the cases of bullous SLE that show linear IgG staining below the lamina densa with circulating IgG autoantibodies to the 290-kD and 145-kD antigens, some patients will show granular staining of IgG at the basement membrane zone without circulating IgG. EBA-like eruptions are rarely seen as a result of penicillamine therapy.

Purely IgA-mediated EBA has been described. The patients resemble linear IgA dermatosis or inflammatory IgG-mediated EBA. Only a minority demonstrate milia or scarring.

Treatment

A review of the literature using Cochrane criteria failed to identify any randomized controlled trials. The disease is often resistant to therapy, but good responses have been reported in some patients treated with systemic steroids alone or in combination with azathioprine or dapsone. Other agents reported to be effective include mycophenolate

mofetil, IVIG, cyclosporin, colchicine, plasmapheresis, and the humanized murine monoclonal anti-Tac antibody daclizumab. Extracorporeal photochemotherapy has been effective in a few patients with refractory disease. Supportive therapy, including control of infection, careful wound management, and maintenance of good nutrition should be emphasized.

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DERMATITIS HERPETIFORMIS (DUHRING DISEASE)

Clinical Features

Dermatitis herpetiformis (DH) is a chronic, relapsing, severely pruritic disease characterized by grouped, symmetrical lesions on extensor surfaces, the scalp, nuchal area, and buttocks. As the lesions as severely pruritic, they generally present as excoriations. The eruption usually occurs on an erythematous base and may be papular, papulovesicular, vesiculobullous (Fig. 21-13), bullous, or urticarial. Linear petechial lesions may be noted on the volar surfaces of the fingers as well as the palms (Fig. 21-14). Pigmented spots alone over the lumbosacral region should arouse suspicion of DH. The mucous membranes are involved in rare cases, mostly when bullae are numerous. Laryngeal lesions may manifest as hoarseness.

Itching and burning are usually intense, and their paroxysmal quality provokes scratching to the point of bleeding and, at times, scarring. Spontaneous remissions lasting as long as a week and terminating abruptly with a new crop of lesions are a characteristic feature of the disease. Perimenstrual flares may occur.

Seventy-seven to 90% of patients with DH and IgA deposits in the skin are HLA-B8 positive, a similar frequency to that observed in gluten-sensitive enteropathy (GSE). HLA antigens DR3 and DQw2 are also increased in frequency.

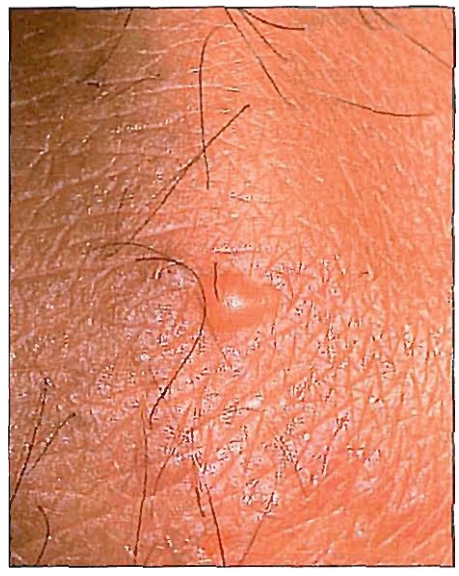

Fig. 21-13 Vesicle of dermatitis herpetiformis on the elbow.

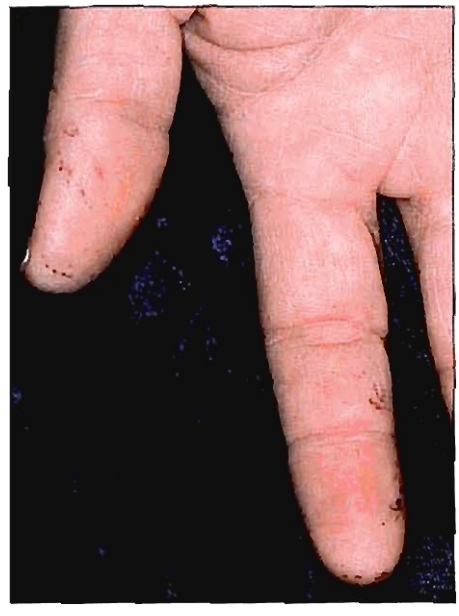

Fig. 21-14 Characteristic linear petechial lesions on the digits in a patient with dermatitis herpetiformis.

Black and Asian patients are infrequent and some studies indicate this may be because of HLA differences. These HLA markers are associated with other autoimmune diseases and are a marker of patients who appear to have an overactive immune response to common antigens and may clear immune complexes slowly. DH is more common in those with affected family members.

DH in childhood is usually similar to the adult type, has identical histologic and immunofluorescent findings, and has a high incidence of HLA-B8 and -DR3 and abnormal jejunal biopsies. Palmer blisters and brown, hemorrhagic, purpuric macules may be more common than in adults. Treatment with sulfones results in prompt response, as in adults.

Gluten, a protein found in cereals except for rice and corn, provokes flares of the disease. Villous atrophy of the jejunum and inflammation of the small bowel occurs. IgA is bound to the skin, and this apparently activates complement, primarily via the alternate pathway. Oral iodides will cause a flare of the disease. Patch tests with 50% potassium iodide in

petrolatum produce a bulla in uncontrolled DH, but only exceptionally in patients controlled by a gluten-free diet or by sulfone therapy.

Associated Disease

Thyroid disorders are increased in incidence in patients with DH. An increased incidence of malignancy, especially small bowel lymphoma has also been noted.

Enteropathy

Seventy to 100% of patients with DH have abnormalities in the jejunal mucosa, but most are asymptomatic. If given a high-gluten diet, virtually all patients with DH develop findings indistinguishable from celiac disease, and DH affects approximately 25% of patients presenting with celiac disease.

The dapsone requirement in DH is usually decreased after 3 to 6 months of a gluten-free diet. The majority of patients who adhere to a strict gluten-free diet can eventually stop their medication or significantly reduce the dosage. A gluten-free diet is not easy to follow.

Diagnosis

The distinction from linear IgA bullous dermatosis is often clinically impossible. Other conditions considered in the differential diagnosis at times are BP, bullous erythema multiforme, scabies, contact dermatitis, atopic dermatitis, nummular eczema, neurotic excoriations, insect bites, and chronic bullous disease of childhood. The finding of IgA in a granular pattern at the dermoepidemal junction with accentuation in the dermal papillae is specific for DH.

Autoantibodies Circulating IgA antibodies against the smooth muscle cell endomysium (anti-endomysial antibodies) are present in 70% of DH patients, in nearly all active celiac disease patients, and almost never in other conditions. Tissue transglutaminase (TTG) is the major autoantigen in GSE. Although anti-TTG antibodies are found in the majority of patients with DH, these patients have antibodies that bind more avidly to a related enzyme, epidermal (type 3) transglutaminase. IgA deposits in the papillary dermis contain epidermal transglutaminase, but not TTG. Dietary exposure to gliadin proteins in wheat and related proteins from barley and rye induce flares of the disease. These proteins are high-affinity substrates for TTG. The two are often tightly bound, which may explain why an antibody response is generated against both gliadin and TTG. Gliadins can also be found in rice, corn, and oats, but these proteins are poor substrates for TTG. Some data suggest that a diet with moderate quantities of oats can be tolerated in patients with controlled DH or GSE.

Epidemiology

This disease has an equal male-to-female incidence. The average age of onset is between 20 and 40 years. It does occur with some frequency in children. Black and Asian persons are rarely affected.

Histopathology

The initial changes are first noted at the tips of the dermal papillae, where edema, focal fibrin, and neutrophilic microabscesses are seen (Fig. 21-15). The cellular infiltrate contains many neutrophils, but may also include a few eosinophils. A subepidermal separation is noted histologically. Ultrastructurally the split may begin in the lamina lucida. In a study of 24 cases of confirmed DH, 37.5% had nonspecific findings on hematoxylin and eosin (H&E), including a lymphocytic infiltrate, ectatic capillaries, and fibrosis in the dermal papillae. Because of the potential for nonspecific biopsy findings, DIF studies are essential. Histologic differentiation of linear IgA bullous dermatosis from DH is extremely difficult unless DIF is performed.

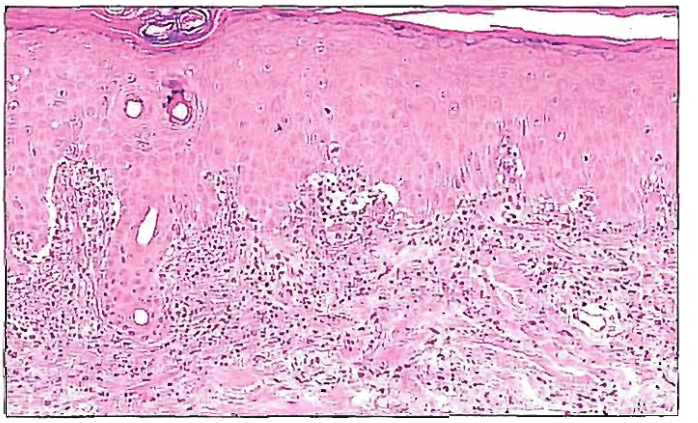

Fig. 21-15 Dermatitis herpetiformis, neutrophilic microabscesses within the dermal papillae.

DIF of noninvolved perilesional skin reveals deposits of IgA alone or together with C3 arranged in a granular pattern at the dermoepidermal junction. The granules may be vertically elongated, giving a "picket-fence" appearance. The deposits are typically accentuated in the dermal papillae. IgM and IgG deposits are occasionally observed in association with IgA. Deposits may be focal, so that multiple biopsies may be needed, and the deposits of antibody are more often seen in previously involved skin or normal-appearing skin adjacent to involved skin. By immunoelectron microscopy IgA is observed either alone or in conjunction with C3, IgG, or IgM as clumps in the upper dermis. A fibrillar staining pattern exists when the immune deposits are along dermal microfibrils. A few patients will have negative DIF despite typical clinical findings and evidence of anti-endomysial antibodies. IIF is rarely positive.

Treatment

The drugs chiefly used are dapsone and sulfapyridine. The most effective sulfone is diaminodiphenylsulfone (dapsone). The dose varies between 50 and 300 mg/day, usually starting with 100 mg/day and increasing gradually to an effective level or until side effects occur. Once a favorable response is attained, the dosage is decreased to the minimum that does not permit recurrence of signs and symptoms. When dapsone is discontinued abruptly, large bullae similar to those seen in BP frequently occur. Hemolytic anemia, leukopenia, methemoglobinemia, agranulocytosis or peripheral neuropathy may occur with dapsone. Acute hemolytic anemia (which may be severe) occurs in patients with glucose-6-phosphate dehydrogenase (GDPD) deficiency, therefore a G6PD level should be done before therapy. In those whose ethnic background makes G6PD deficiency unlikely, some authorities begin dapsone at a low starting dose (25 mg/day) and watch the patient closely for dark urine. The patient should be warned to report by telephone any incident of red or brown urine or

blue nailbeds or lips. A blood count should be done weekly for 4 weeks, bimonthly for the next 3 months, and every 2 to 6 months thereafter. Liver function tests should be monitored bimonthly for the first 4 months, then checked with the hematologic studies every 4 to 6 months.

Agranulocytosis is rare. It typically occurs 1 to 3 months after initiation of drug therapy, and presents with sore throat, aphthae or evidence of infection. The risk of agranulocytosis is higher in older individuals (>60 years) and non-white persons. The incidence varies with the disease. It is rarely seen in leprosy patients but patients with DH have a 25- to 33-fold increased risk.

Sulfapyridine can also be used to treat the disease. After a test dose of 0.5 g of sulfapyridine, one tablet (0.5 g) four times a day is given. The dose is then increased if necessary, or reduced if possible. Usually 1 to 4 g/day is required for good control. The drug is less water soluble than dapsone, and patients should remain hydrated. Sulfasalazine, 500 mg three times a day, increased to 1.5 g three times a day as tolerated, may also be used, since sulfapyridine is a metabolic product. Gastrointestinal intolerance may limit the dosage. In rare patients, it is necessary to find alternatives to the sulfone drugs. Tetracycline/nicotinamide and colchicine have controlled individual patients.

Gluten-Free Diet Patients must strictly avoid wheat, barley, and rye. Moderate amounts of oats may be tolerated. Corn and rice are generally well tolerated, corresponding to the poor binding of their gliadin proteins to TTG. If a gluten-free diet is followed strictly, the patient will almost certainly be able to take less medication or stop it altogether. Some evidence suggests this may decrease the incidence of associated malignancy; however, it is a very difficult diet to follow. The diet will help to achieve a remission. Once a prolonged remission has been obtained, some gluten may be tolerated in a subset of patients. In one study, 38 patients who had followed a gluten-free diet for a mean of 8 years reintroduced gluten to their diets. Thirty-one experienced recurrence within an average of 2 months, but seven remained in remission for a mean follow-up of 12 years. IgA deposits did not recur in their skin. This report suggests that clinical and histologic remission can be maintained in some patients with DH despite the reintroduction of dietary gluten. For most patients, however, a gluten-free diet remains an important aspect of disease management. Support may be obtained from the American Celiac Society/Dietary Support Coalition, Annette Bentley, President, 59 Crystal Avenue, West Orange, NJ 07052-3570, 973-325-8837 (Voice), 973-669-8808 (FAX). A list of celiac societies can be found at http://www.nowheat.com/grfx/nowheat/primer/celisoc.htm or http://www.enabling.org/ia/celiac/groups/groupsus.html. A commercial website with a search engine can be found at http://www.celiac.com. Another commercial source for products can be found at http://www.glutenfreemall.com. A Google search using the terms "celiac society" or "gluten-free diet" is a good starting point for patients with the disease who want more information about the diet and commercially available products.

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LINEAR IGA BULLOUS DERMATOSIS

Linear IgA bullous dermatosis (LAD) is characterized by subepidermal blisters, a neutrophilic infiltrate, and a circulating IgA anti-basement membrane zone antibody with linear basement membrane zone deposits on DIF. Like CP, linear IgA disease is really a group of diseases with a similar immunofluorescent pattern.

Adult Linear IgA Disease

This acquired, autoimmune blistering disease may present with a clinical pattern of vesicles indistinguishable from DH, or with vesicles and bullae in a BP-like appearance. There may be urticarial lesions and bullae may occur on an urticarial base as in BP. Mucous membrane involvement may occur in up to 50% of cases. In some cases, oral and conjunctival lesions dominate the presentation, and scarring may occur as in CP. In the majority of patients, there is no association with enteropathy or with HLA-B8. The disease tends to remit after several years in approximately 60% of patients. IgA is commonly directed against a 97-kD antigen in the lamina lucida. Some patients demonstrate both IgA and IgG antibodies to BP180 and IgA to LAD285. IgA and IgG reactivity have been found to all three portions of the BP180 ectodomain. In some patients, the strongest reactivity is to the C-terminal portion of BP180 (the major antigenic

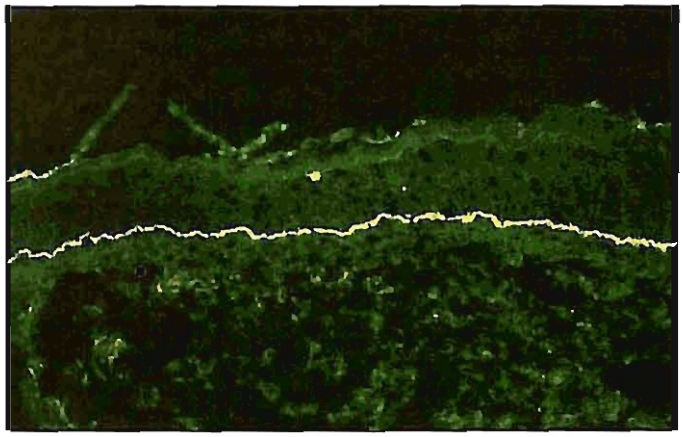

Fig. 21-16 Direct immunofluorescence of linear IgA disease.

area in CP). This may explain cases of clinical overlap with CP. Antigenic targets for LAD are expressed by both keratinocytes and fibroblasts.

Linear IgA dermatosis commonly occurs as a drug-induced disease. In drug-induced disease, the eruption is self-limited, there is less mucosal involvement, and usually no detectable circulating autoantibody. The IgA may be deposited in the subbasal lamina area. Implicated drugs include vancomycin, lithium, amiodarone, carbamazipine, captopril, penicillin, PUVA, furosemide, oxaprozin, IL-2, interferon-γ, phenytoin, diclofenac, statins, tea tree oil, anigotension receptor antagonists, and glibenclamide. The antigen identified may be the 97-kD antigen, the 230-kD BP antigen, or the 180-kD BP antigen.

Some cases have been associated with internal malignancy or infection. Sporadic reports have linked single cases with dermatomyositis, rheumatoid arthritis, and multiple sclerosis, although these are probably fortuitous associations.

Biopsies commonly demonstrate papillary dermal micro-abscess with neutrophils. As in DH, eosinophils may be present. Subepidermal bullae commonly contain a mixture of neutrophils and eosinophils. On DIF, a homogeneous linear (tubular or toothpaste) pattern of IgA is present at the basement membrane zone (Fig. 21-16). Some cases will have both linear IgA and IgG in combination at the basement membrane zone. A lack of C3 may be a clue that both immunoglobulins recognize the 97-kD antigen.

By IIF, only a minority will have circulating IgA auto-antibody with anti-basement membrane specificity, and this is usually present in low titer. On salt-split skin, deposition may occur on the roof, base, or a combination of the two. This correlates with the fact that on immunoelectron microscopy deposition of the autoantibody may be present in the lamina lucida, below the lamina densa, or both. Some patients with sublamina densa deposits have EBA.

In drug-induced disease, the drug must be stopped. Many cases resolve quickly, but some require drug therapy with a corticosteroid or dapsone. Idiopathic disease generally responds to dapsone in doses similar to that described for DH. Other cases require topical or systemic steroids in addition, or as sole treatment. A combination of tetracycline, 2 g/day, and nicotinamide, 1.5 g/day, may be effective. Other patients have responded to mycophenolate mofetil, IVIG, colchicine, or erythromycin. The rare patients with associated GSE may respond to a gluten-free diet.

Allen J, et al: The cellular origins of the linear IgA disease target antigens: an indirect immunofluorescence study using cultured human keratinocytes and fibroblasts. Br J Dermatol 2003;148:945.

Bachot N, et al: Amiodarone-related linear IgA bullous dermatosis. J Am Acad Dermatol 2003;49:E2.

Cooper SM, et al: Linear IgA disease: successful treatment with erythromycin. Clin Exp Dermatol 2002;27:677.

Dellavalle RP, et al: Vancomycin-associated linear IgA bullous dermatosis mimicking toxic epidermal necrolysis. J Am Acad Dermatol 2003;48(5 Suppl):S56.

Egan CA, et al: Linear IgA bullous dermatosis responsive to a gluten-free diet. Am J Gastroenterol 2001;96:1927.

Hollo P, et al: Linear IgA dermatosis associated with chronic clonal myeloproliferative disease. Int J Dermatol 2003;42:143.

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Sato K, et al: Initial presentation and fatal complications of linear IgA bullous dermatosis in the larynx and pharynx. J Laryngol Otol 2005;119:314.

Talhari C, et al: Successful treatment of linear IgA disease with mycophenolate mofetil as a corticosteroid sparing agent. Clin Exp Dermatol 2005;30:297.

Zone JJ: Clinical spectrum, pathogenesis and treatment of linear IgA bullous dermatosis. J Dermatol 2001;28:651.

Childhood Linear IgA Disease (Chronic Bullous Disease of Childhood)

Chronic bullous disease of childhood (CBDC) is an acquired, self-limited bullous disease that may begin by the time the patient is aged 2 or 3 and usually remits by age 13. The average age of onset is 5 years. Bullae develop on either erythematous or normal-appearing skin, preferentially involving the lower trunk, buttocks, genitalia, and thighs. Perioral and scalp lesions are common, and oral mucous membrane lesions may occur in up to 75% of patients. Bullae are often arranged in rosettes or an annular array, the so-called string of pearls configuration (Fig. 21-17). Tense individual bullae similar to those present in BP are also seen. Pruritus is often severe.

The prime histologic finding is the presence of a subepidermal bulla filled with neutrophils. Eosinophils may be present, and in some cases eosinophils predominate. DIF reveals a linear deposition of IgA at the basement membrane zone identical to that seen in the adult forms of the disease. IIF is positive for circulating IgA anti-basement membrane zone antibodies in approximately 50% of cases, usually in low titer. In contrast to adult LAD, children demonstrate an increased frequency of B8, DR3, and DQ2, and may be homozygous for these antigens. As in the adult disease, immunoelectron microscopy and immunomapping studies may demonstrate immune deposits within the lamina lucida, below the lamina densa, or both. As in adult disease, some children have both IgG and IgA deposits. GSE is rare.

Many patients' antibodies target the 97-kD peptide. Some children with subbasal lamina deposits target type VII collagen and have EBA. Patients with only IgA or with both IgG and IgA circulating autoantibodies may target BP230 or BP180. Individual patients may have a combination of IgA against the 97-kD peptide, and IgG against BP230 and BP180. Collagen XVII/BP180 is a transmembrane protein

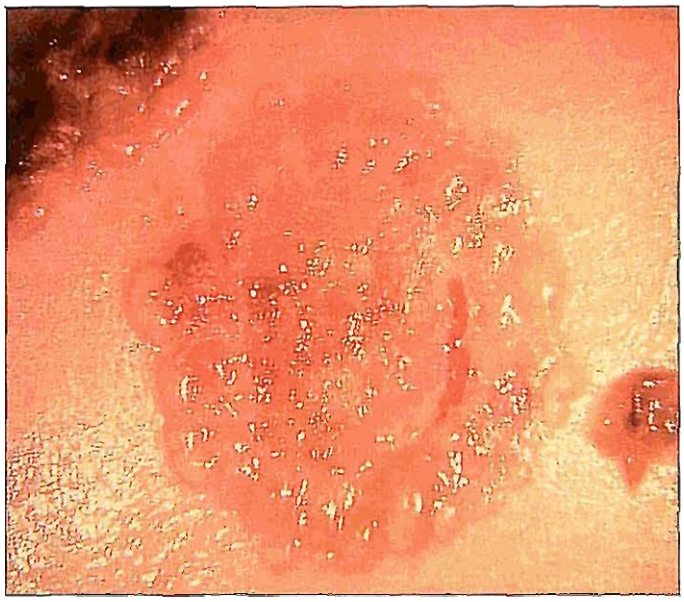

Fig. 21-17 Chronic bullous disease of childhood.

with a soluble 120-kD ectodomain. In linear IgA dermatosis and CBCD, IgA targets the soluble ectodomain more efficiently than the full-length protein. Some sera target the Col15 domain.

The untreated disease runs a variable course, with eventual spontaneous resolution by adolescence being common. Treatment with either dapsone or sulfapyridine is usually successful. Occasional cases respond to topical steroids alone, and systemic steroids are sometimes necessary. Other patients have responded to mycophenolate mofetil, colchicine, or dicloxacillin.

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Collier PM, et al: Adult linear IgA disease and chronic bullous disease of childhood: the association with human lymphocyte antigens Cw7, B8, DR3 and tumour necrosis factor influences disease expression. Br J Dermatol 1999;141:867.

Farley-Li J, et al: Treatment of linear IgA bullous dermatosis of childhood with mycophenolate mofetil. Arch Dermatol 2003;139:1121.

Jablonska S: The therapies for linear IgA bullous dermatosis of childhood. Pediatr Dermatol 1999;16:415.

Schumann H, et al: The shed ectodomain of collagen XVII/BP180 is targeted by autoantibodies in different blistering skin diseases. Am J Pathol 2000;156:685.

Siegfried EC, et al: Chronic bullous disease of childhood: successful treatment with dicloxacillin. J Am Acad Dermatol 1998;39(5 Pt 1):797.

Thappa DM, et al: Chronic bullous dermatosis of childhood. Postgrad Med J 2003;79:437.

TRANSIENT ACANTHOLYTIC DERMATOSIS (GROVER'S DISEASE)

In 1970, Grover described a new dermatosis that occurred predominantly in persons over 50 years of age consisting of a sparse eruption of limited duration. The lesions were fragile vesicles that rapidly turned into crusted and keratotic erosions. He termed the condition transient acantholytic dermatosis (TAD). Since then, the majority of cases have been found to persist or recur, and the term *persistent and recurrent acantholytic dermatosis* may be a more accurate description of the disorder. The distribution is predominantly limited to the chest or shoulder girdle area and upper abdomen, and there is a strong male predominance. The condition often appears or flares during periods of heat, sweating or hospitalization. Many patients are asymptomatic and the condition may be an incidental finding on examination. Other patients complain of pruritus. Asteatotic eczema occurs five times as often among patients with TAD as in controls. The disorder has been described in the setting of a variety of malignancies, but may be associated with the hospitalization rather than the malignancy itself. Patients at strict bedrest appear to have a higher incidence of the disease. The clinical differential diagnosis includes Galli-Galli disease, an acantholytic variant of Dowling-Degos disease that may resemble TAD clinically.

There are five histologic types resembling Darier's disease, PV, PF, benign familial pemphigus, or spongiotic dermatitis. The Darier type predominates. Often two or more types can be found in a single biopsy specimen. DIF studies yield negative or nonspecific results. Although heat and sweating are significant risk factors, only a minority of cases are associated with acrosyringia histologically.

About 50% of patients respond to topical steroids. Control of fevers, hospital discharge, and avoidance of sun and sweating often result in improvement. Sustained remission has been described after a course of systemic corticosteroids. Isotretinoin and dapsone have been successful in some patients. PUVA has been reported to result in an initial flare followed by slow clearance.

Antley CM, et al: Grover's disease (transient acantholytic dermatosis): relationship of acantholysis to acrosyringia. J Cutan Pathol 1998;25:545.

Davis MD, et al: Grover's disease: clinicopathologic review of 72 cases. Mayo Clin Proc 1999;74:229.

Eros N, et al: Successful treatment of transient acantholytic dermatosis with systemic steroids. J Dermatol 1998;25:469.

French LE, et al: Incidence of transient acantholytic dermatosis (Grover's disease) in a hospital setting. Dermatology 1999; 198:410.

Parsons JM: Transient acantholytic dermatosis (Grover's disease): a global perspective. J Am Acad Dermatol 1996; 35(5 Pt 1):653.

Streit M, et al: Transitory acantholytic dermatosis (Grover disease). An analysis of the clinical spectrum based on 21 histologically assessed cases. Hautarzt 2000;51:244.

CHAPTER

22 Nutritional Diseases

A nutritional disease is caused either by insufficiency or, less often, by excess of one or more dietary essentials. Nutritional diseases are particularly common in underdeveloped tropical countries. Infants and children are particularly at risk for deficiency states, especially malnutrition. Frequently, patients have features of several of these disorders if their diets have been generally restricted. An intertiginous or acral eruption, a seborrheic dermatitis-like facial eruption, atrophic glossitis, and alopecia are common features of many nutritional deficiencies. This occurs because these nutrients are essential to overlapping metabolic pathways of fatty acid metabolism, resulting in abnormal arachadonic acid metabolism and abnormal differentiation of the epidermis. The abnormal epidermal differentiation results in impaired epidermal lipid and intercellular junction production and defective barrier function. Impaired disposal of free radicals may also occur. The histologic findings in many types of nutritional dermatoses are also similar.

In developed countries, alcoholism is the main cause of nutritional diseases. Nutritional diseases should also be suspected in postoperative patients; psychiatric patients, including those with anorexia nervosa and bulimia; patients on unusual diets; patients with surgical or inflammatory bowel dysfunction, especially Crohn's disease; and patients with severe oral erosive disease (such as pemphigus) which prevents eating. Cystic fibrosis may be accompanied by nutritional deficiency dermatitis. In the pediatric setting, nutritional deficiency may also occur because of parental ignorance of the nutritional requirements of their infants. The diagnosis of nutritional deficiency is often missed since physicians fail to take adequate dietary histories. The edema of protein malnutrition may mask the problem. The dermatitis produced by elevated glucagon levels from islet cell tumors of the pancreas (necrolytic migratory erythema) and a similar dermatoses seen in hepatitis C infection and other forms of hepatic insufficiency (necrolytic acral erythema and pseudoglucagonoma) probably also represent nutritional deficiency dermatoses. Deficiency states caused by inborn errors of metabolism are discussed in Chapter 26.

VITAMIN A

Hypovitaminosis A (Phrynoderma)

Vitamin A is a fat-soluble vitamin found as retinyl esters in milk, fish oil, liver, and eggs, and as carotenoids in plants. Vitamin A deficiency is common in children in the developing world. It is rare in developed countries, where it is most commonly associated with diseases of fat malabsorption, such as bowel bypass surgery for obesity, pancreatic insufficiency, Crohn's disease, celiac disease, cystic fibrosis, and liver disease. Vitamin A is required for the normal keratinization of many mucosal surfaces. When deficient, the resultant abnormal keratinization leads to increased mortality from inflammatory disease of the gut and lung—diarrhea and pneumonia (especially in rubeola). Vitamin A supplementation of 200,000 IU/day for 2 days is recommended for children with rubeola.

The skin eruption, termed *phrynoderma*, or "toadskin," resembles keratosis pilaris. It consists of keratotic papules of various sizes, distributed over the extremities and shoulders, surrounding and arising from the pilosebaceous follicles. Individual lesions are firm, pigmented papules containing a central intrafollicular keratotic plug, which projects from the follicle as a horny spine and leaves a pit when expressed. Lesions are of two sizes: 1- to 2-mm papules closely resembling keratosis pilaris, and the more diagnostic large 2- to 6-mm crateriform papules filled with a central keratotic plug. These later lesions may simulate a perforating disorder. The eruption of small lesions usually begins on the anterolateral aspect of the thighs or the posterolateral aspect of the upper arms. It then spreads to the extensor surfaces of both the upper and lower extremities, shoulders, abdomen, back, and buttocks, and finally reaches the face and posterior aspect of the neck. The hands and feet are not involved and only occasionally are there lesions on the midline of the trunk or in the axillary and anogenital areas. On the face, the eruption resembles acne because of the presence of many large comedones, but it differs from acne in respect to dryness of the skin. The large dome-shaped nodules are on the elbows and knees. They have a surrounding red or brown rim. The whole skin displays dryness, fine scaling, and hyperpigmentation.

In vitamin A deficiency, eye findings are prominent and often pathognomonic. These include night blindness, an inability to see bright light, xerophthalmia, xerosis corneae, and keratomalacia. The earliest finding is delayed adaptation to the dark (nyctalopia). Sometimes there are circumscribed areas of xerosis of the conjunctiva lateral to the cornea, occasionally forming well-defined white spots (Bitot spots). These are triangular, with the apex toward the canthus. Vitamin A deficiency is a major cause of blindness in children in the developing world. The histologic findings of vitamin A deficiency are hyperkeratosis, horny plugs in the upper portion of the hair follicle, coiled hairs in the upper part of the follicle, severe atrophy of the sebaceous glands, and squamous metaplasia of the secretory cells of the eccrine sweat glands. If the follicles rupture, perifollicular granulomatous inflammation is found.

The diagnosis of vitamin A toxicity is confirmed by determination of the serum retinol level. The treatment is oral vitamin A 100,000 IU/day for 2 to 3 days followed by the recommended dietary requirement. Serum retinol levels are monitored to determine adequacy of supplementation and to avoid vitamin A toxicity.

Hypervitaminosis A

Because the skin findings of hypervitaminosis A are similar to the side effects of synthetic retinoid therapy, they are well recognized by most dermatologists. Children are at greater risk for toxicity than adults. Excess megavitamin ingestion may be the cause. In adults, as little as 25,000 IU/day may lead to toxicity, especially in persons with hepatic compromise from alcoholic, viral, or medication-induced hepatitis. Dialysis patients also are at increased risk. If the patient is taking a synthetic retinoid, all vitamin A supplementation should be stopped.

Most cases of chronic hypervitaminosis A have been reported in children. There is loss of hair and coarseness of the remaining hair, loss of the eyebrows, exfoliative cheilitis, generalized exfoliation and pigmentation of the skin, and clubbing of the fingers. Moderate widespread itching may occur. Hepatomegaly, splenomegaly, hypochromic anemia, depressed serum proteins, and elevated liver function tests may be found. Bone growth may be retarded by premature closure of the epiphyses in children. Pseudotumor cerebri with papilledema may occur very early, before any other signs appear. In infants this may present as a bulging fontanelle.

In adults, the early signs are dryness of the lips and anorexia. These may be followed by joint and bone pains, follicular hyperkeratosis, branny desquamation of the skin, fissuring of the corners of the mouth and nostrils, dryness and loss of scalp hair and eyebrows, and dystrophy of the nails. Fatigue, myalgia, depression, anorexia, headache (from pseudotumor cerebri), strabismus, and weight loss commonly occur. Liver disease may be progressive and may lead to cirrhosis with chronic toxicity. Hypercalcemia commonly occurs in dialysis patients. Retinoids are teratogens, and birth defects may occur with excess vitamin A supplementation during pregnancy.

Bak H, Ahn SK: Pseudoglucagonoma syndrome in a patient with malnutrition. Arch Dermatol 2005;141:914.

Bleasel NR, et al: Vitamin A deficiency phrynoderma: Due to malabsorption and inadequate diet. J Am Acad Dermatol 1999;41:322.

Fishbane S, et al: Hypervitaminosis A in two hemodialysis patients. Am J Kidney Dis 1995;25:346.

Hivnor CM, et al: Necrolytic acral erythema: Response to combination therapy with interferon and ribavirin. J Am Acad Dermatol 2004;50:S121.

Khanna VJ, et al: Necrolytic acral erythema associated with hepatitis C. Arch Dermatol 2000;136:755.

Park YM, et al: Recurrent annular erythematous scaly patches. Arch Dermatol 2002;138:405.

Roe DA: Assessment of risk factors for carotenodermia and cutaneous findings of hypervitaminosis A in college-aged populations. Semin Dermatol 1991;10:303.

Sharieff GX, et al: Pseudotumor cerebri and hypercalcemia resulting from vitamin A toxicity. Ann Emerg Med 1996; 27:518.

Smith KE, Fenske NA: Cutaneous manifestations of alcohol abuse. J Am Acad Dermatol 2000;43:1.

White J, et al: Desquamating migratory erythema caused by nutritional deficiency—4 cases. J Am Acad Dermatol 2004; 50:P159.

VITAMIN D

Although active vitamin D is produced in the skin, deficiency of vitamin D has no skin manifestations, except for alopecia. The elderly have decreased vitamin D cutaneous photosynthesis by reason of decreased sun exposure and poor intake of vitamin D, both of which predispose them to osteomalacia. Aggressive photoprotection may also reduce vitamin D levels. Other patients at risk include those who are debilitated with limited sun exposure, those taking anticonvulsants, and those with fat malabsorption. Supplementation for these patients should be considered. Rickets in malnourished children responds best to combination therapy with vitamin D and calcium supplementation.

Sollitto RB, et al: Normal vitamin D levels can be maintained despite rigorous photoprotection. J Am Acad Dermatol 1997;37:942.

Welsh O, et al: Tropical dermatology. Part II. J Am Acad Dermatol 2002;46:748.

VITAMIN K DEFICIENCY

Dietary deficiency of vitamin K, a fat-soluble vitamin, does not occur in adults because it is synthesized by bacteria in the large intestine. However, deficiency may occur in adults because of malabsorption caused by biliary disease, malabsorption syndromes, cystic fibrosis, or anorexia nervosa. Liver disease of all causes produces deficiency. Drugs such as coumarin, salicylates, cholestyramine, and perhaps the cephalosporins may induce a deficiency state. Newborns of mothers taking coumarin or phenytoin, or premature infants with an uncolonized intestine, can be vitamin K-deficient. The result is a decrease in the vitamin K-dependent clotting factors II, VII, IX, and X. The cutaneous manifestations that result are purpura, hemorrhage, and ecchymosis. Treatment is 5 to 10 mg/day of intramuscular vitamin K for several days. In acute crises, fresh frozen plasma is used.

Humphries JE: Skin necrosis due to vitamin K deficiency. Am J Med 1993;95:453.

Soundararajan R, et al: Skin necrosis and protein C deficiency associated with vitamin K depletion in a patient with renal failure. Am J Med 1992;93:467.

VITAMIN B1 DEFICIENCY

Vitamin B_1 (thiamine) deficiency results in beriberi. The skin manifestations are limited to edema. Peripheral neuropathy is common.

Comabella M, et al: Iatrogenic fulminant beriberi. Lancet 1995; 346:182.

VITAMIN B2 DEFICIENCY

Vitamin B_2 (riboflavin) deficiency is seen most often in alcoholic patients; however, phototherapy for neonatal icterus, acute boric acid ingestion, hypothyroidism, and chlorpromazine use have been reported to cause it also. The classic findings are the oral–ocular–genital syndrome. The lips are prominently affected with angular cheilitis (perlèche)

and cheilosis. The tongue is atrophic and magenta. A seborrheic-like dermatitis with follicular keratosis around the nares, primarily affects the face. Genital dermatitis is worse in men than it is in women who have riboflavin deficiency. There is a confluent dermatitis of the scrotum, sparing the midline, with extension onto the thighs. Photophobia and blepharitis angularis occur. The response to 5 mg/day of riboflavin is dramatic.

Roe DA: Riboflavin deficiency. Semin Dermatol 1991;10:293.

VITAMIN B_6

Pyridoxine Deficiency

Pyridoxine deficiency may occur in cases of uremia and cirrhosis, as well as with the use of certain pharmacologic agents. Skin changes include a seborrheic dermatitis-like eruption, atrophic glossitis with ulceration, angular cheilitis, conjunctivitis, and intertrigo. Occasionally, a pellagra-like eruption may occur. Neurologic symptoms include somnolence, confusion, and neuropathy.

Pyridoxine Excess

Friedman et al reported a patient who ingested large doses of pyridoxine (vitamin B_6) and developed a subepidermal vesicular dermatosis and sensory peripheral neuropathy. The bullous dermatosis resembled epidermolysis bullosa acquisita.

Friedman MA, et al: Subepidermal vesicular dermatosis and sensory peripheral neuropathy caused by pyridoxine abuse. J Am Acad Dermatol 1986;14:915.

VITAMIN B_{12} DEFICIENCY

Vitamin B_{12} (cyanocobalamin) is absorbed through the distal ileum after binding to gastric intrinsic factor in an acid pH. Deficiency is caused mainly by gastrointestinal abnormalities, such as a deficiency of intrinsic factor, achlorhydria, ileal diseases, and malabsorption syndromes resulting from pancreatic disease or sprue. Congenital lack of transcobalamin II can also produce B_{12} deficiency. Because of the large body stores in adults, deficiency occurs 3 to 6 years after gastrointestinal abnormalities.

Glossitis, hyperpigmentation, and canities are the main dermatologic manifestations. The tongue is bright red, sore, and atrophic. The hyperpigmentation is generalized, but it is more commonly accentuated in exposed areas, such as the face and hands, and in the palmar creases and flexures, resembling Addison's disease. The nails may be pigmented. Premature gray hair may occur paradoxically. Megaloblastic anemia is present. Weakness, paresthesias, numbness, ataxia, and other neurologic findings occur.

Parenteral replacement with intramuscular injections, 1 mg/week for 1 month, then 1 mg/month, leads to a reversal of the pigmentary changes in the skin, nails, mucous membranes, and hair. Neurologic defects may or may not improve.

Noppakun N, et al: Reversible hyperpigmentation of skin and nails with white hair due to vitamin B_{12} deficiency. Arch Dermatol 1986;122:896.

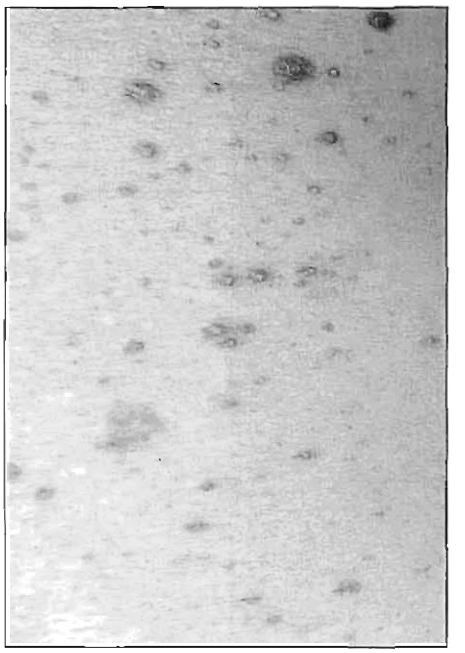

Fig. 22-1 Scurvy, perifollicular hemorrhage and follicular hyperkeratosis.

FOLIC ACID DEFICIENCY

Diffuse hyperpigmentation, glossitis, cheilitis, and megaloblastic anemia, identical to vitamin B_{12} deficiency, occur in folic acid deficiency.

Downham TF, et al: Hyperpigmentation and folate deficiency. Arch Dermatol 1976;112:562.

SCURVY

Scurvy, or vitamin C deficiency, is the deficiency disease most commonly diagnosed by dermatologists, since cutaneous manifestations are early and prominent features. Elderly male alcoholics and psychiatric patients on restrictive diets are most commonly affected.

The four Hs are characteristic of scurvy: hemorrhagic signs, hyperkeratosis of the hair follicles, hypochondriasis, and hematologic abnormalities. Perifollicular petechiae are the characteristic finding (Fig. 22-1). In addition, ecchymoses of various sizes, especially on the lower extremities, are common (Fig. 22-2). These may be associated with tender nodules (subcutaneous and intramuscular hemorrhage) and subperiosteal hemorrhage, leading to pseudoparalysis in children. Woody edema may be present, simulating cellulitis. Subungual, subconjunctival, intramuscular, periosteal, and intra-articular hemorrhage may also occur. The referring diagnosis is often vasculitis.

Another characteristic finding is keratotic plugging of the hair follicles, chiefly on the anterior forearms, abdomen, and posterior thighs. The hair shafts are curled in follicles capped by keratotic plugs. This distinctive finding has been named "corkscrew hairs."

Hemorrhagic gingivitis occurs adjacent to teeth and presents as swelling and bleeding of the gums. The teeth are loose and the breath is foul (Fig. 22-3). Gingival disease may be absent. Edentulous areas do not develop gingivitis, and those with good oral hygiene have less prominent gingival involvement. Epistaxis, delayed wound healing, and

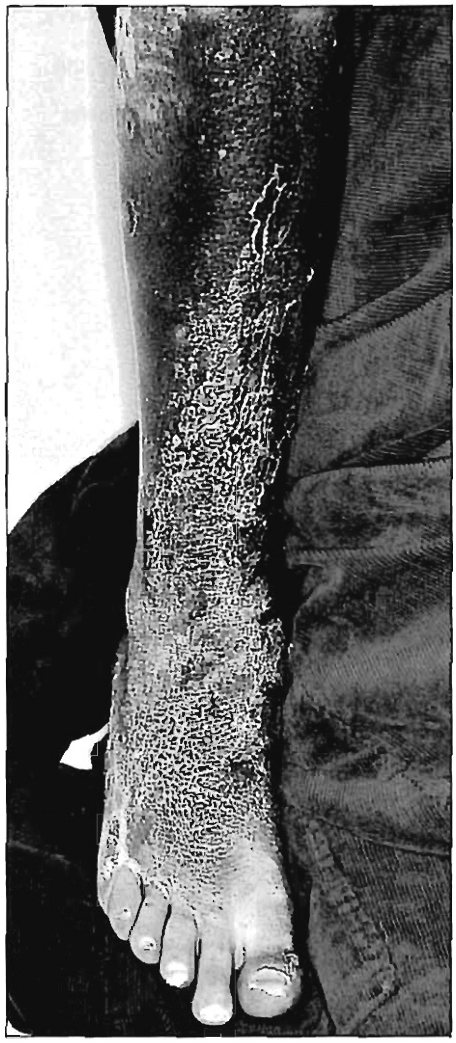

Fig. 22-2 Scurvy, large ecchymosis of the leg.

depression also may occur. Frequently, anemia is present and may be the result of blood loss or associated deficiencies of other nutrients such as folate.

The diagnosis of scurvy is usually made on clinical grounds and confirmed by a positive response to vitamin C supplementation. A biopsy will exclude vasculitis and demonstrate follicular hyperkeratosis, coiled hairs, and perifollicular hemorrhage in the absence of inflammation. Serum ascorbic acid levels may be confirmatory in unusual cases. Treatment is with ascorbic acid, 1000 mg/day for a few days to 1 week, and a maintenance dose of 100 mg/day should be considered.

Chartier TK, et al: Palpable purpura in an elderly man. Arch Dermatol 2003;139:1363.
Christopher K, et al: Early scurvy complicating anorexia nervosa. South Med J 2002;95:1065.
Edge JC, Callen J: Scurvy masquerading as cellulitis. J Am Acad Dermatol 2004;50:P170.
Firth N, Marvan E: Oral lesions in scurvy. Australas Dent J 2001; 46:298.
Hirschmann JG, Raugi GJ: Adult scurvy. J Am Acad Dermatol 1999;41:895.
Kocak M, et al: Case 2. Clin Exp Dermatol 2003;28:337.
Leggett J, Convery R: Scurvy. N Engl J Med 2001;345:1818.

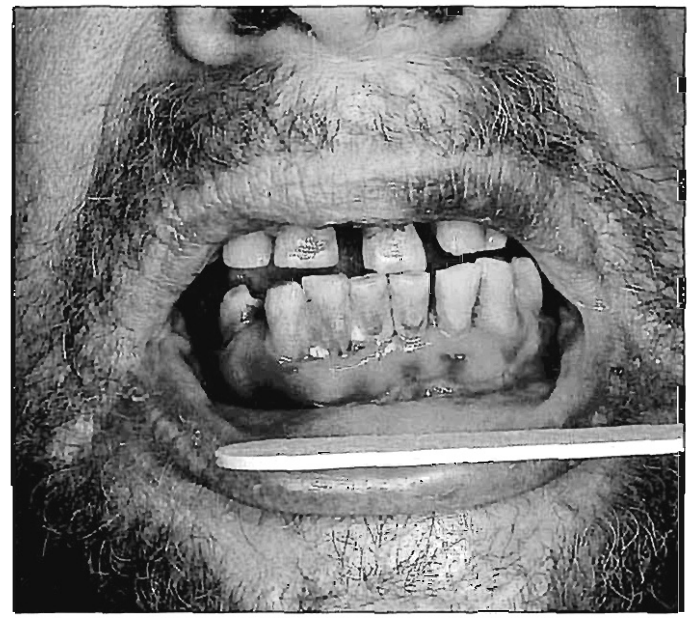

Fig. 22-3 Scurvy, gingivitis.

Levin NA, Greer KE: Scurvy in an unrepentant carnivore. Cutis 2000;66:39.
Nguyen RTD, et al: Scurvy: A cutaneous clinical diagnosis. Australas J Dermatol 2003;44:48.

NIACIN DEFICIENCY (PELLAGRA)

Pellagra usually results from a deficiency of nicotinic acid (niacin, vitamin B_3) or its precursor amino acid, tryptophan. It is associated classically with a diet almost entirely composed of corn, millet, or sorghum. Other vitamin deficiencies (especially pyridoxine) or malnutrition, which interfere with the conversion of tryptophan to niacin, often coexist and are required for the signs and symptoms of pellagra to occur. In developed countries, most cases of pellagra occur in alcoholics. Other possible causes of pellagra are:

- Carcinoid tumors, which divert tryptophan to serotonin
- Hartnup disease (impaired absorption of tryptophan)
- Gastrointestinal disorders, e.g. Crohn and gastrointestinal surgery
- Prolonged intravenous supplementation
- Psychiatric disease, including anorexia nervosa

Pellagra can also be induced by medications, most commonly isoniazid, azathioprine (and its metabolite 6-mercaptopurine), 5-fluorouracil, ethionamide, protionamide, and pyrazinamide. These medications may induce pellagra by interfering with the niacin biosynthesis. The anticonvulsants, including hydantoins, phenobarbital, and carbamazepine may rarely produce pellagra in a dose-dependent fashion.

Clinical Features

Pellagra is a chronic disease affecting the gastrointestinal tract, nervous system, and skin; hence, the mnemonic of the 3 Ds: diarrhea, dementia, and dermatitis.

The most characteristic cutaneous finding is the photosensitive eruption, which worsens in the spring and summer. It occurs symmetrically on the face, neck, and upper chest (Casal necklace); extensor arms; and backs of the hands (Fig. 22-4). Initially, there is erythema and swelling after sun exposure, accompanied by itching and burning or pain. In

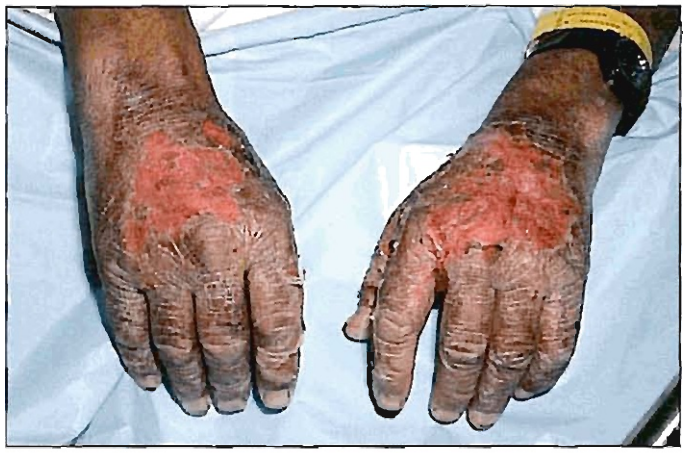

Fig. 22-4 Pellagra, erosive photosensitive eruption.

severe cases, the eruption may be vesicular or bullous (wet pellagra). When compared with normal sunburn, the pellagrous skin takes about four times longer to recover from the acute phototoxic injury. After several phototoxic events, thickening, scaling, and hyperpigmentation of the affected skin occurs. The skin has a copper or mahogany hue. In protracted cases, the skin ultimately becomes dry, smooth, paper-thin, and glassy with a parchment-like consistency. Scarring rarely occurs.

The nose is fairly characteristic. There is dull erythema of the bridge of the nose, with fine, yellow, powdery scales over the follicular orifices (sulfur flakes). The eruption resembles seborrheic dermatitis, except for its location. Plugs of inspissated sebum may project from dilated orifices on the nose, giving it a rough appearance.

At the onset, there is weakness, loss of appetite, abdominal pain, diarrhea, mental depression, and photosensitivity. Skin lesions may be the earliest sign, with phototoxicity being the presenting symptom in some cases. Neurologic and gastrointestinal symptoms can occur without skin changes. In the later stages of the disease, the neurologic symptoms may predominate. Apathy, depression, muscle weakness, paresthesias, headaches, and attacks of dizziness or falling are typical findings. Hallucinations, psychosis, seizures, dementia, neurologic degeneration, and coma may develop. The disease is progressive and can be fatal if untreated.

Pathology

Histologically, the findings in the skin vary according to the stage of the disease. There may be orthokeratosis or slight confluent parakeratosis; basilar pigmentation is increased. Papillary dermal vessels are dilated with papillary dermal edema. The most characteristic finding is pallor and vacuolar changes of the keratinocytes in a band in the upper layers of the stratum malpighii, just below the granular cell layer, which may be attenuated. If marked, a cleft may form in the upper epidermis, correlating with the blistering seen in wet pellagra.

Diagnosis and Treatment

If the characteristic skin findings are present, the diagnosis is not difficult clinically. Dietary treatment to correct the malnutrition is essential. Animal proteins, eggs, milk, and vegetables are beneficial. Supplementation with nicotinamide 100 mg three times a day for several weeks should be given. Fluid and electrolyte loss from diarrhea should be replaced, and in patients with gastrointestinal symptoms, possibly interfering with absorption, initial intravenous supplementation should be considered. Within 24 h after niacin therapy is begun, the skin lesions begin to resolve, confirming the diagnosis. Alcoholism must be treated if present, and the factors that may have led to pellagra must be corrected.

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BIOTIN DEFICIENCY

Biotin is universally available and is produced by intestinal bacteria. Therefore, deficiency is rare but can occur in patients with a short gut or malabsorption. Sometimes it occurs in individuals taking antibiotics or receiving parenteral nutrition. Ingestion of avidin, found in raw egg white, may bind biotin, leading to deficiency. The three autosomal-recessive syndromes holocarboxylase synthetase deficiency (multiple carboxylase deficiency), biotinidase deficiency, and the very rare syndrome of inability to transport biotin into cells all have similar clinical features. Clinical presentation is variable, with some patients manifesting only certain features.

The skin and nervous system are primarily affected. A dermatitis similar to that found in cases of zinc deficiency and essential fatty acid deficiency is seen. It is periorificial and characterized by patchy, red, eroded lesions on the face and groin. *Candida* is regularly present on the lesions. Alopecia, sometimes total, including loss of the eyebrows and eyelashes can occur. Conjunctivitis may be present. Neurologic findings are prominent. In adults, these include depression, lethargy, hallucinations, and limb paresthesias. In infants, neurologic findings include hypotonia, lethargy, a withdrawn behavior, autism, ataxia, seizures, deafness, and developmental delay. Lactic acidosis may be present. The diagnosis of the inherited forms is made by detecting organic aminoaciduria of 3-hydroxyisovaleric acid. Measurement of serum biotinidase can distinguish biotinidase deficiency from holocarboxylase deficiency. Treatment consists of 10 mg of biotin/day, but depending on the severity of the enzyme mutation, higher doses may be required. Skin lesions resolve rapidly, but the neurologic damage may be permanent. One report suggested that valproic acid treatment in children, especially at doses of 40 mg/kg/day or higher, may lead to partial biotinidase deficiency, and that the skin lesions (seborrheic dermatitis-like rash and alopecia) improved with biotin supplementation at 10 mg/day.

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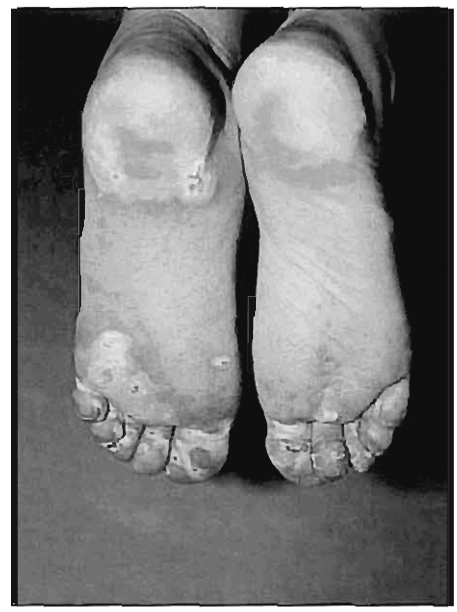

Fig. 22-5 Zinc deficiency, acquired in a patient who had severe nausea following a gastric bypass procedure and was unable to eat.

ZINC DEFICIENCY

Zinc deficiency may be an inherited abnormality, acrodermatitis enteropathica, or it may be acquired. Premature infants are at particular risk because of inadequate body zinc stores, suboptimal absorption, and high zinc requirements. Normally, human breast milk has adequate zinc, and weaning classically precipitates clinical zinc deficiency in premature infants and in infants with acrodermatitis enteropathica. However, clinical zinc deficiency may occur in full-term and premature infants still breastfeeding. This is due to either low maternal breast milk zinc levels or a higher zinc requirement by the infant than the breast milk can provide (even though the zinc level in the breast milk is normal). A rare syndrome of congenital myopathy, recurrent diarrhea, microcephaly, and deafness has been associated with a neonatal bullous eruption characteristic of nutritional deficiency. These children have required very high doses of zinc supplementation.

Parenteral nutrition without adequate zinc content may lead to zinc deficiency. Acquired zinc deficiency also occurs in alcoholics as a result of poor nutritional intake and increased urinary excretion; as a complication of malabsorption, inflammatory bowel disease, or gastrointestinal surgery; and, occasionally, in cases of anorexia nervosa and acquired immunodeficiency syndrome (AIDS). Patients with severe erosive oral disease, such as pemphigus or graft-versus-host disease, may develop zinc deficiency due to malnourishment. Zinc requirements increase during metabolic stress, so symptomatic deficiency may present during infections, after trauma or surgery, with malignancy, during pregnancy, and with renal disease. Diets containing mainly cereal grains are high in phytate, which binds zinc, and have caused endemic zinc deficiency in certain areas of the Middle East and North Africa.

The dermatitis found in all forms of zinc deficiency is pustular and bullous, with an acral and periorifical distribution (Fig. 22-5). On the face, in the groin, and in other flexors there is a patchy, red, dry scaling with exudation and crusting angular cheilitis and stomatitis are present. The periungual areas are erythematous, scaling, and sometimes have superficial, flaccid pustules. Nail dystrophy may result, with thinning of the nails and accentuated longitudinal ridges. Chronic lesions may be more psoriasiform. Generalized alopecia may occur.

Diarrhea is present in most cases. Growth retardation, ophthalmic findings, impaired wound healing, and central nervous system manifestations occur. Patients are particularly irritable and emotionally labile. Many abnormalities of the immune response occur in zinc deficiency.

The histopathologies of acquired and hereditary zinc deficiency are identical. There is vacuolation of the keratinocytes of the upper stratum malpighii. These areas of vacuolation may become confluent, forming a subcorneal bulla. In larger lesions, there may be total epidermal necrosis with subepidermal blister formation. Neutrophils are typically present.

The diagnosis of zinc deficiency should be suspected in at-risk individuals with acral or periorificial dermatitis. In particular, chronic diaper rash with diarrhea in an infant should lead to evaluation for zinc deficiency. The diagnosis can be confirmed by low serum zinc levels. A low serum alkaline phosphatase, a zinc-dependent enzyme, may be a valuable adjunctive test where the serum zinc level is normal or near normal. In some patients, even if the zinc level is in the normal range, if the skin lesions are characteristic, a trial of zinc supplementation should be considered. Replacement is with zinc sulfate 1 to 2 mg/kg/day (50 mg of elemental zinc per 220 mg zinc sulfate tablet). In acquired cases, transient treatment and addressing the underlying condition are adequate. In cases of acrodermatitis enteropathica, supplementation is 3 mg/ kg/day and should be lifelong. Overzealous zinc supplementation should be avoided as it may lead to low serum copper levels.

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ESSENTIAL FATTY ACID DEFICIENCY

Essential fatty acid (EFA) deficiency may develop in multiple settings: low birth weight infants; cystic fibrosis; gastrointestinal abnormalities, including inflammatory bowel disease and intestinal surgery; and prolonged parenteral nutrition without EFA supplementation. The resulting dermatitis is similar to that seen in zinc and biotin deficiency, although characteristically more widespread, but with less periorifacial involvement and mucous membrane and nail changes. There is a generalized xerosis, since EFAs constitute up to one-quarter of the fatty acids of the stratum corneum and are required for normal epidermal barrier function. Widespread erythema and an intertriginous weeping eruption are seen. The hair becomes lighter in color, and diffuse alopecia is present. Poor wound healing, growth failure, and increased risk of infection may occur. This is especially important in patients with cystic fibrosis, who may have inherent abnormalities of essential fatty acid absorption/metabolism independent of their pancreatic function and overall nutritional status. There is a decrease in linoleic acid and an increase in palmitoleic and oleic acids. A ratio of eicosatrienoic acid-to-arachidonic acid of more than 0.4 is diagnostic of EFA deficiency. Intravenous lipid therapy with Intralipid 10% reverses the process. Topical safflower oil emulsion or sunflower seed oil applications may not be able to prevent or treat EFA deficiency and may predispose patients to α-linolenic acid deficiency.

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IRON DEFICIENCY

Iron deficiency is common, especially among actively menstruating women, and particularly if they have little red meat in their diets and have not made an effort to replace their losses with other foods. Mucocutaneous findings include koilonychia, glossitis, angular cheilitis, pruritus, and telogen effluvium diffuse hair loss. Plummer-Vinson syndrome is the combination of microcytic anemia, dysphagia, and glossitis, seen almost entirely in middle-aged women. The lips are thin and the opening of the mouth is small and inelastic, so that there is a rather characteristic appearance. Smooth atrophy of the tongue is pronounced. Koilonychia is present in 40% to 50% of patients, and alopecia may be present.

An esophageal web in the postcricoid area may occur, presenting as difficulty swallowing, or the feeling that food is stuck in the throat. The diagnosis is confirmed by measuring the serum iron level. Treatment consists of iron sulfate supplementation, 325 mg three times a day.

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SELENIUM DEFICIENCY

Selenium deficiency occurs in patients on parenteral nutrition, in areas where soil selenium content is poor, and in low birth weight infants. Manifestations in children include hypopigmentation of the skin and hair (pseudoalbinism). Leukonychia and Terry-like nails have been reported. Cardiomyopathy, muscle pain, and weakness with elevated muscle enzymes are the major features. Treatment consists of 3 μg/kg/day of selenium.

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PROTEIN–ENERGY MALNUTRITION

Protein–energy malnutrition is a spectrum of related disease including marasmus, kwashiorkor, and marasmic kwashiorkor. These conditions are endemic in the developing world. Marasmus represents prolonged deficiency of protein and calories and is diagnosed in children who are below 60% of their ideal body weight without edema or hypoproteinemia. Kwashiorkor occurs with protein deficiency but a relatively adequate caloric intake. It is diagnosed in children between 60% and 80% of their ideal body weight with edema or hypoproteinemia. Marasmic kwashiorkor shows features of both conditions and is diagnosed in children who are less than 60% of their ideal body weight with features of edema or hypoproteinemia.

These conditions are rare in developed countries, but occasionally, kwashiorkor may occur as a result of cystic fibrosis or severe dietary restrictions instituted to improve infantile atopic dermatitis. In the US this may occur when rice beverage, which lacks protein, is substituted for cow's milk and soy in the diets of infants surviving largely on bottle feedings. Most cases, therefore, are in infants younger than 1 year of age.

Marasmus

In cases of marasmus, the skin is dry, wrinkled, and loose because of marked loss of subcutaneous fat. The "monkey

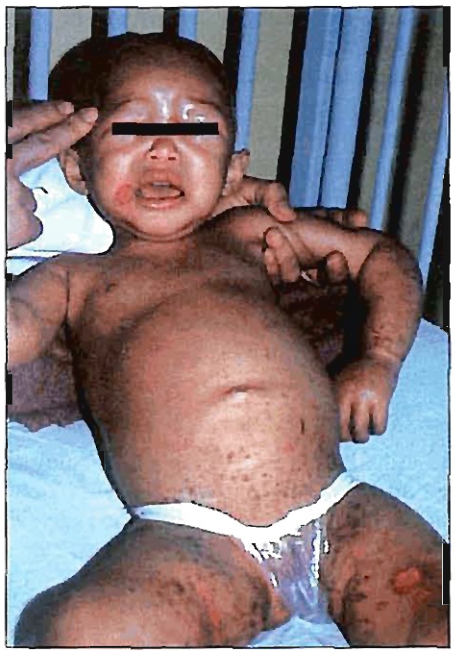

Fig. 22-6
Kwashiorkor, anasarca, hypopigmentation, and scaling skin, in a child who had milk allergy and was given rice milk instead.

facies," caused by loss of the buccal fat pad, is characteristic. In contrast to kwashiorkor, there is no edema or dermatosis.

Kwashiorkor

Kwashiorkor produces hair and skin changes, edema, impaired growth, and the characteristic potbelly (Fig. 22-6). *In cases diagnosed in the US due to dietary restriction* or social chaos, edema has masked growth failure, resulting in the diagnosis of malnutrition being delayed. The hair and skin changes are usually striking. Africans call the victims of kwashiorkor "red children." The hair is hypopigmented, varying in color from a reddish-yellow to gray or even white. The hair is dry and lusterless; curly hair becomes soft and straight; and marked scaling (crackled hair) is seen. Especially striking is the flag sign, affecting long, normally dark hair. The hair grown during periods of poor nutrition is pale, so that alternating bands of pale and dark hair can be seen along a single strand, indicating alternating periods of good and poor nutrition. The nails are soft and thin.

The skin lesions are hypopigmented on dark skin and erythematous or purple on fair skin. Lesions first appear in areas of friction or pressure: *the flexures, groin, buttocks,* and elbows. Hyperpigmented patches occur with slightly raised edges. As they progress, they resemble old, dark, deteriorating enamel paint with peeling or desquamation. This has been described variously as "crazy pavement," "crackled skin," "mosaic skin," "enamel paint," and "flaky paint." In severe cases, the peeling leaves pale, ulcerated hypopigmented areas with hyperpigmented borders.

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Liu T, et al: Kwashiorkor in the United States. Arch Dermatol 2001;137:630.

CAROTENEMIA AND LYCOPENEMIA

Excessive ingestion of carrots, squash, spinach, green beans, rutabagas, pumpkins, yellow turnips, sweet potatoes, or papaya may lead to a yellowish discoloration of the skin, which is especially prominent on the palms, soles, and central face. The sclerae are spared. In lycopenemia, excess *ingestion of red foods, such as tomatoes, beets,* chili beans, and various fruits and berries, leads to a reddish discoloration of the skin. Carotenemia may also be seen in hypothyroidism.

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CHAPTER

23 Diseases of Subcutaneous Fat

An inflammatory disorder that is primarily localized in the subcutaneous fat is termed a *panniculitis*. This group of disorders may be challenging both for the clinician and the dermatopathologist. Clinically, in all forms of panniculitis, lesions present as subcutaneous nodules. Histopathologically, the subcutaneous fat is a rather homogenous tissue and inflammatory processes may show considerable overlap. One way of classifying panniculitis is to separate erythema nodosum (EN), as the prototypical septal panniculitis, from those processes that primarily involve the fat lobules—the lobular panniculitides. Some lobular panniculitides are due to vasculitedes (such as polyarteritis nodosa), which are discussed in other chapters. The remaining lobular panniculitides are categorized by their pathogenesis. Weber-Christian disease, Rothmann-Makai disease, lipomembranous or membranocystic panniculitis, and eosinophilic panniculitis are reaction patterns, and are not specific entities. Neutrophilic panniculitis appears to represent a variant of Sweet syndrome with primary involvement of the panniculus.

Given the depth of lesions in the panniculus, the choice of biopsy is critical in establishing the diagnosis. An incisional or excisional biopsy, narrow at the skin surface and wider in the panniculus, is the optimal procedure. An alternative double-punch method, using a 6- to 8-mm punch first, followed by a 4- to 6-mm punch at the depth of the first punch, may be considered, but is less ideal. Panniculitis is one area of dermatopathology where the skill of the dermatopathologist is critical in establishing good clinicopathologic correlation. If the biopsy report from an adequate biopsy specimen does not match the clinical findings, repeat the biopsy, or ask for a second opinion on the original specimen.

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SEPTAL PANNICULITIS (ACUTE AND CHRONIC ERYTHEMA NODOSUM)

EN is the most common inflammatory panniculitis. It occurs in two forms: acute, which is common, and chronic, which is rare. Acute EN may occur at any age and in both sexes, but most cases occur in young adult women (female-to-male ratio, 3–6:1). The eruption consists of bilateral, symmetrical, deep, tender nodules and plaques 1 to 10 cm in diameter. Usually there are up to 10 lesions, but in severe cases many more may be found. Initially, the skin over the nodules is red, smooth, slightly elevated, and shiny (Fig. 23-1). The most common location is the pretibial area and lateral shins. In general, the lesions should be primarily on the anterior rather than posterior calf. Lesions may also be seen on the upper legs, extensor arms, neck, and rarely the face. The onset is acute, frequently associated with malaise, leg edema, and arthritis or arthralgia (usually of the ankles, knees, or wrists). Fever, headache, episcleritis, conjunctivitis, and various gastrointestinal complaints may also be present. Over a few days, the lesions flatten, leaving a purple or blue-green color resembling a deep bruise (erythema contusiforme). Ulceration does not occur, and the lesions resolve without atrophy or scarring. The natural history is for the nodules to last a few days or weeks, appearing in crops, and then slowly involute.

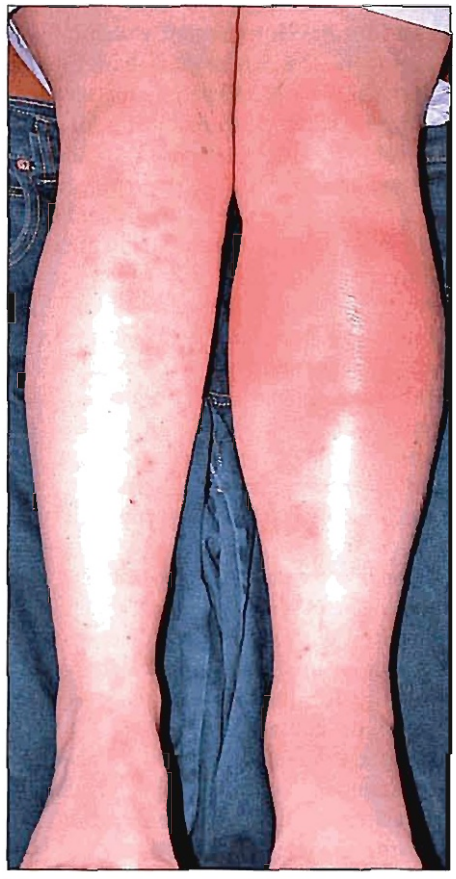

Fig. 23-1 Erythema nodosum, erythematous tender nodules on the anterior shins.

EN is much less common in children than adults, and affects boys and girls equally.

Acute EN is a reactive process. It is commonly associated with a streptococcal infection and in children this is by far the most common percipitant. Tuberculosis remains an important cause in areas where tuberculosis is endemic. Intestinal infection with *Yersinia, Salmonella,* or *Shigella* may precipitate EN. Other infectious causes include systemic fungal infections (coccidioidomycosis, histoplasmosis, sporotrichosis, and blastomycosis) and toxoplasmosis. EN-like lesions have been described in other infectious diseases such as *Helicobacter* septicemia, brucellosis, psittacosis, cat-scratch disease, and many others. Since these organisms are fastidious, it has not always been possible to exclude the possibility that the EN-like lesions seen in these diseases actually represent septic foci in the panniculus. Sarcoidosis may present with fever, cough, joint pains, hilar adenopathy, and EN. This symptom complex, known as *Lofgren syndrome*, is especially common in Scandinavian, Irish, and Puerto Rican women. It generally responds well to therapy and runs a self-limited course. EN is frequently seen in patients with inflammatory bowel disease, more commonly Crohn's than ulcerative colitis. EN has been rarely reported in association with various hematologic malignancies, but this is less common than Sweet syndrome or pyoderma gangrenosum.

Drugs may also induce EN. The bromides, iodides, and sulfonamides were once the most frequent causative agents. Currently, oral contraceptives and hormone replacement therapy are the most common medications inducing EN. This association, the predominance in young women, and the occurrence of EN in pregnancy suggest that estrogens may predispose to the development of EN. Echinacea herbal therapy can also induce EN.

EN-like lesions have been described in Behçet syndrome and Sweet syndrome, and probably represent these inflammatory processes occurring in the fat, rather than the coexistence of two disorders. Histologically, the subcutaneous lesions of Behçet syndrome show features different from EN—a lobular or mixed lobular and septal pattern, and most importantly, a vasculitis which may be lymphocytic, leukocytoclastic or involve a small arteriole. This vasculitis is proposed to be the primary event producing the subcutaneous lesions in Behçet syndrome.

A more chronic variant of EN, called chronic EN, EN migrans, or subacute migratory panniculitis of Vilanova and Piñol, is well described. This form of septal panniculitis is much less common than acute EN. It is distinguished from acute EN by the following features:

1. Lesions tend to occur in older women
2. Lesions are unilateral or asymmetrical if bilateral
3. Lesions are not associated with systemic symptoms except arthralgias
4. Lesions are painless or less tender than acute EN lesions
5. Lesions are not associated with underlying diseases
6. Lesions begin as a single lesion that tends to resolve, but migrates centrifugally, forming annular plaques of subcutaneous nodules with central clearing
7. Lesions have a prolonged course of months to years

In the differential diagnosis of EN, other forms of panniculitis must be considered. Erythema induratum (EI) usually affects primarily the posterior calves alone and runs a more chronic course, with the possibility of ulceration and scarring. Syphilitic gummas, as well as the nodules of sporotrichosis are, as a rule, unilateral. Subcutaneous fat necrosis associated with pancreatitis and nodular vasculitis may also occur on the shins, but associated clinical features and/or histologic features will allow the differentiation to be made. Subacute infectious processes, such as *Helicobacter* cellulits and atypical mycobacterial infection, may closely mimic EN. In most cases, the classic picture of the acute onset of symmetrical, red, tender nodules on the anterior shins of a young woman will allow the diagnosis of EN to be easily made without a biopsy. However, if the case is atypical or does not evolve typically, a biopsy should be performed. In cases where the diagnosis of EN has been made in error, either the clinical features were atypical and a biopsy was not performed or was inadequate (punch biopsy), or the biopsy was misinterpreted by the pathologist.

EN is a septal panniculitis: the inflammatory infiltrate principally involves the connective-tissue septa between fat lobules throughout the evolution of the lesion. The infiltrate may be composed of either neutrophils (early) or lymphocytes and other mononuclear cells (later), or a mixture, depending on the stage at which the lesion is biopsied. In older lesions histiocytes and multinucleate giant cells may predominate. Fat lobules are only secondarily affected by the inflammation, but some foamy histiocytes may be seen in the evolution of the lesions. Meischer radial granulomas, aggregates of histiocytes around stellate clefts, are characteristic but not diagnostic of EN. Leukocytoclastic vasculitis is not a histologic feature of EN. In chronic EN septal fibrosis and septal granulomas of epithelioid macrophages are seen.

The management of EN involves three components: identifying the trigger, rest and elevation of the affected extremities; and specific anti-inflammatory medications. Since streptococcus is a common trigger, throat culture and ASO titer are indicated. A complete history of any preceding illness will often lead to clues. Preceding diarrhea might suggest *Yersinia* infection, for example. A travel and exposure history are especially important when considering endemic fungal infections. Four per cent of patients with histoplasmosis present with EN, so in endemic areas this cause should be excluded. Early treatment of the infectious cause does not appear to shorten the duration of the EN, although EN triggered by infections tends to last longer if the infection is more chronic—streptococcal-induced EN will tend to last a shorter period than tuberculosis-triggered EN. Bed rest is of great value and may be all that is required in mild cases. In children this is especially true. Gentle support hose are also helpful. Curtailing vigorous exercise during the acute attacks will shorten the course, and restriction of physical activities might prevent exacerbations and recurrences. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin are often helpful. Potassium iodide is a safe and effective treatment. As a supersaturated solution, five drops three times a day, increased by one drop per dose per day up to 15 drops three times a day, is one easy-to-remember dose schedule. As a tablet, the dose is one 300-mg tablet three times a day. Induction of hypothyroidism by prolonged iodide therapy should be watched for. Once controlled, the therapy is gradually reduced over 2 to 3 weeks. Intralesional corticosteroid injections will control persistent lesions. Systemic steroids will result in rapid

resolution of lesions, if not contraindicated by the underlying precipitating cause. In acute lesions, colchicine is often rapidly effective at a dose of 0.6 mg twice a day. For chronic EN, SSKI is often effective. In refractory cases, antimalarials may be tried.

The prognosis in acute EN usually is good, the attack running its course in 3 to 6 weeks. Recurrences do occur, especially if the underlying condition or infection is still present, or if physical activity is resumed too quickly. Chronic or atypical lesions should suggest an alternative diagnosis and require a biopsy.

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LOBULAR PANNICULITIS

VESSEL-BASED LOBULAR PANNICULITIS

Inflammation or thrombosis of blood vessels may lead to fat necrosis due to ischemia. This can occur in the primary vasculopathies, such as polyarteritis nodosa and Churg-Strauss, in metabolic disorders such as oxalosis and calciphylaxis, with atheromatous emboli, with heparin and Coumadin necrosis, and with various coagulopathies. These entities are discussed in other chapters.

Nodular Vasculitis

Clinically and histologically, nodular vasculitis is identical to EI. The two differ only by the presence of tuberculosis as a precipitating factor in EI. Nodular vasculitis presents as tender, subcutaneous nodules of the calves of middle-aged, thick-legged women. Venous insufficiency may be present. Lesions are bilateral and less red and tender than EN; they often ulcerate, drain oily liquid, and recur over years.

The early lesions may show a suppurative vasculopathy, proposed by various authors to be an arteritis, a venulitis, or both. In some cases, no vasculitis is found, and (despite the name) the presence of a vasculitis is *not* required to establish the diagnosis of nodular vasculitis. Nodular vasculitis results in substantial lobular necrosis of adipocytes with suppuration. Necrosis of the lobule results in loss of the lipocyte membrane and pooling of lipid into variably sized round aggregates. As lesions evolve, the fat becomes increasingly necrotic, forming microcysts, and suppuration progresses to the point where it may perforate through the epidermis, forming ulceration. Granulomatous inflammation appears adjacent to areas of fat necrosis, and eventually lesions resolve with fibrosis.

Nodular vasculitis must be distinguished from EI. Because clinical and pathologic features are identical, the differentiation is made by searching for tuberculous infection in the patient, by applying a tuberculin skin test. If this is positive, the appropriate diagnosis is EI. Polymerase chain reaction (PCR) of the affected tissue may reveal the DNA of *Mycobacterium tuberculosis* in 50% to 70% of cases of EI. As a tuberculid, EI is a manifestation of cellular immunity to tuberculosis, and the PPD will always be positive. PCR of the tissue is *not* recommended in cases which are tuberculin skin test negative.

EI requires antibiotic therapy for the underlying tuberculosis. Treatment of nodular vasculitis is usually SSKI, as outlined for EN. This is effective in about half of cases. In the others, trials of colchicine, antimalarials, NSAIDs, and systemic steroids may be attempted. Support stockings, elevation, and treatment of associated venous insufficiency may also improve nodular vasculitis.

Sclerosing Panniculitis (Hypodermitis Sclerodermiformis, Lipodermatosclerosis, Stasis Panniculitis)

Sclerosing panniculitis occurs primarily on the medial lower third of the lower legs of women older than 40, with an above average body mass index. It may be bilateral. If not bilateral, the left leg only is affected, or the process is more severe on the left leg. If the right leg is primarily affected, deep venous thrombosis currently or in the past or a venous injury to the right leg must be considered. Typically, there is marked woody induration in a stocking distribution resulting in calves that resemble inverted champagne bottles. This induration results from fibrosis in the subcutaneous fat which may occur without the primary inflammatory panniculitis ever being clinically observed. It occurs multifocally and microscopically throughout the affected area. This pattern was called hypodermitis sclerodermiformis. When the areas of fat necrosis are larger, they present as erythematous, tender, subcutaneous nodules or plaques. This is designated sclerosing panniculitis.

It is now recognized that these are two aspects of the same disease with a common pathogenesis—venous insufficiency. These patients may have venous varicosities, superficial thrombophlebitis, deep venous thrombosis, or several of these conditions. Even when venous disease is not clinically evident, evaluation of the venous system of the lower leg will frequently reveal insufficiency. Laboratory evaluation may reveal a genetic mutation in the fibrinolytic system resulting in increased thrombosis in these patients. Venous insufficiency results in hypoxia, necrosis of fat, inflammation, and eventual fibrosis. If hypoxemia is present from other causes such as pulmonary disease, sclerosing panniculitis may be more severe.

The histologic features of sclerosing panniculitis are characteristic, but not all features may be seen on every biopsy, since the histologic features change over time within the lesion. The overlying dermis frequently shows changes of stasis with nodular proliferation of thick-walled vessels, hemosiderin deposition, fibrosis, and atrophy. In early lesions there is ischemic necrosis in the center of the fat lobules

manifested as "ghost cells"—pale cell walls with no nuclei. There is a sparse lymphocytic infiltrate in the fat septa. As the lesions evolve, the septa are thickened and fibrosed, and there is a mixed inflammatory infiltrate of lymphocytes, plasma cells, and macrophages. Foamy histiocytes are present around the areas of fat necrosis. Fat microcysts are characteristic (but not diagnostic) and appear as small cysts with feathery eosinophilic remnants of adipocytes lining the cyst cavity and resembling frost on a window, so-called lipomembranous fat necrosis. In later lesions these microcysts collapse and are replaced by fibrosis. Despite these characteristic features, biopsy should be avoided in these patients. Biopsies heal poorly and may lead to chronic leg ulcers. If a biopsy must be performed, it should be from the most proximal edge of involvement.

This diagnosis can be clinically confirmed if a careful vascular evaluation is performed. The location on the lower medial calf is unusual for EN. Most other panniculitides favor the posterior mid-calf. The gradual progression from the ankles proximally is characteristic of sclerosing panniculitis and not other forms of lobular panniculitis.

The treatment of sclerosing panniculitis may be difficult. Fibrotic areas may be irreversible. Graded compression stockings and elevation, standard treatments for venous insufficiency, are most effective in this condition. Application of pressure dressings such as an Unna boot can produce dramatic, if temporary, improvement. Greater compression—Unna boot with Coban and a foam buttress (bolster material to apply extra pressure to the red inflamed area) or the Profore boot—can be beneficial. Unfortunately, some patients cannot tolerate compression because of the pain of the lesions. Pentoxyphylline in doses of 400 to 800 mg three times a day is useful, especially in cases not responding to compression and elevation alone, or in patients who are initially intolerant of compression dressings. Apparently by enhancing the fibrinolytic capacity of affected patients, stanozolol, 2 to 5 mg or oxandrolone 10 mg twice a day, may benefit some patients. It is rarely required if appropriate pressure dressings are applied and the patient is able to take full doses of pentoxyphylline. Stanazol and oxandrolone may be virilizing for women and should be avoided if possible in women of childbearing potential. Stanazol may induce hepatitis.

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Fernandez-Lopez E, et al: Membranous fat necrosis: a non-specific histological finding. Eur J Dermatol 2002;12:82.

Herouy Y: Lipodermatosclerosis and compression stockings. J Am Acad Dermatol 2000;42:307.

Segal S, et al: Treatment of lipodermatosclerosis with oxandrolone in a patient with stanozolol-induced hepatoxicity. J Am Acad Dermatol 2000;43:558.

Stacey MC, et al: Pericapillary fibrin deposits and skin hypoxia precede the changes of lipodermatosclerosis in limbs at increased risk of developing a venous ulcer. Cardiovasc Surg 2000;8:372.

PHYSICAL PANNICULITIS

This category includes processes in the fat that occur from physical factors. Some are characterized by the presence of needle-like clefts—sclerema neonatorum, subcutaneous fat necrosis, and post-steroid panniculitis. Infants and children are most frequently affected, and in all these disorders metabolic differences in fat are apparently pathogenically important. Hypothermia or cold is frequently associated in some forms (cold panniculitis, sclerema, and subcutaneous fat necrosis). It may be difficult in some cases to clearly separate mild cases of sclerema neonatorum from subcutaneous fat necrosis, or differentiate cold panniculitis from subcutaneous fat necrosis of the newborn if the lesions are at sites of cold exposure. This is not surprising, since they may be pathogenically related. In general cold panniculitis refers to localized cases where there is a history of local cold exposure, sclerema to cases presenting in severely ill children soon after birth with a poor prognosis, and subcutaneous fat necrosis (the most common variant) to cases with more limited lesions occurring in the first 6 weeks of life, sometimes with associated hypercalcemia. Traumatic fat necrosis occurs from damage to the subcutaneous fat resulting from trauma. All these conditions are treated supportively, and in all except sclerema neonatorum, spontaneous and complete recovery is expected.

Sclerema Neonatorum

Sclerema neonatorum is the most severe and rarest disorder in this group. It affects premature neonates who are gravely ill for other reasons. Affected neonates usually die, unless the underlying diseases can be reversed. In the first few days of life, the skin begins to harden, usually initially on the buttocks or lower extremities, and rapidly spreads to involve the whole body. The skin on the palms, soles, and genitalia is spared. The skin becomes dry, livid, cold, rigid, and board-like, so that the mobility of the parts is limited. The skin in the involved areas cannot be picked up. The skin of the entire body may appear half frozen and is yellowish white. Visceral fat may also be involved.

Histologically, adipocytes are enlarged and filled with needle-like clefts in a radial array. Affected fat cells undergo necrosis. There is sparse inflammation, and histiocytes containing needle-like clefts are rare, possibly because most children die before granulomas can form.

Subcutaneous Fat Necrosis of the Newborn

Subcutaneous fat necrosis of the newborn (SFN) occurs during the first 4 weeks of life (half in the first week) in term or post-term infants. A history of fetal distress, birth asphyxia, and meconium aspiration is common. Maternal cocaine use, severe neonatal anemia, thrombocytopenia, septicemia, and hypothermia have also been associated. SFN following delivery by emergency cesarian section and speaks against trauma as playing a role in SFN. Painful, firm to rubbery, erythematous nodules appear, usually on the upper back, buttocks, cheeks, or proximal extremities (Fig. 23-2). Lesions may fuse to form plaques and resolve spontaneously within 3 months with no scarring. In general, the infants remain well; however, hypercalcemia has occurred in more than 50% of recently reported cases, and in 4 of 11 consecutive cases seen at one institution. The hypercalcemia may appear weeks to months after the appearance and resolution of the skin lesions. Periodic serial serum calcium determinations for the first 3 to 4 months of life have been recommended. The pathogenesis of the hypercalcemia in SFN may be due to elevated prostaglandin E levels or inappropriately high levels of 1,25-hydroxyvitamin D. The mechanism of

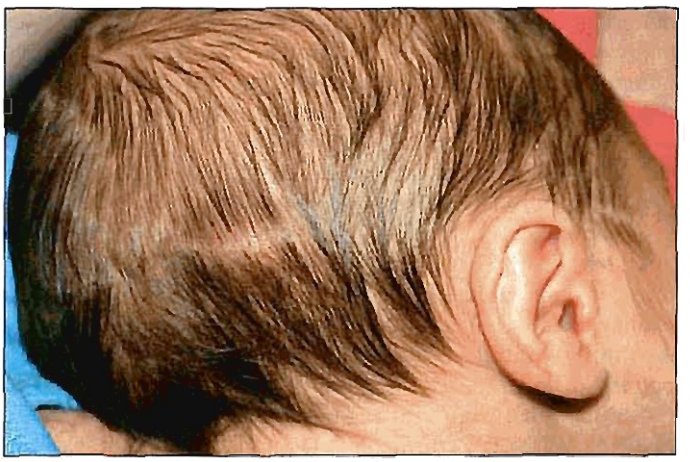

Fig. 23-2 Subcutaneous fat necrosis.

hypercalcemia in SFN has been postulated to be similar to that seen in other granulomatous conditions, such as sarcoidosis. Hypercalcemia may result in failure to thrive, irritability, apathy, hypotonia, seizures, and renal failure. The hypercalcemia is treated with hyperhydration, calcium wasting diuretics (furosemide), and formulas low in calcium and vitamin D. Systemic steroids, calcitonin, and etidronate (bisphosphonate) may also be effective, when other methods fail to reduce the hypercalcemia.

Histologically, subcutaneous fat necrosis is a lobular panniculitis, with granular necrosis of adipocytes. Needle-shaped clefts are arranged radially within histiocytes, and multinucleate foamy histiocytes are present. Lesions may resolve with calcification and fibrosis. Fine-needle aspiration has confirmed this diagnosis and characteristic magnetic resonance imaging (MRI) findings have been reported.

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Carraccio C, et al: Subcutaneous fat necrosis of the newborn: link to maternal use of cocaine during pregnancy. Clin Pediatr 1994;33:317.

Chuang SD, et al: Subcutaneous fat necrosis of the newborn complicating hypothermic cardiac surgery. Br J Dermatol 1995;132:805.

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Gu LL, et al: Nephrocalcinosis and nephrolithiasis due to subcutaneous fat necrosis with hypercalcemia in two full-term asphyxiated neonates. Pediatr Radiol 1995;25:142.

Gupta RK, et al: Fine needle aspiration cytodiagnosis of subcutaneous fat necrosis of the newborn. Acta Cytol 1995; 39:759.

Jardine D, et al: Sclerema neonatorum and subcutaneous fat necrosis of the newborn in the same infant. Eur J Pediatr 1990;150:125.

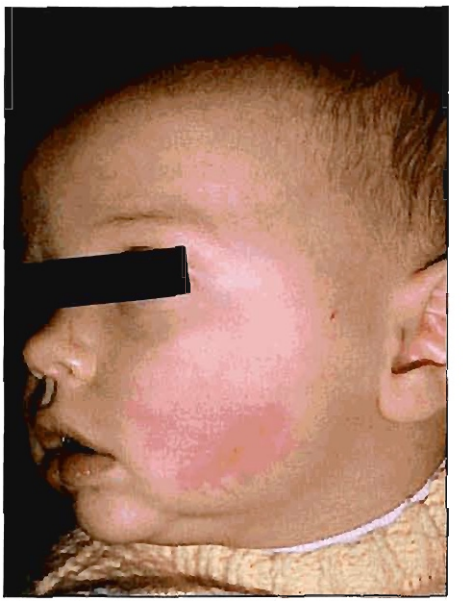

Fig. 23-3 Cold panniculitis (popsicle panniculitis).

Lum CK, et al: Asymptomatic hypercalcemia in subcutaneous fat necrosis. Clin Pediatr 1999;38:547.

Sharata H, et al: Subcutaneous fat necrosis, hypercalcemia, and prostaglandin E. Pediatr Dermatol 1995;12:43.

Tran JT, Sheth AP: Complications of subcutaneous fat necrosis of the newborn: A case report and review of the literature. Pediatr Dermatol 2003;20:257.

Varan B, et al: Subcutaneous fat necrosis of the newborn associated with anemia. Pediatr Dermatol 1999;16:381.

Wiadrowski TP, Marshman G: Subcutaneous fat necrosis of the newborn following hypothermia and complicated by pain and hypercalcaemia. Australas J Dermatol 2001;42:207.

Cold Panniculitis

Infants and young children are particularly predisposed to cold panniculitis. It has been described in children who suck on ice or popsicles (popsicle panniculitis) (Fig. 23-3), in the scrotum of prepubertal males, and in infants treated for supraventricular tachycardia with the application of cold packs to the face. Most reported affected infants have been Black. Lesions occur within a few days of the cold application and appear as slightly erythematous, nontender, firm subcutaneous nodules. Equestrian panniculitis on the upper outer thighs of women riding horses in the cold appears to represent a form of perniosis rather than true panniculitis (see Chapter 3). The typical patient with fat necrosis of the scrotum is a prepubertal (9–14-year-old) boy, who is heavy-set or even obese, with scrotal swelling, usually bilateral, associated with mild-to-moderate pain. The gait is often guarded and broad based. There is a lack of systemic complaints and no symptoms related to voiding. The scrotal masses are bilateral and symmetrical in most cases. However, the lesions may be unilateral and there may be more than two. The masses are firm, tender, and do not transmit light. The overlying scrotal skin will be normal or red. Cryptorchidism is not unusual. The most common location of the lesions is near the perineum, consistent with the area of greatest concentration of scrotal fat in children. The adult scrotum lacks this fatty tissue. Without treatment lesions resolve over several days to weeks.

Histologically, there is necrosis of adipocytes within lobules of the upper subcutaneous fat adjacent to the lower dermis. A mixed inflammatory infiltrate of lymphocytes, neutrophils, and foam cells is present, and microcysts sometimes occur. This histology is not specific and the diagnosis relies largely on obtaining a history of cold exposure.

Ter Poorten JC, et al: Cold panniculitis in a neonate. J Am Acad Dermatol 1995;33:383.

Post-Steroid Panniculitis

This rare form of panniculitis occurs predominately in children treated acutely with high doses of systemic corticosteroids during rapid corticosteroid withdrawal. Substantial weight gain has usually occurred during the corticosteroid therapy. Firm subcutaneous nodules begin to appear within a month of tapering the corticosteroids. Areas of abundant subcutaneous fat are favored—the cheeks, trunk, and proximal extremities. Most cases resolve spontaneously within weeks, but if severe, the steroids must be reinstituted and tapered more slowly.

Histologically, the changes are identical to those seen in subcutaneous fat necrosis of the newborn. There is a lobular panniculitis with necrosis of adipocytes and needle-shaped clefts in both adipocytes and histiocytes. Foamy histiocytes are also present.

Silverman RA, et al: Poststeroid panniculitis. Pediatr Dermatol 1992;5:92.

Traumatic Panniculitis

Accidental trauma to the skin may induce necrosis of the fat. This is most common on the trunk and breasts of women. The prior history of trauma is frequently not recalled. Lesions present like a lipoma, as a firm, mobile subcutaneous mass (formerly reported as mobile encapsulated lipoma). Airbag injury may induce fat necrosis. The term *myospherulosis* (spherulocytosis) has been used to describe subcutaneous cystic lesions induced by trauma with hemorrhage into areas of high lipid content. Long-acting antibiotics formulated in oil bases were associated with myospherulosis. The structures resemble the sporangia of rhinosporidiosis, but represent degenerated red blood cells rather than true fungal organisms. Accidental trauma to the upper anteriolateral thigh from a desk or chair may result in semicircular bands of atrophy of fat called lipoatrophia semicircularis.

Histologically, there is a granulomatous lobular panniculitis with foamy histiocytes, membranous fat necrosis, and microcysts. Lesions heal with fibrosis of the septa. In myospherulosis, large round structures containing many smaller round eosinophilic bodies are noted. These represent degenerated erythrocytes.

Pozo L, et al: Multilobulated abdominal nodule. Arch Dermatol 2002;138:1509.

Wong JJ, Greenberg RD: Upper extremity nodules. Arch Dermatol 2004;140:234.

Factitial Panniculitis

Self-induced panniculitis is rarely reported, but it is not uncommon. It may be induced by the injection of organic materials, povidone, feces, saliva, vaginal fluid, and oils. In many cases, ulceration will occur. Factitial trauma may also induce a panniculitis. Medical personnel are at risk because they have ready access to syringes and needles. Pointed, detailed questioning of the patient may identify inconsistencies in the history, or the underlying cause for the behavior (e.g. attention seeking, revenge, malingering).

The clinician must have a high index of suspicion in cases in which the clinical pattern is not characteristic of a known form of panniculitis. Inspection of early lesions for tell-tale healing injection sites may help confirm the diagnosis. A biopsy is often required. Culture may demonstrate a consistent pattern of fecal, oral or vaginal flora. Careful evaluation of the biopsy material with polarization may identify foreign material. When the suspicion is high and no foreign material can be seen in the tissue, special evaluation by incineration and mass spectroscopy may identify the injected substance. Electron microscopy with x-ray emission spectrography can identify inorganic substances. Radiographs may demonstrate fractured needles or foreign bodies.

Kossard S, et al: Povidone panniculitis. Arch Dermatol 1980; 116:704.

Sclerosing Lipogranuloma

Sclerosing lipogranuloma describes the granulomatous and fibrotic reaction that occurs in the panniculus from the injection of silicone or mineral oils. Topical application of an antibacterial ointment to an open wound can rarely result in the formation of lipogranuloma. In most cases the injections are intentional and cosmetic. The time from injection to onset of symptoms may be months to more than 10 years.

Lesions are usually localized to the penis, scrotum, breasts, nose and buttocks, often after an attempt to augment the area by injection. The overlying skin is hyperpigmented and erythematous. Lesions are frequently diagnosed initially as cellulitis. On palpation, the skin is indurated and cannot be picked up between the fingers. The subcutaneous tissue is indurated, thickened, and lumpy. In some cases, there will be focal ulceration. The injected material will frequently migrate locally, extending beyond the sites of implantation. In some cases it is carried to other tissues, specifically the lymphoreticular system and lungs. Hepatosplenomegaly and pulmonary fibrosis may occur.

Histologically, the panniculus is replaced by the injected material, which is in various sized vacuoles, giving the affected tissue a "Swiss cheese" appearance. Because the material is usually washed out during the tissue processing, the material itself is not seen, only the spaces it occupied in the tissue in vivo. The vacuoles are surrounded by histiocytes, many of which have ingested the material, giving their cytoplasm a vacuolated appearance. Fibrosis may be prominent. Frozen section can be used to demonstrate the lipid.

Cabral AR, et al: Clinical, histopathological, immunological and fibroblast studies in 30 patients with subcutaneous injections of modelants including silicone and mineral oils. Rev Invest Clin 1994;46:257.

Heltzer JM, et al: Diffuse nodular eyelid lipogranuloma following sutureless transconjunctival blepharoplasty dressed with topical ointment. Ophthal Plast Reconstr Surg 1999;15:438.

Hohaus K, et al: Mineral oil granuloma of the penis. J Eur Acad Dermatol Venereol 2003;17:585.
Lazarov A, et al: Dermal spherulosis (myospherulosis) after topical treatment for psoriasis. J Am Acad Dermatol 1994;30:265.
Ricchiuti VS, et al: Sclerosing lipogranuloma of the testis. Urology 2002;60:515.
Rudolph CM, et al: Foreign body granulomas due to injectable aesthetic microimplants. Am J Surg Pathol 1999;23:113.
Sinrachtanant C, et al: Sclerosing lipogranuloma of the nose: a new treatment using adipose tissue transplantation. Facial Plast Surg 2003;19:363.

ENZYME-RELATED PANNICULITIS

This category includes panniculitis induced by enzymes that damage fat (pancreatic panniculitis) and panniculitis caused by the absence of an enzyme critical in preventing tissue inflammation after injury (α_1-antitrypsin).

PANCREATIC PANNICULITIS (SUBCUTANEOUS FAT NECROSIS)

Subcutaneous fat necrosis is most commonly associated with pancreatitis or pancreatic carcinoma, and more rarely with anatomic pancreatic abnormalities, pseudocysts, or drug-induced pancreatitis. Men outnumber women 2:1 in cases of pancreatitis and 7:1 in cases of pancreatic carcinoma. In cases associated with pancreatic carcinoma, acinar cell carcinoma is most common. Even metastatic pancreatic carcinoma with no residual tumor in the pancreas may induce the syndrome. In 40% of cases, the skin lesions are the first symptom of the underlying pancreatic pathology and therefore represent an important clue to the diagnosis.

Skin lesions appear as tender or painless erythematous subcutaneous nodules from 1 to 5 cm in diameter (Fig. 23-4). The lower leg is the most common location, being affected in more than 90% of cases. Subcutaneous fat elsewhere may also be affected, except rarely on the head and neck. The number of lesions is usually fewer than 10 but may number in the hundreds. In most cases the lesions involute, leaving an atrophic scar. If the fat necrosis is severe, however, the lesion develops into a sterile abscess that may break down, draining a thick, brown, oily material.

Subcutaneous fat necrosis is frequently accompanied by a constellation of findings related to fat necrosis in other organs. Importantly, abdominal symptoms may be completely absent. Arthritis is found in 54% to 88% of cases, and may be monoarticular, oligoarticular, and rarely polyarticular. The arthritis may be intermittent, migratory, or persistent, and is usually in joints adjacent to the lesions of panniculitis. Examination of the joint fluid reveals the presence of free fatty acids, suggesting it is due to fat necrosis adjacent to the joint space. Other findings are medullary fat necrosis of bone, polyserositis, and pulmonary infiltrates or embolism.

Laboratory evaluation is useful in establishing the diagnosis. In most patients the amylase or lipase, or both, are elevated. In many cases, however, one of the tests may be normal and the other abnormal, so both tests must be performed. Sixty percent of patients with pancreatic carcinoma and subcutaneous fat necrosis will have a peripheral eosinophilia.

The histologic features of pancreatic panniculitis are diagnostic. They include focal areas of fat necrosis with anucleate "ghost cells;" finely stippled basophilic material, representing calcium, within the residual rim of the necrotic cells and at the periphery of the affected foci; and a dense inflammatory polymorphous infiltrate at the periphery of the affected fat. The affected necrotic areas are relatively acellular. Several reports have suggested that the early features are those of a septal panniculitis, resembling EN. This may have represented sampling error but does indicate that if the initial sample is not diagnostic another, perhaps more adequate sample of a more advanced lesion, should be considered.

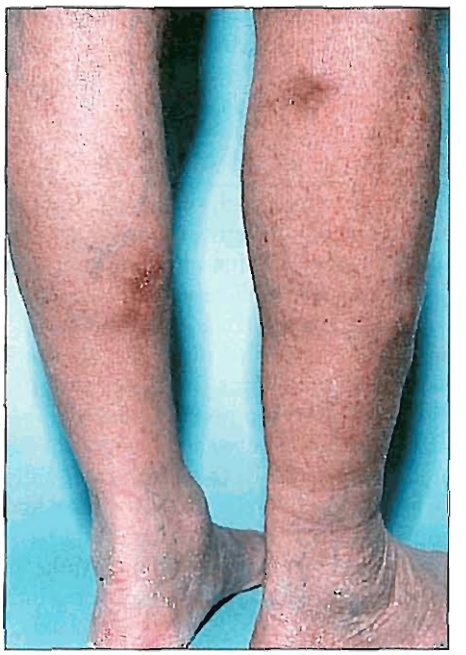

Fig. 23-4 Pancreatic fat necrosis.

The necrosis of fat at all affected sites is at least in part due to the release of fat-digesting enzymes, lipases, from the affected pancreatic tissue. These lipases spread hematogenously to the affected sites.

EN represents the primary differential consideration, since pancreatic panniculitis may not have abdominal symptoms, also favors the lower legs, and may be accompanied by joint symptoms. The distinction can be made by skin biopsy, serum amylase, and lipase determinations, and especially if eosinophilia is present, a search for a pancreatic neoplasm.

Treatment revolves mainly around treating the cause of the pancreatitis. Obstruction or stenosis of ducts should be repaired, pseudocysts drained, and in the case of pancreatic carcinoma, octreotide administered, if necessary.

Ball NJ, et al: Possible origin of pancreatic fat necrosis as a septal panniculitis. J Am Acad Dermatol 1996;34:362.
Cheng KS, et al: Recurrent panniculitis as the first clinical manifestation of recurrent acute pancreatitis secondary to cholelithiasis. J R Soc Med 1996;89:105.
Dahl PR, et al: Pancreatic panniculitis. J Am Acad Dermatol 1995;33:413.
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Ohno Y, et al: A case of subcutaneous nodular fat necrosis with lipase-secreting acinar cell carcinoma. Int J Dermatol 2003; 42:384.

Shbeeb MI, et al: Subcutaneous fat necrosis and polyarthritis associated with pancreatic disease. Arthritis Rheum 1996; 39:1922.

α_1-ANTITRYPSIN DEFICIENCY PANNICULITIS

α_1-Antitrypsin is the most abundant antiprotease in circulation and a potent and irreversible inactivator of neutrophil elastase. Heterozygous deficiency of this enzyme occurs in 1 in 50 persons and homozygous deficiency in 1 in 2500 persons of European descent. Emphysema and liver disease are the most common manifestations of deficiency. A small percentage of patients with homozygous deficiency and the PiZZ or PiSZ phenotypes will develop panniculitis.

The panniculitis usually appears between the ages of 20 and 40 but can occur in childhood. Both sexes are equally affected. Lesions appear after relatively minor trauma and present as painful nodules on the extremities or trunk. They may spontaneously drain an oily, brown liquid. Multiple draining sinus tracts can occur, with lesions coalescing into large draining plaques.

The histologic findings in this form of panniculitis are dependent on the stage of the lesion. Early lesions show neutrophils splaying the collagen of the reticular dermis and subcutaneous septae. More fully evolved lesions show dissolution of the septae, with islands of normal fat "floating" in the spaces that represented the destroyed septae. This later finding is considered diagnostic by some. Elastic tissue stains may reveal decreased elastic tissue in the affected areas.

The clinical and histologic differential diagnosis is factitial panniculitis. This is not surprising since trauma produces both lesions and in the case of the enzyme deficiency, the inflammation-produced enzymes are simply not inactivated, leading to more pronounced lesions than would be expected from that degree of trauma.

Replacement of the deficient enzyme will lead to resolution of the skin lesions, but is costly. Dapsone and doxycycline can also be therapeutic apparently by their ability to reduce neutrophil chemotaxis. Colchicine can be attempted if dapsone is not tolerated. These agents can reduce the requirement for enzyme replacement and should be considered as maintenance treatment in previously affected patients. Systemic steroids may exacerbate the panniculitis. Liver transplantation leads to normal levels of the enzyme and resolution of the panniculitis.

Chng WJ, Henderson CA: Suppurative panniculitis associated with alpha 1-antitrypsin deficiency (PiSZ phenotype) treated with doxycycline. Br J Dermatol 2001;144:1262.

Chowdhury MMU, et al: Severe panniculitis caused by homozygous ZZ α1-antitrypsin deficiency treated successfully with human purified enzyme (Prolastin). Br J Dermatol 2002; 147:1258.

Geller JD, et al: A subtle clue to the histopathologic diagnosis of early alpha 1-antitrypsin deficiency panniculitis. J Am Acad Dermatol 1994;31:241.

Needham M, Stockley RA: α_1-Antitrypsin deficiency—3: Clinical manifestations and natural history. Thorax 2004;59:441.

Parr DG, et al: Panniculitis secondary to extravasation of clarithromycin in a patient with α_1-antitrypsin deficiency (phenotype PiZ). Br J Dermatol 2003;149:410.

CYTOPHAGIC HISTIOCYTIC PANNICULITIS

Cytophagic histiocytic panniculitis (CHP) is a multisystem disease characterized by widespread erythematous, painful subcutaneous nodules, which may occasionally become ecchymotic or break down and form crusted ulcerations. There is a progressive febrile illness, with hepatosplenomegaly, pancytopenia, hypertriglyceridemia, and liver dysfunction. These result from the proliferation of benign appearing histiocytes, which have a marked phagocytic capacity and extensively involve the reticuloendothelial system. Some patients progress to a terminal phase characterized by profound cytopenia, liver failure, and a terminal hemorrhagic diathesis.

Cytophagic histiocytic panniculitis represents a spectrum of disease that occurs in children and adults. Some cases are triggered by viral infections (Epstein-Barr virus [EBV] and human immunodeficiency virus [HIV]), and others represent subcutaneous B- or T-cell lymphomas. The benign cases are reportedly EBV negative and the lymphoma-associated cases are EBV positive.

Histologically, there is infiltration of the lobules of subcutaneous fat by histiocytes and inflammatory cells (primarily helper T-cells), with fat necrosis and hemorrhage. The characteristic cell is a "bean bag" cell: a histiocyte stuffed with phagocytized red blood cells, lymphocytes, neutrophils, platelets, or fragments of these cells. These "bean bag" cells are not diagnostic of CHP and can be seen uncommonly in other panniculitides, especially lupus profundus. The presence of atypical lymphocytes or the detection of a clonal B- or T-cell proliferation supports the diagnosis of subcutaneous lymphoma in cases of CHP.

The treatment of CHP is difficult. If malignancy cannot be detected, cyclosporin has been very effective in all reported cases treated with this agent, inducing a permanent remission. If malignancy is detected, aggressive chemotherapy and perhaps bone marrow transplantation may be considered.

Craig AJ, et al: Cytophagic histiocytic panniculitis. J Am Acad Dermatol 1998;39:721.

Iwatsuki K, et al: Latent Epstein-Barr virus infection is frequently detected in subcutaneous lymphoma associated with hemophagocytosis but not in nonfatal cytophagic histiocytic panniculitis. Arch Dermatol 1997;133:787.

Ostrov BE, et al: Successful treatment of severe cytophagic histiocytic panniculitis with cyclosporine A. Semin Arthritis Rheum 1996;25:404.

Zollner TM, et al: Monitoring of phagocytic activity in histocytic cytophagic panniculitis. J Am Acad Dermatol 2001;44:120.

MISCELLANEOUS FORMS OF PANNICULITIS

GOUTY PANNICULITIS

Uric acid crystals may deposit initially in the subcutaneous fat, leading to lesions resembling other forms of panniculitis. Histologically, there is a lobular panniculitis with necrosis of adipocytes and infiltration of polymorphonuclear leukocytes. Feathery needle-like crystals in sheaves are present.

LeBoit PE, et al: Gout presenting as lobular panniculitis. Am J Dermatopathol 1987;9:334.

LIPODYSTROPHY (LIPOATROPHY)

The lipodystrophies are conditions in which there is markedly reduced subcutaneous fat. They can be generalized (total), partial, or localized, and may be congenital, or acquired. In the congenital types, women are more commonly and severely affected. Hypertriglyceridemia and diabetes mellitus with insulin resistance occur in many of the congenital and acquired forms of lipodystrophy. These syndromes were quite rare until the 1990s. With the advent of combination antiviral therapy for HIV infection (highly active antiretroviral therapy [HAART]) acquired lipodystrophy has become very common in geographic regions where HIV infection is prevalent. In addition, localized fat loss can be a consequence of therapeutic injections into the fat.

Congenital Lipodystrophies

Congenital Generalized Lipodystrophy Congenital generalized liposystrophy, also known as *Beradinelli-Seip syndrome*, is a rare autosomal-recessive condition. From birth there is an extreme paucity of fat in the subcutaneous tissue and other adipose tissues, giving affected persons a generalized muscular appearance. The mechanical fat of the palms, soles, joints, orbits, and scalp are not affected in some types of this syndrome. The children have a voracious appetite. They have increased height and height velocity, advanced bone age, muscular hypertrophy, and a masculine habitus. This habitus plus enlargement of the genitalia in infancy (clitoromegaly) can lead to the misdiagnosis of precocious puberty. Scalp hair is abundant and curly, and there is generalized hypertrichosis and hyperhidrosis. The abdomen is protuberant and the liver and spleen are enlarged. The overall appearance is acromegalic due to enlargement of the mandible, hands, and feet. Acanthosis nigricans is invariably present and often generalized. Hyperinsulinemia, insulin resistance, and diabetes appear often around puberty. The diabetes mellitus resists insulin and oral hypoglycemic therapy, but ketoacidosis does not occur. Hypertriglyceridemia occurs and can produce eruptive xanthomas; pancreatitis; and fatty liver, which may eventuate in cirrhosis. Hypertrophic cardiomyopathy and mild mental retardation may occur. Lifespan is shortened, with patients frequently dying in young adulthood from complications of diabetes, liver or heart disease. Congenital generalized lipodystrophy is due to two genetic defects, classified as type 1 and type 2 respectively. Type 1 patients have homozygous or compound heterozygous mutation of the AGPAT2 gene encoding 1-acylglycerol-3-phosphate O-acyl transferase 2. This enzyme is involved in the formation of triglycerides and phospholipids. Type 2 patients have mutations in the seipin gene. The role of seipin in causing this phenotype is unknown. Patients with seipin mutations are more likely to have mental retardation, hypertrophic cardiomyopathy, and also lack mechanical adipose tissue. Serum leptin and adiponectin levels are extremely low in both types. If leptin levels are low, leptin replacement decreases serum triglycerides and improves hyperglycemia. Twenty percent of patients with congenital generalized lipodystrophy do not have mutations in these two genes, suggesting there are other genetic causes.

Familial Partial Lipodystrophy Familial partial lipodystrophy is a heterogenous autosomal-dominant group of disorders with distinct phenotypes. The most common variant is the Dunnigan type. Patients are normal at birth, but at around the time of puberty there is gradual loss of subcutaneous tissue from the arms and legs, and variably from the chest and anterior abdomen. Fat gain occurs in the face, neck, and intra-abdominally, resulting in a cushingoid appearance. Diabetes mellitus, hypertriglyceridemia, and atherosclerosis occur more frequently in female patients. The hypertriglyceridemia may result in pancreatitis and fatty liver, but cirrhosis has not been reported. The genetic defect in the Dunnigan variant of partial lipodystrophy is in the gene encoding lamins A and C (LMNA). Lamins are intermediate filaments integral to the nuclear envelope. The site of the mutation determines the phenotype expressed. Myopathy, muscular dystrophy, cardiomyopathy, and conducting system disturbances can occur in a minority of patients.

A second characterized form of familial partial lipodystrophy is related to mutations in the PPAR γ gene. This rare syndrome is associated with marked loss of subcutaneous tissue of the forearms and calves and less prominently on the upper arms and thighs. The trunk is spared and there is no excess fat on the neck. Diabetes mellitus, hypertriglyceridemia, hypertension, and hisuitism also occur. Other forms of familial partial lipodystrophies not associated with the above two mutations have been described, suggesting additional genetic causes of this syndrome.

Mandibuloacral dysplasia is an extremely rare autosomal-recessive condition with hypoplasia of the mandible and clavicle, acro-osteolysis, joint contractures, mottled cutaneous pigmentation, skin atrophy, alopecia, a bird-like facies, and dental anomalies. Two distinct patterns of lipodystrophy occur. Type A is characterized by loss of subcutaneous fat from the arms and legs, but normal-to-excess fat of the face and neck. Type B has a more generalized lipodystrophy. Hyperinsulinemia, insulin resistance, diabetes mellitus, and hyperlipidemia occur in some patients. Mutations in the LMNA gene have been reported in type A patients. Mutations in the zinc metalloproteinase (ZMPSTE24), which is involved in the processing of prelamin A, have also been responsible for mandibuloacral dysplasia. Autosomal-recessive neonatal progeroid syndrome is characterized by near total absence of fat from birth, with sparing of the sacral and gluteal areas.

Acquired Lipodystrophy

There are several forms of acquired lipodystrophy. Although they appear later in life, are not inherited, and no genetic mutation has yet been described to be causal, they closely resemble the genetically determined diseases. Acquired lipodystrophy can be partial or generalized. In addition, hyperinsulinemia, hyperlipidemia, and diabetes mellitus may occur in patients with acquired lipodystrophy. Management involves controlling the hyperinsulinemia and its complications.

Acquired Partial Lipodystrophy (Barraquer-Simons Syndrome) Until HAART-associated lipodystrophy appeared, this was the most common form of lipodystrophy. Females outnumber males 4:1. It presents in the first and second decades. This progressive fat disorder is characterized by a diffuse and progressive loss of the subcutaneous fat that usually begins in the face and scalp and progresses down-

ward as far as the iliac crests, sparing the lower extremities. The upper half of the body looks emaciated and the cheeks sink in (Fig. 23-5A). There is an apparent, and sometimes real, adiposity of the buttocks, thighs, and legs, especially in affected women (Fig. 23-5B). The onset is insidious, with no discomfort or inflammation in the areas of fat loss. A few patients have developed other autoimmune diseases, including systemic lupus erythematosus and juvenile dermatomyositis. Histologically, the skin is normal except for the absence of fat. Most patients with this form of lipodystrophy have reduced levels of C3 resulting from the presence of a circulating polyclonal IgG called "C3 nephritic factor." Proteinuria caused by membranoproliferative glomerulonephritis occurs in about 20% of patients, appearing about 8 years after the onset of the lipodystrophy. C3 nephritic factor stabilizes C3b,Bb (C3 convertase), leading to unopposed activation of the alternative complement system and excessive consumption of C3.

Acquired Generalized Lipodystrophy This rare form of lipodystrophy appears during childhood or adolescence. Females outnumber males 3:1. The fat loss affects large areas of the body, particularly the face, arms, and legs. Mechanical fat of the palms and soles may be lost, but ocular and bone marrow fat are spared. Acanthosis nigricans is present. Hepatic steatosis and voracious appetite may be present. Cirrhosis occurs in about 20% of patients due to hepatitic steatosis or autoimmune hepatitis. Diabetes mellitus and hypertriglyceridemia may occur.

About 25% of patients will have a preceding inflammatory panniculitis at the onset of the syndrome. These patients tend to have less severe manifestations. Another 25% of patients with acquired generalized lipodystrophy have an associated connective tissue disease, especially juvenile dermatomyositis. Half of the patients give no history of panniculitis and have no connective tissue disease. One case has been associated with an abnormality of chromosome 10.

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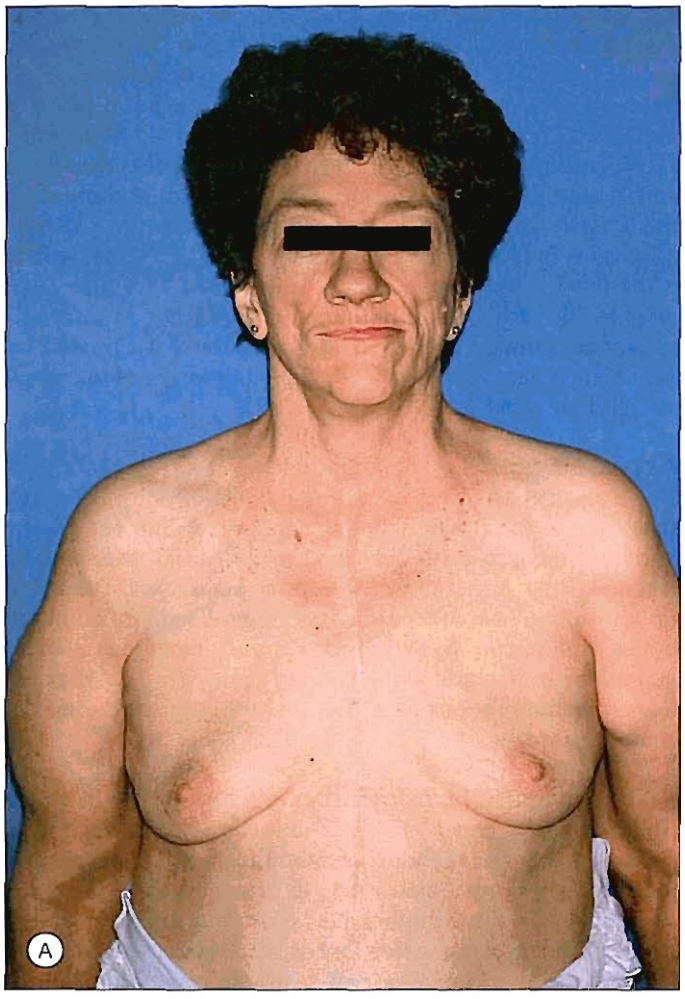
Centrifugal Abdominal Lipodystrophy

Most cases of "lipodystrophia centrifugalis abdominalis infantilis," as described by Imamura et al, have been reported from a single region of Japan. The cause is un-



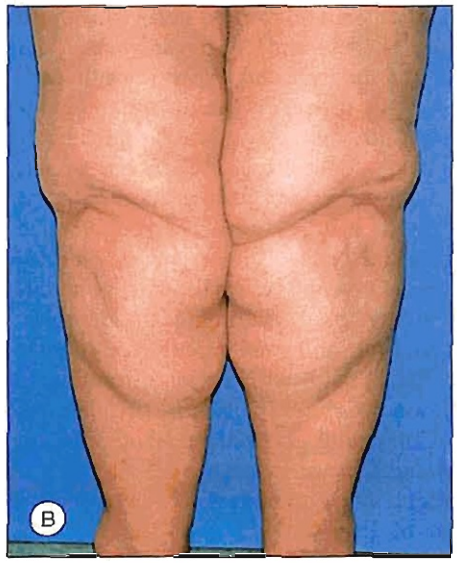


Fig. 23-5 Partial lipodystrophy, acquired. *A*, Face and *B*, hypertrophy of subcutaneous fat on the lower half of the body.

known. It is almost invariably a disease of childhood; 90% of cases begin at age 3. Girls outnumber boys 2:1. It is characterized by depression of the skin caused by loss of fat in the groin (80% of cases) or axilla (20% of cases). The atrophic area enlarges slowly centrifugally for 3 to 8 years in most cases, often stopping with the onset of puberty. In 80% of cases the depressed area was surrounded by a discrete, erythematous border with scale. One-third of patients have multiple lesions and regional lymph nodes are enlarged in 65% of cases. The affected children are otherwise well. When the lesion stops expanding, the erythematous rim and lymphadenopathy disappear. After the progression stops, the skin returns to normal within a year or two.

Muller S, et al: Lipodystrophia centrifugalis abdominalis infantilis in a 4-year-old caucasian girl: association with partial IgA deficiency and autoantibodies. Br J Dermatol 1999;140:1161.

Lipoatrophia Annularis (Ferreira-Marques)

Lipoatrophia annularis affects primarily women and usually affects the upper extremity. The lipoatrophy may be preceded by erythema, a bracelet-shaped swelling, and tenderness of the entire extremity. This is followed by loss of subcutaneous fat so that the arm is divided into two parts by a depressed, atrophic, bracelet-like constriction. The depressed band is usually about 1 cm wide and up to 2 cm in depth. Arthralgias and pain of the affected extremity precede and accompany the process. The band persists for up to 20 years. The histology shows atrophy of the subcutaneous fat. The cause is unknown.

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Localized Lipodystrophy

Six months to 2 years after the initiation of insulin injections, localized atrophy of fat may develop at the sites, more frequently in children and women than in men. This dystrophic change may resolve if patients are switched to human insulin. Much less often, insulin injections may result in lipohypertrophy. Rarely, injections of other medications may result in lipoatrophy.

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Kayikcioglu A, et al: Semicircular lipoatrophy after intragluteal injection of benzathine penicillin. J Pediatr 1996;129:166.

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HIV-Associated Lipodystrophy

In up to 80% of HIV-infected patients, most of whom are being treated with combination anti-HIV therapy (HAART), an unusual form of fat redistribution occurs. The fat of the face, especially the buccal fat pads, buttocks, and limbs is lost. There is increased fat deposition in other areas, especially the neck, upper back (buffalo hump), and intra-abdominally. It is related to non-nucleoside reverse transcriptase inhibitors which also inhibit the γ DNA polymerase of mitochondria leading to adipocyte apoptosis. As with the other acquired and inherited forms of lipodystrophy, patients may suffer from hypertriglyceridemia, hypercholesterolemia, and insulin resistance, especially if a protease inhibitor is a part of their treatment. Metformin therapy at a dose of 500 to 850 mg twice a day combined with exercise reduces the body mass index and waist circumference, as well as insulin resistance. Various injectables may provide cosmetic improvement.

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Rodwell GEJ, et al: Fat redistribution in HIV disease. J Am Acad Dermatol 2000;42:727.

Sattler F: Body habitus changes related to lipodystrophy. Clin Infect Dis 2003;36:S84.

CHAPTER

24 Endocrine Diseases

The skin interacts with the endocrine system in many ways. Some of these are discussed in this chapter.

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Grando SA: Physiology of endocrine skin interactions. J Am Acad Dermatol 1993;28:981.

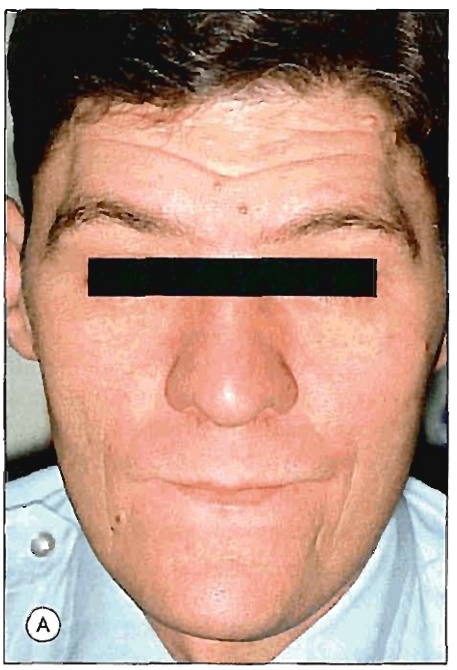
Jabbour S: Cutaneous manifestations of endocrine disorders. Am J Clin Dermatol 2003;4:315.

Thiboutot DM: Dermatological manifestations of endocrine disorders. J Clin Endocrinol Metab 1995;80:3082.

ACROMEGALY

Excess growth hormone in prepubertal children leads to gigantism, whereas once the epiphysial growth plates close, such excess leads to acromegaly. In acromegaly, changes in the soft tissues and bones form a characteristic syndrome. In association with the well-known changes in the facial features caused by gigantic hypertrophy of the chin, nose, and supraorbital ridges, there is thickening, reddening, and wrinkling of the forehead, and exaggeration of the nasolabial grooves (Fig. 24-1A). The lips and tongue are thick. Cutis verticis gyrata is present in approximately 30% of patients. The hands and feet enlarge (Fig. 24-1B), and there is gradual growth of the fingertips until they resemble drumsticks. There is diffuse hypertrophy of the skin. This is at least partly due to deposition of colloidal iron-positive material in the papillae and reticular dermis. This increased skin thickness can be demonstrated in lateral radiographs of the heel, with reversal toward normal after treatment. Skin thickness does not correlate well with growth hormone levels at the time of diagnosis. Hypertrichosis, hyperpigmentation, and hyperhidrosis occur in many patients. The clinical changes may suggest the leonine facies of leprosy, as well as Paget's disease, myxedema, and pachydermoperiostosis. Acromegaloid facial appearance syndrome is an inherited condition where only the facial changes are present, and no abnormality of growth hormone exist. Pseudoacromegaly is an acquired condition which may be seen in patients with severe insulin-resistant diabetes, which appears to be a fibroblast defect, or in patients on long-term minoxidil.

The cause of acromegaly is hypersecretion of growth hormone by the pituitary, usually because of a mixed chromophobe and eosinophilic adenoma of the gland. Rare cases of ectopic growth-hormone–releasing hormone producing tumors of the lung and pancreas have been reported. The peak age of diagnosis is in the 40s. Measurement of serum insulin-like growth factor (somatomedin C) and serum growth hormone after a glucose load and a magnetic resonance imaging (MRI) of the pituitary are diagnostic tests. It may occur as one of the manifestations of Carney complex or



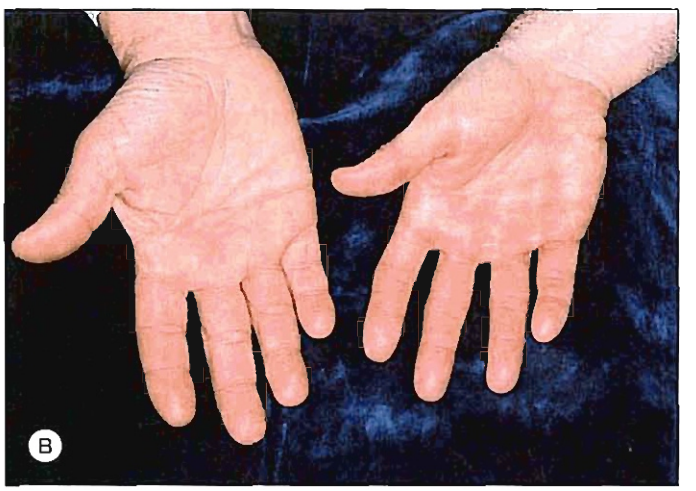


Fig. 24-1 *A* and *B*, Acromegaly. *B*. Patient with acromegaly on the left compared to normal sized hand on the right.

multiple endocrine neoplasia-1.

The currently preferred treatment is a combination of transphenoidal microsurgical excision of the tumor followed by medical therapy for residual disease. Octreotide and lanreotide are potent, long-acting inhibitors of growth hormone (somatostatin analogs) that are given as once a month or biweekly intramuscular depot injections. Fatigue, paresthesias, and headaches improve rapidly. With continuous treatment, soft-tissue swelling and facial coarsening improve as growth hormone levels decline in almost all patients. After 18 to 24 months of therapy 50% of patients will completely normalize, with the exception of hyperhidrosis, which persists in most patients. The dopamine agonist bromocriptine suppresses growth hormone secretion and is used as an adjuvant medical therapy in some cases. Radiation is generally reserved for recalcitrant cases.

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CUSHING SYNDROME

Chronic excess of glucocorticoids leads to a wide variety of signs and symptoms. Among the most prominent features of this syndrome is central obesity, affecting the face, neck, trunk, and markedly the abdomen, but sparing the limbs. There is classically deposition of fat over the upper back, referred to as a buffalo hump. This may be treated with liposuction. The face becomes moon-shaped, being wide and round. The peak age of onset is in the 20s and 30s.

The striking and distressing skin changes include hypertrichosis, dryness, fragility of the skin, facial acne, susceptibility to superficial dermatophyte and pityrosporon infections, a plethora over the cheeks, anterior neck, and V of the chest, and the characteristic purplish, atrophic striae on the abdomen (Fig. 24-2) and thighs. Women, who are affected four times more frequently than men in noniatrogenic cases, develop facial and body hypertrichosis, with thinning of the scalp hair. The thinning of the skin can be demonstrated and measured in lateral radiographs of the heels. There is reversal with treatment. Occasionally, there may be livedo reticularis, purpura, ecchymosis, or brownish pigmentation. Poikiloderma-like changes have been observed. Opportunistic fungal infections occur; these may be with organisms that are not normally pathogenic or be uncommon presentations of common infections.

There is usually hypertension and marked generalized arteriosclerosis, with progressive weakness, prostration, and pains in the back, limbs, and abdomen; also kyphosis of the dorsal spine occurs, accentuating the buffalo appearance. Osteoporosis occurs and there is generally a loss of libido. In 20% of patients a disturbance in carbohydrate metabolism develops with hyperglycemia, glycosuria, and diabetes mellitus.

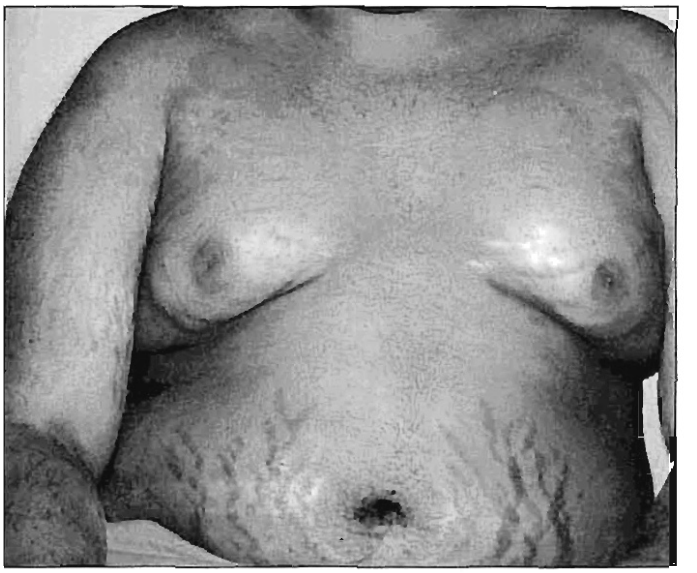

Fig. 24-2 Cushing syndrome.

These varied symptoms indicate a marked and widespread disturbance caused by the hyperactive adrenal cortex. When microadenomas of the pituitary produce these clinical findings, it is referred to as Cushing's disease. This accounts for only 10% of patients; most adenomas are chromophobic. Forty to 60% of additional cases are due to increased adrenocorticotropic hormone (ACTH) production by the pituitary, but no adenoma is identified. Adrenal adenomas and carcinomas, and ectopic production of ACTH by other tumors, account for the remainder of cases of noniatrogenic Cushing syndrome. Iatrogenic Cushing syndrome is usually secondary to systemic administration of corticosteroids; however, absorption from topically applied steroids may occur, especially in children. Primary pigmented nodular adrenocortical disease leading to Cushing syndrome occurs in 30% of patients with Carney complex.

A rapid screening test for Cushing syndrome consists of oral administration of 1 mg of dexamethasone at 11 PM followed at 8 AM by a fluorometric determination of plasma cortisol. A cortisol level below 3 μg/dL essentially rules out Cushing syndrome, except for the iatrogenic variety, in which there is adrenocortical hypoplasia, and the serum cortisol level is very low even without dexamethasone suppression. If this test is positive it must be confirmed by doing a 24-h urinary free cortisol test. A value of at least three times the upper limit of normal is 95% to 100% sensitive and specific. A serum ACTH is then obtained to determine if the source is the adrenals, pituitary or ectopic tumor (low, normal or high, and very high, respectively). Treatment is primarily surgical removal of the tumor; however, radiation, chemotherapy or medication that blocks steroid synthesis are occasionally employed.

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ADDISON'S DISEASE

Adrenal insufficiency is manifested in the skin primarily by hyperpigmentation (Fig. 24-3). It is diffuse but most prominently observed in sun-exposed areas and sites exposed to recurrent trauma or pressure. The axillae, perineum, and nipples are also affected. Palmar crease darkening in patients of lighter skin type, scar hyperpigmentation, and darkening of nevi, mucous membranes, hair, and nails may all be seen. An eruptive onset of multiple new nevi may be an early sign of Addison's disease. Occasionally, pigmentation may not occur; this is referred to as white Addison's disease. Decreased axillary and pubic hair is seen in women as their androgen production primarily occurs in the adrenals. Fibrosis and calcification of the pinnae of the ears are rare complications.

Systemic signs such as weight loss, nausea, vomiting, diarrhea, weakness, fatigue, and hypotension add specificity to the cutaneous abnormalities. Addison's disease is usually the result of autoantibody destruction of adrenocortical tissue; however, infection, hemorrhage, or infiltration may be the cause of adrenal insufficiency. In young boys suspected of having Addison's disease, adrenoleukodystrophy must be considered. Hyperpigmentation may precede neurologic signs, so very-long-chain fatty acids should be determined. Addison's disease may be part of a polyglandular autoimmune disease in which various combinations of hypoparathyroidism, chronic candidiasis, and vitiligo or autoimmune thyroiditis and diabetes may occur.

Diagnosis is made by obtaining a serum cortisol followed by stimulation with cosyntropin. Failure to see an elevation above 20 µg/dL in 1 h is diagnostic. Plasma ACTH is elevated in primary insufficiency but normal to low in patients with secondary adrenal insufficiency, where the damage is in the hypothalamic/pituitary axis. The adrenals should be imaged with CT to exclude infiltration or infection. Treatment is the replacement of the glucocorticoids and mineralocorticoids.

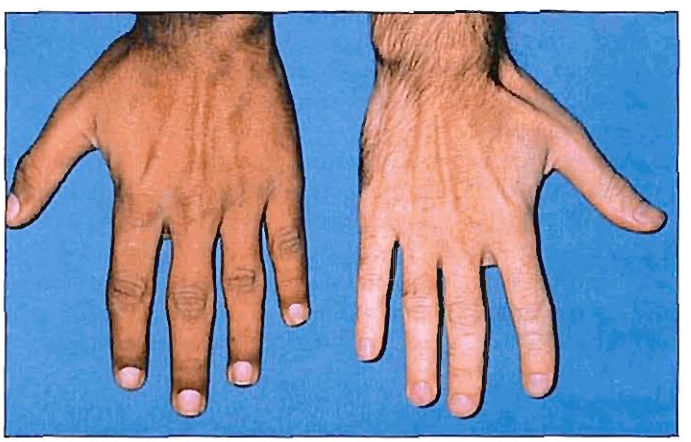

Fig. 24-3 Hyperpigmentation in Addison disease.

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PANHYPOPITUITARISM AND GROWTH HORMONE DEFICIENCY

Pituitary failure results in many changes in the skin, hair, and nails as a result of the absence of pituitary hormone action on these sites. Pale, thin, dry skin is seen. Hypohidrosis is present. Diffuse loss of body hair, with axillary, pubic, and head hair being especially thin, is present. The nails are thin, fragile, and opaque, and grow slowly. Compromise of the pituitary is usually caused by a pituitary tumor, although infiltration, infection, trauma, hemorrhage or hypothalamic tumors, may be the etiology. Thyroid hormone, glucocorticoids, sex steroids, and growth hormones are low and require replacement. A pituitary MRI will screen for tumors or infiltrative processes.

Diseases of the pituitary that cause panhypopituitarism may also lead to growth hormone deficiency as an isolated finding. This condition may begin in childhood, in which case short stature is the most prominent problem, while in adults weight gain, decreased energy, decreased strength, and psychosocial disorders predominate. Children have sparse hair growth and frontal recession and pili torti et canaliculi and trichorrhexis nodsa are present in some patients. In children the most common finding is an idiopathic decrease in secretion of growth hormone from the pituitary, while in adults there is usually pituitary pathology demonstrable by MRI, as described above. An insulin tolerance test is the most common diagnostic test. Treatment is with growth hormone replacement.

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ANDROGEN-DEPENDENT SYNDROMES

The androgen-dependent syndromes are caused by the excessive production of adrenal or gonadal androgens by adrenal adenomas, carcinoma or hyperplasia, Leydig cell tumors in men, and arrhenoblastomas and polycystic ovarian syndrome (PCOS) in women. The latter is defined as the association of biochemical or clinical androgenism with chronic anovulation without specific underlying disease of the adrenal or pituitary glands.

The cutaneous signs of excessive androgen in women include acne, hirsutism, temporal baldness, seborrhea, enlargement of the clitoris, and decreased breast size. Hyperpigmentation of the skin, areolae, genitalia, palmar creases, and buccal mucosa develops in some patients. Acanthosis nigricans is common in PCOS. A deepening voice, increased muscle mass, galactorrhea, and irregular or absent periods are other signs of androgen excess in women.

In the congenital adrenogenital syndrome, excess androgen is produced by an inherited defect in any of the five enzymatic steps required to convert cholesterol to cortisol. The formation of inadequate amounts of cortisol stimulates the pituitary to secrete excessive ACTH, which stimulates excess androgen production. In boys, precocious puberty results. In girls, masculinization occurs, with the prominent cutaneous signs of excess androgen production (Fig. 24-4). Among these may be childhood acne. It may begin before age 9 and manifest as primarily comedonal lesions in the central face associated with advanced bone age. Many children with this presentation of acne, however, reveal no abnormality. Accelerated bone growth with early closure of the epiphyseal plates results in short stature. Early appearance of pubic and axillary hair is also seen.

Testing includes serum total testosterone and dehydroepiandrosterone sulfate (DHEA-S). If the total testosterone is greater than 200 ng/dL, ovarian imaging is indicated to assess for an ovarian tumor. If DHEA-S is two to three times the upper limit, an adrenal mass should be suspected and a computed tomographic (CT) scan of the adrenals is needed. In congenital adrenal hyperplasia, testing should include levels of cortisol, aldosterone, and precursor hormones, and in some case cortrysin stimulation tests. Nonclassic adrenal hyperplasia is most commonly related to 21-hydroxylase deficiency, and may present as PCOS. It is best diagnosed by a corticotropin-stimulated 17-hydroxyprogesterone (17-HP) level greater than 10 ng/mL (30.3 nmol/L). The diagnosis can be confirmed by genotyping of the CYP21 gene. The baseline 17-HP level has been used as a screening test. Although the sensitivity and specificity of the test has been challenged, levels of 17-HP lower than 2 ng/mL (6.0 nmol/L) have a fairly good negative predictive value and those greater than 4 ng/mL (12.0 nmol/L) have a fairly good positive predictive value. The question remains whether treatment with corticosteroid replacement results in better outcomes than empiric antiandrogen therapy.

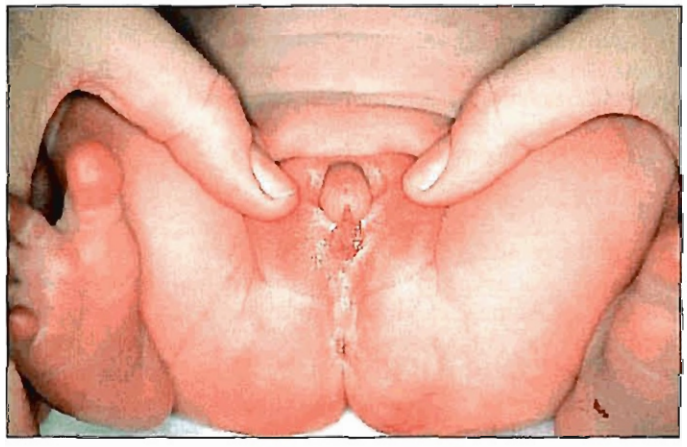

Fig. 24-4 Adrenogenital syndrome.

Treatment of the cutaneous signs of androgen excess is successful with the androgen-blocking agents cyproterone acetate, flutamide, and finasteride. Spironolactone, which competes for the androgen cytosol receptors, has proved useful as a systemic antiandrogen in the treatment of hirsutism and acne. Adrenal–androgenic female pattern alopecia may improve with topical minoxidil or spironolactone. Chorionic villous biopsy may identify homozygous adrenogenital female fetuses and allow for dexamethasone therapy to prevent intrauterine virilization of the external genitalia.

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HYPOTHYROIDISM

Hypothyroidism is a deficiency of circulating thyroid hormone, or rarely peripheral resistance to hormonal action. Deficiency may be caused by iodine deficiency, late-stage Hashimoto autoimmune thyroiditis, pituitary or hypothalamic disease causing central hypothyroidism, or it may be iatrogenic secondary to surgery, radioactive iodine treatment or drug therapy with lithium, interferon or bexarotene. The condition produces various clinical manifestations, depending on when in life it occurs and on its severity. Middle-aged women are the most commonly affected adults. Patients with Turner and Down syndrome are predisposed to hypothyroidism and the production of thyroid autoantibodies. There is a wide array of immunologic conditions associated with Hashimoto thyroiditis such as autoimmune polyglandular syndrome type II/III, vitiligo, connective tissue disease, and autoimmune urticaria.

An autosomal-recessive variant of ectodermal dysplasia reported as ANOTHER (alopecia, nail dystrophy, ophthalmic complications, thyroid dysfunction, hypohidrosis, ephelides and enteropathy, and respiratory tract infections) syndrome has been described and thyroid tumors are a component of Carney complex and multiple endocrine neoplasia-2a and -2b.

Cretinism

Thyroid deficiency in fetal life produces the characteristic picture of cretinism at birth and in the next few months of

life. Depending on the degree of thyroid deficiency, a wide variety of signs and symptoms may be evident. The main consequence of extreme thyroid deficiency is cretinism and its attendant mental retardation, but much more prevalent are lesser degrees of intellectual and neurologic deficits seen in areas where iodized salt is still not routinely available.

The person with cretinism has cool, dry, pasty white to yellowish skin. Disturbances in the amount, texture, and distribution of the hair with patchy alopecia are common. Pigmentation is less than normal after exposure to sunlight. Sweating is greatly diminished. The lips are pale, thick, and protuberant. The tongue is usually enlarged, and there is delayed dentition. Wide-set eyes, a broad, flat nose, and periorbital puffiness characterize the face. A protuberant abdomen with umbilical hernia; acral swelling; coarse, dry, brittle nails; a clavicular fat pad; and hypothermia with cutis marmorata are also seen.

Myxedema

When lack of secretion of thyroid hormone is severe, the systemic mucinosis called *myxedema* is produced. The skin becomes rough and dry, and in severe cases of primary myxedema, ichthyosis vulgaris may be simulated. The facial skin is puffy; the expression is often dull and flat; macroglossia, swollen lips, and a broad nose are present; and chronic periorbital infiltration secondary to deposits of mucopolysaccharides frequently develops (Fig. 24-5A). Such infiltrate can lead to a cutis verticis gyrata appearance of the scalp. Carotenemia may cause a yellow tint in the skin that is especially prominent on the palms and soles. Diffuse hair loss is common, and the outer third of the eyebrows is shed (Fig. 24-5B). The hair becomes coarse and brittle. The free edges of the nails break easily, and onycholysis may occur.

Mild Hypothyroidism

Lesser degrees of deficiency are common and far less easily diagnosed. Coldness of hands and feet in the absence of vascular disease, sensitivity to cool weather, lack of sweating, tendency to put on weight, need for extra sleep, drowsiness in the daytime, or constipation all suggest possible hypothyroidism and the need for appropriate tests. Palmoplantar keratoderma may be a sign of hypothyroidism and will resolve after thyroid replacement is given.

Diagnosis and Treatment

An increased thyroid-stimulating hormone (TSH) test is the best diagnostic test for primary hypothyroidism. T3 and T4 are low, and in Hashimoto thyroiditis, the most common cause of hypothyroidism in the US, thyroid peroxidase antibodies are present in 95% of patients. In those with positive antibodies but normal thyroid function, hypothyroidism will develop at a rate of 5% per year. Thyroid hormone replacement will reverse the skin findings of hypothyroidism.

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HYPERTHYROIDISM

Excessive quantities of circulating thyroid hormone may be caused by a multinodular toxic goiter or a single toxic thyroid nodule, early Hashimoto autoimmune thyroiditis, a TSH-secreting pituitary adenoma, or Graves thyroiditis. The latter

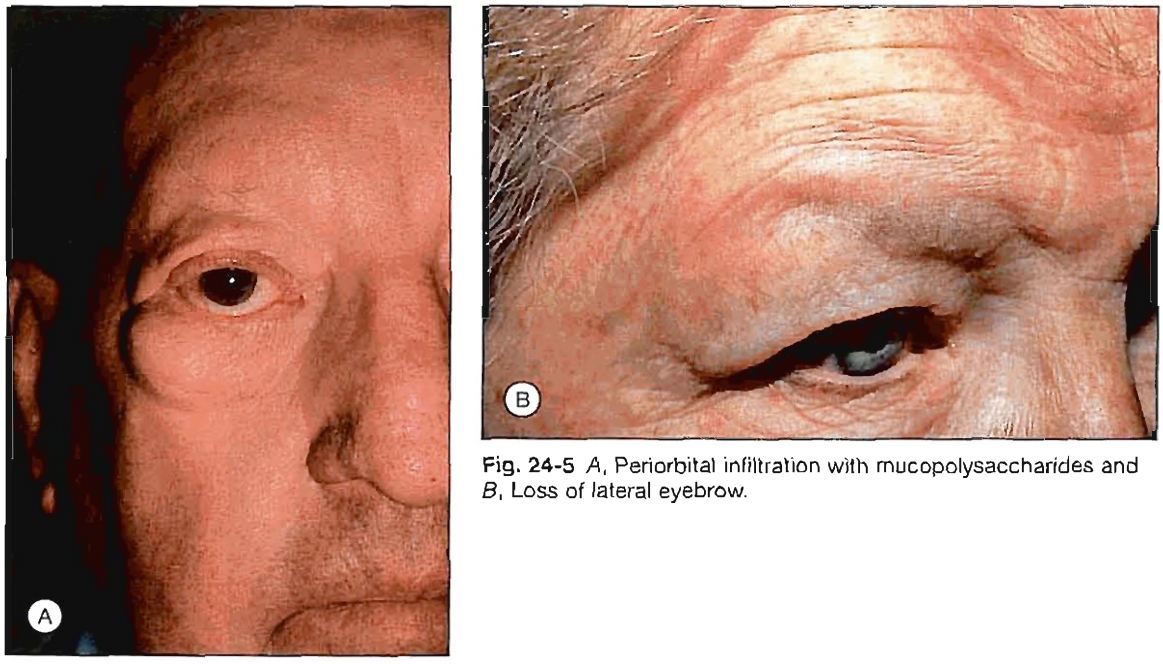
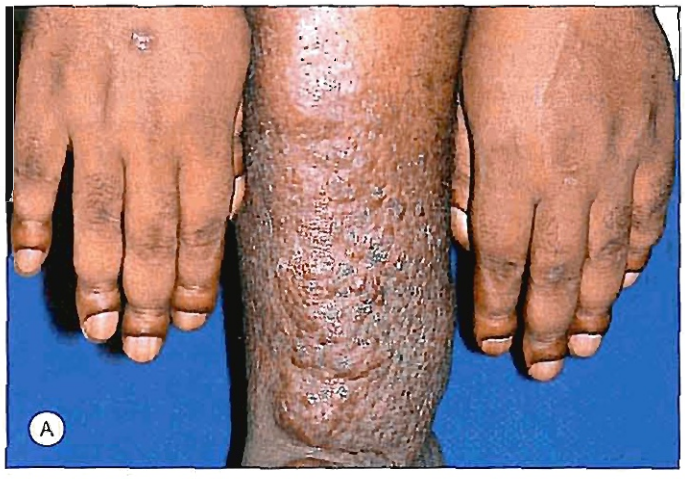


Fig. 24-5 *A*, Periorbital infiltration with mucopolysaccharides and *B*, Loss of lateral eyebrow.

is mediated by thyroid stimulating antibodies that bind to the TSH receptor, mimic the effects of TSH, and induce hyperthyroidism. There are many skin changes common to all forms of hyperthyroidism. The cutaneous surface is warm, moist, and smooth textured. Palmar erythema or facial flushing may be seen. The hair is thin and has a downy texture, and nonscarring diffuse alopecia may be observed. The skin may darken to produce a bronzed appearance or melanoderma; sometimes melasma of the cheeks is seen. Nail changes are present in approximately 5% of patients with Plummer nails, a concave contour of the plate with distal onycholysis, being characteristic. Hyperhidrosis may be noted.

Graves' disease has a female-to-male ratio of 7:1, and the peak age at onset is 20 to 30 years. It is the most common cause of noniatrogenic hyperthyroidism. Ophthalmopathy, pretibial myxedema, and thyroid acropachy are findings nearly always limited to Graves patients (Fig. 24-6). Thyroid acropachy, seen in approximately 0.1% to 1% of Graves patients, is characterized by digital clubbing, soft-tissue swelling of the hands and feet, and diaphyseal proliferation of the periosteum in acral and distal long bones (tibia, fibula, ulna, and radius). It usually occurs after treatment of hyperthyroidism and is usually associated with exophthalmos and pretibial myxedema. It may, however, occasionally precede the thyrotoxicosis and has been recognized in euthyroid and hypothyroid patients. It can be confused clinically with acromegaly, pachydermoperiostosis, pulmonary osteoarthropathy, or osteoperiostitis, but the radiologic findings are pathognomonic.



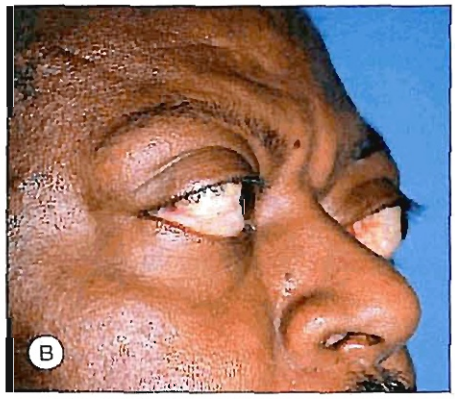


Fig. 24-6 *A*, Thyroid acropachy and pretibial myxedema, *and B, exophthalmos.*

Pretibial myxedema, consisting of bilateral, localized, cutaneous accumulations of glycosaminoglycans, occurs in 4% of patients who have or have had Graves' disease (Fig. 24-7). The morphology may vary from a nonpitting infiltration to nodules, plaques, and even an elephantiasic form where the skin is thickened, firm, and hyperpigmented from just below the knees to the feet. It may uncommonly also occur during the course of Hashimoto thyroiditis and primary hypothyroidism. Patients with pretibial myxedema regularly have associated ophthalmopathy and occasionally have thyroid acropachy. While not usually clinically apparent, approximately half of patients with Graves' disease have mucopolysaccharide deposition in the preradial area of the extensor aspects of the forearms. Lesions of the shoulder, hands, thigh, and scalp have been reported.

Improvement in the plaques of pretibial myxedema has resulted from intralesional injections of triamcinolone acetonide, with high potency topical steroids under occlusion. Systemic steroids are usually not helpful. Compression stockings or complete decongestive physiotherapy, a combination of manual lymphatic drainage, bandaging, and exercise, are useful and safe. Improvement with intravenous immunoglobulin of the skin, eye, and immunologic parameters has been reported in small series of patients. Pentoxifylline, octreotide, plasmapheresis, and cytotoxic drugs have all been reported to help in small numbers of patients, but negative reports also exist.

Vitiligo is associated with hyperthyroidism in 7% of patients with Graves' disease and is seen with an increased frequency in Hashimoto thyroiditis. Urticaria may be seen in patients with thyroid autoantibodies and may clear with the administration of thyroid hormone, even in euthyroid patients. A wide range of other autoimmune disorders may be seen in patients with Graves or Hashimoto autoimmune thyroiditis.

The TSH level is low in all patients except those with a TSH-secreting pituitary adenoma. Free T3 and T4 are elevated. Anti-TSH antibodies are present in nearly all Graves patients but the presence of a diffuse goiter with classic signs

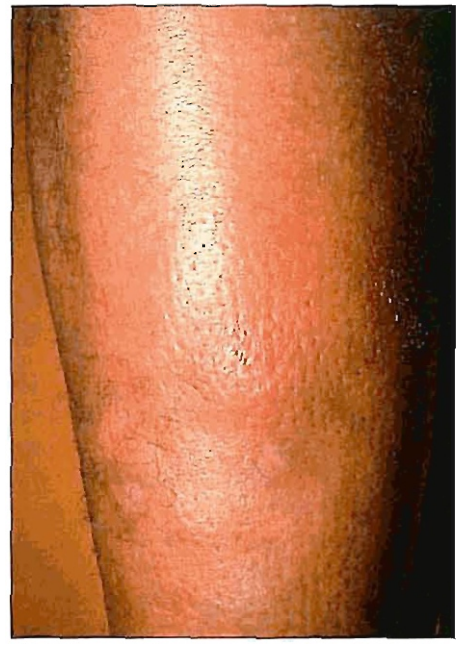


Fig. 24-7 Pretibial myxedema. (Courtesy of Lawrence Lieblich, MD)

precludes the need to order this test in most patients. A 24-h radioiodine scan will also help define the etiology. Treatment is with radioactive iodine or antithyroid drugs such as methimazole or propylthiouracil.

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HYPOPARATHYROIDISM

Varied changes in the skin and its appendages may be evident. Most pronounced is faulty dentition when hypoparathyroidism is present during development of the permanent teeth. The skin is dry and scaly. A diffuse scantiness of the hair and complete absence of axillary and pubic hair may be found. The nails are brittle and malformed. Onycholysis with fungal infection may be present. Of patients with idiopathic hypoparathyroidism, 15% develop mucocutaneous candidiasis. Hypoparathyroidism is the most frequent endocrine abnormality present in patients with the APECED (autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy) syndrome. In autoimmune polyendocrinopathy syndrome type I, hypoparathyroidism is present in association with Addison's disease and chronic candidiasis. Hypoparathyroidism may additionally occur in DiGeorge syndrome, or with infiltration or inadvertent surgical removal during thyroid surgery. Hypoparathyroidism with resultant hypocalcemia has been reported to trigger bouts of impetigo herpetiformis or pustular psoriasis.

Pseudohypoparathyroidism (PH) is an autosomal-dominant or X-linked inherited disorder characterized by end-organ unresponsiveness to parathyroid hormone. The parathyroid hormone and phosphorus levels are high, whereas the serum calcium is low. The typical clinical findings include short stature; obesity; round face; prominent forehead; low nasal bridge; attached earlobes; short neck; short, wide nails; delayed dentition; mental deficiency; amenorrhea; blue sclera; and cataracts. Brachycephaly, microcephaly, and shortened metacarpals or metatarsals, especially of the fourth and fifth digits, occur because of premature epiphyseal closure. The latter results in short, stubby fingers and toes, with dimpling over the metacarpophalangeal joints (Albright's sign) (Fig. 24-8). Subcutaneous calcification and ossification occur commonly in this disorder as it may in pseudopseudohypoparathyroidism (PPH), which has the same phenotype but patients have normal serum and calcium levels. PH and PPH are two types of Albright hereditary osteodystrophy. In PH type 1a there is a defect in a G protein that couples receptors for several hormones to adenylate cyclase. This causes a generalized resistance to agents acting through the cAMP pathway and explains the frequent association of hypothyroidism and hypogonadism.

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HYPERPARATHYROIDISM

Whereas parathyroid hormone (PTH) regulates calcium levels, calcinosis cutis may develop from excess PTH. This can occur when the serum calcium/phosphorus product is greater than 65 mg/dL. This may manifest as large subcutaneous nodules or white, often linearly arranged, papules centered about joints. Additionally, calciphylaxis, while most common in the setting of secondary hyperparathyroidism and renal failure, may be seen occasionally in primary hyperparathyroidism.

Multiple endocrine neoplasia (MEN) type I is characterized by tumors of the parathyroids, endocrine pancreas, anterior pituitary, thyroid, and adrenal glands. The most commonly observed abnormality is hypercalcemia from hypersecreting tumors of the parathyroid glands. This autosomal-dominantly inherited disease usually presents in the fourth decade of life with clinical symptoms related to hypersecretion of hormone. They may also manifest multiple angiofibromas, collagenomas, café-au-lait macules, lipomas, confetti-like hypopigmentation, and gingival macules. The angiofibromas are smaller and less numerous than those present in tuberous sclerosis. The tumors in both MEN I and tuberous sclerosis apparently arise because of abnormalities within a tumor suppressor gene. The MEN I gene, which is present on chromosome 11, has a protein product termed *menin* whose function is yet to be delineated. Additionally, approximately 20% to 40% of cases of sporadic parathyroid adenomas have been linked to overexpression of cyclin D1, a key regulator of the cell cycle.

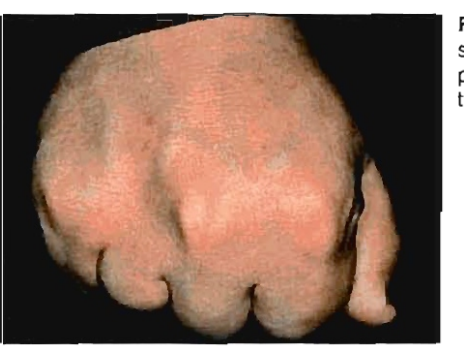

Fig. 24-8 Albright's sign in pseudopseudohypoparathyroidism.

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ACANTHOSIS NIGRICANS

Acanthosis nigricans is characterized by hyperpigmentation and velvet-textured plaques, which are symmetrically distributed. The regions affected may be the face, neck, axillae (Fig. 24-9), external genitals, groin, inner aspects of the thighs, flexor and extensor surface of the elbows and knees, dorsal joints of the hands, umbilicus, and anus. With extensive involvement, lesions can be found on the areolae, conjunctiva, lips, and buccal mucosa, and around the umbilicus. Rarely, the involvement may be almost universal. The color of the patches is grayish, brownish, or black. The palms or soles may show thickening of the palmar skin with exaggeration of the dermatoglyphs. In severe cases a rougose hypertrophy occurs and can be a sign of malignancy. Small, papillomatous, nonpigmented lesions and pigmented macules may occasionally be found in the mucous membranes of the mouth, pharynx, and vagina. Acrochordons are a frequent accompaniment in the axillae and groin

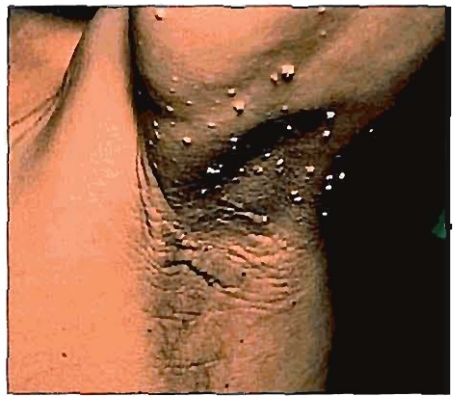


Fig. 24-9 Acanthosis nigricans.

Type I: Acanthosis Nigricans Associated with Malignancy

The "malignant" type of acanthosis nigricans may either precede (18%), accompany (60%), or follow (22%) the onset of the internal cancer. This rare type generally is the most striking clinically, both from the standpoint of extent of involvement and the pronounced nature of the lesions (Fig. 24-10). Most cases are associated with adenocarcinoma, especially of the gastrointestinal tract (60% stomach), lung, and breast; less often the gallbladder, pancreas, esophagus, liver, prostate, kidney, colon, rectum, uterus, and ovaries. Other types of cancer and lymphomas may be seen also. A few cases of this type of acanthosis nigricans have been observed in childhood, but most begin after puberty or in adulthood. This type should be highly suspected if widespread lesions develop in a nonobese male aged over 40.

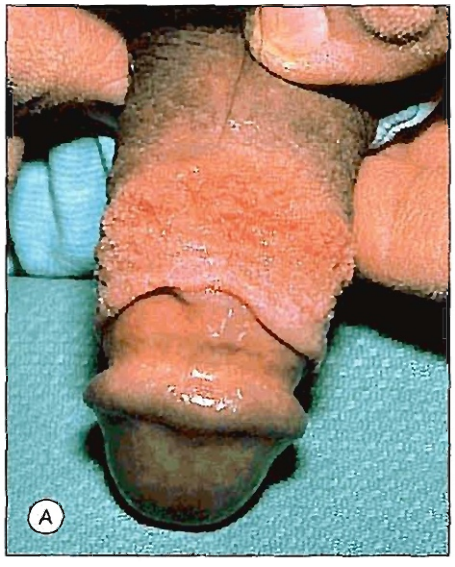
Tripe palms (acanthosis palmaris) are characterized by thickened, velvety palms with pronounced dermatoglyphics; 95% occur in patients with cancer and 77% are seen in conjunction with acanthosis nigricans (Fig. 24-11). In 40% of these cases, tripe palms is the presenting sign of an undiagnosed malignancy. If only the palms are involved, lung cancer is most common, whereas in tripe palms associated with acanthosis nigricans gastric cancer is most frequent.

Type II: Familial Acanthosis Nigricans

This exceedingly rare type is present at birth or may develop during childhood. It is commonly accentuated at puberty. It is not associated with an internal cancer and is inherited in an autosomal-dominant manner.

Type III: Acanthosis Nigricans Associated with Obesity, Insulin-Resistant States, and Endocrinopathy

Type III is the most common variety of acanthosis nigricans. It presents as a grayish, velvety thickening of the skin of



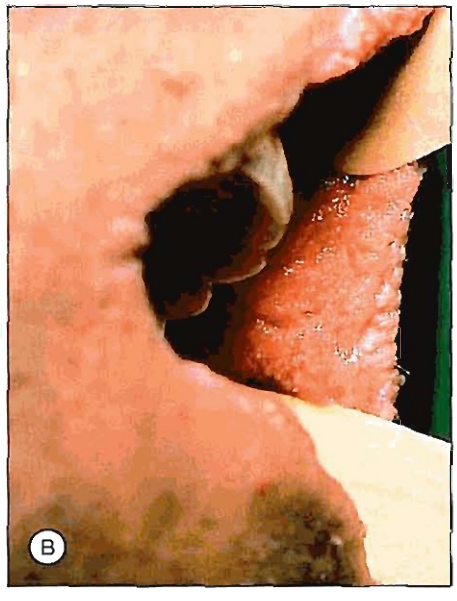


Fig. 24-10 *A* and *B*, Extensive acanthosis nigricans in a patient with stomach cancer.

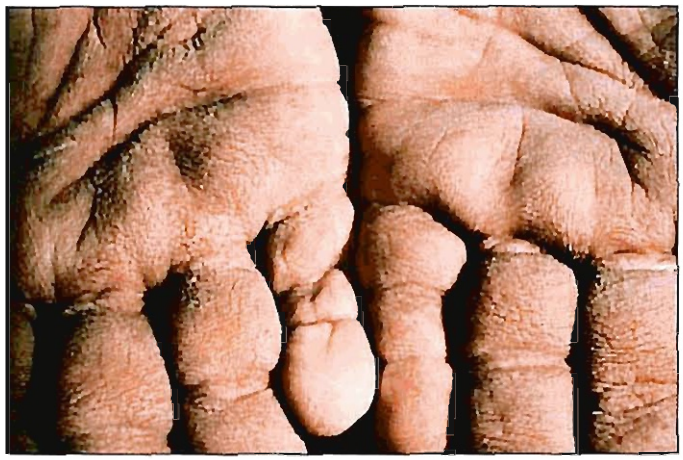


Fig. 24-11 Tripe palms. (Courtesy of James Fitzpatrick, MD)

Fig. 24-12 Obesity-related acanthosis nigricans.

the sides of the neck, axillae, and groins. It occurs in obese persons with or without endocrine disorders (Fig. 24-12). It also occurs in acromegaly and gigantism, pseudoacromegaly, Stein-Leventhal syndrome, Cushing syndrome, diabetes mellitus, hypothyroidism, Addison's disease, hyperandrogenic states, hypogonadal syndromes, and the various well-recognized insulin-resistant states, including lipoatrophic diabetes, leprechaunism, pinealoma (Rabson-Mendenhall syndrome), acral hypertrophy syndrome; type A syndrome, where there is a defect in insulin-receptor, postreceptor pathways, or a lamin A mutation and type B syndrome, where autoantibodies to the insulin receptor are present. Whereas both types A and B syndrome occur most commonly in black females, type A predominates in young children with hyperandrogenic manifestations. Type B syndrome is seen in middle-aged patients with autoimmune disease (Fig. 24-13). Most, if not all, patients with this type of acanthosis nigricans may have either clinical or subclinical insulin resistance, and patients should have a glucose and insulin level drawn simultaneously. In adults a glucose-to-insulin ratio less than 4.5 is abnormal, while in prepubertal children less than 7 is abnormal. Many of the conditions associated with insulin resistance and acanthosis nigricans manifest as hyperandrogenism and have been dubbed the HAIR-AN syndrome. In one group of women with hirsutism, obesity, and hyperandrogenism, vulvar acanthosis nigricans was present in all patients, with other sites less frequently involved.

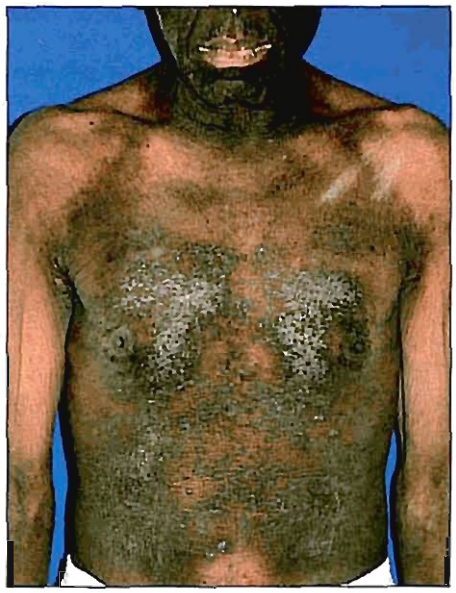


Fig. 24-13 Diffuse acanthosis nigricans in type B syndrome.

Acanthosis nigricans may occur in various syndromes such as Bloom syndrome, Alström syndrome, ataxia-telangiectasia, Costello syndrome, MORFAN syndrome (mental retardation, overgrowth, remarkable face, and AN), Capozucca syndrome, Prader-Willi syndrome, Beare-Stevenson cutis gyrata syndrome, Down syndrome, Crouzon syndrome, Hermansky-Pudlack syndrome, Rud syndrome, and Wilson's disease. Drugs known to induce acanthosis nigricans are nicotinic acid, niacinamide, somatotrophin, testosterone, triazinate, diethylstilbestrol, triazinate, oral contraceptives, and glucocorticoids. Approximately 10% of renal transplant patients have acanthosis nigricans.

The histopathology shows papillomatosis without thickening of the Malpighian layer. The term *acanthosis* was applied here to indicate the clinical, not the histologic, bristly thickening of the skin. Hyperkeratosis and slight hyperpigmentation of the basal layer is present in most cases; it appears, however, that the clinically observed hyperpigmentation is due to hyperkeratosis and clinical thickening rather than to melanin.

The differential diagnosis includes intertriginous granular parakeratosis and several disorders of reticulated hyperpigmentation, including confluent and reticulated papillomatosis (Gougerot-Carteaud syndrome), Dowling-Degos' disease, Haber syndrome, and acropigmentatio reticularis of Kitamura. Granular parakeratosis presents as eryhthematous to brownish hyperkeratotic papules and plaques of the intertriginous regions. It is most often seen in middle-aged women in the axillae; however, the inguinal folds and submamamary areas may be involved. Histology reveals a thickened stratum corneum, severe compact parakeratosis with retention of keratohyalin granules, and vascular proliferation and ectasia. The cause is likely an irritant response to rubbing or to antiperspirants or deodorants. Dowling-Degos' disease is a familial nevoid anomaly with delayed onset in adult life. There is progressive, brown–black hyperpigmentation of flexures with associated soft fibromas and follicular hyperkeratoses. Pitted acneform scars occur periorally.

Treatment of the type associated with malignancy consists of finding and removing the causal tumor. Early recognition and treatment may be life-saving. The type occurring with obesity usually improves with weight loss. If there is associated endocrinopathy, it must be treated as well. One patient with lipodystrophic diabetes improved during dietary supplementation with fish oil. Etretinate, metformin, tretinoin, calcipotriol, urea, salicyclic acid, CO_2 laser ablation, and long-pulsed alexandrite laser therapy have been reported as successful treatments in individual cases.

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CHAPTER

25 Abnormalities of Dermal Fibrous and Elastic Tissue

COLLAGEN

Many types of collagens have been identified in tissues of vertebrates (Table 25-1). There are four families of collagens. *Fibrillar collagens* (types I, II, III, V, and XI) form fibrils that are among the most abundant proteins in the body. Type I collagen accounts for 60% to 90% of the dry weight of skin, ligaments, and demineralized bone.

Type III collagen is abundant in fetal skin and blood vessels. It comprises 35% of the collagen in normal adult skin, but up to 40% in inflamed skin in the setting of contact dermatitis. *Basement membrane-associated collagen* is made up of types IV and VII. *Fiber-associated collagens* (types VIII, IX, and XIV) are found on the surface of type I and II collagens and are believed to serve as flexible spacers among fibrils. *Fibril-associated collagens with interrupted triple helices* (FACITs) do not form fibrils themselves but are found attached to the surfaces of preexisting fibrils of the fibril-forming collagens. FACITs are composed of types IX, XII, XIV, XVI, XIX, XX and XXI. *Network-forming collagens* are sheets formed from types VIII and X. Studies on types XV, XVII, and XIX demonstrate their widespread presence in basement membranes, particularly vascular endothelium, which may represent a new subgroup of collagens associated with angiogenic and pathologic processes. Type XVII collagen is also known as BP180, and contains the target antigens for several immunobullous diseases. Type VII collagen contains the target antigens for bullous lupus and epidermolysis bullosa aquisita. Type II collagen contains the target antigens for relapsing polychondritis.

The regulation of collagen synthesis and degradation is complex. Dermal fibrosis is largely related to increases in type I collagen mediated by proα1 and proα2 collagen genes. Transforming growth factor-β (TGF-β) results in increased type I procollagen synthesis. Angiotensin II type 1 receptor stimulation increases collagen production and inhibits collagen degradation, whereas type 2 receptor stimulation exerts the reverse effects.

Table 25-1 Collagen types

Collagen type	Gene*	Chromosome	Tissue distribution
I	COL1A1-2	17q21.3–q22	Skin, bone, tendon
I-trimer			Tumors, cell cultures, skin, liver
II	COL2A1	7q21.3–q22	Cartilage, vitreous
III	COL3A1	12q13–q14	Fetal skin, blood vessels, intestines
IV	COL4A1–6	13q34, 2q35–q37, Xq22	Basement membranes
V	COL5A1–3	9q34.2–q34.3	Ubiquitous
VI	COL6A1–3	21q22.3, 2q37	Aortic intima, placenta
VII	COL7A1	3p21	Amnion, anchoring fibrils
VIII	COL8A1–2	3q12–q13.1, 1p32.3–p34.3	Endothelial cell cultures
IX	COL9A1–3	6q12–q14, 1p32	Cartilage, type II collagen tissue
X	COL10A1	6q12–q22	Cartilage
XI	COL11A1–2, COL2A1	1p21	Cartilage, skin
XII	COL12A1	6	Skin, cartilage, cornea, limbal
XIII	COL13A1	10q22	Ubiquitous
XIV	COL14A1	8q23	Ubiquitous, fetal hair follicles, basement membranes
XV	COL15A1	9q21–22	Skin hemidesmosomes, kidney, liver, spleen
XVI	COL16A1	1p34–35	Ubiquitous
XVII	COL17A1	10q24.3	Skin hemidesmosomes (BP180)
XVIII	COL18A1	21q22.3	Ubiquitous, basement membranes
XIX	COL19A1	6q12–q14	Ubiquitous, basement membranes
XX	COL20A1		Corneal epithelium, embryonic skin, sternal cartilage, and tendon
XXI	COL21A1	6p11.2–12.3	Blood vessel walls
XXII			
XXIII			Rat prostate carcinoma cells
XXIV			Fetal cornea and bone
XXV			Precursor to Alzheimer amyloid plaque component
XXVI			Testis and ovary
XXVII			Chondrocytes, developing tissues including stomach, lung, gonad, skin, cochlea, and teeth

*Hyphenation denotes a series of genes, i.e. COL14A1-2 means COL14A1 and COL14A2.

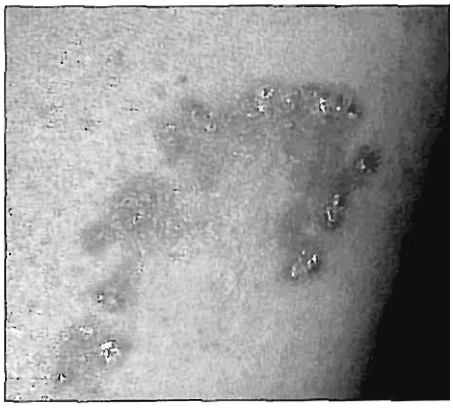

Fig. 25-1 Elastosis perforans serpiginosa.

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ELASTOSIS PERFORANS SERPIGINOSA

In 1953, Lutz described a chronic papular keratotic eruption in an arciform shape located on the sides of the nape of the neck (Fig. 25-1). The papules range from 2 to 5 mm in diameter, and are grouped in a serpiginous or horseshoe-shaped arrangement. Although the lesions typically occur on the neck, other sites may be involved, such as the upper arms, face, lower extremities, and rarely the trunk. Disseminated lesions may occur in Down syndrome. Elastosis perforans serpiginosa (EPS) is most common in young adults. Men outnumber women 4:1. The disease runs a variable course with spontaneous resolution often occurring from 6 months to 5 years after onset. Often, atrophic scarring remains.

Approximately one-third of cases occur in patients with associated diseases, the most frequent concomitant disorder being Down syndrome. Approximately 1% of patients with Down syndrome have EPS, and the lesions are likely to be more extensive and persistent than in other patients. Ehlers-Danlos syndrome, osteogenesis imperfecta, Marfan syndrome, Rothmund-Thomson syndrome, acrogeria, systemic sclerosis, morphea, XYY syndrome, and renal disease have also been associated with EPS. Reports of EPS associated with pseudoxanthoma elasticum are probably examples of perforating pseudoxanthoma elasticum. Several patients with Wilson's disease have developed EPS after prolonged treatment with penicillamine.

The distinctive histopathologic changes consist of elongated, tortuous channels in the epidermis into which eosinophilic elastic fibers perforate. The fibers are extruded from the dermis. There is degeneration and alteration of the elastic tissue in the adjacent papillary dermis with an accompanying inflammatory response. In penicillamine-associated disease, the fibers may have an irregular (bramble-bush) contour when examined with electron microscopy.

Treatment is difficult, but individual lesions may resolve following liquid nitrogen cryotherapy. Some cases have responded to CO_2, Er:YAG, or pulsed dye laser therapy. Topical retinoids, such as tazarotene, have been reported to be of benefit in some patients.

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REACTIVE PERFORATING COLLAGENOSIS

In 1967, Mehregan reported a rare, familial, nonpruritic skin disorder characterized by papules that grow to a diameter of 4 to 6 mm and develop a central area of umbilication in which keratinous material is lodged. The discrete papules may be numerous and involve sites of frequent trauma such as the backs of the hands, forearms, elbows, and knees. The lesion reaches a maximum size of about 6 mm in 4 weeks and then regresses spontaneously in 6 to 8 weeks. The lesions are broader than those of EPS and a broad crust containing collagen fibers is extruded centrally. Koebnerization is often observed. Young children are most frequently affected. Most reports support an autosomal-recessive mode of inheritance; however, a family in which it appeared to be inherited by autosomal dominance has been reported. Acquired reactive perforating collagenosis is discussed in Chapter 33 within the discussion of acquired perforating dermatosis.

No specific treatment is indicated, since the lesions involute spontaneously. Tretinoin 0.1% cream may be effective.

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PSEUDOXANTHOMA ELASTICUM

Pseudoxanthoma elasticum (PXE) is an inherited disorder involving the connective tissue of the skin, eye, and cardiovascular system. Many cases appear to be sporadic. In familial cases, both a recessive and a dominant inheritance pattern

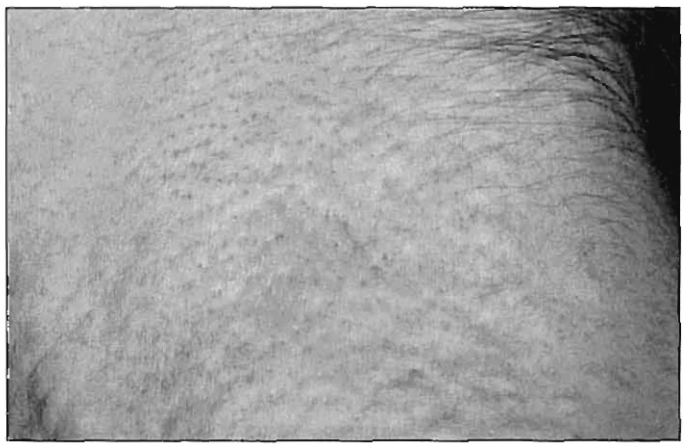

Fig. 25-2 Pseudoxanthoma elasticum.

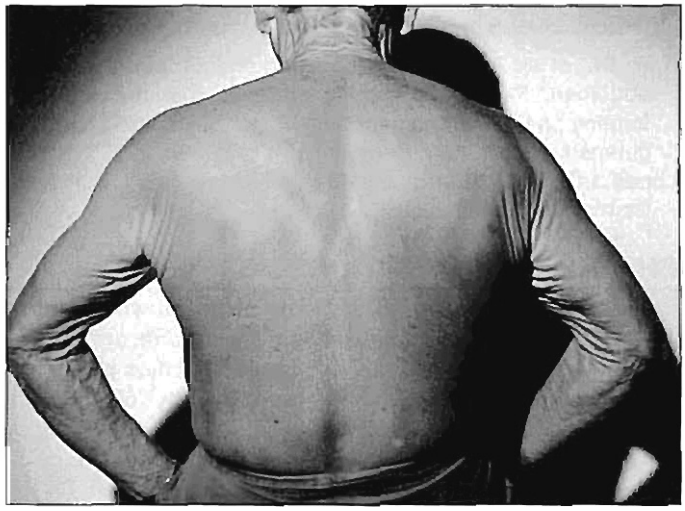

Fig. 25-3 Pseudoxanthoma elasticum.

have been reported, with the recessive form apparently more common. The skin changes generally present as small, circumscribed, yellow to cream-colored papules on the sides of the neck and flexures, giving the skin a "plucked chicken skin" appearance (Fig. 25-2). Lax, redundant folds of skin may be present (Fig. 25-3). Nuchal comedones and milia en plaque may also be seen. Characteristic exaggerated nasolabial folds and mental creases are common. Mental creases appearing in patients under the age of 30 years are highly suggestive of PXE. In addition, the inguinal, periumbilical, and periauricular skin, as well as the mucosa of the soft palate, inner lip, stomach, rectum, and vagina may be involved.

The characteristic retinal change is the angioid streak, which is the result of breaks in Bruch's elastic membrane. PXE can be demonstrated in more than half of patients with angioid streaks, and 85% of PXE patients will have retinal findings. The angioid streaks appear earlier than the skin changes, so that most cases are discovered by ophthalmologists. Angioid streaks may be the only sign of the disease for years. In such patients biopsies of the midportions of old scars may be diagnostic of PXE. The association of the skin lesions with angioid streaks is called *Grönblad-Strandberg syndrome*. Angioid streaks may also be seen in Ehlers-Danlos syndrome, Paget's disease of bone, diabetes, hemochromatosis, hemolytic anemia, hypercalcinosis, solar elastosis, neurofibromatosis, Sturge-Weber syndrome, tuberous sclerosis, myopia, sickle-cell anemia, trauma, lead poisoning, hyperphosphatemia, pituitary disorders, and intracranial disorders. PXE, Paget's disease of the bone, and sickle-cell disease account for the vast majority of patients with angioid streaks.

On funduscopic examination a reddish-brown band is evident around the optic disk, from which glistening streaks extend. With fluorescent photography early fluorescence of the angioid streaks and macular lesions are noted. In addition, there may be hemorrhages and exudates. Progressive loss of vision often starts after minor trauma to the eye. Drusen-like spots are commonly present, and show increased autofluorescence, unlike age-related drusen.

Vascular involvement commonly leads to hemorrhage. These vascular events are caused by the degeneration of the elastic fibers in the vascular media. Gastric hemorrhage occurs in 10% of patients, and viewed by gastroscopy diffuse rather than focal bleeding is common. Epistaxis occurs frequently, but hematuria is rare. PXE affects the elastic tissue of the cardiac valves, myocardium, and pericardium. In one study, mitral valve prolapse was found in 71% of 14 patients examined. Hypertension occurs in many patients older than age 30. Any patient with hypertension at a young age should be examined for stigmata of PXE. Leg cramps and intermittent claudication occur prematurely, and peripheral pulses are diminished or absent. Calcification of peripheral arteries is seen in many patients over age 30 and may be detected by radiograph. Accelerated coronary artery disease can occur, especially in association with hypertension.

Mutations in the ABCC6 gene on the short arm of chromosome 16 have been implicated in the pathogenesis of pseudoxanthoma elasticum. ABCC6 encodes an ATP-binding cassette transporter and multidrug resistance protein. Although the most prominent manifestations of the disease are in the skin, eye, gut, and heart, mineralization of elastic fibers can be found in many organs.

Histologically, elastic fibers are fragmented and mineralized with calcium. They stain gray–blue with hematoxylin and eosin (H&E), and are twisted, curled, and broken, suggesting "raveled wool." Blind biopsies of scars or axillary skin in patients with a family history of PXE or with angioid streaks may sometimes show early changes of PXE. Calcium stains are helpful in identifying early disease.

The differential diagnosis includes PXE-like papillary dermal elastolysis, perforating calcific elastosis, and cutis laxa. Patients with PXE-like papillary dermal elastolysis may have cobble-stoned, yellow papules on the neck, similar to PXE, but lack any retinal or vascular alterations and the typical fragmentation of elastic fibers with calcium deposition on histology. Penicillamine may induce similar clinical and histologic features in patients with Wilson's disease or homocystinuria.

No definitive therapy is available. Some data suggest that patients benefit from limiting dietary calcium and phosphorus to the minimal daily requirement.

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PERFORATING CALCIFIC ELASTOSIS

Also known as *periumbilical perforating PXE* and *localized acquired cutaneous PXE*, perforating calcific elastosis is an acquired, localized cutaneous disorder, most frequently found in obese, multiparous, middle-aged women. Lax, well-circumscribed, reticulated or cobble-stoned plaques occur in the periumbilical region with keratotic surface papules. It is a distinct disorder that shares some features of PXE. Like PXE there may be calcific elastosis in the mid-dermis; however, hereditary PXE rarely causes perforating channels. None of the systemic features of PXE occurs in perforating calcific elastosis.

It is suggested that repeated trauma of pregnancy, obesity, and/or abdominal surgery promotes elastic fiber degeneration, resulting in localized disease. PXE can cause periumbilical lesions, and in the absence of documented perforation, evaluations to exclude PXE should be performed. There is no effective therapy.

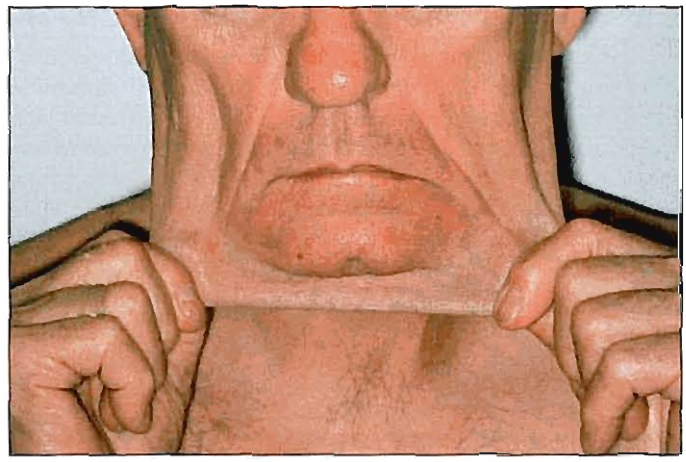

Fig. 25-4 Ehlers-Danlos syndrome.

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EHLERS-DANLOS SYNDROMES

Ehlers-Danlos syndromes (EDSs), also known as *cutis hyperelastica, India rubber skin*, and *elastic skin*, are a group of genetically distinct connective tissue disorders characterized by excessive stretchability and fragility of the skin (Fig. 25-4) with hyperextensibility of the joints, and a tendency toward easy scar formation and formation of fibrous or calcified pseudotumors. Atrophic scarring on the distal fingers

Table 25-2 Features of Ehlers-Danlos syndromes

Ehlers-Danlos type	Gene	Inheritance*	Molecular abnormality	Clinical features
I	COL5A1–2†	AD	Type V collagen	Gravis type: joint laxity, skin hyperextensibility
II	COL5A1–2	AD	Type V collagen	Mitis type: same as EDS 1 but less severe
III	TNXB haploid	AD	Unknown	Hypermobility
IV	COL3A1	AD AR	Type III procollagen	Thin skin, bruising, ruptured blood vessels and viscera
V			Unknown	Skin hyperextensibility, easy bruising
V1	LH1, PLOD	AR	Lysyl hydroxylase deficiency	Severe eye defects and scoliosis
VIIA, VIIB	COL1A1–2	AD	Type I procollagen	Arthrochalasis, subluxations, moderate skin stretchability
VIIC		AR	Procollagen peptidase deficiency	Dermatosparaxis, severe stretchability, redundant skin
VIII	Heterogenous, only some map to chromosome 12p13	AD	Unknown	Same as EDS types I and II, periodontitis
Old-type IX, reclassified as a variant of Menkes' disease/occipital horn syndrome	ATP7A	X-linked	Lysyl oxidase	Abnormal facies, skeletal abnormalities including occipital horns, chronic diarrhea, and genitourinary abnormalities
X (new-type IX)		AR	Fibronectin	Bruising
Old-type XI (new-type X)				Familial joint hypermobility syndrome Relationship to EDS unclear

*AD, autosomal dominant; AR, autosomal recessive.
†COL5A1-2 means COL5A1 and COL5A2 genes.

and wide atrophic "fish mouth" scars are typical. Patients demonstrate reduced thickness of the dermis as determined by high-resolution 20-MHz ultrasound. The reduction in thickness is most marked on the chest and distal lower leg. Classically, EDS has been divided into 10 numeric types, the salient features of which are listed in Table 25-2. Type IX EDS, an allelic variant of Menkes' disease, is now reclassified as the *occipital horn syndrome* and is identical to X-linked cutis laxa. It is related to mutations in an X-linked gene, ATP7A.

Types I, II, III, V, VII, and VIII EDS have hyperextensible skin. In these patients, the integument may be stretched out like a rubber band and snaps back with equal resilience. This rubbery skin is most pronounced on the elbows, neck, and sides of the abdomen. The skin is velvety in appearance and feels like wet chamois cloth. Minor trauma may produce a gaping "fish-mouth" wound with large hematomas underneath. The subcutaneous calcifications are 2- to 8-mm oval nodules, mostly on the legs. Two types of nodules occur in patients with EDS. Molluscoid pseudotumors are soft, fleshy nodules seen in easily traumatized areas such as the ulnar forearms and shins. Spheroids are hard subcutaneous nodules that become calcified. They are probably the result of fat necrosis. Trauma over the shins, knees, hands, and elbows produces cigarette-paper-thin scars. Approximately 50% of these patients can touch the tip of the nose with their tongue (Gorlin's sign), compared with 10% of persons without the disorder. Aortic root dilation is seen in up to 20% of patients with EDS. It is more common in types I and II than in type III.

Patients with type IV EDS have thin, translucent skin, characteristic facial features, and vascular fragility. They are prone to arterial rupture and often have extensive bruising. Perforations of the intestines and uterus may occur. Atlanto-axial subluxation has been noted. Protein analysis of collagen III in cultured fibroblasts usually shows a defect. Some type IV patients demonstrate no abnormalities of collagen III, although a mutation in the COL3A1 gene is identified. Type V patients have clinical features that are similar to the Gravis/Mitis form. Patients with type VI EDS may have microcornea, retinal detachment, and glaucoma, as well as scoliosis. In normal individuals, the ratio of hydroxylysylpyridinoline (HP) to lysylpyridinoline (LP) in urine is about 10:1. In patients with type VI EDS, the HP/LP ratio is reduced, ranging from 1:3 to 1:7.

In type VIIA and VIIB EDS there is marked joint hypermobility and moderate cutaneous elasticity. Joint dislocations of the large joints, such as the hips, are common. Type VIIC EDS, the autosomal-recessive form, is referred to as *dermatosparaxis*. Patients with this type have severe skin fragility and sagging, redundant skin. Type VIII EDS manifests as periodontitis as well as easy bruising. When type IX EDS was redefined as a variant of Menkes syndrome, old-type X EDS was reclassified by some authors as new type IX. It is characterized by hypermobile joints, easy bruising, fish-mouth scars, mitral valve prolapse, and platelets resistant to aggregation with collagen and adenosine diphosphate (ADP) reagents. A qualitative deficiency of fibronectin was the suggested cause, although never confirmed. Since the deletion of old-type IX, old-type XI has been reclassified by some as new-type X, or the familial joint hypermobility syndrome.

Because of the confusion concerning the numbered types, an alternate classification scheme has been proposed that groups EDS by associated signs and symptoms, as well as known genetic mutations. This new classification combines numeric types I and II because they share the same mutations (Box 25.1).

Box 25-1 New classification for Ehlers-Danlos syndrome (EDS)

1. Classic type (Gravis—EDS type I, and Mitis II)*
2. Hypermobility type (hypermobile—EDS III)
3. Vascular types (arterial-ecchymotic—EDS type IV, Qatarian EDS)†
4. Kyphoscoliosis type (ocular-scoliotic—EDS type VI)
5. Arthrochalasia type (arthrochalasis multiplex congenita—EDS type VIIA and VIIB)
6. Dermatosparaxis type (human dermatosparaxis—EDS type VIIC)
7. Miscellaneous forms (X-linked—EDS type V, periodontitis; EDS type VIII, fibronectin-deficient EDS; EDS type X, familial hypermobility syndrome [formerly EDS type XI]; progeroid EDS; and unspecified forms). Some progeroid EDS is related to galactosyltransferase I deficiency.

*Mutations in the genes for collagen α1(V) chain (COL5A1), collagen α2(V) chain (COL5A2), tenascin-X (TNX), and collagen α1(I) chain (COL1A1) have been characterized in patients with classical EDS. All are autosomal dominant, except the tenascin-X-related type, which is autosomal recessive.

†A distinct vascular type of EDS was described in an extended family in Qatar. Features of the syndrome include skin hyperextensibility, joint hypermobility, tortuous systemic arteries, epicanthic folds, flat saggy cheeks, elongated faces, micrognathia, hernias, an elongated aortic arch, aortic aneurysms, bifid pulmonary artery, pulmonic stenosis, hypotonia, and arterial rupture. Linkage to the major loci of other types of EDS was excluded.

Histology

Collagen fibers may appear fine. Factor XIIIa-positive dermal dendrocytes may be markedly reduced in the adventitial dermis and almost absent in the reticular dermis.

Treatment

Patients must be counseled to avoid trauma. Intestinal perforations in EDS type IV have been managed with porcine small intestinal submucosa grafts. Matrix metalloproteinase inhibitors produce changes in connective tissue, and are being evaluated as possible therapeutic agents.

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MARFAN SYNDROME

Marfan syndrome is an autosomal-dominant disorder of connective tissue caused by mutations in the gene encoding fibrillin-1. It is one of the more common inherited diseases, with estimated incidence rates of 1 in 10,000 in the US. Among the important abnormalities are tall stature, loose-jointedness, a dolichocephalic skull, high-arched palate, arachnodactyly, pigeon breast, pes planus, poor muscle tone, and large, deformed ears. The aorta, chordae tendineae, and aortic and mitral valves are often involved. Ascending aortic aneurysm and mitral valve prolapse are commonly seen. Ectopia lentis, extensive striae over the hips and shoulders, dental anomalies, and, rarely, elastosis perforans serpiginosa have been reported. Several cases document the occasional occurrence of spontaneous pneumothorax and congenital lung abnormalities.

Marfan syndrome is caused by a gene defect localized to chromosome 15 and producing abnormal elastic tissue in fibrillin 1 (aorta adventitia, the suspending ligaments of the lens, skin) and fibrillin 2 (elastin orientation in cartilage, aortic media, bronchi, and all tissues rich in elastin). Gene defects include substitutions, deletions, duplication missense, frameshift, splice site, and nonsense mutations. Ectopia lentis is more common in patients whose mutations involve a cysteine substitution in the gene for fibrillin 1, and less prevalent in those with premature termination mutations.

Death may result from aortic root aneurysm rupture or dissection. Echocardiography is helpful for early detection of cardiovascular involvement. Surgical intervention may be required for aneurysms of the aortic root or for aortic dissection. Long-term administration of propranolol may significantly reduce the rate of aortic dilatation. Antisense ribozymes are promising for gene therapy.

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HOMOCYSTINURIA

Homocystinuria, an inborn error in the metabolism of methionine, is characterized by the presence of homocystine in the urine and deficiency of the enzyme cystathionine synthetase. Cystathionine β-synthase is a heme-containing enzyme that catalyses pyridoxal 5′-phosphate-dependent conversion of serine and homocysteine to cystathionine. Over 130 gene mutations have been described. The defect results in increased levels of homocysteine and methionine, and decreased levels of cysteine. The incidence of the disorder varies from 1 in 344,000 worldwide to 1 in 65,000 in Ireland where the disorder is more common. Among the signs of homocystinuria are ectopia lentis, genu valgum, kyphoscoliosis, pigeon breast deformity, and frequent fractures. Generalized osteoporosis, arterial and venous thrombosis, and mental retardation are features of homocystinuria not found in Marfan syndrome. Half of all patients will have a serious vascular event before the age of 30, and 25% experience a serious event before the age of 16.

The facial skin has a characteristic flush, especially on the malar areas, and the color has a tendency to become violaceous when the patient is reclining. Elsewhere the skin is blotchy red, suggestive of livedo reticularis. The hair is typically fine, sparse, and blond, and the teeth are irregularly aligned. Downward dislocation of the lens, as opposed to the upward displacement seen in Marfan syndrome, is a prominent feature. Treatment with pyridoxine, folic acid, and vitamin B_{12} produces variable results. A methionine-restricted, cysteine-supplemented diet is generally recommended. Unfortunately, some methionine-free baby formulas contain significant amounts of homocysteine and should be reformulated. Betaine supplementation has been shown to be effective. Wheat flour is rich in betaine, but the amounts ingested are smaller than those needed to treat the disease. It has been recommended that methionine-free formulas be supplemented with 150 mg/dL of betaine. Alfalfa and bean sprouts contain ample homocysteine, and excessive amounts should be avoided. Other vegetables do not contain large amounts of homocysteine. Vitamin C ameliorates endothelial dysfunction, and the effect appears to be independent of homocysteine concentration. Some of the beneficial effects of folate are also independent of homocysteine lowering.

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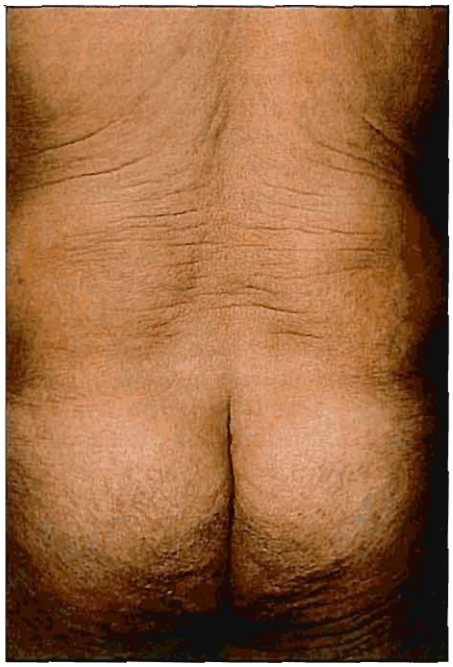

Fig. 25-5 Cutis laxa.

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CUTIS LAXA (GENERALIZED ELASTOLYSIS)

Cutis laxa, also known as *dermatomegaly*, *dermatolysis*, *chalazoderma*, and *pachydermatocele*, is characterized by inelastic loose, redundant skin (Fig. 25-5). Around the eyelids, cheeks, and neck the drooping skin produces a bloodhound-like facies. Usually the entire integument is involved. The shoulder girdle skin may look like that of a St Bernard dog. The abdomen is frequently the site of large, pendulous folds.

There are two well-described genetic forms of cutis laxa, the autosomal-dominant and -recessive types. The dominant form is primarily a cutaneous, cosmetic form, with a good prognosis. The recessive form is more common, and is associated with significant internal involvement, including hernias, diverticula, pulmonary emphysema, cor pulmonale, aortic aneurysm, dental caries, large fontanelles, and osteoporosis. Pulmonary emphysema, cor pulmonale, and right-sided heart failure are often seen already in infancy. Frameshift mutations in the elastin gene have been reported in autosomal-dominant disease. Both homozygous and heterozygous missense mutations in the fibulin-5 gene have been reported in some patients with the disease, especially in families with the recessive form. X-linked recessive cutis laxa is now known as the *occipital horn syndrome* (formerly type IX EDS). It is caused by a mutation in the copper-binding ion transporting ATPase, ATP7A, and is allelic to another X-linked disorder, Menkes' disease. Nonfamilial cases (Fig. 25-6) have been associated with urticaria, lupus erythematosus, glomerulonephritis, plasma cell dyscrasias, and systemic amyloidosis. These acquired cases may have a preceding inflammatory phase with large numbers of interstitial neutrophils, eosinophils, or macrophages engulfing

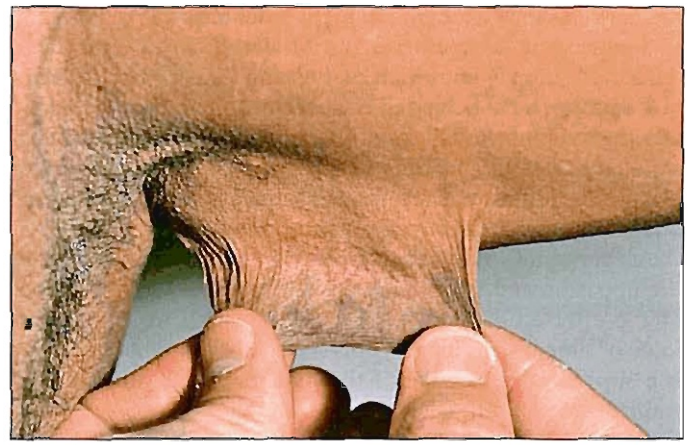

Fig. 25-6 Acquired cutis laxa.

elastic fibers. Isolated acral disease has been associated with myeloma and rheumatoid arthritis.

The Costello syndrome is characterized by increased prenatal growth, postnatal growth retardation, coarse facies, loose skin that resembles cutis laxa, cardiomyopathy, and gregarious personality. Patients are predisposed to abdominal and pelvic rhabdomyosarcoma in childhood. The disorder appears to be inherited as an autosomal-dominant trait.

The de Barsy syndrome is associated with severe cutis laxa, mental and growth retardation, joint laxity, ocular abnormalities, and skeletal disease.

Mid-dermal elastolysis is an acquired, noninherited condition that usually affects young women. Wide areas of skin demonstrate atrophic wrinkling. Histologically, elastic tissue is absent from the mid-dermis. Many cases appear to be induced or aggravated by ultraviolet light exposure.

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BLEPHAROCHALASIS

In blepharochalasis the eyelid skin becomes lax and falls in redundant folds over the lid margins. The condition may affect young adults, where a preceding inflammatory phase presents with episodes of lid swelling. Most cases are bilateral, but unilateral involvement may occur. Rarely, elastolysis of

the earlobes may accompany blepharochalasis. It is generally sporadic, but a dominantly inherited form has been described. Biopsy shows lack of elastic fibers, and abundant IgA deposits have been demonstrated in some cases, possibly binding to fibulin and fibronectin. Sequelae include excess thin skin, fat herniation, lacrimal gland prolapse, ptosis, blepharophimosis, pseudoepicanthic fold, proptosis, conjunctival injection and cysts, entropion, and ectropion.

Ascher syndrome consists of progressive enlargement of the upper lip and blepharochalasis. The minor salivary glands of the affected areas are inflamed, resulting in superfluous folds of mucosa, giving the appearance of a double lip. There is a superficial resemblance to angioedema. Treatment is by surgical correction.

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Schaeppi H, et al: Unilateral blepharochalasis with IgA-deposits. Hautarzt 2002;53:613.

ANETODERMA (MACULAR ATROPHY)

Anetoderma is characterized by localized loss of elastic tissue resulting in herniation of subcutaneous tissue. The lesions protrude from the skin (Fig. 25-7), and on palpation have less resistance than the surrounding skin, producing the "button hole" sign identical to a neurofibroma. The surface skin may be slightly shiny, white, and crinkly. The usual locations are the trunk, especially on the shoulders, upper arms, and thighs. The intervening skin is normal.

Up to half of cases have an accompanying abnormality, such as lupus, antiphospholipid antibodies, Graves' disease, scleroderma, hypocomplementemia, hypergammaglobulinemia, autoimmune hemolysis, and infection with the human immunodeficiency virus (HIV). Screening for antiphospholipid antibodies is of particular importance, as they may produce a prothrombotic state, and some patients fulfill criteria for the antiphospholipid syndrome. The antibodies may be detected as anticardiolipin antibodies, anti-β2-glycoprotein-I antibodies or a lupus anticoagulant. Patients may experience recurrent fetal loss, recurrent stokes, or recurrent deep vein thrombosis. Some cases of anetoderma may be related to borreliosis. Rare familial cases have been noted. Secondary anetoderma may be related to previous lesions of acne, secondary syphilis, measles, lupus erythematosus, leprosy, sarcoidosis, tuberous xanthoma, varicella, and lymphoreticular malignancy.

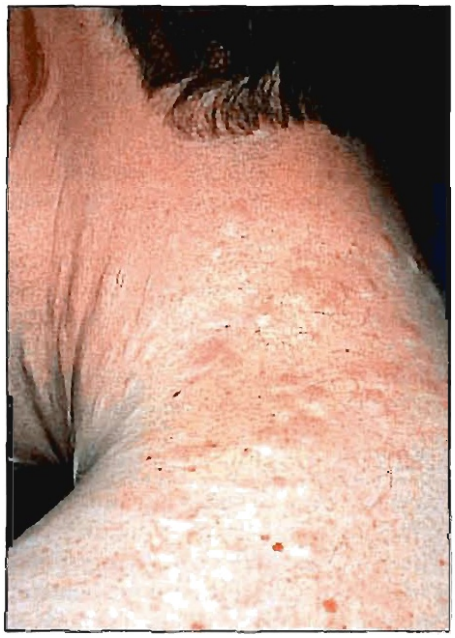

Fig. 25-7
Anetoderma.

Anetoderma of prematurity (congenital anetoderma) occurs in premature infants and may be related to pressure, adhesives, or changes in flow of ions or water under monitor leads. Intrauterine borreliosis has also been implicated.

Histologically, a loss of elastic tissue is noted with special stains. In the late stage, the skin looks normal in H&E sections. In the acute stage, a neutrophilic, lymphoid or granulomatous response may be noted.

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STRIAE DISTENSAE

Striae distensae are depressed lines or bands of thin, reddened skin, which later become white, smooth, shiny, and depressed. Elastotic striae have a yellow-gold iridescent appearance. Striae occur in response to changes in weight or muscle mass and skin tension, such as that induced by weight lifting. They are common on the abdomen during and after pregnancy (striae gravidarum) and on the breasts after lactation. They also occur on the buttocks and thighs, the inguinal areas, and over the knees and elbows in children during the growth spurt of puberty. Cushing syndrome, either endogenous or induced by systemic steroid treatment, is a frequent cause of striae, and they may occur after application of potent topical corticosteroid preparations, especially under occlusion or in folds. Striae are common in patients with Marfan syndrome.

The histologic findings are variable and depend on the stage of development. In some early lesions, perivascular and interstitial infiltration of lymphocytes and sometimes eosinophils is noted. In older lesions the primary changes are in the connective tissue. The collagen of the upper dermis is decreased, and thin collagen bundles lie parallel to the overlying epidermis as in a scar. Elastic tissue often appears increased, but this may be due to a loss of collagen in many cases. Dilated upper dermal vessels may be prominent.

Over time striae become less noticeable. Topical tretinoin and vascular lasers may produce some improvement in

Fig. 25-8 Linear focal elastosis on the lower back of an elderly man.

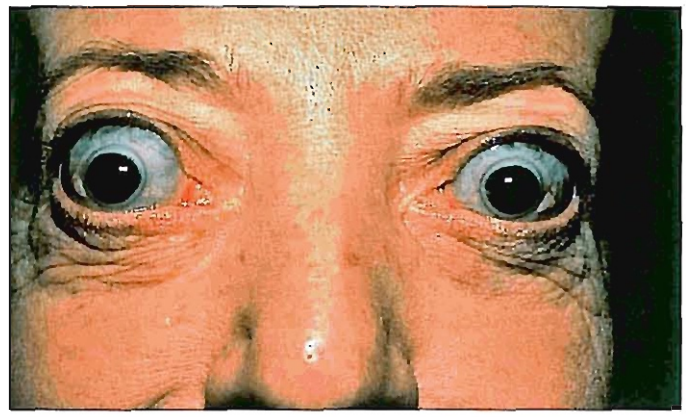

Fig. 25-9 Blue sclera of osteogenesis imperfecta in a patient with Grave's disease. (Courtesy Lawrence Lieblich)

appearance, although the benefits are more marked in the early erythematous phase. Lasers (585 nm) result in a moderate decrease in erythema in striae rubra. Although the total collagen per gram of dry weight increases in striae treated with pulsed dye laser, this change may not result in a clinically evidenced change in striae alba. Intense pulsed light has also demonstrated potential for improvement in the appearance of some striae, although darker skin types have greater risk and lower efficacy.

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LINEAR FOCAL ELASTOSIS (ELASTOTIC STRIAE)

This variant presents with asymptomatic, palpable or atrophic, yellow lines (Fig. 25-8) of the middle and lower back, thighs, arms and breasts. The condition is more common in males. Histologically, there are increased elastic fibers characterized by thin, wavy, elongated, as well as fragmented, elastic fiber bundles. Electron microscopy reveals elongated thin, irregular shaped, swollen elastic fibers with degenerative changes.

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ACRODERMATITIS CHRONICA ATROPHICANS

Patients with acrodermatitis chronica atrophicans present with diffuse thinning of the skin on the extremities, sometimes associated with fibrous bands. It is reviewed in Chapter 14, since it results from infection with *Borrelia*.

OSTEOGENESIS IMPERFECTA

Osteogenesis imperfecta (OI), also known as *Lobstein syndrome*, affects the bones, joints, eyes, ears, and skin. It is estimated to affect approximately 10,000 persons in the US (4–5 in 100,000). There are seven recognized forms based on differences in clinical presentation and bone architecture. Types I and IV have only an autosomal-dominant inheritance, whereas types II and III have both autosomal-dominant and autosomal-recessive forms. Fifty percent of OI patients have the type I form. The type II form is lethal, and deaths usually occur within the first week of life.

The brittle bones result from a defect in the collagenous matrix. Fractures occur early in life, sometimes in utero. Loose-jointedness may be striking, and dislocation of joints can be a problem. Blue sclerae, when present, are a valuable diagnostic clue (Fig. 25-9). Scoliosis and defective teeth may be present. Deafness develops in many by the second decade of life and is audiologically indistinguishable from otosclerosis. The skin is thin and translucent, and healing wounds result in spreading atrophic scars. Elastosis perforans serpiginosa may occur. Some patients experience unusual bruisability, probably due to a structural defect in either the blood vessel wall or the supporting dermal connective tissue.

The basic defect is abnormal collagen synthesis, resulting in type I collagen of abnormal structure. Most forms of OI result from mutations in the genes for the proα1or proα2 chains of type I collagen. Types V, VI, and VII are not associated with type I collagen gene defects. In type I (blue scleral dominant) there is diminished type I collagen with a mutation of COL1A1 gene; in type II (perinatal lethal) there is diminished type I collagen synthesis and decreased integrity of the helical domain of the α1 (I) gene; in type III (progressive deforming) there is delayed secretion of type I collagen with altered mannosylation; and in type IV (white sclerae dominant) there is a defective proα1 (I) gene.

The major causes of death, attributed to OI, are respiratory failure secondary to severe kyphoscoliosis and head trauma, mostly observed in type III disease. Patients with type I and type IV disease have a normal lifespan. Brack

syndrome is a combination of osteogenesis imperfecta and arthrogryposis multiplex.

Treatment includes surgical intervention, such as intramedullarly stabilization. Bisphosphonates and calcitriol are the most effective pharmacologic agents. Specifically, cyclical pamidronate therapy has been shown to suppress bone turnover, reduce bone pain and fracture incidence, and increase bone density and level of ambulation. Gene therapy is promising, but is complicated by the genetic heterogeneity of the disease. Most of the OI mutations result in a mutant allele product that interferes with the function of the normal allele. This sort of abnormality presents greater challenges for gene therapy than simple replacement of a missing enzyme.

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CHAPTER

26 Errors in Metabolism

Amyloid is a material deposited in the skin and other organs that is eosinophilic, homogeneous, and hyaline in appearance. It represents beta-pleated sheet forms of various host-synthesized molecules processed into this configuration by host cells.

Amyloidosis can be classified as primary (which often has skin manifestations), secondary (which has very rare skin manifestations), primary localized amyloidosis (also called *primary cutaneous amyloidosis* when the skin is affected), and secondary cutaneous or tumor-associated amyloidosis. Rare familial syndromes may be complicated by secondary amyloidosis or have genetic defects that lead to amyloid deposition (heredofamilial amyloidosis). Classification of cutaneous amyloidoses is shown below.

I. Systemic amyloidosis
   A. Primary (myeloma-associated) systemic amyloidosis
   B. Secondary systemic amyloidosis
II. Cutaneous amyloidosis
   A. Macular amyloidosis
   B. Lichen amyloidosis
   C. Nodular amyloidosis
   D. Secondary (tumor-associated) cutaneous amyloidosis
III. Heredofamilial amyloidosis

All forms of amyloid have relatively identical histologic and electron microscopic findings. The amyloid in all forms is made up of three distinct components: protein-derived amyloid fibers, amyloid P component (about 15% of amyloid), and ground substance. It is the protein-derived amyloid fibers that differ among the various forms of amyloid.

Amyloid is weakly periodic acid-Schiff (PAS) positive and diastase resistant, Congo-red positive, purple with crystal violet, and positive with thioflavin T. Amyloid stained with Congo red exhibits apple-green birefringence under polarized light. Secondary systemic amyloid (AA amyloid) loses its birefringence after treatment with potassium permanganate, whereas primary and localized cutaneous forms do not.

Amyloid stains an intense, bright orange with cotton dyes such as Pagoda red, RIT Scarlet No. 5, or RIT Cardinal red No. 9. Ultrastructurally, amyloid has a characteristic fibrillar structure that consists of straight, nonbranching, nonanastomosing, often irregularly arranged filaments 60 to 100 nm in diameter. If the type of amyloid is known, specific antibodies against the protein component can be used. Only 50% of cases of primary systemic amyloidosis stain with antisera to κ or λ chains, because the amyloid protein frequently contains only the variable portion of the immunoglobulin light chain. Because amyloid substance P is present in all forms of amyloid, immunoperoxidase staining against this component will stain all forms of amyloid. In addition, since serum amyloid P (SAP) is avidly bound to amyloid, radiolabeled highly purified SAP can be used to localize amyloidosis, determine the extent of organ infiltration, study progression of disease, and see if therapy reduces the amount of amyloid in various organs.

SYSTEMIC AMYLOIDOSES

Primary Systemic Amyloidosis

Primary systemic amyloidosis involves mesenchymal tissue, the tongue, heart, gastrointestinal tract, and skin. Cutaneous manifestations occur in approximately 40% of cases of primary systemic amyloidosis. Myeloma-associated amyloidosis is included in this category. The amyloid fibril proteins in primary systemic (so-called immunocytic or plasma cell dyscrasia-associated) amyloidosis are composed of protein AL. This is derived from the immunoglobulin light chains, usually of the λ subtype, and is often only a fragment of the light chain, particularly from the amino terminal end or variable region. Ninety percent of patients will also have this immunoglobulin fragment in the serum or urine. This same type of amyloid, AL, is also found in nodular or tumefactive cutaneous amyloidosis, which is best considered a localized plasmacytoma-producing amyloid.

In primary systemic amyloidosis, the cutaneous eruption usually begins as shiny, smooth, firm, flat-topped, or spherical papules of waxy color, which, because of their tenseness, have the appearance of translucent vesicles. These lesions coalesce to form nodules and plaques of various sizes and, in some cases, bandlike lesions. The regions about the eyes, nose, mouth, and mucocutaneous junctions are commonly involved. Vulvar lesions (Fig. 26-1) may resemble giant condylomata.

Purpuric lesions and ecchymoses occur in about 15% of patients and are the most common cutaneous manifestation of primary systemic amyloidosis. They result from amyloid infiltration of blood vessels. Purpura chiefly affects the eyelids, limbs, and oral cavity. Purpura typically occurs after trauma (pinch purpura). Purpuric lesions also classically appear after actions or procedures that result in increased pressure in the vessels of the face, such as after vomiting, coughing, proctoscopic examination, or pulmonary function testing.

Glossitis, with macroglossia, occurs in at least 20% of cases, may be an early symptom, and can lead to dysphagia. The tongue becomes greatly enlarged, and furrows develop (Fig. 26-2). The lateral aspects show indentations from the teeth. Papules or nodules, sometimes with hemorrhage, occur on the tongue.

Bullous amyloidosis is a rare but important clinical manifestation of amyloidosis. Skin fragility and tense, hemorrhagic bullae appear at areas of trauma, usually the hands, forearms, and feet. Lesions heal with scarring and milia. Histolo-

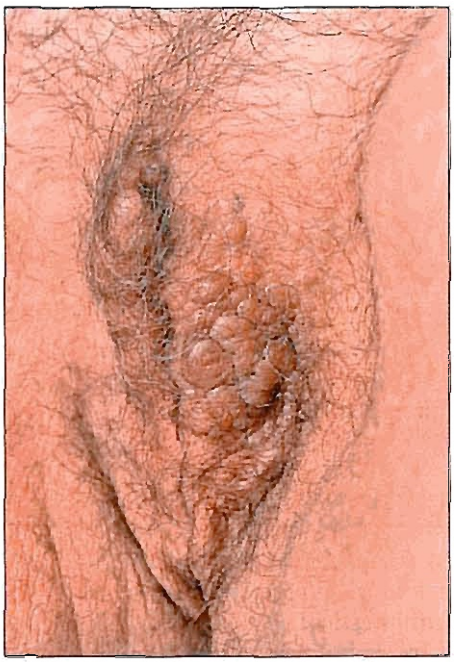

Fig. 26-1 Vulvar amyloid deposits.

gically, the lesions are subepidermal and pauci-inflammatory. Epidermolysis bullosa acquisita and porphyria cutanea tarda are the differential diagnoses. Amyloid staining may yield negative results, and direct immunofluorescence (DIF) may be falsely positive (because of AL protein deposition at the dermoepidermal junction). The diagnosis is confirmed by evaluation of the patient's serum and urine for immunoglobulin fragments and by electron microscopy of the skin biopsies, which will demonstrate the amyloid.

A diffuse or patchy alopecia, cutis verticis gyrata, a scleroderma-like, scleromyxedema-like, or a cutis laxa-like appearance have also rarely been described. Cutis laxa-like findings may be generalized or localized to the acral parts. The nail matrix may be infiltrated resulting in atrophy of the nail plate, presenting as longitudinal striae, partial anonychia, splitting, and crumbling of the nail plate. Cordlike thickening along blood vessels can also occur.

Patients may present with or develop a plethora of systemic findings. Most characteristically they develop carpal tunnel syndrome, other peripheral neuropathies, a rheumatoid arthritis-like arthropathy of the small joints, orthostatic hypotension, gastrointestinal bleeding, nephrotic syndrome, and cardiac disease. These patients may appear to have prominent deltoid muscles as a result of deposition of amyloid in the muscles (shoulder pad sign). Cardiac arrhythmias and congestive heart failure are common causes of death.

The prognosis for patients with primary systemic amyloidosis is poor. The median survival averages 43 months. Those presenting with neurologic findings survive longer than patients presenting with cardiac disease.

Treatment is improving but still relies heavily on systemic chemotherapy (usually melphalan). Secondary malignancies may complicate alkylating therapy. Hematopoetic stem cell transplantation after high-dose melphalan has led to remission in some patients.

Secondary Systemic Amyloidosis

Secondary systemic amyloidosis is amyloid involvement of the adrenals, liver, spleen, and kidney as a result of some

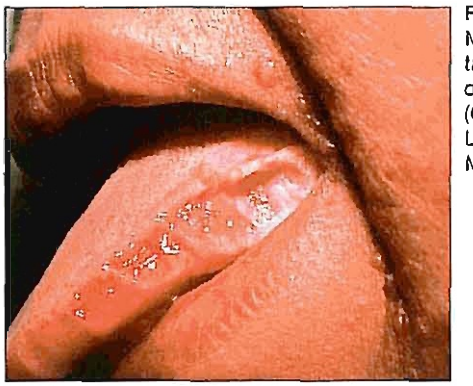

Fig. 26-2 Macroglossia and translucent papules of the tongue. (Courtesy of Lawrence Lieblich, MD)

chronic disease, such as tuberculosis, lepromatous leprosy, Hodgkin's disease, Behçet's disease, rheumatoid arthritis, ulcerative colitis, schistosomiasis, or syphilis. The parenchymatous organs are involved, but the skin is not. Certain dermatoses, such as hidradenitis suppurativa, stasis ulcers, psoriatic arthritis, and dystrophic epidermolysis bullosa may be complicated by systemic amyloidosis.

The amyloid fibrils in secondary systemic amyloidosis, and in the type associated with Muckle-Wells syndrome and with familial Mediterranean fever, are designated AA. The protein component is unrelated to immunoglobulin. Its precursor is serum amyloid A protein (SAA), which is an acute-phase reactant that is increased in various inflammatory states. Biopsy of normal skin in secondary systemic amyloidosis may be positive for perivascular amyloid in slightly more than half the cases. The treatment of secondary systemic amyloidosis is to treat the underlying condition optimally.

In patients undergoing hemodialysis, carpal tunnel syndrome is frequent; its prevalence is related to the duration of dialysis. This finding is now known to be associated with amyloid deposition in synovium, causing not only carpal tunnel syndrome but also trigger finger, bone cysts, and spondyloarthropathy. The protein component of dialysis-related amyloidosis is β2-microglobulin, altered by uremia.

CUTANEOUS AMYLOIDOSIS

Primary Cutaneous Amyloidosis

The primary cutaneous amyloidoses have been divided into two forms—macular and lichen amyloid. Most patients have only one form, but rarely, patients may be seen with both patterns. Chronic rubbing of the skin resulting from pruritus or the use of nylon brushes during bathing (frictional amyloidosis) appears contributory. Individuals of Asian, Hispanic, or Middle Eastern ancestry seem to be predisposed. The deposited amyloid material contains keratin as its protein component, strongly suggesting that traumatic damage to basal keratinocytes results in the deposits. Why only certain individuals are affected is unknown. A rare form localized to the conchae has been described.

The histologic picture of both forms of primary cutaneous amyloidosis is similar, the only difference being the size of the amyloid deposits and the extent of the overlying epidermal changes. The overlying epidermis is frequently hyperkeratotic. Focal necrotic keratinocytes may be observed in the basal cell layer. Dermal papillae are expanded by

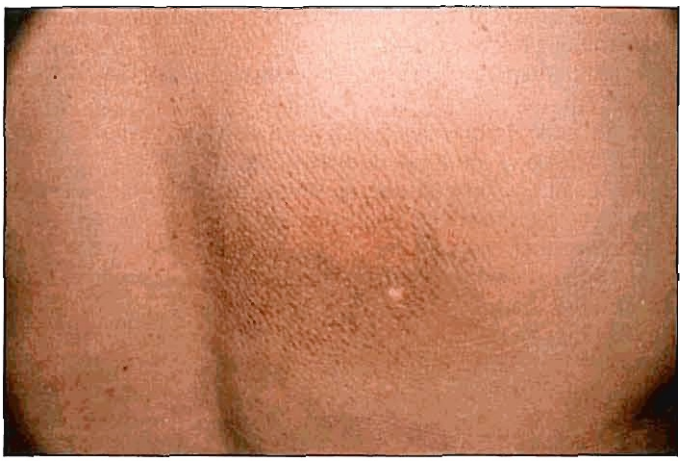

Fig. 26-3 Macular amyloid. (Courtesy of Lawrence Lieblich, MD)

amorphous deposits of amyloid that abut immediately below the epidermis. Melanin deposits are classically present in the amyloid. In all cases of postinflammatory hyperpigmentation with incontinence of pigment, the texture of the areas of dermal melanosis should be examined carefully to exclude amyloidosis. Systemic amyloidosis is excluded by the absence of amyloid deposits around blood vessels. Special stains may be used to confirm the diagnosis, but this is rarely required if the classic histology is found. In difficult cases, immunoperoxidase stains for keratin will stain the amyloid deposits and confirm the diagnosis of primary cutaneous amyloidosis. DIF may demonstrate immunoglobulin (usually IgM) in a globular pattern in the keratin-derived cutaneous amyloidoses, but this is caused by passive absorption rather than by specific deposition. This phenomenon is seen in all disorders with prominent apoptosis of keratinocytes.

Macular Amyloidosis Typical cases exhibit moderately pruritic, brown, rippled macules characteristically located in the interscapular region of the back (Fig. 26-3). Pigmentation is typically not uniform, giving the lesions a "salt and pepper" or rippled appearance. Notalgia paresthetica is localized to the same sites, and most cases of macular amyloid between the scapulae probably result from rubbing dysesthetic areas of notalgia paresthetica. Occasionally, the thighs, shins, arms, breasts, and buttocks may be involved, and these more diffuse cases are usually associated with diffuse pruritus. Macular amyloidosis is a chronic condition.

Lichen Amyloidosis Lichen amyloidosis is characterized by the appearance of paroxysmally itchy lichenoid papules, typically appearing bilaterally on the shins (Fig. 26-4). The primary lesions are small, brown, discrete, slightly scaly papules that group to form infiltrated large moniliform plaques. It may, less commonly, occur on the thighs, forearms, and even the upper back.

Treatment of the primary cutaneous amyloidoses is frequently unsatisfactory. Reducing friction to the skin is critical. Identifying the cause of the rubbing, whether it is habit, pruritus, or neuropathy (as in notalgia paresthetica), directs treatment. Occlusion plays a major role, because it both enhances topical treatments and provides a physical block to prevent trauma to the skin. Administration of topical high-potency corticosteroid agents can be beneficial, as can intralesional corticosteroid therapy when small areas are involved. Topical tacrolimus 0.1% ointment, PUVA, UVB, and calcipotriol benefit individual patients. Oral retinoids, cyclophosphamide, and dermabrasion have also been reported to be beneficial.

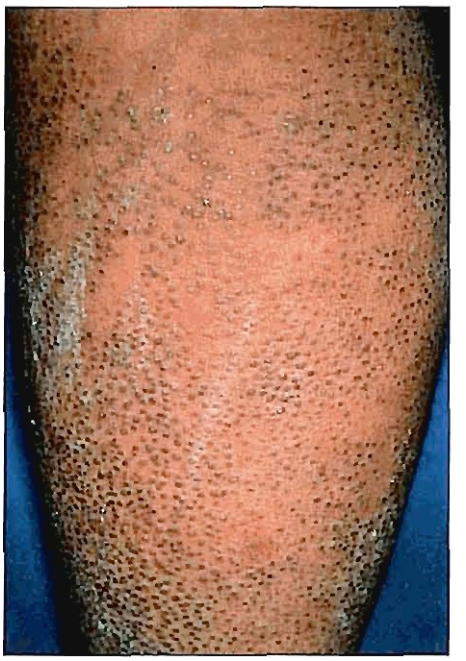

Fig. 26-4 Lichen amyloidosis.

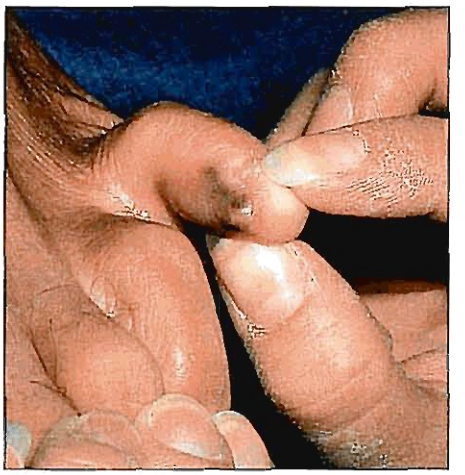

Fig. 26-5 Nodular amyloidosis.

Nodular Amyloidosis Nodular amyloidosis is a rare form of primary localized cutaneous amyloidosis in which single, or rarely, multiple nodules or tumefactions preferentially involve the acral areas (Fig. 26-5); however, trunk, genital, or facial lesions may be seen. The overlying epidermis may appear atrophic, and lesions may resemble large bullae. The dermis and subcutis may be diffusely infiltrated with amyloid. The lesions may contain numerous plasma cells and are best considered isolated plasmacytomas. The amyloid in these patients is immunoglobulin-derived AL, as is seen in primary systemic amyloidosis, and is unrelated to keratinocyte-related amyloid or to AA amyloid. Progression to systemic amyloidosis may occur, but is rare. Treatment is physical removal or destruction of the lesion with shave removal and desiccation or CO_2 laser.

Secondary Cutaneous Amyloidosis

Following PUVA therapy and in benign and malignant cutaneous neoplasms, deposits of amyloid may be found. Most frequently, the associated neoplasms are nonmelanoma skin cancers or seborrheic keratoses. In all cases, this is keratin-derived amyloid.

FAMILIAL SYNDROMES ASSOCIATED WITH AMYLOIDOSIS (HEREDOFAMILIAL AMYLOIDOSIS)

Familial syndromes have been reported that have either systemic or localized amyloidosis. In familial Mediterranean fever and Muckle-Wells syndrome, the amyloid protein is AA; these are hereditary inflammatory diseases commonly complicated by secondary systemic amyloidosis. Multiple endocrine neoplasia 2A (MEN 2A) and familial medullary thyroid carcinoma are genetic diseases caused by activating mutations of the RET protooncogene. Affected patients can manifest keratin-derived amyloid. Most commonly this is lichen amyloidosis with pruritus being present since infancy. MEN 2A should be considered when a child or adolescent presents with nostalgia paresthetica or macular or lichen amyloidosis. Family history, calcitonin, calcium, parathyroid hormone levels, and urinary catecholamines and metanephrines will screen for the associated problems and RET mutations may be assessed. Poikiloderma-like cutaneous amyloidosis and other very rare hereditary variants of cutaneous amyloidosis exist.

Most forms of familial amyloidosis, however, present with neurologic disease and are designated *familial amyloidotic polyneuropathy*. Peripheral neuropathy, and, less commonly, autonomic neuropathy and cardiomyopathy occur. Several types of hereditary amyloidoses have been identified: two forms are caused by genetic defects in transthyretin. These are autosomal-dominant syndromes, and most affected patients are heterozygotes. Others are caused by a genetic defects in apolipoprotein A-I or A-II, by a defect in gelsolin, fibrinogen A α, Cystatin C or lysozome.

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PORPHYRIAS

Porphyrinogens are the building blocks of all the hemoproteins, including hemoglobin and the cytochrome enzymes. They are produced primarily in the liver and bone marrow. In certain inherited and acquired disease states, called the *porphyrias*, these intermediate metabolites of hemoglobin synthesis are increased.

Each form of porphyria has now been associated with a deficiency in an enzyme in the metabolic pathway of heme synthesis. Cutaneous disease, characterized by photosensitivity, is observed in some forms of porphyria. The photosensitivity in porphyria is caused by the absorption of UV radiation in the Soret band (400–410 nm) by increased porphyrins. These activated porphyrins are unstable, and as they return to a ground state, they transfer energy to oxygen, creating reactive oxygen species. These unstable oxygen species interact with biologic systems, primarily plasma and lysosomal membranes, causing tissue damage. Mediators released from mast cells and polymorphonuclear leukocytes, acting through complement, eicosanoids, or factor XII pathways may augment tissue effects.

Understanding the biosynthetic pathway of heme has clarified the biochemical basis of the porphyrias. Delta-aminolevulinic acid (dALA) is synthesized in the mitochondria via dALA synthetase. From it are formed, successively, porphobilinogen, uroporphyrin III, coproporphyrin III, and protoporphyrin IX. This re-enters the mitochondrion, to be acted on by ferrochelatase to produce heme. Each step in this process is catalyzed by a specific enzyme. Heme, by negative feedback, represses the production, or activity, of dALA synthetase. If heme is inadequate, dALA synthetase activity may be increased, leading to the production of more porphyrins. Because this enzyme system is inducible, medications that increase the cytochrome drug metabolizing system in the liver can lead to exacerbation of the porphyrias by increasing the production of the porphyrin intermediates.

The current grouping of the porphyrias is based on the primary site of increased porphyrin production, either liver or bone marrow—the hepatic or erythropoietic porphyrias, respectively. Some include a hepatoerythropoietic category.

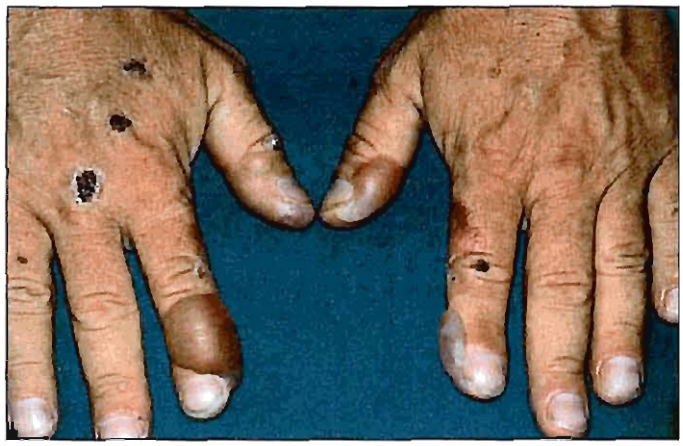

Fig. 26-6 Porphyria cutanea tarda.

Congenital erythropoietic porphyria, erythropoietic protoporphyria, and erythropoietic coproporphyria are the erythropoietic forms. Acute intermittent porphyria, ALA dehydratase deficiency, hereditary coproporphyria, variegate porphyria, and porphyria cutanea tarda are the hepatic forms. Hepatoerythrocytic porphyria has been classified as either a hepatic or hepatoerythropoietic type.

The porphyrias are diagnosed by identifying characteristic clinical and biochemical abnormalities, typically elevated levels of porphyrins in the urine, serum, red blood cell, or stool. Because there is some clinical overlap, biochemical testing should be performed to confirm any diagnosis of porphyria. The clinical syndromes may be chronic or have intermittent exacerbations with relative quiescent periods. The latter are called the *acute porphyrias*.

PORPHYRIA CUTANEA TARDA

Porphyria cutanea tarda (PCT) is the most common type of porphyria. It is characterized by photosensitivity resulting in bullae, especially on sun-exposed parts (Fig. 26-6). The dorsal hands and forearms, ears, and face are primarily affected. The bullae are not surrounded by erythema, and rupture easily to form erosions or shallow ulcers. These heal with scarring, milia, and dyspigmentation. Lesions on the legs, especially the shins and dorsal feet, occur primarily in women. In addition, patients frequently complain of skin fragility in affected areas. There is hyperpigmentation of the skin, especially of the face, neck, and hands. Hypertrichosis of the face, especially over the cheeks and temples, is seen. The face and neck, especially in the periorbital area, may show a pink to violaceous tint. Sclerodermatous thickenings may develop on the back of the neck, in the preauricular areas (Fig. 26-7), or on the thorax, fingers, and scalp. In the latter instance, there is associated alopecia. A direct relationship between the levels of uroporphyrins in the urine and sclerodermatous changes has been reported.

Liver disease is frequently present in patients with PCT. A history of alcoholism is common. Hepatitis C virus (HCV) infection has been found in 17% (Northern Europe), 20% (Australia/New Zealand), 65% (Southern Europe), and 94% (US) of patients with PCT. All PCT patients should be screened for HCV infection. Iron overload in the liver is frequently found in patients with PCT. This may be as a consequence of chemical or viral liver damage, or because 20% of patients with PCT are homozygous for the C282Y

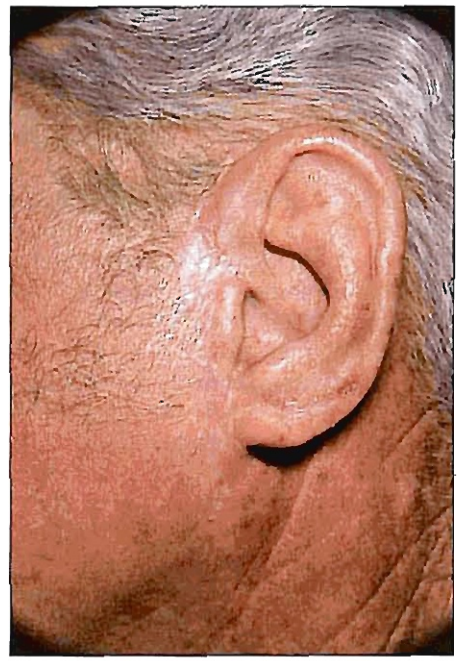

Fig. 26-7 Porphyria cutanea tarda with sclerosis.

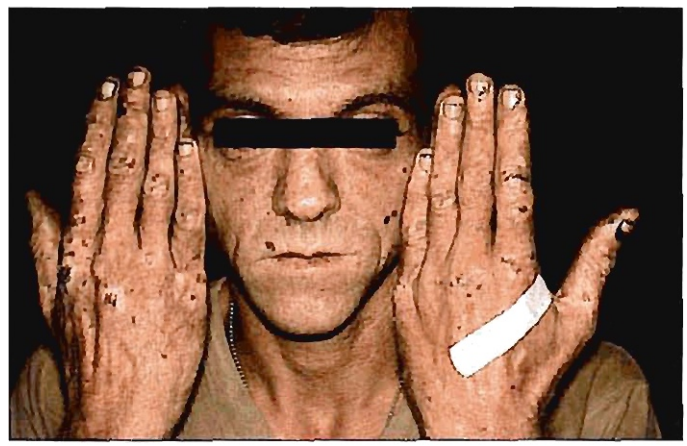

Fig. 26-8 Porphyria cutanea tarda with hemochromatosis. (Courtesy of Curt Samlaska, MD)

mutation (and a few with the H63D mutation) causing hemochromatosis (Fig. 26-8). This leads to increases in serum iron, ferratin, and hepatic iron overload. Hepatocellular carcinoma may rarely produce PCT.

PCT has been frequently associated with other diseases. It is estimated that diabetes mellitus occurs in 15% to 20% of patients with PCT. Numerous cases of lupus erythematosus concomitant with PCT have been reported. Patients may have systemic and/or purely cutaneous lupus, and either disease may present initially. The pathogenesis of this association is unclear.

PCT occurs not infrequently in patients infected with the human immunodeficiency virus (HIV). This is not solely related to coexistent HCV infection, which is increased in some risk groups of HIV-infected persons. Subtle porphyrin abnormalities are found in HIV disease, but the porphyrin levels are well below those capable of inducing clinical disease. Other risk factors, such as alcoholism, should be evaluated and the existence of PCT should not be attributed to the HIV disease alone. However, effective anti-HIV therapy has led to improvement of PCT in one HIV/HCV-infected patient.

Estrogen treatment is associated with the appearance of PCT by an unknown mechanism. Before oral contraceptives were introduced, PCT cases occurred predominantly among men, but in most recent series, 60% of cases occurred in men and 40% in women. Men treated with estrogens for prostate cancer may develop PCT.

PCT is caused by a deficiency in the enzyme uroporphyrinogen decarboxylase. Several types have been described. The most common is the sporadic, nonfamilial form, which represents about 80% or more of cases. Enzymatic activity of uroporphyrinogen decarboxylase is abnormal in the liver but normal in other tissues. With remission, the enzyme activity in the liver may return to normal. Patients present most commonly in midlife, averaging 45 years at disease onset.

The second, or familial type, is an autosomal-dominantly inherited deficiency of uroporphyrinogen decarboxylase in the liver and red blood cells of patients, and also of clinically unaffected family members. There is an approximate 50% decrease in both the activity and concentration of the enzyme. Multiple genetic defects have been reported producing the same phenotype. Familial PCT tends to present at an earlier age, and development of PCT before age 20 strongly suggests familial PCT. A third form, acquired toxic PCT, is associated with acute or chronic exposure to hepatotoxins, specifically polyhalogenated hydrocarbons, such as hexachlorobenzene and dioxin. These patients have biochemical and clinical features identical to those of patients with sporadic and familial PCT.

A diagnosis of PCT can be strongly suspected on clinical grounds. A useful confirmatory test that can be performed in the office is the characteristic pink or coral-red fluorescence of a random urine specimen under a Wood's light. A 24-h collected urine specimen usually contains less than 100 μg of porphyrins in a normal individual; in PCT it may range from 300 to several 1000 μg. The ratio of uroporphyrins-to-coproporphyrins in PCT is typically 3:1 to 5:1, distinguishing PCT from variegate porphyria.

Biopsy of a blister reveals a noninflammatory subepidermal bulla with an undulating, festooned base. PAS-positive thickening of blood vessel walls in the upper and mid-dermis is present. A useful and highly characteristic—but not diagnostic—feature is the presence of the so-called caterpillar bodies. These eosinophilic, elongated, wavy structures are present in the lower and mid-epidermis and lie parallel to the basement membrane zone. They stain positively with PAS and are positive for type IV collagen and laminin, suggesting they represent basement membrane material present in the epidermis. DIF of involved skin shows IgG and C3 at the dermoepidermal junction and in the vessel walls in a linear pattern.

Initial treatment of PCT involves removal of all precipitating environmental agents such as alcohol and medications. This may lead to sufficient improvement that further therapy is not required. Chemical sunscreens are of little value since they do not typically absorb radiation in the near-visible UVA range. Barrier sunscreens such as titanium dioxide and zinc oxide may be more beneficial, but physical barriers such as hats and gloves may be encouraged while therapy is initiated.

Phlebotomy is the treatment of choice for PCT. Uroporphyrinogen decarboxylase is inhibited by iron, and removal of hepatic iron may therefore lead to recovery of enzyme activity. Typically, phlebotomy of 500 mL at 2-week intervals is performed until the hemoglobin reaches 10 g/dL or the serum iron 50 to 60 μg/dL. Ideally, serum ferritin will become normal also. Urinary porphyrin excretion initially increases, but gradually, 24-h uroporphyrin levels are markedly reduced, with most patients able to achieve normal levels. This process takes several months, usually requiring a total of 6 to 10 phlebotomies. As the porphyrins fall, the skin lesions also involute. Initially, blistering improves, then skin fragility decreases, and finally the cutaneous sclerosis and hypertrichosis can eventually reverse. A common error in management is coadministration of oral iron supplementation during the phlebotomies to treat the anemia.

Antimalarials are an alternative to phlebotomy and may be combined with phlebotomy in difficult cases. Full doses of antimalarials may produce a severe hepatotoxic reaction. The initial dose is 125 mg of chloroquine twice a week. Improvement is gradual, but can be more rapid than phlebotomy.

After both phlebotomy and antimalarial therapy, a remission is induced that may last many years. If the patient relapses, these treatments can be repeated. Alternative treatments, which are rarely required, include desferrioxamine (iron chelation) and erythropoietin treatment. Erythropoietin may be combined with phlebotomy. PCT in renal failure may respond to erythropoietin and low volume phlebotomy or to renal transplantation. If HCV infection coexists, interferon-α treatment of the HCV infection may lead to improvement of the PCT.

PSEUDOPORPHYRIA

In certain settings patients develop blistering and skin fragility identical to PCT with the histologic features of PCT but with normal urine and serum porphyrins. Hypertrichosis, dyspigmentation, and cutaneous sclerosis do not occur. This condition is called *pseudoporphyria*. Most commonly this is caused by medications, typically a nonsteroidal anti-inflammatory drug (NSAID), usually naproxen. Other NSAIDs, such as nebumetone and rofecoxib, tetracycline (Fig. 26-9), and multiple other medications can cause a similar picture. Sunbed use can also cause pseudo-PCT. Some patients on hemodialysis develop a similar PCT-like picture.

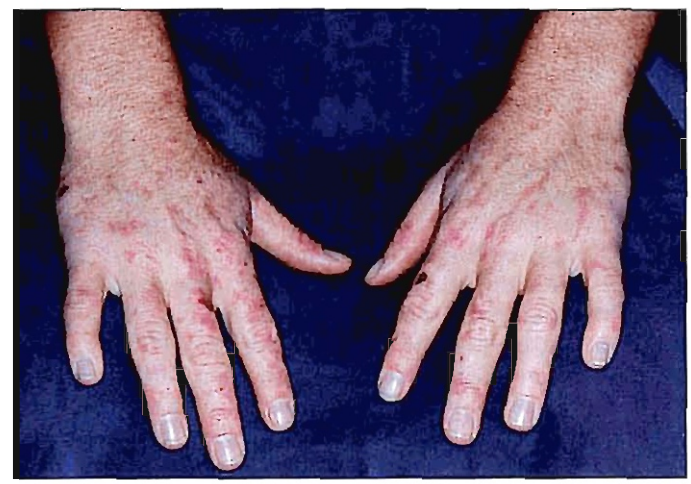

Fig. 26-9 Pseudoporphyria cutanea tarda from tetracycline in a young woman.

Less commonly, dialysis patients develop true PCT. In the anuric dialysis patient, true PCT and pseudo-PCT are distinguished by analysis of serum porphyrins in a laboratory knowledgeable in the normal porphyrin levels in patients undergoing hemodialysis. The treatment of pseudoporphyria is physical sun protection and discontinuance of any inciting medication. Ibuprofen is a safer alternative NSAID which usually does not cause pseudoporphyria. Those cases induced by medications usually resolve over several months; the management of those associated with hemodialysis is much more difficult; however, remission by the administration of *N*-acetylcysteine, 400 mg of powder dissolved in orange juice twice a day, has been reported.

HEPATOERYTHROPOIETIC PORPHYRIA

Hepatoerythropoietic porphyria (HEP) is a very rare form of porphyria that is inherited as an autosomal-recessive trait. HEP is the homozygous form of PCT. It is caused by a homozygous or compound heterozygous deficiency of uroporphyrinogen decarboxylase, which is about 10% of normal in both the liver and erythrocytes. The biochemical abnormalities are similar, but more marked, than those in PCT, but the clinical features are similar to congenital erythropoietic porphyria. Dark urine is usually present from birth, but may be noted later. In infancy vesicles occur in sun-exposed skin, followed by sclerodermoid scarring, hypertrichosis, pigmentation, red fluorescence of the teeth under Wood's light examination, and nail damage. Neurologic disease has been reported in one patient. The diagnosis is confirmed by abnormal urinary uroporphyrins, as seen in PCT, elevated erythrocyte protoporphyrins, and increased coproporphyrins in the feces. In congenital erythropoietic porphyria, uroporphyrins are elevated in the erythrocytes, allowing differentiation from HEP. Sun protection is necessary.

ACUTE INTERMITTENT PORPHYRIA

Acute intermittent porphyria (AIP), the second most common form of porphyria, is characterized by periodic attacks of abdominal colic, gastrointestinal disturbances, paralyses, and psychiatric disorders. Skin lesions do not occur, since the elevated porphyrin precursors are not photosensitizers. It is inherited as an autosomal-dominant trait and is caused by a deficiency in porphobilinogen deaminase, which has 50% activity in affected persons. Only 10% of those with the genetic defect develop disease, but all may be at risk for primary liver cancer. AIP is particularly common in Scandinavia, especially Lapland. AIP usually presents after puberty in young adulthood, and women outnumber men 1.5 to 2:1.

Severe abdominal colic is most often the initial symptom of AIP. Usually there is no abdominal wall rigidity, although tenderness and distension are present. Nausea, vomiting, and diarrhea or constipation accompany the abdominal pain. Peripheral neuropathy, mostly motor, is present. Severe pain in the legs occurs. Optic atrophy, diaphragmatic weakness, respiratory paralysis, flaccid quadriplegia, facial palsy, and dysphagia are but a few of the many neurologic signs. Psychiatric disturbances are varied and frequently apparent. Attacks may be induced by numerous medications.

A diagnosis of AIP is established by finding elevated levels of urinary porphobilinogen (PBG) and increased dALA in the plasma and urine. Erythrocyte and fecal porphyrin levels are normal.

No specific treatment is available for AIP. It is important for the patient to avoid such precipitating factors as a wide variety of medications, including sex steroid hormones, and to maintain adequate nutrition. Glucose loading has been used extensively and appears to be beneficial in many cases. Hematin infusions, in the form of heme arginate, results in clinical improvement and a marked decrease in ALA and PBG excretion. Early treatment may ameliorate attacks. The phenothiazines (chlorpromazine) may be helpful for pain; opiates and propoxyphene are also useful for analgesia.

VARIEGATE PORPHYRIA

Variegate porphyria (VP) is also known as *mixed porphyria*, *South African genetic porphyria*, and *mixed hepatic porphyria*. VP has an autosomal-dominant inheritance, with a high penetrance. It results from a decrease in activity of protoporphyrinogen oxidase. The majority of affected relatives have silent VP, in which there is reduced enzyme activity but no clinical lesions. Such persons should be identified and counseled to avoid known precipitating medications.

VP is characterized by the combination of the skin lesions of PCT and the gastrointestinal and neurologic disease of AIP. Seventy percent of patients develop skin lesions; in 50%, this is the presenting finding. Vesicles and bullae with erosions, especially on sun-exposed areas, are the chief manifestations. In addition, hypertrichosis is seen in the temporal area, especially in women. Hyperpigmentation of sun-exposed areas is also a feature. Facial scarring and thickening of the skin may give the patient a prematurely aged appearance.

The presence of VP should be suspected in a patient when findings indicate both PCT and AIP, especially if he/she is of South African ancestry. Fecal coproporphyrins and protoporphyrins are always elevated, and during attacks urine porphobilinogen and ALA are elevated. Urinary coproporphyrins are increased over uroporphyrins, distinguishing VP from PCT. A finding in the plasma of a unique fluorescence at 626 nm is characteristic of VP and distinguishes it from all other forms of porphyria. Treatment is symptomatic and as outlined for PCT and AIP.

HEREDITARY COPROPORPHYRIA

Hereditary coproporphyria (HCP) is a rare, autosomal-dominant porphyria resulting from a deficiency of coproporphyrinogen oxidase (CPO). About one-third of patients are photosensitive, with blistering similar to but less severe than in VP. Affected persons are prone to attacks with gastrointestinal and neurologic symptoms similar to those seen in AIP and VP. Fecal coproporphyrin is always increased; urinary coproporphyrin, ALA, and PBG are increased only during attacks.

Harderoporphyria is caused by a homozygous defect of CPO with patients having 10% of normal activity. Children present with photosensitivity, hypertrichosis, and hemolytic anemia. Harderoporphyrin is the natural intermediate between coproporphyrinogen and protoporphyrinogen.

ERYTHROPOIETIC PROTOPORPHYRIA

Erythropoietic protoporphyria (EPP) is an inherited disorder with both autosomal-dominant and -recessive forms. The ferrochelatase activity is 10% to 25% of normal in affected

persons. EPP typically presents early in childhood (2–5 years old), but presentation late in adulthood can occur.

Unique among the more common forms of porphyria is an immediate burning of the skin on sun exposure. Because the elevated protoporphyrin IX absorbs both in the Soret band and at 500 to 600 nm, visible light through window glass or in the operating room may precipitate symptoms. Infants cry when exposed to sunlight. Erythema, plaque-like edema, and wheals such as those seen in hydroa aestivale or solar urticaria can be seen. These lesions appear solely on sun-exposed areas. In severe cases, purpura is seen in the sun-exposed areas.

With repeated exposure, the skin develops a weather-beaten appearance. Shallow linear or elliptical scars, waxy thickening and pebbling of the skin on the nose, cheeks, and over metacarpophalangeal joints, and atrophy of the rims of the ears have been described.

Many EPP patients have mildly elevated liver function tests. Severe liver disease develops in 10% of patients, and 1% of EPP patients die of liver failure. Excessive porphyrins are deposited in the liver, porphyrin gallstones are frequently found, and affected livers are cirrhotic. Autosomal-recessive inheritance of EPP may be a risk factor for the development of liver failure. Liver failure requires liver transplantation. A mild microcytic anemia is present in 25% of patients with EPP, but therapy with iron should be used only if iron deficiency is detected, since it may exacerbate symptoms.

Histologically, there is prominent ground-glass, PAS-positive material in the upper dermis, mostly perivascularly. This material is type IV collagen. On DIF, IgG and C3 may be found perivascularly.

A diagnosis of EPP can usually be suspected on clinical grounds, especially if both the acute symptoms and chronic skin changes are found. Because protoporphyrin IX is not water soluble, urine porphyrin levels are normal. Erythrocyte protoporphyrin is elevated, and can be detected by red blood cell (RBC) fluorescence. Erythrocyte, plasma, and fecal protoporphyrin can also be assayed to confirm the diagnosis. Erythrocyte protoporphyrin levels in affected persons may range from several 100 to several 1000 μg/100 mL of packed RBC (normal values, <35 μg/100 mL of packed RBCs).

The differential diagnosis of EPP includes hydroa vacciniforme, xeroderma pigmentosa, and solar urticaria. In infancy, before the appearance of the chronic skin changes, erythrocyte porphyrins may need to be screened to confirm the diagnosis. Once chronic changes are present, a skin biopsy will confirm the diagnosis.

The treatment consists of protection from exposure to sunlight with clothing and barrier sunscreens with titanium dioxide or zinc oxide. Beta-carotene, 60 to 180 mg/day in adults and 30 to 90 mg/day for children, to maintain a serum level of 600 μg/100 mL, provides some protection for most cases. As the child grows, the dose must be increased to maintain adequate tissue levels. Cysteine at a dose of 500 mg twice a day can reduce symptoms. Transfusions of washed packed RBCs may be used to treat anemia, if the patient is symptomatic.

Cholestyramine, oral bile acids, hematin, and a high-carbohydrate diet have all been proposed to prevent or slow the progression of liver disease, but no definitive therapy has been developed.

CONGENITAL ERYTHROPOIETIC PORPHYRIA

Congenital erythropoietic porphyria (CEP) is a rare form of porphyria, also known as *erythropoietic porphyria* or *Gunther's disease*. It is inherited as an autosomal-recessive trait and is caused by a homozygous defect of the enzyme uroporphyrinogen III synthase.

CEP presents soon after birth with the appearance of red urine (noticeable on diapers). Severe photosensitivity occurs, and may result in immediate pain and burning so that the affected child screams when exposed to the sun. Redness, swelling, and blistering occur and result in scarring of the face, dorsal hands, and scalp (with subsequent alopecia). Ectropion can occur with subsequent corneal damage and loss of vision. Erythrodontia of both deciduous and permanent teeth is also characteristic. This phenomenon is demonstrated by the coral-red fluorescence of the teeth when exposed to a Wood's light. Mutilating scars, especially on the face, and the hypertrichosis of the cheeks with profuse eyebrows, and long eyelashes occurs. Other features seen in CEP include growth retardation, hemolytic anemia, thrombocytopenia, porphyrin gallstones, osteopenia, and increased fracturing of bones.

A diagnosis of CEP can be easily suspected when an infant has dark urine and is severely photosensitive. Milder forms of the disease resemble adult PCT and may present in adult life. Abnormally high amounts of uroporphyrin I and coproporphyrin I are found in urine, stool, and red cells. There is stable red fluorescence of erythrocytes. On biopsy there is a subepidermal bulla identical to that seen in PCT.

Treatment is strict avoidance of sunlight, and sometimes splenectomy for the hemolytic anemia. Oral activated charcoal is efficacious; presumably it retards the absorption of endogenous porphyrins. Repeated transfusions of packed red cells, enough to maintain the hematocrit level at 33%, turns off the demand for heme and reduces porphyrin production. Bone marrow transplantation can be an effective treatment.

TRANSIENT ERYTHROPORPHYRIA OF INFANCY (PURPURIC PHOTOTHERAPY-INDUCED ERUPTION)

Paller et al reported seven infants exposed to 380 to 700 nm blue lights for the treatment of indirect hyperbilirubinemia who developed marked purpura in skin exposed to UV light. Extensive blistering and erosions occurred in one case. Biopsies of the skin show hemorrhage without epidermal changes in the cases associated with purpura, and a pauci-inflammatory, subepidermal bulla in the case with blistering. The infants had all received transfusions. Elevated plasma coproporphyrins and protoporphyrins were found in the four infants examined. The pathogenesis is unknown.

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CALCINOSIS CUTIS

Cutaneous calcification results from deposits of calcium and phosphorous in the skin. Calcinosis cutis is divided into four forms. *Dystrophic calcinosis* includes conditions in which calcification occurs in damaged tissue (usually collagen or elastic tissue). Serum calcium and phosphorus levels are normal. Dermatomyositis is a classic example. *Metastatic calcification* refers to deposition of calcium resulting from elevated serum levels of calcium or phosphorus. Hyperparathyroidism is an example of this form of calcification. *Iatrogenic and traumatic calcinosis* is associated with medical procedures or occupational exposures that may involve both tissue damage and local elevated calcium concentrations. *Idiopathic calcinosis cutis* refers to those forms of cutaneous calcification of unknown cause with normal serum calcium. In osteoma cutis, true bone is formed in the skin.

DYSTROPHIC CALCINOSIS CUTIS

This type occurs in a preexisting lesion or inflammatory process. Systemic calcium metabolism is normal, and lesions affect the skin only. This may be divided into localized (calcinosis circumscripta) and widespread (calcinosis universalis) types. Localized calcinosis cutis may present as small deposits of chalky granular material around the fingers and on the elbows. This may spontaneously extrude from the skin. It occurs most commonly in limited scleroderma (the CREST syndrome: calcinosis cutis, Raynaud's phenomenon, esophageal disorders, sclerodactyly, and telangiectasia) (Fig. 26-10), but may be seen in progressive systemic sclerosis and systemic lupus erythematosus. Pancreatic and lupus panniculitis typically demonstrate dystrophic calcification, but the process tends to remain microscopic. Patients with Werner syndrome and PCT may also develop calcifications within the scleroderma-like lesions. Various benign and malignant neoplasms may develop calcification or ossification. Pilomatrixomas, pilar cysts, nevi, mixed tumors, melanomas, and atypical fibroxanthomas are the most commonly reported of these. In the above cases, calcification is in the dermis or subcutaneous tissue; however, in one patient with well-defined infiltrated white plaques of the labia majora and

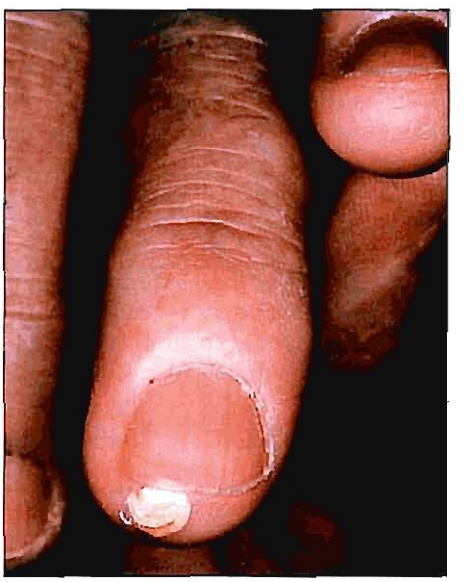

Fig. 26-10
Calcinosis cutis in CREST syndrome.

genital mucosa who had chronic irritation from urinary incontinence and a vesicovaginal fistula, calcification occurred in the epithelium.

Calcinosis universalis is usually seen in children with dermatomyositis. It affects the skin, muscles, and tendons, as well as more diffusely. This calcification can persist for many years after the dermatomyositis is inactive. Calcinosis cutis in dermatomyositis may occur in adults, particularly those with a delay in diagnosis, or who receive inconsistent treatment, or who have the tumor necrosis factor-α-308A allele. Idiopathic cases of calcinosis universalis have been reported. Dystrophic calcification is treated with limited surgical removal as needed to control discomfort. Bisphosphonates, calcium-channel blockers, warfarin, colchicines, probenecid, and a low calcium, low phosphate diet combined with aluminum hydroxide have been reported to be of benefit in the treatment of calcinosis cutis in individual patients.

METASTATIC CALCINOSIS CUTIS

This rare entity is characterized by calcifications in the skin, elevated serum calcium, and sometimes hyperphosphatemia. Metastatic calcinosis is often associated with bone loss or destruction, the bone providing the source of the elevated serum calcium. Conditions associated with metastatic calcinosis include parathyroid neoplasms, primary hyperparathyroidism, chronic renal failure, hypervitaminosis D, sarcoidosis, and excessive intake of milk and alkali. Destruction of bone by osteomyelitis, leukemia, Paget's disease of the bone, myeloma, and metastatic carcinoma may lead to elevated serum calcium and metastatic calcification. In calcinosis cutis with hyperparathyroidism, the skin manifestations are numerous, small, firm, white papules, about 1 to 4 mm in diameter, occurring symmetrically in the popliteal fossae, over the iliac crests, and in the posterior axillary lines.

The most common metabolic condition associated with metastatic calcification is renal failure. Usually there is an elevated phosphorus level and secondary hyperparathyroidism, resulting in high calcium and phosphorous production and deposition of calcium phosphate in tissues. Less commonly, cutaneous calcification in renal disease can occur with normal serum calcium and phosphorus levels. Three forms of cutaneous calcification in renal disease have been described: tumoral calcinosis, calcifying panniculitis, and calciphylaxis. Tumoral calcinosis is a very rare complication of renal disease. Managing the metabolic abnormalities may lead to resolution of the large deposits of calcium.

Often calcifying panniculitis and calciphylaxis occur in the same patient at the same time, suggesting that they may be of a common pathogenesis. Isolated, firm, indurated nodules, usually on the legs or thighs, in the subcutaneous fat have been called *calcifying panniculitis*. Usually they are seen with the most severe complication of the abnormal calcium and phosphorus metabolism of renal disease, calciphylaxis. This life-threatening condition, which leads to livedo reticularis and ischemic tissue necrosis, is discussed in Chapter 35.

IATROGENIC AND TRAUMATIC CALCINOSIS CUTIS

Medical procedures that may inadvertently introduce calcium into tissue in association with tissue trauma may lead to cutaneous calcification. This has been reported after extravasation of calcium chloride or calcium gluconate infusion, and after electroencephalography or electromyography. The electrode paste is high in calcium, and the skin is traumatized during the procedure, leading to calcifications at the sites of electrode insertion. The most common setting is on the scalp of children. Lesions spontaneously resolve over months. Performing frequent heel sticks in neonates has led to similar lesions. Injections of low molecular weight calcium-containing heparins in patients suffering from renal failure may develop calcification at the sites of injection.

Traumatic calcinosis may occur as a result of occupational exposure to calcium-containing materials, as in the cases reported in oil-field workers and coal miners. Exposure of the skin to cloth sacks of calcium chloride, limewater compresses, and refrigerant calcium chloride can all cause calcinosis cutis.

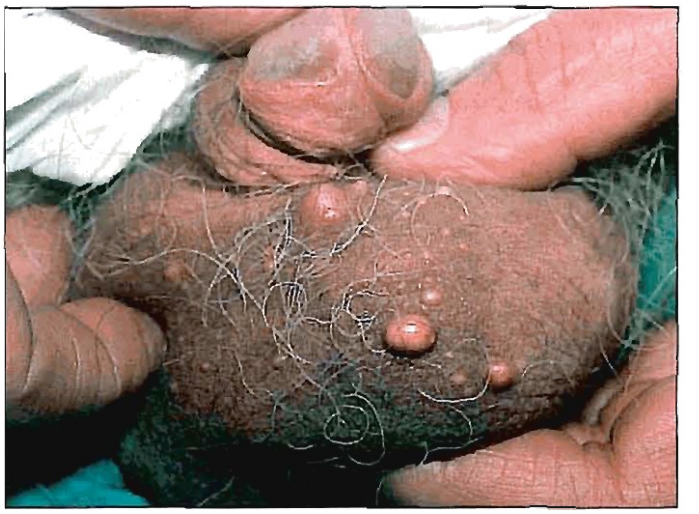

Fig. 26-11 Scrotal calcinosis.

IDIOPATHIC CALCINOSIS CUTIS

Idiopathic Scrotal Calcinosis

Idiopathic scrotal calcinosis is the most common form of idiopathic calcinosis cutis. Lesions present in young to middle-aged adult men as multiple, asymptomatic, firm, round, yellow papules from several millimeters up to 1 cm in diameter (Fig. 26-11). The papules resemble infundibular follicular cysts. Similar lesions may be seen less commonly in girls or women on the labia majora or areola. Histologically, there are localized deposits of calcium surrounded by foreign body reaction. At least some are calcified scrotal infundibular cysts. Why they have such a high proclivity to calcification at this anatomic location is unclear. Treatment is not required, but surgical removal cures individual lesions.

Subepidermal Calcified Nodule

Subepidermal calcified nodule is an uncommon but distinct type of idiopathic calcinosis; it occurs most frequently as one or a few lesions on the scalp or face of children (Fig. 26-12). Males outnumber females by nearly 2:1, and the average age at onset is 7 years. Lesions present as fixed, uninflamed papules that look very much like those of molluscum contagiosum with a central umbilication. A similar condition, milia-like idiopathic calcinosis cutis, has a wider distribution (hands,

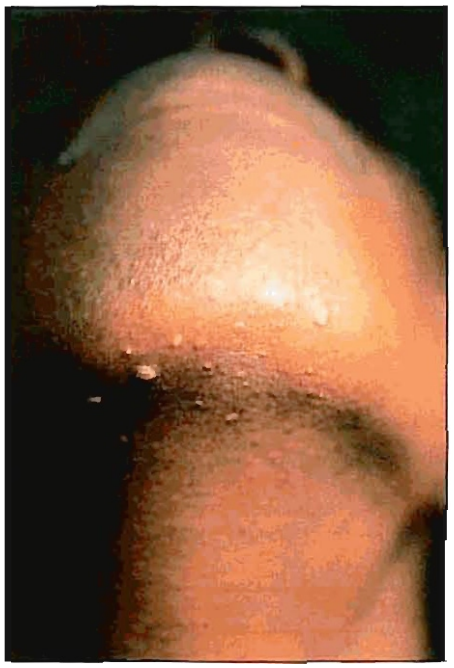

Fig. 26-12 Subepidermal calcified nodules.

feet, elbows, knees are common sites). Two-thirds of patients have Down syndrome. Treatment is not required, but surgical removal will cure any individual lesion.

Tumoral Calcinosis

Tumoral calcinosis is a rare disease of unknown cause that can be divided into two forms. The idiopathic, primary, or normophosphatemic form is seen in young adults, primarily in African natives. It is not familial, lesions are usually solitary, and antecedent trauma is frequently present. Primary hyperphosphatemic tumoral calcinosis is a familial disease, primarily of black males. Most cases present before the second decade of life. Three-quarters of these individuals have affected siblings, but the exact mode of inheritance is unknown. Multiple lesions predominate, and there is no preceding history of trauma. The serum calcium level is normal, but serum phosphorus and calcitriol levels are elevated.

Lesions in both types present as large subcutaneous masses of calcium overlying pressure areas and large joints, usually the hips, elbows, shoulders, or knees. Skin involvement, apart from the tumoral masses, is extremely rare but may occur as localized calcinosis cutis. The internal organs are not involved, and serum calcium levels are generally normal. Surgical excision has been the mainstay of therapy; however, recurrences are frequent after incomplete removal. Various dietary restrictions to lower calcium and phosphorus intake have shown some success.

OSTEOMA CUTIS

Bone formation within the skin may be primary in cases where there was no preceding lesion; metastatic (associated with abnormalities of parathyroid metabolism); or dystrophic, where ossification occurs in a preexisting lesion or inflammatory process.

Primary osteoma cutis includes four genetic disorders, fibrodysplasia ossificans progressiva, progressive osseous heteroplasia, widespread or single, platelike osteoma cutis, and Albright hereditary osteodystrophy. Additionally, single

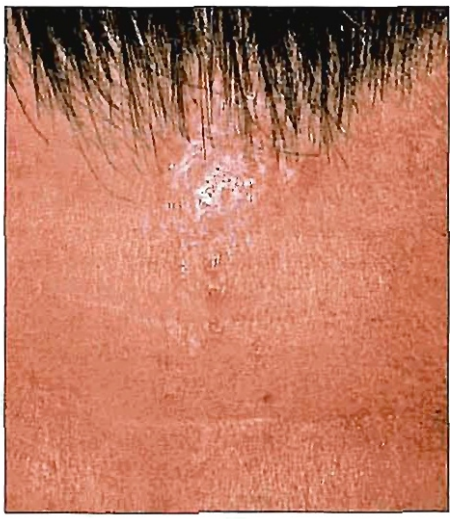

Fig. 26-13 Osteoma cutis. (Courtesy of Curt Samlaska, MD)

osteomas may occur as an idiopathic event in later life, or multiple miliary osteomas of the face can be seen, usually in women (Fig. 26-13). Some feel the latter are dystrophic because they occur in patients with acne and are associated with scars. If tetracycline or minocycline is ingested for treatment of the acne, the cutaneous osteomas may be pigmented. Improvement with topical tretinoin, erbium:YAG laser or with incision, curettage, and primary closure has been reported in theses miliary osteomas.

Patients with fibrodysplasia ossificans progressiva develop osteoma cutis as endochondral bone formation associated with deep connective tissue and skeletal muscle involvement. They have dystrophic great toes, baldness, mental retardation, and deafness. The prognosis is poor due to the progressive and deep nature of the lesions, leading to extreme morbidity and early death due to restricted movement of the chest. Mutations in the noggin gene in the 17q 21-22 region have been documented in several families.

Progressive osseous heteroplasia is a rare form of cutaneous ossification initially seen between birth and 6 months of age, often in the first month of life. Females are preferentially affected. Lesions begin as small papules that can coalesce to large plaques. Sometimes these plaques will have small firm calcified papules overlying them. Lesions are randomly distributed and may be unilateral or only involve one anatomic area. There is no preceding trauma or inflammatory phase. Serum calcium, phosphorus, parathyroid hormone and calcitriol are normal, but alkaline phosphatase, lactate dehydrogenase (LDH), and creatine phosphokinase (CPK) may be elevated, indicating increased bone formation (alkaline phosphatase) or muscle destruction (CPK and LDH). Histologically, the lesions reveal intramembranous bone formation and can affect the soft tissues as well as skin. Only calcification without ossification may be found in superficial dermal biopsies, so a deep biopsy, including subcutaneous fat, may be required to confirm the diagnosis. The condition is progressive and can lead to serious sequelae, including ulceration, infection, and severe pain. Platelike osteoma cutis also occurs in newborns or young children, is unassociated with dysmorphic features or abnormalities of calcium or phosphorus metabolism, has intramembranous bone formation histologically, but is nonprogressive. These disorders are most likely polar ends of a spectrum of disease, as one family

has been described with members having either condition, and they both have been associated with mutations in the α-subunit of the stimulatory G protein that interacts with adenyl cyclase.

Albright hereditary osteodystrophy is described in Chapter 24. It is characterized by childhood development of intramembranous bone formation in the dermis and subcutaneous tissue. The cutaneous ossifications may be noted soon after birth and are usually multiple, small, superficial plaques. They favor the scalp, hands, feet, periarticular regions, abdomen, and chest wall. Small lesions are of little consequence, but large subcutaneous masses may disrupt underlying structures. There may be characteristic dysmorphic features and the presence of pseudo- or pseudopseudohpyoparathyroidism. It also is associated with mutations of the GNAS1 gene.

Dystrophic osteoma cutis occurs most frequently in pilomatricomas; however, other lesions in which bone formation may occur are basal cell epithelioma, intradermal nevi, mixed tumor of the skin, scars, scleroderma, and dermatomyositis.

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LIPID DISTURBANCES

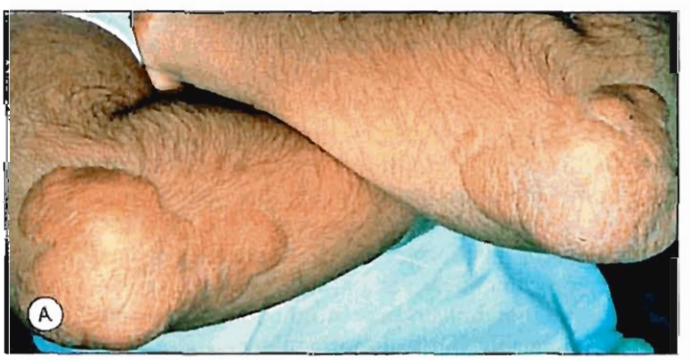
XANTHOMATOSIS

Xanthomatosis is a cutaneous manifestation of lipidosis in which the plasma lipoproteins and free fatty acids are changed quantitatively. There is accumulation of lipids in large foam cells in the tissues. Cholesterol or triglycerides are usually found, but when cholesterol levels are normal, β-sitosterol, campesterol, stigmasterol (plant sterols), or cholestanol may rarely be at fault.

The names for cutaneous manifestations of xanthomatosis are based on clinical morphology. Several different genetic diseases may present with similar cutaneous xanthoma patterns. The morphologies are relatively specific for the associated elevated lipid, however, with eruptive xanthomas seen with hypertriglyceridemia and other forms of xanthomas seen with elevations in cholesterol.

Xanthoma Tuberosum

Tuberous xanthomata are variously found as flat or elevated and rounded, grouped, yellowish or orange nodules located over the joints, particularly on the elbows and knees (Fig. 26-14). The lesions are indurated and tend to coalesce. They may also occur over the face, knuckles, toe joints, axillary and inguinal folds, and buttocks. Solitary lesions may occur. Early lesions are usually bright yellow or erythe-



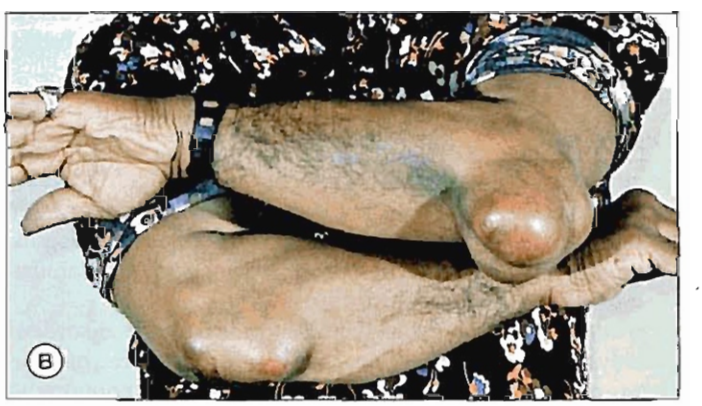


Fig. 26-14 *A* and *B*, Tuberous xanthomas.

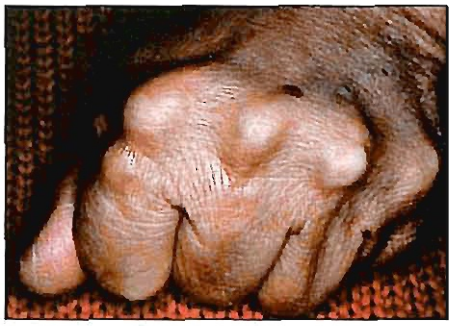


Fig. 26-15 Tendonous xanthomas.

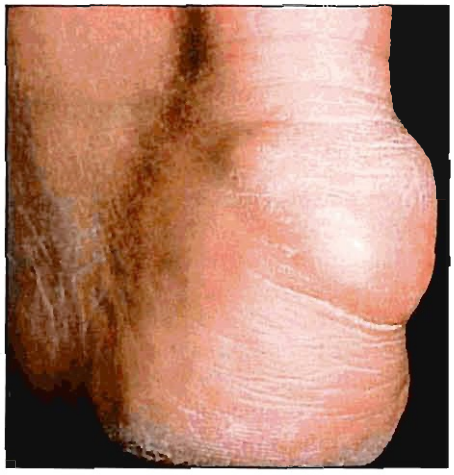
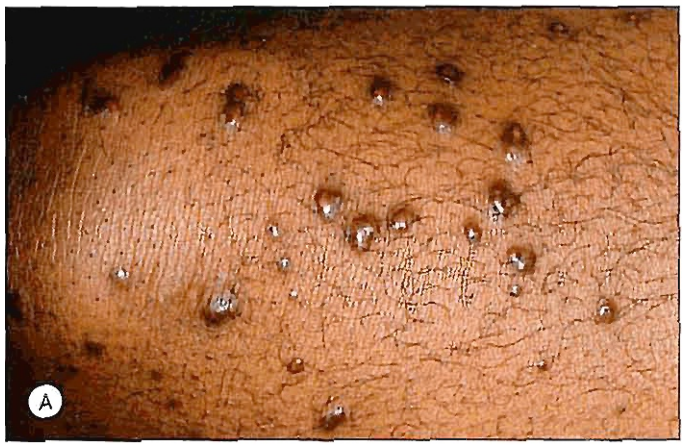


Fig. 26-16 Tendonous xanthomas.



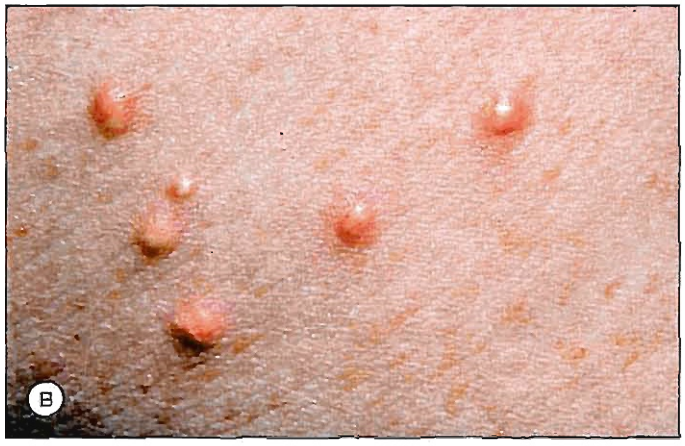


Fig. 26-17 *A* and *B*, Eruptive xanthomas.

matous; older lesions tend to become fibrotic and lose their color. Pedunculated, fissured, and suppurative nodules may also be seen.

Xanthoma tuberosum is associated with primary hyperlipoproteinemias with elevated cholesterol levels, such as familial hypercholesterolemia and familial dysbetalipoproteinemia. It also occurs in biliary cirrhosis, myxedema, phytosterolemia, and normocholesterolemic dysbetalipoproteinemia.

Xanthoma Tendinosum

Papules or nodules 5 to 25 mm in diameter are found in the tendons, more especially in extensor tendons on the backs of the hands (Fig. 26-15) and dorsa of the feet and in the Achilles tendons (Fig. 26-16). These predominate in conditions with elevated cholesterol, such as the primary hyperlipoproteinemias of familial hypercholesterolemia, familial defective apolipoprotein B-100, and familial dysbetalipoproteinemia. They are usually seen in association with tuberous xanthomas and xanthelasma. They also occur in obstructive liver disease, diabetes, myxedema, cerebrotendinous xanthomatosis, and phytosterolemia.

Eruptive Xanthoma

Xanthoma eruptivum consists of small, yellowish-orange to reddish-brown papules that appear in crops over the entire body (Fig. 26-17). These occur in association with markedly elevated triglycerides. Causes for such elevations are genetic deficiency of lipoprotein lipase, familial deficiency of apoprotein CII, familial inhibitor of lipoprotein lipase, and endogenous familial hypertriglyceridemia. Certain diseases or drugs raise the triglyceride level either by increased production, decreased catabolism, or decreased excretion. These include diabetes mellitus, obesity, pancreatitis, chronic renal failure, hypothyroidism, and treatment with estrogens, corticosteroids, or systemic retinoids.

The papules may be surrounded by an erythematous halo and may be grouped in various favored locations such as the buttocks, flexor surfaces of the arms and thighs, knees, inguinal and axillary folds, and oral mucosa. Koebnerization may occur. Pruritus is variable.

Xanthoma Planum (Plane Xanthoma)

These xanthomas appear as flat macules or slightly elevated plaques with a yellowish-tan or orange coloration of the skin that is spread diffusely over large areas. They are frequently associated with biliary cirrhosis and myeloma but have been described in patients with high-density lipoprotein (HDL) deficiency (isolated A-1 apolipoprotein deficiency type), monoclonal gammopathy, lymphoma, leukemia, and in xanthomas following erythroderma. Characteristically, plane xanthomas may occur about the eyelids, neck, trunk, shoulders, or axillae (Fig. 26-18). These well-defined macular patches may be situated on the inner surface of the thighs and antecubital and popliteal spaces. Xanthelasma palpebrarum may be associated with xanthoma planum elsewhere.

Palmar Xanthomas

These consist of nodules and irregular yellowish plaques involving the palms and flexural surfaces of the fingers (Fig. 26-19). Striated xanthomas appear as yellowish streaks that follow the distribution of creases of the palms and soles. These lesions are seen in familial dysbetalipoproteinemia, multiple myeloma, and biliary cirrhosis.

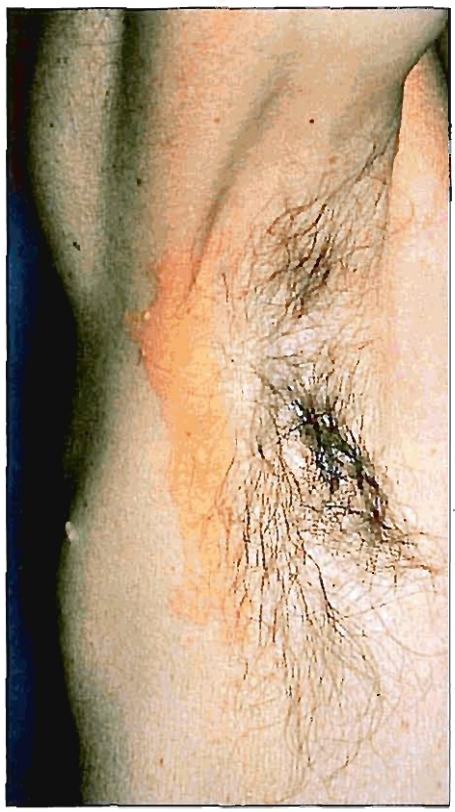


Fig. 26-18 Planar xanthoma.

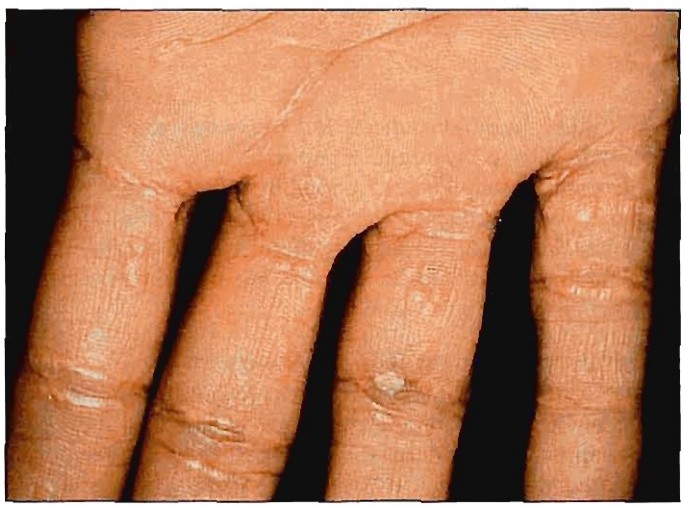


Fig. 26-19 Xanthomas of the palmar striae. (Courtesy of James Fitzpatrick, MD)

Xanthelasma Palpebrarum (Xanthelasma)

Xanthelasma is the most common type of xanthoma. It occurs on the eyelids and is characterized by soft, chamois-colored or yellowish orange oblong plaques, usually near the inner canthi (Fig. 26-20). The xanthelasmata vary from 2 to 30 mm in length. Frequent symmetry, with a tendency to be permanent, progressive, multiple, and coalescent, is also characteristic. Frequently xanthelasmata are associated with other types of xanthomas, but they are usually present without any other disease.

The disorder is encountered chiefly in patients of middle age. It is common among women who have hepatic or biliary disorders. Xanthelasma may be seen in familial hypercholesterolemia, familial defective apolipoprotein B-100, and familial dysbetalipoproteinemia; however, half or more of the patients are normolipemic. It is a common finding in generalized xanthoma planum, in obstructive liver disease, myxedema, diabetes, and phytosterolemia.

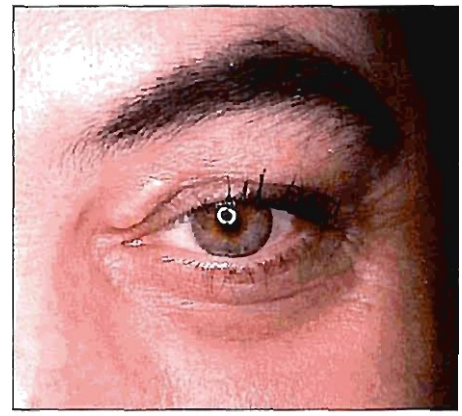


Fig. 26-20 Xanthelasma.

Several studies have found abnormalities in apolipoprotein E phenotypes or other lipoproteins more frequently than in controls. New patients with xanthelasma should be evaluated with a full lipoprotein profile, as well as a careful history and physical examination. Patients with a young age at onset and a family history of hyperlipidemias are at higher risk of having lipid abnormalities.

Treatment of xanthelasma is discussed here because of its uniqueness among the xanthomas, in that surgical therapy is often successful. The best method is surgical excision. The anesthetized lesion is grasped with mouse-tooth forceps and clipped off with scissors, and the skin edges undermined and sutured with fine silk. Excellent cosmetic results are obtained, even if the wound is not closed. Fulguration, trichloracetic acid cauterization, and CO_2 and erbium:YAG laser treatments are other methods. Complete removal of the lesions does not preclude the possibility that other new lesions will develop.

Tuberoeruptive Xanthomas

These xanthomas are red papules and nodules that appear inflamed and tend to coalesce. They are associated with familial dysbetalipoproteinemia.

Nodular Xanthomas

These are multiple, yellowish, dome-shaped lesions, 4 to 5 mm or larger in diameter; they may be discrete or confluent and may occur on the earlobes, neck, elbows, and knees. They are usually associated with biliary cirrhosis and atresia of the bile ducts.

The histologic features in all varieties of xanthoma are similar, characterized by the presence of numerous large xanthoma or foam cells, which are phagocytes (fat-laden histiocytes). They may be multinucleated. In addition to the foam cells, giant cells of the Touton type occur. Clefts representing cholesterol and fatty acids dissolved by embedding agents may be noted. There is generally a connective tissue reaction about the nests of foam cells, and in old lesions most of the foam cells are replaced with fibrosis. To demonstrate lipids in the histologic sections, frozen sections should be stained with lipid stains (scarlet red).

PRIMARY HYPERLIPOPROTEINEMIAS

Cutaneous xanthomas are usually manifestations of a disorder of lipid metabolism. The blood lipids, with the exception of free fatty acids, are bound to circulating plasma proteins and are mainly cholesterol, phospholipid, and triglyceride. The total serum lipids have a range of 400 to 1000 mg%. Of this, serum cholesterol values vary according to age. Generally, a serum cholesterol below 200 mg/dL is normal, while a level of more than 240 mg/dL requires further evaluation. A triglyceride level of more than 250 mg/dL is considered abnormal.

Lipoprotein fractions may be demonstrated by paper electrophoresis. Four lipoprotein bands may be evident: the α-lipoprotein band (HDL), β-lipoprotein (low-density lipoprotein, LDL), preβ-lipoprotein (very-low-density lipoprotein, VLDL), and the chylomicron band. When the lipoproteins are subjected to ultracentrifugation it is found that the HDLs are composed mostly of phospholipid and esterified cholesterol. The LDLs are composed mostly of cholesterols. The VLDL fraction is the main carriers of endogenous triglycerides. The lowest density chylomicrons are the exogenous triglycerides.

Frederickson classified hyperlipoproteinemias into six types on the basis of electrophoretic patterns, as follows:

Type I: Excess chylomicrons
Type IIa: Excess β-lipoprotein
Type IIb: Excess β-lipoprotein with slightly elevated VLDLs
Type III: Increased intermediate-density (remnant) lipoprotein
Type IV: Increased preβ-lipoprotein
Type V: Increased preβ-lipoproteins and chylomicrons

Although this phenotypic classification has been useful for many years, advances in the understanding of lipoprotein metabolism and transport, coupled with new knowledge of molecular defects which result in these phenotypes, has led to the use of a genetic classification of lipoproteinemias.

Lipoprotein metabolism may be viewed based on the lipid source: an exogenous and an endogenous category. Exogenous lipids in the diet are absorbed and incorporated into triglyceride-rich chylomicrons. These are hydrolyzed by the action of lipoprotein lipase and certain cofactors, among them apoprotein CII. The resulting remnants are taken up by the liver. Endogenously produced VLDLs are synthesized in the liver and (again through the action of lipoprotein lipase) are connected to cholesterol-rich intermediate-density lipoproteins (IDLs) and eventually into LDLs.

These are then available for uptake by peripheral tissues, as well as by the liver. The uptake of LDL, IDL, and chylomicron remnants is dependent on specific receptors. Abnormalities of lipoprotein lipase, the apolipoproteins, cofactors, receptors, or stimulators or retarders of endogenous production or catabolism, whether on a genetic or sporadic basis, may accelerate or block the pathway in different areas. If blockade occurs early and results in elevation of triglyceride-rich particles, eruptive xanthoma may result. If a defect occurs later in the pathway, and cholesterol-rich particles accumulate, xanthelasma, tuberous xanthomas, and tendinous xanthomas are to be expected, along with premature atherosclerotic cardiovascular disease.

Lipoprotein Lipase Deficiency

Lipoprotein lipase deficiency causes type I disease (chylomicronemia) early in life. It is rare, results from a homozygous defect, and is associated with highly elevated triglycerides. With levels above 2000 mg/dL, a high risk of pancreatitis and eruptive xanthomas (Fig. 26-21) exists. As patients grow older, their VLDLs (type V) become elevated. Dietary modification is the only effective treatment.

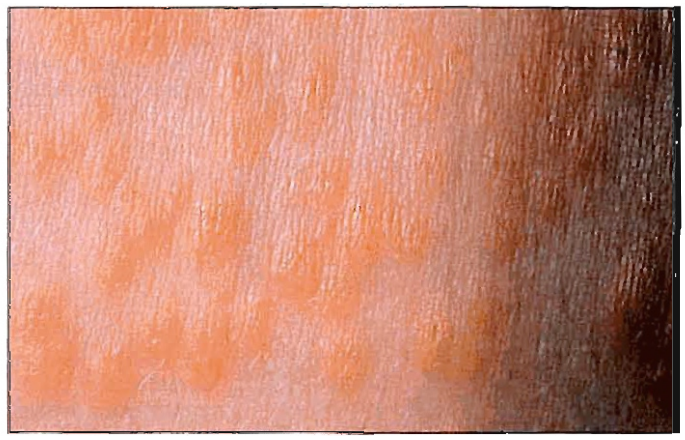


Fig. 26-21 Eruptive xanthomas in lipoprotein lipase deficiency.

Familial Apoprotein CII Deficiency

Patients with the rare familial apoprotein CII deficiency lack lipoprotein lipase activator; very high triglyceride levels, up to 10,000 mg/dL, result. They are at risk for pancreatitis and eruptive xanthomas; management again is through dietary reduction of fats.

Familial Hypertriglyceridemia

In familial hypertriglyceridemia, increased hepatic production of VLDLs occurs first (type IV), but overloaded removal mechanisms result in accumulation of dietary lipids, and chylomicrons accumulate, so a type V pattern results. Eruptive xanthomas are common, and atherosclerotic heart disease may occur. Cholelithiasis, polyarthritis, and arthralgia frequently occur.

Familial Hypercholesterolemia

Familial hypercholesterolemia is Frederickson type II disease: LDLs are found in high levels in the plasma; there may be a moderate increase in VLDLs and in the triglycerides that they carry. There is overproduction of LDL cholesterol (caused by loss of normal feedback inhibition) and impaired removal of it (because of impaired formation of LDL receptors). There is elevated plasma β-lipoprotein from birth in heterozygotes, and symptoms begin in the third to sixth decade, when tendinous or less commonly tuberous xanthomas appear. Atherosclerotic coronary heart disease begins in the 30s and 40s in men and a decade later in women. Statins are the treatment of choice.

Homozygotes generally develop coronary atherosclerosis before the age of 15, as their cholesterol levels are in the 800 to 1000 mg/dL range. Tendinous xanthomas, tuberous xanthomas, and xanthelasma appear in childhood. Characteristic xanthomatous plaques occur, which may be generalized (Fig. 26-22), but typically involve intertriginous areas such as the interdigital spaces (Fig. 26-23) or the intergluteal cleft. Cultured amniotic fluid cells permit prenatal diagnosis in homozygotes. LDL-apheresis or liver transplantation are treatments employed for this homozygous type. Autosomal-

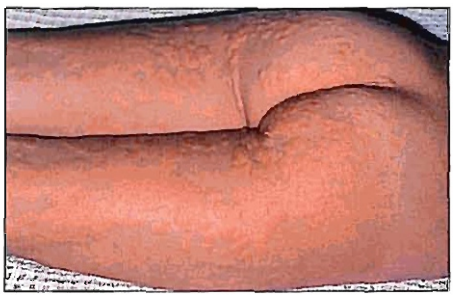


Fig. 26-22 Xanthomas in homozygous familial hypercholesterolemia.

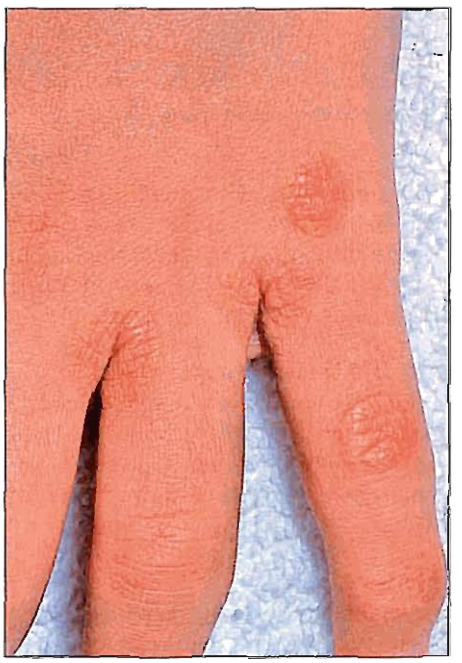


Fig. 26-23 Interdigital xanthomas in homozygous familial hypercholesterolemia.

recessive hypercholesterolemia is a rare condition in which the internalization of the LDL receptor on cells is defective. This leads to clinical disease which is similar, but generally less severe than, homozygous familial hypercholesterolemia.

Familial Defective Apolipoprotein B-100

In this condition, a structural defect in apolipoprotein B-100 means it binds poorly to LDL receptors, allowing for accumulation of LDL. In the more common heterozygous form, hypercholesterolemia occurs, tendinous xanthomas and xanthelasma may be seen, and premature coronary heart disease develops. In the rare homozygous form there are higher levels of cholesterol present but not to the heights seen in homozygous familial hypercholesterolemia. Statins are an effective intervention.

Familial Dysbetalipoproteinemia (Broad Beta Disease)

In this disorder, remnant lipoproteins increase, LDLs and HDLs are reduced, and triglyceride and cholesterol levels are increased. The cholesterol-rich IDLs form a broad band on electrophoresis, extending from preβ-lipoproteins to β-lipoproteins: hence broad beta disease. The presence of an abnormal form of apolipoprotein E, apolipoprotein E2, allows for the definitive diagnosis to be made. Xanthomas (tuberous, eruptive, palmar, or tendinous) are common; xanthelasmas are infrequent. Atherosclerosis is common, as are diabetes, gout, and obesity. Familial apolipoprotein E deficiency is a rare disease that is associated with marked atherosclerosis and xanthomatosis.

Familial Combined Hyperlipidemia or Multiple-Type Hyperlipoproteinemia

This, the most common of the genetic lipoproteinemias, has a high risk of myocardial infarction and diabetes, and a low incidence of tuberous or tendinous xanthomas.

SECONDARY HYPERLIPOPROTEINEMIA

Obstructive Liver Disease (Xanthomatous Biliary Cirrhosis)

This type of hyperlipoproteinemia shows an increase of the serum phospholipid and cholesterol, giving a type II lipoprotein pattern. This is caused by the presence of lipoprotein X, which is secreted by the liver in cholestasis. It has the ability to carry large quantities of free cholesterol and phospholipids. The triglycerides are not elevated and the plasma is clear, showing no chylomicrons.

The xanthomatous lesions are plane xanthomas, with lesions on the face, flexor surfaces of the extremities, and trunk. Striate palmar and plantar lesions, and xanthelasmas are also seen. Tuberous xanthomas may also occur. Pruritus is extremely severe. Hepatomegaly and jaundice are present. Cholestyramine is of help in allaying pruritus.

Alagille syndrome is a congenital disorder characterized by intrahepatic bile ductular atresia, patent extrahepatic bile ducts, a characteristic facies (prominent forehead; deeply set eyes; straight nose; small, pointed chin), cardiac murmur, vertebral and ocular abnormalities, low intelligence, and hypogonadism. It is an autosomal-dominantly inherited condition. There is persistent cholestasis early in life with pruritus and hyperbilirubinemia. Lipid levels elevate by the age of 2 and planar or papular xanthomas may occur. This is a treatable condition with cholestyramine and fat-soluble vitamins leading to prolonged improvement.

Hematopoietic Diseases

Xanthomas may occur secondarily in myelomas; Waldenström macroglobulinemia; cryoglobulinemia, and occasionally, lymphoma; and hemochromatosis. These xanthomas are usually generalized plane xanthomas of the eyelids, periorbital areas, sides of the neck, shoulders, and upper back. The lipoproteinemia may be of type I, V, or IIa pattern. In some patients no lipoprotein abnormality is present. These patients may have paraproteins that bind to the lipoproteins, preventing their metabolism.

Xanthoma Diabeticorum

Eruptive xanthomas may occur secondarily, especially in young persons unresponsive to insulin. Cardiovascular disease and hepatomegaly are common. Insulin is necessary for the normal plasma triglyceride clearing action of lipoprotein lipase. Therefore, in insulin deficiency, an acquired lipoprotein lipase deficiency exists, which leads to impaired clearance of chylomicrons or VLDLs, or both. This results in a type I, IV, or V lipoprotein pattern and hypertriglyceridemia. When the diabetes is brought under control, the triglyceride levels are lowered and prompt involution of the lesions is seen. Weight reduction and carbohydrate intake

restriction are also helpful. Identical phenomena may occur in von Gierke's disease, a form of glycogen storage disease in which there is a lack of hepatic glucose-6-phosphatase.

Chronic Renal Failure

If plasma protein levels are reduced by urinary loss in the nephrotic syndrome (or by plasmapheresis or repeated bleeding), a compensatory increase of lipoproteins may occur, with hyperlipidemia and various kinds of xanthoma.

Renal failure with or without dialysis may cause hypertriglyceridemia. In long-term dialysis there is increased cardiovascular disease because of increased levels of VLDL, as well as lowered HDLs. Type IV and V profiles are most commonly seen.

Myxedema

Lipoprotein lipase needs thyroid hormone to work, and its failure may lead to type I, IV or V disease; also thyroid hormone deficiency may lead to hypercholesterolemia, because thyroid hormone is needed in the oxidation of hepatic cholesterol to bile salts. Xanthelasma and xanthomas are common in myxedema.

Pancreatitis

Hyperlipidemia in the hyperchylomicronemic syndromes (types I and V) may cause pancreatitis; it may be recurrent, and pancreatic necrosis and death may occur. Alternatively, pancreatitis (perhaps initiated by ethanol) may cause type I or V hyperlipoproteinemia by inducing insulin deficiency and a relative lack of lipoprotein lipase activity.

Medication-Induced Hyperlipoproteinemia

Estrogens, by decreasing lipoprotein lipase activity and increasing VLDL synthesis, may cause type I or type IV patterns. Eruptive xanthomas may occur. Oral prednisone may induce insulin deficiency and cause type IV or V patterns to develop. Oral retinoids, indomethacin, highly active antiretroviral therapy (HAART) and olanzapine may also cause eruptive xanthomas.

Normolipoproteinemic Xanthomatoses

The normolipoproteinemic xanthomatoses are conditions in which serum cholesterol and lipoproteins are normal, yet secondary lipid deposition in the skin occurs. Hematopoietic conditions, particularly monoclonal gammopathies and myeloma, may be associated with normolipoproteinemic planar xanthomas.

Cerebrotendinous Xanthomatosis Cerebrotendinous xanthomatosis is an autosomal-recessive disease caused by an accumulation of cholestanol in plasma lipoproteins and xanthomatous tissue. The underlying abnormality is a mutation in the sterol 27-hydroxylase gene (CYP27A) leading to incomplete oxidation of cholesterol to bile acids. Cholestanol, an intermediate, accumulates as a result. It accumulates in tendons, brain, heart, lungs, and ocular lenses. There may be tendinous xanthomas, especially of the Achilles tendons; progressive neurologic dysfunction; cerebellar ataxia; dementia; spinal cord paresis; cataracts; atherosclerotic coronary disease; and endocrine abnormalities. Urinary gas chromatography is a specific test for this disease. The condition is treated with chenodeoxycholic acid and cholic acid.

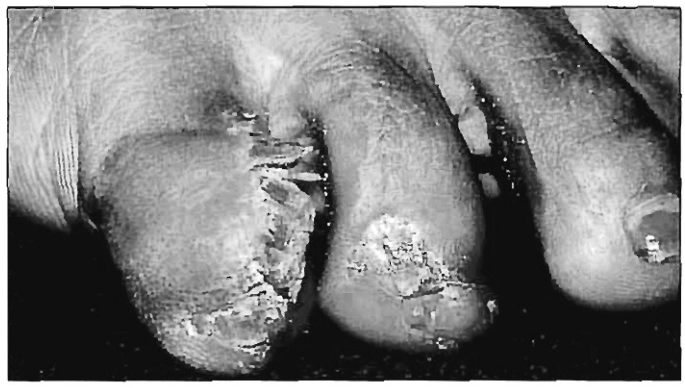


Fig. 26-24 Verruciform xanthoma.

Phytosterolemia In phytosterolemia, a rare disorder, plant sterols such as β-sitosterol, stigmasterol, and campesterol are absorbed from the gastrointestinal tract in excessive amounts. This autosomal-recessive disorder is caused by mutations in the genes encoding the ABCG5 and ABCG8 transporters, which are needed to pump sterols out to intestinal cells in the lumen of the gut. The plant sterols accumulate in the body as xanthelasmas, tendinous xanthomas, and tuberous xanthomas. In most patients there is also type IIa hyperlipoproteinemia. There is a risk of hemolysis, arthritis, and premature atherosclerosis.

Verruciform Xanthoma Verruciform xanthoma (VX) is an uncommon lesion that occurs as a reddish-orange or paler hyperkeratotic plaque or papillomatous growth with a pebbly or verrucous surface. The most common site is the oral mucosa. It has also been reported on other mucosal surfaces, genitalia, lower extremities (Fig. 26-24), and elsewhere. The type of epidermal nevus that is present in CHILD syndrome may have characteristics of VX. Additionally, VX has been reported in psoriatic lesions undergoing PUVA therapy and in psoriasiform skin lesions in an HIV-positive patient. Histologically, there is acanthosis without atypia, parakeratosis, and xanthoma cells in the papillary dermis. The etiology is unknown.

Familial α-Lipoprotein Deficiency (Tangier Disease) Tangier disease is caused by mutations in the cell-membrane protein ABCA1, which mediates the secretion of excess cholesterol from cells into the HDL metabolic pathway. This results in a profound deficiency of HDL, an accumulation of cholesterol in tissue macrophages, and prevention of atherosclerosis. The characteristic clinical finding is yellow, enlarged tonsils from accumulation of lipid in this localized area. Xanthomas do not occur; however, there is diffuse accumulation of cholesterol esters in the skin, as well as the intestines, thymus, bone marrow, lymph nodes, and spleen. ABC (ATP-binding cassette) transporters generally have transmembrane domains that move substrates across cell membranes. Defects in 14 of the over 50 known ABC transporters cause 13 genetic diseases, including cystic fibrosis, age-related macular degeneration, phytosterolemia, and adrenoleukodystrophy.

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NIEMANN-PICK DISEASE

This rare autosomal-recessive condition has six recognized subtypes. The originally described severely affected infants of Ashkenazi Jewish background have type A disease. Type B disease, which also results from mutations in the gene on chromosome 11 encoding for acid sphingomyelinase, is a non-neuropathic form that is the so-called adult type. Sphingomyelin (which is a ceramide phospholipid) and other lipids accumulate in the monocyte–macrophage system leading to shared systemic findings, such as hepatosplenomegaly, lymphadenopathy, pancytopenia, and pulmonary disease. There are two subtypes of C and type D (Nova Scotia), which result from defects in cholesterol metabolism.

Cutaneous changes in those patients with acid sphingomyelinase gene mutations are seen in type A patients. They are uncommon and consist of distinctive yellowish coloration of the skin and, in rare patients, skin-colored to tan papules. These latter lesions involve the head and upper extremities, and histologically contain foamy histiocytes, scattered multinucleateted cells, and a few lymphocytes. Inclusions may be observed in sweat gland epithelium. Black macular patches may occur on the mucous membranes.

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GAUCHER'S DISEASE

Gaucher's disease is a rare autosomal-recessive disorder of the reticuloendothelial system. Acid-β-glucosidase is lacking, with a resulting accumulation of glucocerebrosides in the brain and in the reticuloendothelial cells of the liver, spleen, and marrow. In rare cases, Gaucher's disease is caused by mutations in the prosaposin gene which encodes the saposin C activator protein, which is necessary for optimal activity of β-glucosidase. The disease occurs at any age, but three forms are recognized: type 1 (adult type), without neurologic involvement; type 2 disease, the infantile form, with acute early neurologic manifestations; and type 3, the juvenile chronic neuropathic type.

Some type 2 patients have congenital ichthyosis that precedes neurologic manifestations, and some are born with a collodian membrane. Epidermal ultrastructural and biochemical abnormalities occur in all type 2 patients. Hepatosplenomegaly, rarefaction of the long bones, pingueculae of the sclera, and a distinctive bronze coloration of the skin from melanin characterize the adult type. A deeper pigmentation may extend from the knees to the feet (Fig. 26-25). This is often caused by hemosiderin and may be accompanied by thrombocytopenia and splenomegaly.

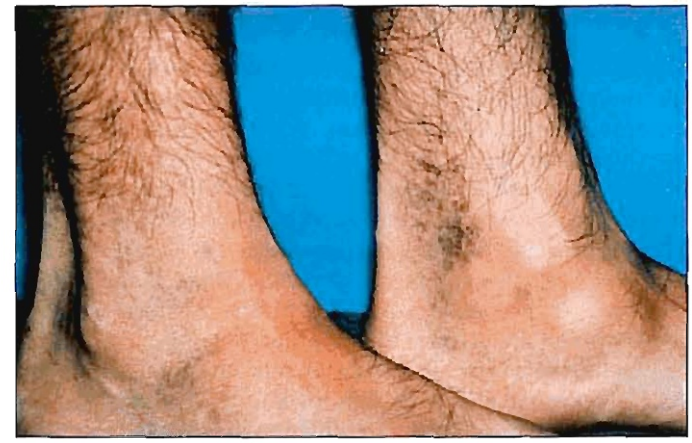

Fig. 26-25 Gaucher pigmentation of the lower leg.

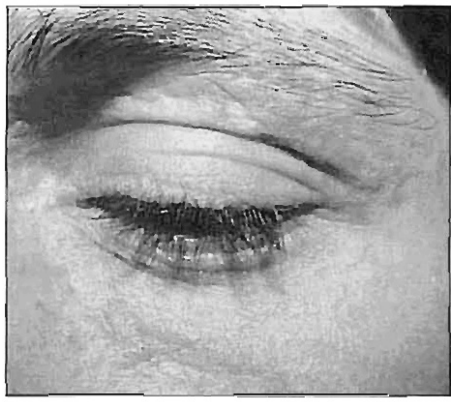

Fig. 26-26 Papules of the eyelid in lipoid proteinosis. (Courtesy of Eric Krause, MD)

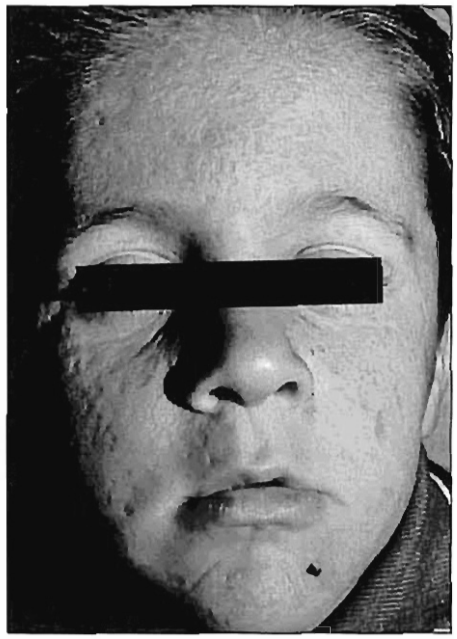

Fig. 26-27 Acnelform scarring in lipoid proteinosis.

The disease occurs most frequently among Ashkenazi Jews. Approximately 1 in 20 carry the defective gene, the lack of which leads to the accumulation of glucocerebroside in histiocytes in the bone marrow and spleen, and Kupffer cells in the liver, forming Gaucher cells. These are large, 20 to 100 μm in diameter, with one nucleus or a few small nuclei and pale cytoplasm that stains faintly for fat but is PAS positive. Elevated plasma acid phosphatase occurs and is a useful clue to the diagnosis. There is thinning of the cortex of the long bones.

Bone marrow transplantation performed before neurologic deficits occur has a high mortality rate (20–50%), but when successful has halted neurologic progression. Enzyme therapy is successful in treating some of the manifestations of the adult form, but it is limited by cost. Substrate-reduction therapy using the glycolipid synthesis inhibitor *N*-butyldeoxynojirimycin is also available. Symptomatic treatment includes radiation therapy to the long bones to relieve bone pain and splenectomy for hypersplenism (anemia and thrombocytopenia, with petechiae and bruising). With the identification of the gene defect, carrier screening and prenatal diagnosis are possible.

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LIPOID PROTEINOSIS

Also known as *Urbach-Wiethe disease* and *hyalinosis cutis et mucosae*, this rare autosomal-recessive disturbance is characterized by yellowish-white infiltrative deposits on the inner surfaces of the lips, undersurface of the tongue, fauces, and uvula. Other parts of the upper respiratory tract are also affected. In the early stage, crops of bullae and pustules occur; these heal, leaving acne-like scars (Fig. 26-26). Changes in the larynx lead to a marked degree of hoarseness, which usually appears within the first few weeks of life. Failure to cry and a hoarse, gravelly voice are suggestive signs.

The patient's tongue is "like wood" and moves only with difficulty. The patient is unable to protrude the tongue. Marked changes occur in the epiglottis. The vocal cords are thickened by an infiltration of grayish-yellow material, giving rise to the hoarseness observed so early. In some patients, similar yellowish and cream-colored deposits are sometimes observed on the labia majora, urethral orifice, scrotum, gluteal folds, and axillae. Severe xerostomia and poor salivation may result from infiltration of the salivary glands. Patchy alopecia is common.

Hyperkeratotic wartlike or nodular lesions are found on the dorsal aspects of the hands, fingers, elbows, and knees. The eyelid margins contain small, yellowish, transparent, pearly papules in about two-thirds of patients (Fig. 26-27). Drusen of Bruch's membrane are seen in the fundi in half the patients. Sickle-shaped calcifications dorsal and lateral to the sella turcica in skull x-ray films are pathognomonic.

Distinctive histologic features include extreme dilation of the blood vessels, thickening of their walls, progressive hyalinization of sweat glands, and infiltration of the dermis and subcutaneous tissue with extracellular hyaline deposits, which are also demonstrable in the vessel walls. Normal skin and mucous membranes also show changes of endothelial proliferation of the subpapillary vessels and a homogeneous thickening of the walls of the deeper vessels. Type IV collagen and laminin are increased around vessels.

The disease is caused by mutations in the extracellular matrix protein 1. Differentiation from erythropoietic protoporphyria may be difficult, especially histologically. Topical steroids, surgical removal of selected deposits, and occasional reports of improvement with systemic retinoids are treatments of limited benefit. One patient improved after 2 years of D-penicillamine treatment. While occasional patients die of respiratory obstruction in infancy, the disease is otherwise compatible with a normal lifespan.

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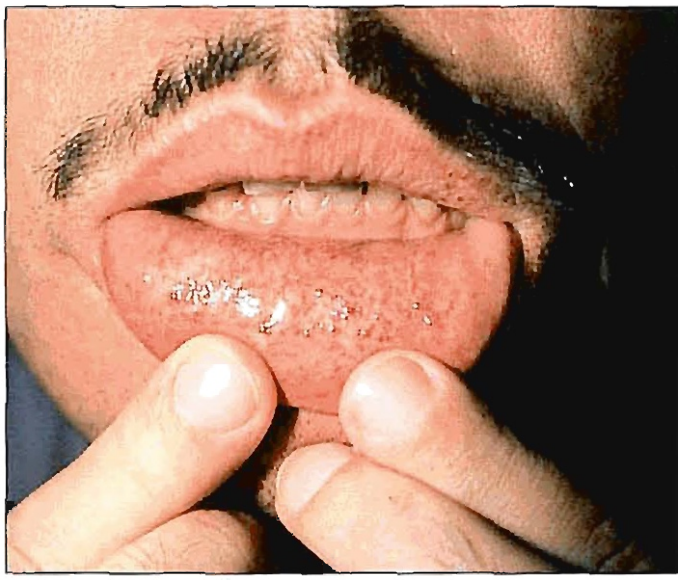

Fig. 26-28 Fabry disease.

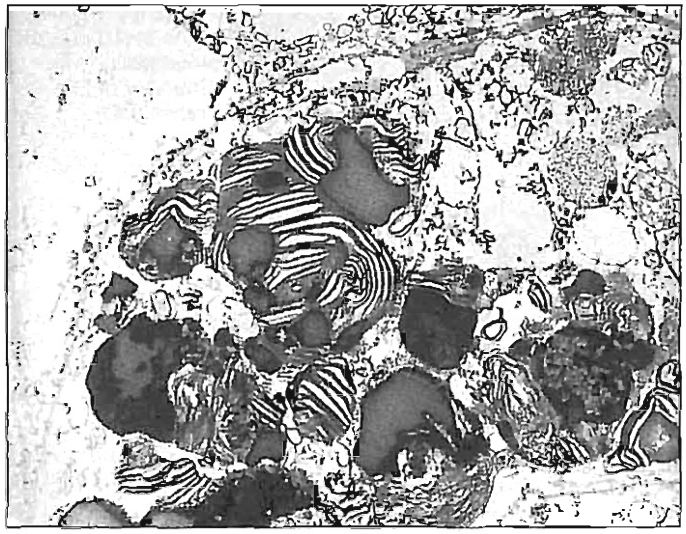

Fig. 26-29 Zebra bodies in Fabry disease.

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ANGIOKERATOMA CORPORIS DIFFUSUM (FABRY DISEASE)

Also known as *Anderson-Fabry disease*, in angiokeratoma corporis diffusum (ACD), a storage disease, glycosphingolipids accumulates in the skin and viscera. The skin lesions are widespread punctate telangiectatic vascular papules that on first inspection suggest purpura. Some show hyperkeratotic tops, but this is less prominent than in other forms of angiokeratoma. Myriad tiny telangiectatic papules are seen, especially on the lower extremities, scrotum and penis, lower trunk, axillae, ears, oral mucous membranes (Fig. 26-28), and lips, where the small, sometimes linear, angiokeratomas are most numerous on the midline of the lower lip. Hair growth is scanty.

The deposits of glycolipids (ceramide trihexoside) occur in the endothelial cells, fibroblasts, and pericytes of the dermis, and in the heart, kidneys, and autonomic nervous system. Cardiac disease (cardiomyopathy) and renal insufficiency bring death, usually in the fifth decade. The disease may be limited to one organ, such as the heart or kidney. Edema of the ankles, paralyses, paresthesias manifested by a burning sensation of the hands and feet, and hypohidrosis are often present. Abnormal vascular structures are noted in the conjunctiva and eye-grounds. Distinctive whorl-like opacities of the cornea occur in 90%, and 50% develop characteristic spokelike cataracts in the posterior capsular location. The urine, in addition to albuminuria, may show "Maltese cross" material on polaroscopy, and glycolipids may be seen in the form of "mulberry cells" in the sediment.

The cause of the disease is a deficiency of α-galactosidase A. Inheritance is by an X-linked recessive route. Female heterozygotes may show evidence of the disease in varying degrees; approximately 30% have angiokeratomas. The diagnosis can be confirmed by finding diminished levels of α-galactosidase A in leukocytes, serum, tears, skin fibroblasts, or amniotic fluid cells.

Histologically, there is dilation of capillaries in the papillary dermis, resulting in endothelium-lined lacunae filled with blood and surrounded by acanthotic and hyperkeratotic epidermis. Electron microscopy reveals characteristic electron-dense bodies in endothelial cells, pericytes, and fibroblasts (Fig. 26-29). They are also present in normal skin of affected adults and children.

Laser treatment of the angiokeratomas is cosmetically helpful. Phenytoin, neurontin, and carbamazepine afford significant relief of pain. Enzyme replacement therapy is safe and can reverse substrate storage in the lysozyme.

FUCOSIDOSIS

Angiokeratomas identical to those of Fabry disease occur in this rare disorder. It can be distinguished clinically by the frequent presence of coarse thickening of the skin of the face, severe mental retardation, weakness, spasticity, and seizures.

Histologically, there are granule-filled vacuoles in endothelial and other cells. The defect, a lack of α-L-fucosidase, is transmitted as an autosomal-recessive trait. Progressive mental and motor deterioration begins in infancy and progresses, with death by age 18 to 20 as a rule.

SIALIDOSIS

Another disease manifesting Fabry-like angiokeratomas is caused by mutations in the sialidase gene NEU1, resulting in intracellular accumulation of sialiated oligosaccharides. Mental retardation, myoclonus, cerebellar ataxia, skeletal abnormalities, and coarse facies occur.

B-MANNOSIDASE DEFICIENCY

This is a rare autosomal-recessive disorder of glycoprotein metabolism. In addition to the Fabry-like angiokeratomas, mental retardation, hearing loss, aggressive behavior,

peripheral neuropathy, recurrent infections, epilepsy, coarse facies, and skeletal abnormalities are often present.

Several patients with other rare autosomal-recessive lysosomal enzyme disorders, such as galactosialidosis, aspartylglycosaminuria, GM_1 gangliosidosis (β-galactosidase deficiency which may also manifest extensive dermal melanocytosis), and α-*N*-acetylgalactosaminidase deficiency (Kanzaki disease) have been reported to have Fabry-like angiokeratomas. Finally, several patients without any detectable enzyme deficiency have been reported. Among them was a family with autosomal-dominantly inherited Fabry-like angiokeratomas associated with arteriovenous malformations. It should be emphasized that there are many normal patients who have widespread small petechia-like lesions that erupt in adulthood. This is a variant of cherry angiomas.

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NECROBIOSIS LIPOIDICA (NECROBIOSIS LIPOIDICA DIABETICORUM)

Necrobiosis lipoidica is characterized by well-circumscribed, firm, depressed, waxy, yellow–brown, lesions on the skin of persons who may also have diabetes mellitus. Women are three times more commonly affected than men.

The earliest changes are sharply bordered, elevated, small red papules; these may be capped by a slight scale and do not disappear under diascopic pressure. Later, the lesions develop into irregularly round or oval scleroderma-like lesions with well-defined borders and a smooth, glistening (glazed) surface. The center becomes depressed and sulfur-yellow, so that a firm yellowish lesion forms, surrounded by a broad violet–red or pink border. In the yellow portion numerous telangiectases are evident. Ulceration is not unusual. Rarely, squamous cell carcinoma may occur in chronic ulcers.

The most common location of the lesions is the shins (Fig. 26-30); about 85% occur on the legs. A much less common site is the forearms, and they have been reported on the trunk, face, scalp, palms, and soles. Only rarely are sites exclusive of the legs present.

Sixty percent of patients with necrobiosis lipoidica have diabetes mellitus; another 20% will have glucose intolerance or a family history of diabetes. In 15%, necrobiosis lipoidica precedes the onset of frank diabetes by an average of 2 years. Control of the diabetes does not influence the course of the disease. Its incidence is 3 to 7 in 1000 diabetic patients.

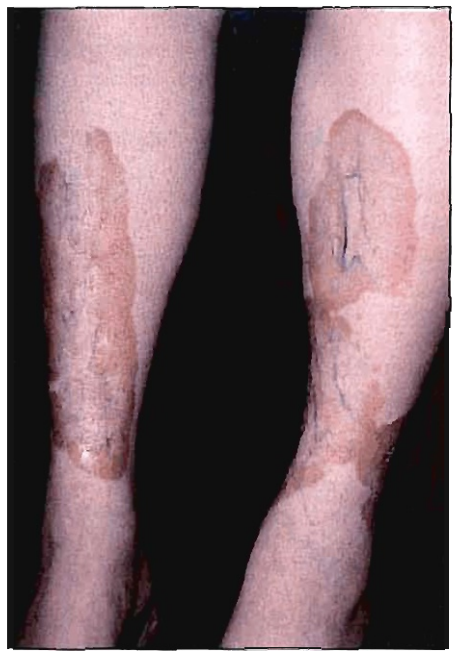

Fig. 26-30
Necrobiosis lipoidica diabeticorum.

The average age of onset is 34 years—22 years, on average, in insulin-dependent patients and 49 years in non–insulin-dependent patients.

Histologically, well-developed lesions of necrobiosis lipoidica demonstrate a superficial, deep, and interstitial inflammatory process that involves the whole reticular dermis and often the panniculus. Because the dermis is firm, punch biopsy specimens appear rectangular rather than tapered. The inflammatory cells include lymphocytes, histiocytes, multinucleate giant cells, and plasma cells. At low magnification there are layered palisaded granulomas with pale pink degenerated collagen alternating with ampophilic staining histiocytes. In contradistinction to granuloma annulare, mucin is not increased in the centers of the granulomas. The overlying epidermis tends to be thinned, with loss of the normal rete ridge pattern.

Treatment, after control of the diabetes is achieved, is not completely satisfactory. The best results have occurred after intralesional injections of triamcinolone suspension into the inflammatory papules and active advancing edges. Injection into the yellow center is of little benefit and may result in ulceration. Concerns about atrophy limit topical steroid use; however, in the actively inflamed early stage potent topical steroids with occlusion have produced resolution. Some cases have benefited from excision and skin grafts, but others have had recurrences in or at the edges of the grafts.

One series of six cases reported that systemic corticosteroids given over a 5-week period were effective in all patients treated and there was no recurrence after a mean follow-up of 7 months. Control of the diabetes was achieved by oral hypoglycemics or insulin. The atrophy did not improve. Pentoxifylline, chloroquine, nicotinamide, ticlopidine, topical PUVA, topical tacrolimus, cyclosporin, and tretinoin have been reported to be helpful in individual cases. Other case reports document that hyperbaric oxygen, topically applied bovine collagen, and cyclosporin are helpful in healing chronic ulcers. Spontaneous resolution may occur in 13% to 19% of patients after 6 to 12 years.

Clayton TH, et al: Successful treatment of chronic ulcerated necrobiasis lipoidica with 0.1% tacrolimus ointment. Br J Dermatol 2005;152:581.
Ferringer T, et al: Cutaneous manifestations of diabetes mellitus. Dermatol Clin 2002;20:483.
Gudi VS, et al: Squamous cell carcinoma in area of NLD. Clin Exp Dermatol 2000;25:597.
Lowitt MH, et al: Necrobiosis lipoidica. J Am Acad Dermatol 1991;25:735.
Nguyen K, et al: NLD treated with chloroquine. J Am Acad Dermatol 2002;46:S34.
Patel GK, et al: Severe disabling Koebnerizing ulcerated necrobiosis lipoidica successfully managed with topical PUVA. Br J Dermatol 2000;143:668.

OTHER DIABETIC DERMADROMES

In addition to necrobiosis lipoidica, there are many cutaneous signs in this common endocrinopathy.

Diabetic Dermopathy (Shin Spots)

Dull-red papules that progress to well-circumscribed, small, round, atrophic, hyperpigmented lesions on the shins are the most common cutaneous sign of diabetes. Although they occur individually in people who do not have diabetes, if four or more are present the specificity is high for microvascular disease in other tissues. They are present in 50% of people with diabetes, most commonly men.

Diabetic Bullae

Noninflammatory, spontaneous, painless blistering, most often in acral locations, is characteristic (Fig. 26-31). Lesions heal spontaneously in 4 to 5 weeks, usually without scarring.

Both sub- and intra-epidermal locations have been reported as the site of blister formation, but in the authors' experience lesions are subepidermal. Electron microscopic studies show separation at the lamina lucida level. DIF is negative. UV light, trauma, neuropathy, and cation imbalance have all been hypothesized to be inciting factors to the blistering. There is a reduced threshold to suction-induced blistering in insulin-dependent diabetics.

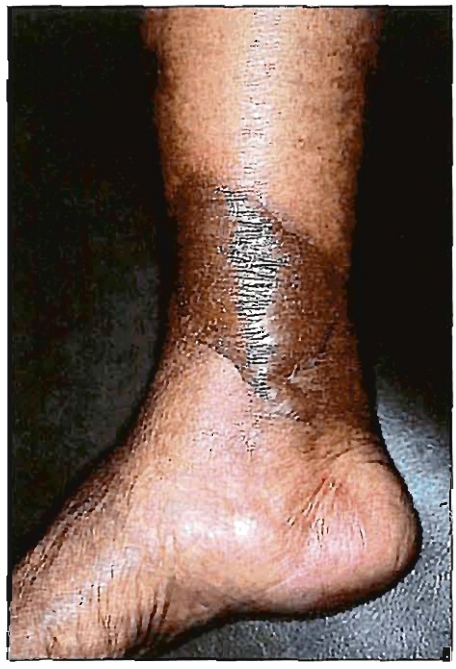

Fig. 26-31 Bullous eruption of diabetes.

Carotenosis

Carotenosis is a yellowish discoloration of the skin, especially of the palms and soles (Fig. 26-32), that is sometimes seen in diabetic patients. Of the 50% of diabetic persons who have carotenemia, about 10% have carotenosis. The sclerae remain white. There may be night blindness (delayed dark adaptation) as a result of reduced conversion of carotene to vitamin A in the liver.

Limited Joint Mobility and Waxy Skin

Limited joint mobility and waxy skin are important not only because of the 30% to 50% prevalence of these conditions in diabetic patients with long-standing disease, but also because they are associated with microvascular complications, such as nephropathy and retinopathy. Joint symptoms begin with limitation of joint mobility in the fifth finger at the metacarpophalangeal and proximal joints and progress radially to the other fingers. It is bilateral, symmetrical, and painless. Involvement of the feet also occurs and is thought to contribute to the development of chronic ulcerations. Such open sores on the neuropathic, microvascularly compromised, infection-prone diabetic foot pose a constant threat to life and limb.

Other Associated Conditions in Patients with Diabetes

Various abnormalities associated with diabetes are erysipelas-like erythema of the legs or feet; sweating disturbances; paresthesias of the legs; mal perforans ulcerations; a predisposition to certain infections such as mucormycosis, group B streptococcal infections, nonclostridial gas gangrene, and malignant external otitis resulting from *Pseudomonas*; disseminated granuloma annulare; eruptive xanthomas; clear cell syringomas; eruptive xanthomas; rubeosis of the face; lipodystrophy; acquired perforating disorders; acanthosis nigricans; skin tags; Dupuytren contracture; and finger-pebbling.

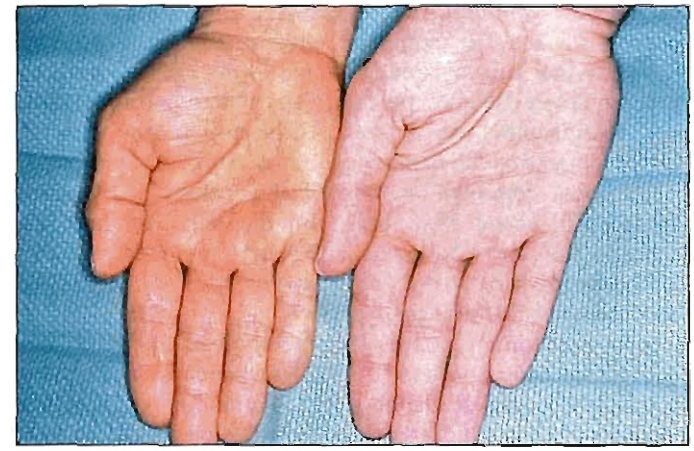

Fig. 26-32 Carotenemia, yellow palm shown next to normal palm. (Courtesy of James Fitzpatrick, MD)

Arkkila PE, et al: Dupuytren's disease in type 1 diabetic patients. Clin Exp Rheumatol 1996;14:59.
Aye M, et al: Dermatological care of the diabetic foot. Am J Clin Dermatol 2002;3:463.
Boulton AJM, et al: Neuropathic diabetic foot ulcers. N Engl J Med 2004;351:48.
Ferringer T, et al: Cutaneous manifestations of diabetes mellitus. Dermatol Clin 2002;20:483.
Huntley AC: Finger pebbles: a common finding in diabetes mellitus. J Am Acad Dermatol 1986;14:612.
Jabbour SA: Cutaneous manifestations of endocrine disorders. Am J Clin Dermatol 2003;4:315.
Kakourou T, et al: Limited joint mobility and lipodystrophy in children and adolescents with insulin-dependent diabetes mellitus. Pediatr Dermatol 1994;11:310.
Lipsky BA, et al: Diabetic bullae. Int J Dermatol 2000;39:196.
Sibbald RG, et al: Skin and diabetes. Endocrinol Metab Clin North Am 1996;25:463.

OTHER METABOLIC DISORDERS

CITRULLINEMIA

Citrullinemia occurs in two forms. Type I is caused by a deficiency of the enzyme argininosuccinic acid synthetase. This enzyme converts citrulline and aspartic acid to argininosuccinic acid, as a part of the urea cycle. Low plasma arginine levels result, and the hypothesis is that since keratin is 16% arginine, dermatitis may occur. Neonates who present with severe deficiencies and hyperammonemic crises may develop erosive, erythematous, scaling patches, and plaques prominent in the perioral, lower abdominal, diaper, and buttock regions. This eruption clears with arginine supplementation. Short, sparse hair may also be present. Cirtullinemia type II is due to a defect in the SCL25A13 gene and is seen nearly exclusively in adult Japanese patients.

In carbamoyl phosphate synthetase deficiency, low plasma arginine levels may also occur, and similar cutaneous findings have been reported in this second metabolic defect of the urea cycle.

Diets high in arginine will heal the skin lesions.

Goldblum OM, et al: Neonatal citrullinemia associated with cutaneous manifestations and arginine deficiency. J Am Acad Dermatol 1986;14:321.
Takeoka M, et al: Carbamyl phosphate synthetase 1 deficiency. Pediatr Neurol 2001;24:193.
Tokatli A, et al: Citrullinemia. Turk J Pediatr 1998;40:185.

HARTNUP DISEASE

Hartnup disease is an inborn error of tryptophan excretion; it was named after the Hartnup family, in which it was first noted. The outstanding findings are a pellagra-like dermatitis following exposure to sunlight, intermittent cerebellar ataxia, psychiatric manifestations, and constant aminoaciduria.

The dermatitis occurs on exposed parts of the skin, chiefly the face, neck, hands, and legs. The erythematous scaly patches flare up into a hot, red, exudative state after exposure to sunlight, followed after subsidence by hyperpigmentation. Stomatitis and vulvitis also occur. The disease becomes milder with increasing age. Hartnup disease is an autosomal-recessive trait. Large amounts of indole-3-acetic acid and indican are secreted in the urine. Hartnup disease is caused by mutations in the SLC6A19 gene on chromosome 5. SLC6A19 transports neutral amino acids across the apical membrane of epithelial cells. The skin lesions respond to niacinamide, 200 mg/day.

Galadari E, et al: Hartnup disease. Int J Dermatol 1993;32:904.
Oakley A, et al: Hartnup disease presenting in an adult. Clin Exp Dermatol 1994;19:407.
Seow HF, et al: Hartnup disorder is caused by mutations in the gene encoding the neutral amino acid transporter SLC6A19. Nat Genet 2004;36:1003.

PROLIDASE DEFICIENCY

Prolidase deficiency is an autosomal-recessive inherited inborn error of metabolism. Prolidase, or peptidase D, cleaves dipeptides containing C-terminal proline or hydroxyproline. When this enzyme is deficient, the normal recycling of proline residues obtained from collagen degradation is impaired. A build-up of iminodipeptides results, with disturbances in connective tissue metabolism and excretion of large amounts of iminodipeptides in the urine. Also, the absence of prolidase activity causes the activation of a necrosis-like cellular death, which may be responsible for the skin lesions.

Clinically, 85% of patients have some dermatologic manifestations. The most important cutaneous signs, which almost always appear before the affected person is 12 years old, are skin fragility, ulceration, and scarring of the lower extremities; photosensitivity and telangiectasia; poliosis; scaly, erythematous, maculopapular, and purpuric lesions; and thickening of the skin with lymphedema. Systemic signs and symptoms include mental deficiency, splenomegaly, and recurrent infections. An unusual facial appearance is noted at times, with low hairline, frontal bossing, and saddle nose. Prolidase measurement may be determined in erythrocytes, leukocytes, or fibroblasts. Many therapeutic options have been described, such as oral supplements of manganese and ascorbic acid, both modulators of prolidase activity; however, results of treatment are highly variable. Apheresis exchange repeated monthly may improve the leg ulcers. In long-standing ulcerations squamous cell carcinomas may occur.

Bissonnette R, et al: Prolidase deficiency. J Am Acad Dermatol 1993;29:818.
Fimiani M, et al: Squamous cell carcinoma of the leg in a patient with prolidase deficiency. Br J Dermatol 1999;140:362.
Lupi A, et al: Therapeutic apheresis exchange in two patients with prolidase deficiency. Br J Dermatol 2002;147:1237.

PHENYLKETONURIA

Phenylketonuria, an autosomal-recessive disorder of phenylalanine metabolism, is characterized by mental deficiency; epileptic seizures; the presence of phenylpyruvic acid in the urine; pigmentary dilution of skin, hair, and eyes; pseudoscleroderma; and dermatitis (Fig. 26-33). It is most common in white persons. Phenylalanine hydroxylase is lacking in the liver and also in peripheral lymphocytes. Phenylalanine is therefore not oxidized to tyrosine.

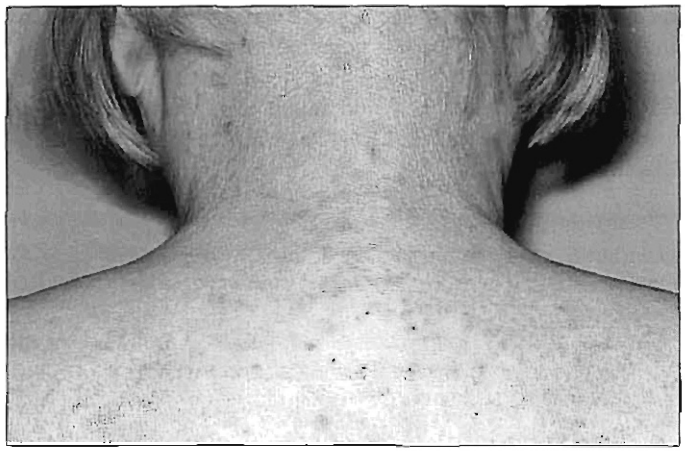

Fig. 26-33 Light skinned, light haired PKU patient with dermatitis. (Courtesy of Jeff Miller, MD)

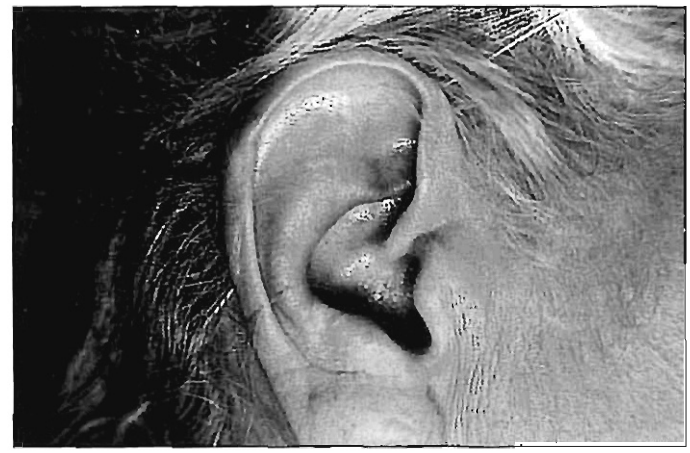

Fig. 26-34 Ochronotic pigmentation of ear cartilage.

Affected children are blue eyed, with blond hair and fair skin. They are usually extremely sensitive to light, and about 50% have an eczematous dermatitis. It is clinically similar to atopic dermatitis, with a predilection for the flexures. It is worst in the youngest patients, may improve with dietary treatment, and has been exacerbated by phenylalanine challenge in a carrier of the recessive gene. Skin lesions may be sclerodermatous in nature. Indurations of the thighs and buttocks are present early in infancy and increase with time. After many years the lesions soften and become atrophic.

Blood levels of phenylalanine are high. The presence of phenylpyruvic acid in the urine is demonstrated by a characteristic deep-green color when a few drops of ferric chloride solution are added to it. Green diapers occur in histidinemia as well as in phenylketonuria.

In developed countries universal screening is practiced so dietary therapy with phenylalanine restriction combined with supplementation of tyrosine and other amino acids may be instituted. This prevents the manifestations of the disease. If compliance is poor, the manifestations, including eczema, may develop at any age, followed by improvement of the skin with reinstitution of the diet.

Belloso LM, et al: Cutaneous findings in a 51-year-od man with phenylketonuria. J Am Acad Dermatol 2003;49:S190.

Nova MP, et al: Scleroderma-like skin indurations in a child with phenylketonuria. J Am Acad Dermatol 1992;26:329.

ALKAPTONURIA AND OCHRONOSIS

Alkaptonuria, inherited as an autosomal-recessive trait, is caused by the lack of renal and hepatic homogentisic acid oxidase, the enzyme necessary for the catabolism of homogentisic acid to acetoacetic and fumaric acids. It is characterized by the excretion of homogentisic acid in the urine to produce a black-staining urine, the deposition of a grossly brown–black pigment in the connective tissue, and ochronotic arthropathy.

In patients with alkaptonuria the voided urine is dark and on standing turns black from the homogentisic acid. For many years the dark urine may be the only indication of the presence of alkaptonuria. In the meantime, large amounts of homogentisic acid are accumulated in the body tissues. By the third decade of life the deposition of pigment becomes apparent. Cartilage is preferentially affected. The early sign is the pigmentation of the sclera (Osler's sign) and the cartilage of the ears (Fig. 26-34). Later the cartilage of the nose and tendons, especially those on the hands, become discolored.

Blue or mottled brown macules appear on the skin. The bluish macules have a predilection for the fingers, ears, nose, genital regions, apices of the axillae, and buccal and vaginal mucosa. Palmoplantar pigmentation may occur. The sweat glands are rich in ochronotic pigment granules, and the intradermal injection of epinephrine into the skin of the axillary vault will yield brown–black sweat droplets in the follicular orifices. The cerumen is often black. Internally, the larynx, great vessels, and valves of the heart, kidneys, esophagus, tonsils, and dura mater may be involved.

Histologically, there are large, irregular ochre bodies within the reticular dermis. They represent degenerated elastic fibers with deposition of ochronotic pigment and stain black with crystal violet or methylene blue.

Ochronotic arthropathy involves the spinal joints first, resembling osteoarthritis. Next affected are the knees, shoulders, and hips. Radiographic films show a characteristic appearance of early calcification of the intervertebral disk and later narrowing of the intervertebral spaces with eventual disk collapse.

There is no effective treatment. Nitisinone, used in treating tyrosinemai type I, inhibits the enzyme that produces homogentisic acid. Its safety and efficacy in alkaptonuria is being investigated.

Exogenous Ochronosis

Topically applied phenolic intermediates such as hydroquinone, carbolic acid (phenol), picric acid, and resorcinol may produce exogenous ochronosis (Fig. 26-35). Hydroquinone specifically inhibits the enzyme homogentisic acid oxidase locally, resulting in accumulation of this substance on the collagen fibers in tissues where it is applied. Histologically, exogenous ochronosis and alkaptonuria have identical changes on skin biopsy (Fig. 26-36). Treatment with dermabrasion and the CO_2 and Q-switched alexandrite lasers.

Bellew SG, et al: Treatment of exogenous ochronisis with a Q-switched alexandrite (755 mm) laser. Dermatol Surg 2004; 30:555.

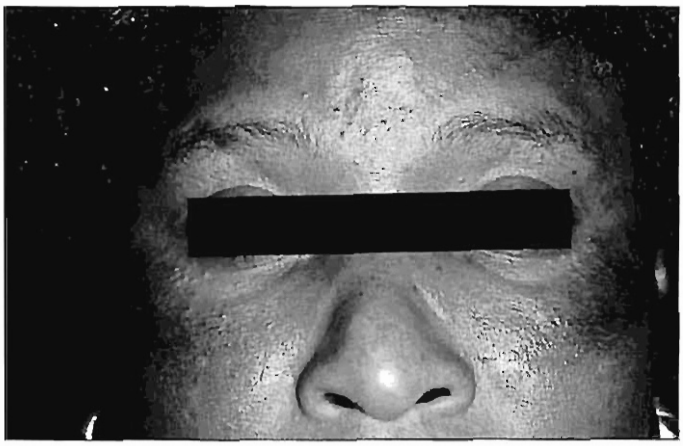

Fig. 26-35 Exogenous ochronosis.

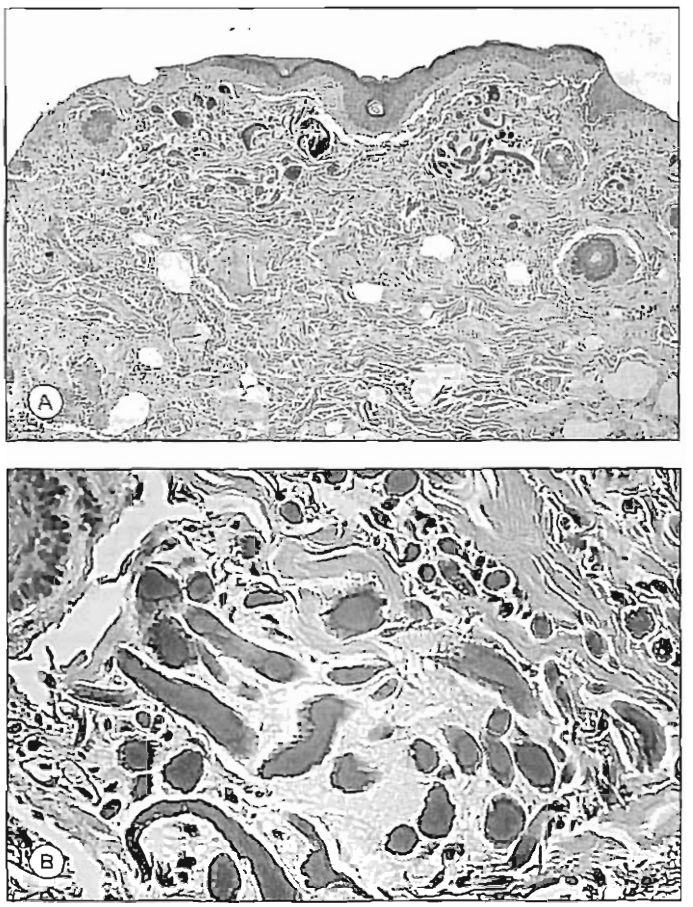

Fig. 26-36 *A* and *B*, Large ochre bodies in the dermis in exogenous ochronosis.

Bongiomo MR, et al: Exogenous ochronosis and striae atrophicae following the use of bleaching creams. Int J Dermatol 2005;44:112.

Gutzmer R, et al: Alkaptonuric ochronosis. J Am Acad Dermatol 1997;37:305.

Lubics A, et al: Extensive bluish gray skin pigmentation and severe arthropathy. Arch Dermatol 2000;36:548.

Micali G, et al: Endogenous ochronosis (alkaptonuria). Arch Dermatol 1998;134:98.

Phornphutkul C, et al: Natural history of alkaptonuria. N Engl J Med 2002;347:2111.

Turiansky GW, et al: Bluish patches on the ears and axillae with dark urine. Int J Dermatol 2001;40:333.

WILSON'S DISEASE (HEPATOLENTICULAR DEGENERATION)

Wilson's disease is an autosomal-recessive derangement of copper transport. Affected persons develop hepatomegaly, splenomegaly, and neuropsychiatric changes. Slurred speech, a squeaky voice, salivation, dysphagia, tremors, incoordination, and spasticity may all occur. There is progressive, fatal hepatic and central nervous system degeneration. The body retains an excessive amount of copper, leading to damage to the liver and brain. As a result, azure lunulae (sky-blue moons) of the nails occur in 10% of patients, and the smoky, greenish-brown Kayser-Fleischer rings develop at the edges of the corneas. Hyperpigmentation develops on the lower extremities in most patients. A vague greenish discoloration of the skin on the face, neck, and genitalia may also be present. An idiopathic blistering eruption that ceased with treatment of Wilson's disease has been reported. Skin changes of cirrhosis (vascular spiders and palmar erythema) may occur. Low ceruloplasmin level in the serum is diagnostic.

The disease is caused by the synthesis of a defective copper-transporting enzyme, P-type ATPase (ATP7B), leading to accumulation of copper in the brain, liver, and kidney. The treatment is D-penicillamine, which removes copper by chelating it. The dose is 1 or 2 g/day orally. Potential side effects include pemphigus, cutis laxa, and elastosis perforans serpiginosa, which has been reported repeatedly in Wilson patients on penicillamine. Treatment must be continued for life.

Baban NK, et al: Wilson's disease. South Med J 1997;90:535.

Yoo HW: Identification of novel mutations and the three most common mutations in the human ATP7B gene of Korean patients with Wilson disease. Genet Med 2002;4:43S.

TYROSINEMIA II (RICHNER–HANHART SYNDROME)

Tyrosinemia is an autosomal-recessive syndrome resulting from a deficiency of hepatic tyrosine aminotransferase. Serum tyrosine ranges from 200 to 300 µmol/100 mL (normal, ≤10). Clinical features are mild-to-severe keratitis, and hyperkeratotic and erosive lesions of palms and soles, often with mental retardation. Photophobia and tearing commonly occur as the keratitis begins, and ultimately neovascularization is seen. Painful palmar and plantar erosions and hyperkeratoses usually appear within the first year of life, weeks to months after the eye lesions. Thigh skin, grafted to the heel, is spared. A low tyrosine, low phenylalanine diet may improve or prevent the eye and skin lesions but may or may not benefit the mental retardation.

El-Essa MA, et al: Tyrosinaemia type II. J Inherit Metab Dis 2001;24:824.

Jimenez-Acosta F: Painful plantar calluses and mental retardation. Arch Dermatol 1994;130:507.

Rabinowitz LG, et al: Painful keratoderma and photophobia. J Pediatr 1995;126:266.

Tallab TM: Richner–Hanhart syndrome. J Am Acad Dermatol 1996;35:857.

HURLER SYNDROME (MUCOPOLYSACCHARIDOSIS I)

Hurler syndrome, or gargoylism, is an autosomal-recessive disorder of mucopolysaccharide metabolism. A deficiency of α-L-iduronidase is the causative defect. It is characterized by mental retardation, hepatosplenomegaly, umbilical and inguinal hernia, genital infantilism, corneal opacities, and skin abnormalities. Patients with Hurler syndrome have gargoyle-like features, with a broad saddle nose, thick lips, and a large tongue. The skin is thickened, with ridges and grooves, especially on the upper half of the body. Fine lanugo hair is profusely distributed all over the body. Large, coarse hair is prominent, especially on the extremities. Dermal melanocytosis characterized by extensive, blue pigmentation with both a dorsal and ventral distribution, indistinct borders, and a persistent and/or progressive course occurs in some patients with lysosomal storage disease, including patients with Hurler syndrome, Hunter syndrome, and GM1-gangliosidosis type 1. The skeletal system is deformed, with hydrocephalus, kyphosis, and gibbus (cat-back shape). The hands are broad and have clawlike fingers. The joints are distorted.

The two acid mucopolysaccharides, dermatan sulfate and heparan sulfate, are produced excessively in gargoylism, so that in many tissues there is an accumulation, and they are excreted in the urine in large amounts. Dried urine on filter paper will show a purple color when acetic acid followed by toluidine blue reagent is added.

Prenatal diagnosis is possible. Bone marrow transplantation is the most effective treatment of Hurler syndrome. It can prevent dementia if performed early enough. Enzyme replacement therapy with recombinant human α-L-idronidase is also effective in treating the attenuated forms of Hurler syndrome (those without neuronal involvement).

Brooks DA: Alpha-l-iduronidase and enzyme replacement therapy for mucopolysaccharidosis I. Expert Opin Biol Ther 2002;2:967.

Hanson M, et al: Association of dermal melanocytosis with lysosomal storage disease. Arch Dermatol 2003;139:916.

HUNTER SYNDROME

Hunter syndrome is X-linked mucopolysaccharidosis (MPS) II. The clinical features are similar to those of Hurler syndrome and are characterized by an excessive storage and excretion of mucopolysaccharides. The relative mildness and mode of inheritance distinguish it from Hurler syndrome. The pebbly lesions of MPS II in the skin over the inferior angles of the scapulas represent the only diagnostic skin changes of the MPSs. These are firm, flesh-colored to white papules and nodules, which coalesce (Fig. 26-37). They are most common on the back, but may be seen on the pectoral areas, nape of the neck, and lateral aspects of the arms and thighs. They generally occur at about age 10. Additionally, the dermal melanocytosis described above with Hurler syndrome may occur in Hunter syndrome.

The deficient enzyme is iduronate-2-sulfatase. Dermatan sulfate and heparin sulfate are excreted in the urine in large amounts. Hematopoietic stem cell transplantation has limited efficacy but does result in the disappearance of the pebbly lesions within a month of the procedure.

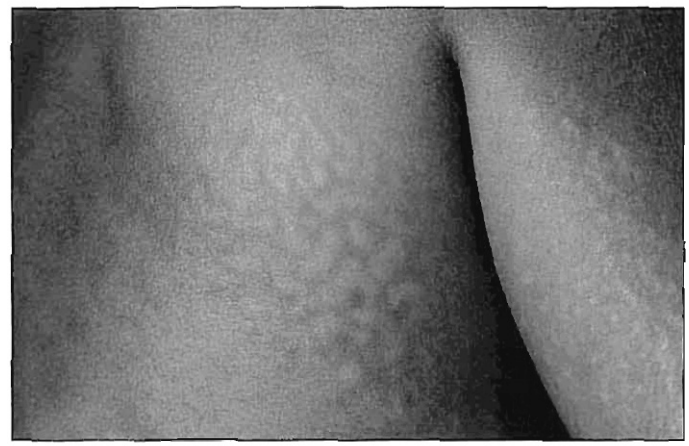

Fig. 26-37 Hunter syndrome papules.

Ito K, et al: The effect of haematopoietic stem cell transplant on papules with "pebbly" appearance in Hunter's syndrome. Br J Dermatol 2004;151:207.

Ochiai T, et al: Significance of extensive Mongolian spots in Hunter's syndrome. Br J Dermatol 2003;148:1173.

Zivony DI, et al: Ivory-colored papules in a young boy. Arch Dermatol 1995;131:81.

MORQUIO'S DISEASE (MUCOPOLYSACCHARIDOSIS IV)

This autosomal-recessive disorder is characterized by dwarfism, prognathism, corneal opacities, deafness, progressive kyphoscoliosis, flat feet, and knock-knees. The standing position is a crouch. There is increased excretion of keratan sulfate. The enzyme deficiencies are galactosamine-6-sulfate sulfatase in Morquio A and β-galactosidase in Morquio B.

Chudley AE, et al: Genetic landmarks through philately. Clin Genet 2002;62:438.

Urban Z, et al: Elastic-fiber pathologies. Am J Hum Genet 2000;67:4.

HYALURONIDASE DEFICIENCY (MUCOPOLYSACCHARIDOSIS IX)

A deficiency of hyaluronidase, caused by mutations in HYAL1, leads to short stature, erosions of the acetabula, and multiple periauricular soft-tissue masses. There is no neurologic or visceral involvement. Hyaluronan is an extracellular matrix component important for cell migration, cellular proliferation and differentiation, and is a structural component of connective tissue. Turnover of this glycosaminoglycan is dependent upon hyaluronidases, each of which has different tissue expression patterns, likely explaining the mild phenotype of this newly described condition.

Trigs-Raine B, et al: Mutations in HYAL1, a member of a tandemly distributed multigene family encoding disparate hyaluonidase activities, cause a newly described lysosomal disorder, mucopolysaccharidosis IX. Proc Natl Acad Sci USA 1999;96:6296.

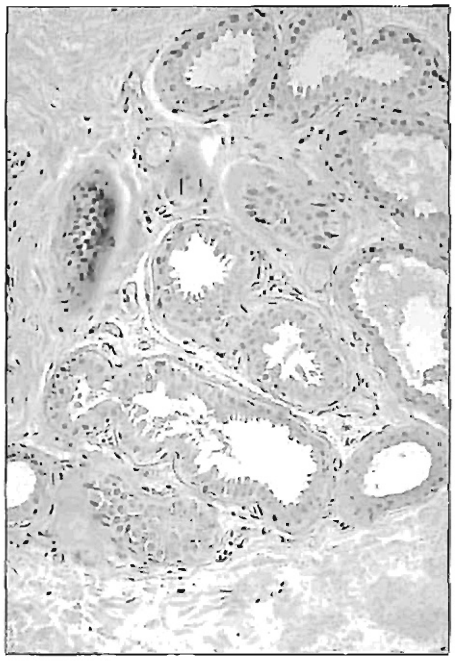

Fig. 26-38 PAS-stained inclusions in Lafora disease.

LAFORA'S DISEASE

Lafora's disease is an autosomal-recessive form of progressive epilepsy beginning at puberty. It is characterized by myoclonic jerks followed by progressive ataxia, dysphagia, dysarthria, dementia, and death in early adulthood. Diagnosis is established in the proper clinical setting by demonstration of characteristic PAS-positive cytoplasmic inclusion bodies in the eccrine ducts, axillary apocrine myoepithelial cells (Fig. 26-38), and peripheral nerves. The best site to biopsy is the axilla. Other conditions in which similar polyglucosan inclusions can be seen include normal aging (amyloid bodies), double athetosis syndrome, amyotrophic lateral sclerosis, and glycogen storage disease, type IV.

Cutaneous manifestations are rare. Papulonodular lesions on the ears and indurated, thickened plaques on the arms have been reported. Large amounts of acid mucopolysaccharides were demonstrated histologically in these lesions. In 80% of patients the disease is caused by a mutation in the EPM2A gene, which encodes lafin protein tyrosine phosphatase Abnormalities in an additional locus, EPM2B, which encodes the laforin binding partner protein malin, suggests an alteration in microtubular axonal and dendritic transport to be causative. There is no treatment.

Chan EM, et al: Mutations in NHLRC1 cause progressive myoclonus epilepsy. Nat Genet 2003;35:125.

Karimipour D, et al: Lafora's disease. J Am Acad Dermatol 1999; 41:790.

CADASIL SYNDROME

Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy is a neurovascular disease of young and middle-aged people. Children have cognitive impairment, young adults depression and migrane headaches, and those in their 40s and 50s experience multi-infarct dementia. One patient developed generalized hemorrhagic macules and papules. There is deposition of a granular eosinophilc material, NOTCH 3, in the media of arterial walls due to mutations in the NOTCH intercellular signaling pathways. This may be demonstrated on skin biopsy by electron microscopy or by a specific immunostain.

Gridley T: Notch signaling and inherited disease syndromes. Hum Mol Genet 2003;12:R9.

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Rumbaugh JA, et al: CADASIL. J Am Acad Dermatol 2000; 43:1128.

Walsh JS, et al: CADASIL. J Am Acad Dermatol 2000;43:1125.

FARBER DISEASE

Also known as *fibrocytic dysmucopolysaccharidosis* and *lipogranulomatosis,* Farber disease is characterized by periarticular swellings; a weak, hoarse cry; pulmonary failure; painful joint deformities; and motor and mental retardation. The onset is during the first months of life; death can be expected before the age of 2.

The rubbery subcutaneous nodules have a distinct yellowish hue and are 1 to 2 cm in diameter. They are usually located over the joints, lumbar spine, scalp, and weight-bearing areas. Histologically, they are granulomas. Diagnosis can be aided by finding Farber bodies (curvilinear bodies) within the cytoplasm or phagosomes of fibroblasts, histiocytes, or endothelial cells, banana-shaped bodies within Schwann cells, and zebra bodies within endothelial cells and neurons. There is an accumulation of ceramide and its degradation products in foam cells due to a specific deficiency of lysosomal ceramidase.

Levade T, et al: Neurodegenerative course in ceramidase deficiency (Farber disease) correlates with the residual lysosomal ceramide turnover in cultured living patient cells. J Neurol Sci 1995;134:108.

Rauch HJ, et al: Banana bodies in disseminated lipogranulomatosis (Farber disease). Am J Dermatopathol 1983;5:263.

ADRENOLEUKODYSTROPHY (SCHILDER'S DISEASE)

Adrenoleukodystrophy (ALD) is an X-linked disorder in which cerebral white matter becomes progressively demyelinated and serious adrenocortical insufficiency usually occurs. Skin hyperpigmentation often calls attention to the adrenal disease, and mental deterioration indicates the even graver diagnosis of ALD. A mild ichthyotic appearance to the skin of the trunk and legs and sparse hair with trichorrhexis nodosa-like features may occur. Skin biopsies may show characteristic vacuolization of eccrine secretory coils (duct cells being spared), and biopsies of the skin and conjunctiva may show diagnostic clefts in Schwann cells surrounding myelinated axons. Mutations are in the ABCD1 gene, leading to abnormalities in a peroxisomal ABC half-transporter, involved in the import of very long-chain fatty acids into the peroxisome. Bone marrow transplantation may prevent dementia and result in a better quality of life.

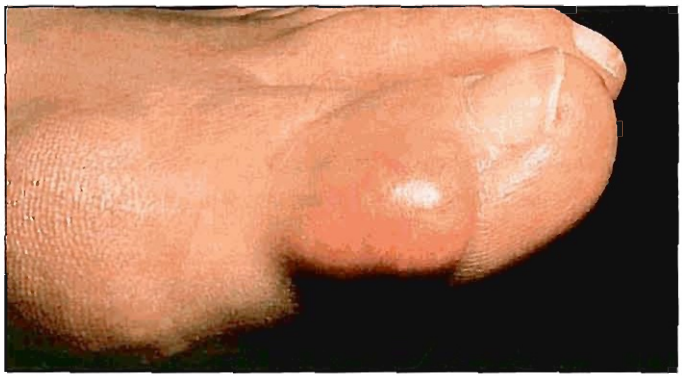

Fig. 26-39 Gouty tophus. (*Courtesy of James Fitzpatrick, MD*)

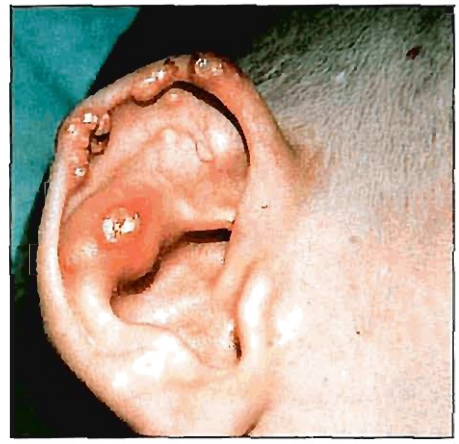

Fig. 26-40 Lesch-Nyhan syndrome.

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GOUT

Classic gout presents as an acute monoarthritis, usually of the great toe or knee, in a middle-aged to elderly man with hyperuricemia. In such patients with chronic disease, usually present for more than 10 years, monosodium urate monohydrate may be deposited in the subcutaneous tissues, forming nodules called tophi. These vary from pinhead- to pea-sized or, rarely, even baseball-sized. They are commonly found on the rims of the ears and over the distal interphalangeal articulations (Fig. 26-39). Tophi are of a yellow or cream color. In the course of time they tend to break down and discharge sodium urate crystals, afterward healing and perhaps breaking down again. The diagnosis is verified histologically by finding the characteristic long, needle-shaped crystals of monosodium urate. Because routine processing dissolves these deposits, fixation in absolute ethanol or freezing is optimal for their demonstration. Atypical gout occurs as a polyarticular chronic arthritis, often of the hands. It occurs equally in women as in men, and there may be tophi, frequently overlying Hebreden nodes, at presentation. Another risk group is organ transplant patients of whom 10% develop gout. Acute arthritis is treated with NSAIDs, prednisone or colchicines, while long-term management is with uricosuric agents or xanthine oxidase inhibitors.

LESCH-NYHAN SYNDROME

Also known as *juvenile gout*, Lesch-Nyhan syndrome is a rare, X-linked, recessively-inherited disorder characterized by childhood hyperuricemia, gout, tophi (Fig. 26-40), choreoathetosis, progressive mental retardation, and self-mutilation.

The cutaneous lesions are distinctive. Massive self-mutilation of lips with the teeth occurs. The fingers are also badly chewed. The ears and nose are occasionally mutilated. An early diagnostic clue is orange crystals in the diaper. The blood uric acid is increased and allopurinol, 200 to 400 mg/day, is given. There is a marked deficiency in an enzyme of purine metabolism, hypoxanthine guanine phosphoribosyltransferase (HGPRT).

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Jinnah HA, et al: The spectrum of inherited mutations causing HPRT deficiency. Mutat Res 2000;463:309.
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CHAPTER

27 Genodermatoses and Congenital Anomalies

Genetic disorders are often grouped into three categories: chromosomal, single gene, and polygenetic. Chromosomal disorders can be numerical, such as trisomy and monosomy, or structural, resulting from translocations or deletions. Most genodermatoses show single-gene or mendelian inheritance (autosomal-dominant, autosomal-recessive, or X-linked recessive genes). Polygenetic syndromes often involve complex interactions of genes.

Autosomal-dominant conditions require only a single gene to produce a given phenotype. Usually the patient has one affected parent or is affected by a new mutation. The disease is transmitted from generation to generation. Autosomal-recessive traits require a homozygous state to produce the abnormality. The pedigree will often reveal parental consanguinity. Parents will be clinically unaffected but often have affected relatives. X-linked conditions occur when the mutant gene is carried on the X chromosome. If a disease is X-linked recessive, the loss is evident in males (XY) who do not have a second X chromosome to express the normal allele. Therefore, X-linked recessive traits occur almost exclusively in males. They cannot transmit the disease to sons (who inherit their Y chromosome), but all their daughters will be carriers. Carrier females who are heterozygous (having one normal and one abnormal X chromosome) occasionally show some subtle evidence of the disease. This occurs as a result of Lyonization (the physiologic segmental inactivation of one of the X-chromosomes). X-linked dominant disease states are commonly lethal in males. Survival is possible in females who retain a normal allele. As the mutation is commonly lethal in many affected cell lines, females commonly demonstrate loss of normal tissue in the affected segments (loss of digits, microphthalmia, loss of teeth). X-linked dominant traits result in pedigrees in which more than one female is affected but no males express the disease. Rarely, males may survive, especially if they have Kleinfelter syndrome (XXY).

Mosaicism is the presence of two or more genetically distinct cell lines in a single individual. It may occur as a result of physiologic inactivation of one X-chromosome (Lyonization) or as the result of post-zygotic somatic mutation. Mosaicism often presents in a linear and whorled pattern along the lines of Blaschko. In mosaic states, genes that are detrimental to a cell population during fetal development often result in thin segments that are overgrown by the adjacent normal tissue. Genes that confer a growth advantage during fetal development (e.g. mutated tumor suppressor genes) may result in broader plaque-type lesions that have grown beyond the boundaries of a typical Blaschko segment.

In autosomal-dominant conditions, a normal allele remains, but is not enough to prevent disease. Loss of heterozygosity (LOH) is the segmental loss of this remaining normal allele. LOH may give rise to segments of the body with an exaggerated presentation of the syndrome. The affected area corresponds to a Blaschko segment or plaque. The forehead plaque of tuberous sclerosis is related to a mutation in a tumor suppressor gene. The loss of the tumor suppressor gene imparts a growth advantage and loss of heterozygosity leaves no suppressor gene product in the segment. As a result, the affected segment grows beyond its Blaschko boundaries forming a broad plaque.

When a patient presents with segmental distribution of a disorder, it is critical to determine if the disorder is a result of mosaicism or LOH. In the latter case, the abnormal allele is present throughout the body, with loss of the normal remaining allele in the affected segment. In a patient who presents with segmental neurofibromatosis, but has Lisch nodules or axillary freckling, LOH rather than mosaicism is likely to account for the segmental presentation. The risk of passing the gene to a child is roughly 50:50. A geneticist should be involved during discussions of risk of transmission, as the mechanisms may be complex. Patients with mosaicism based on post-zygotic somatic gene mutation may have gonadal mosaicism and be capable of passing on the gene. Gonadal mosaicism is more likely when more than one segment is present on different regions of the body. During embryonic development, cells are dedicated to produce segments of the body at about the time of gastrulation (when a cavity forms in the embryo). Prior to gastrulation, every cell is pleuripotent and can give rise to an entire organism, or contribute to multiple sites of the body. Blaschko segments in different regions suggest a mutation that occurred prior to gastrulation when the involved cell lines could contribute to different parts of the body, including the gonads.

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X-LINKED, MOSAIC, AND RELATED DISORDERS

INCONTINENTIA PIGMENTI

Also known as *Bloch-Sulzberger disease*, incontinentia pigmenti is an X-linked dominant condition characterized by spattered pigmentation on the trunk preceded by vesicular and verrucous changes. It appears in girls during the first weeks after birth. Most lesions are evident by the time the infant is 4 to 6 weeks old. A vesicular phase is present in 87% of cases. This first stage begins in most individuals before 6 weeks of age and is replaced by verrucous lesions after several weeks to months in two-thirds of patients. Although these usually resolve by 1 year of age, lesions may persist for many years. In the third, or pigmentary, phase, pigmented macules in streaks, sprays, splatters, and whorls follow the lines of Blaschko. The pigmentary stage may last for many years and then fade away, leaving no sequelae. A fourth stage may be seen in some adult women, manifesting subtle, faint, hypochromic or atrophic linear lesions, most commonly on the extremities.

Histologically, the vesicular stage is characterized by spongiosis with eosinophils. As the lesions mature, clusters of dyskeratotic cells appear within the epidermis. Dyskeratotic cells predominate in the verrucous stage, and pigmented incontinence (dermal melanophages) predominates in hyperpigmented lesions.

Other cutaneous changes include patchy alopecia at the vertex of the scalp, atrophic changes simulating acrodermatitis chronica atrophicans on the hands, onychodystrophy, subungual tumors with underlying lytic bone lesions, and palmoplantar hyperhidrosis. Extracutaneous manifestations occur in 70% to 90% of patients. Most commonly involved are the teeth (up to 90%), bones (40%), central nervous system (CNS) (33%), and eyes (35%). Immune dysfunction with defective neutrophil chemotaxis and elevated IgE has been reported. Eosinophilia is common.

Dental abnormalities usually manifest by the time the individual is 2 years old. Dental defects include delayed eruption, partial anodontia (43%), microdontia, and cone- or peg-shaped teeth (30%). The most common CNS findings are seizures (13%), mental retardation (12%), spastic paralysis (11%), microcephaly, destructive encephalopathy, and motor retardation. The eye changes include strabismus, cataracts, retinal detachments, optic atrophy, blue sclerae, and exudative chorioretinitis. Skeletal abnormalities include syndactyly, skull deformities, dwarfism, spina bifida, club foot, supernumerary ribs, hemiatrophy, and shortening of the legs and arms.

Incontinentia pigmenti is caused by a mutation in the NEMO gene on the X chromosome, localized to Xq28. The gene is generally lethal in male fetuses, although males with Klinefelter syndrome (47,XXY) may survive. Mosaicism may also account for some cases in males.

Incontinentia pigmenti achromians differs in that it is a negative image, with hypopigmentation (see below). It has autosomal-dominant in inheritance, no vesicular or verrucous stages, and a higher incidence of CNS abnormalities. Patients with linear and whorled nevoid hypermelanosis lack the vesicular and verrucous phases.

There is no treatment for incontinentia pigmenti. Use of ruby lasers to treat pigmented lesions in infants and young children is not necessary and may worsen the condition. Usually the end stage of streaks of incontinentia pigmenti start to fade at age 2, and by adulthood there may be little residual pigmentation.

NAEGELI-FRANCESCHETTI-JADASSOHN SYNDROME

Also known as the *chromatophore nevus of Naegeli*, Naegeli-Franceschetti-Jadassohn syndrome differs from incontinentia pigmenti in that the pigmentation is reticular and there are no preceding inflammatory changes, vesiculation, or verrucous lesions. Vasomotor changes and hypohidrosis are present. There is reticulate pigmentation involving the neck, flexural skin, and perioral and periorbital areas. Diffuse keratoderma and punctiform accentuation of the palms and soles may occur. Dermatoglyphics are abnormal, producing atrophic or absent ridges on fingerprints.

Congenital malalignment of the great toenails may be found. Dental abnormalities are common, and many patients are edentulous. Both sexes are equally affected, and the syndrome appears to be transmitted as an autosomal-dominant trait, with linkage to chromosome 17q.

Hadj-Rabia S, et al: Clinical study of 40 cases of incontinentia pigmenti. Arch Dermatol 2003;139:1163.

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Phan TA, et al: Incontinentia pigmenti case series: clinical spectrum of incontinentia pigmenti in 53 female patients and their relatives. Clin Exp Dermatol 2005;30:474.

Sprecher E, et al: Refined mapping of Naegeli-Franceschetti-Jadassohn syndrome to a 6 cM interval on chromosome 17q11.2–q21 and investigation of candidate genes. J Invest Dermatol 2002;119:692.

INCONTINENTIA PIGMENTI ACHROMIANS (HYPOMELANOSIS OF ITO)

Incontinentia pigmenti achromians (IPA) is characterized by various patterns of bilateral or unilateral hypopigmentation following the lines of Blaschko. The lesions suggest the "negative image" of incontinentia pigmenti and usually develop by the first year of life. The female-to-male ratio is about 2.5:1. Three-quarters of affected individuals have associated anomalies of the CNS, eyes, hair, teeth, skin, nails, musculoskeletal system, or internal organs. Patients may manifest psychomotor or mental retardation, autism, microcephaly, coarse facies, and dysmorphic ears. Some patients have had associated Sturge-Weber syndrome-like leptomeningeal angiomatosis.

More than half of these patients have chromosomal abnormalities, with most demonstrating mosaicism for aneuploidy or unbalanced translocations. Several patients have demonstrated trisomy 13 mosaicism. No inflammatory changes or vesiculation are found before the development of the hypopigmentation. There is no treatment, but eventual repigmentation is the rule.

Failla P, et al: Hypomelanosis of Ito: a syndrome requiring a multisystem approach. Australas J Dermatol 1997;38:65.

Garcia Muret MP, et al: Hypomelanosis of Ito with Sturge-Weber syndrome-like leptomeningeal angiomatosis. Pediatr Dermatol 2002;19:536.

LINEAR AND WHORLED NEVOID HYPERMELANOSIS

This disorder of pigmentation develops within a few weeks of birth and progresses for 1 to 2 years before stabilizing. There is linear and whorled hyperpigmentation following the lines of Blaschko without preceding bullae or verrucous lesions. Sparing of mucous membranes, eyes, palms, and soles is noted. Congenital anomalies, such as mental retardation, cerebral palsy, atrial septal defects, dextrocardia, auricular atresia, and patent ductus arteriosus may be present. Bilateral giant cerebral aneurysms have been reported. There is no sexual predilection. Biopsy of pigmented areas demonstrates increased pigmentation of the basal layer and prominence of melanocytes without incontinence of pigment.

Most cases appear to be sporadic although familial cases have been reported. Sporadic forms have been attributed to mosaicism. Because of confusion with other pigmented disorders, such as incontinentia pigmenti, early linear epidermal nevi, hypomelanosis of Ito, and nevus depigmentosus, it is likely that linear and whorled nevoid hypermelanosis may be more common than previously appreciated.

Megarbane A, et al: Linear and whorled nevoid hypermelanosis with bilateral giant cerebral aneurysms. Am J Med Genet 2002;112:95.

Mendiratta V, et al: Linear and whorled nevoid hypermelanosis. J Dermatol 2001;28:58.

CHONDRODYSPLASIA PUNCTATA

A variant of the original *Conradi-Hünermann syndrome* or *chondrodystrophia calcificans congenita*, chondrodysplasia punctata is characterized by ichthyosis of the skin similar to that of the collodion baby, followed by hyperkeratotic "whirl and swirl" patterns on erythematous skin. In addition to reddening, the waxy, shiny skin has hyperkeratotic scales of a peculiar crushed-eggshell configuration. As the child grows, follicular atrophoderma and pseudopelade develop. Usually the ichthyosis clears within the first year of life but may leave behind hyperpigmentation similar to that seen in incontinentia pigmenti. An additional feature is minor nail defects, such as platonychia and onychoschizia.

There are four forms of chondrodysplasia punctata, which are classified by their inheritance patterns. The Conradi-Hünermann type is associated with autosomal-dominant inheritance, facial dysmorphia with a low nasal bridge, short stature, mild disease, cataracts, and few skin lesions. The rhizomelic form has autosomal-recessive inheritance, marked shortening of the extremities, cataracts, ichthyosis, and nasal hypoplasia; the patient dies in infancy. The X-linked recessive type has been described as part of contiguous gene deletion syndromes, with short stature, telebrachydactyly, and nasal hypoplasia. The X-linked dominant form (Happle syndrome, Conradi-Hünermann-Happle syndrome, or CDPX2) is lethal in males. Happle syndrome (X-linked dominant chondrodysplasia punctata) has ichthyosiform erythroderma along the lines of Blaschko, cataracts, asymmetrical limb shortening, and calcified stippling of the epiphyses of long bones. Follicular atrophoderma replaces the erythroderma after the first year.

The skeletal defects revealed on radiographic evaluation show irregular calcified stippling of the cartilaginous epiphyses in the long bones, costal cartilages, and vertebral diaphysis. The stippling occurs in the fetus and persists until age 3 or 4. The humeri and femurs may be shortened, and there may be joint dysplasia. Histologic evaluation of the ichthyotic lesions reveals a thinned, granular cell layer, calcification of keratotic follicular plugs, and focal hyperpigmentation of basal keratinocytes. The keratotic follicular plugs and calcium deposits are characteristic of this disease and very helpful in establishing the diagnosis in newborns. The syndrome is caused by mutations in an emopamil-binding protein, important in the cholesterol biosynthesis pathway.

Basbug M, et al: Prenatal ultrasonographic diagnosis of rhizomelic chondrodysplasia punctata by detection of rhizomelic shortening and bilateral cataracts. Fetal Diagn Ther 2005; 30:171.

Hoang MP, et al: Ichthyosis and keratotic follicular plugs containing dystrophic calcification in newborns: distinctive histopathologic features of X-linked dominant chondrodysplasia punctata (Conradi-Hünermann-Happle syndrome). Am J Dermatopathol 2004;26:53.

Whittock NV, et al: Molecular prenatal diagnosis in a case of an X-linked dominant chondrodysplasia punctata. Prenat Diagn 2003;23:701.

KLINEFELTER SYNDROME

Klinefelter syndrome, the most common sex chromosome disorder, consists of hypogonadism, gynecomastia, eunuchoidism, small or absent testicles, and elevated gonadotropins. There may be a low frontal hairline, sparse body hair with only a few hairs in the axillary and pubic areas, scanty or absent facial hair in men, and shortening of the fifth digit of both hands.

Thrombophlebitis and recurrent or chronic leg ulcerations may be a presenting manifestation; these may be more common than previously reported. The cause of the hypercoagulable state is believed to be an increase in plasminogen activator inhibitor-1 levels. Patients are at an increased risk of a variety of cancers, especially male breast cancer, hematologic malignancies, and sarcomas (retinoblastoma and rhabdomyosarcoma).

Many of these patients are tall; some are obese. Dull mentality or misbehavior is frequent, and psychiatric disorders occur in about one-third of these patients. Klinefelter syndrome is most frequently associated with an XXY sex chromosome pattern, although other variations occur as the number of X chromosomes increases. Marked improvement in appearance has been achieved by the injection of testosterone.

XXYY GENOTYPE

The XXYY genotype is considered to be a variant of Klinefelter syndrome. In addition to the changes seen in Klinefelter, there are vascular changes, such as cutaneous angiomas, acrocyanosis, and peripheral vascular disease leading to stasis dermatitis.

Manning MA, et al: Diagnosis and management of the adolescent boy with Klinefelter syndrome. Adolesc Med 2002; 13:367.

Swerdlow AJ, et al: Cancer incidence and morality in men with *Klinefelter syndrome: a cohort study.* J Natl Cancer Inst 2005;97:1204.

TURNER SYNDROME

Turner syndrome, also known as *gonadal dysgenesis*, is characterized by a webbed neck, low posterior hairline margin, increased carrying angle at the elbow (cubitus valgus), congenital lymphedema, and a triangular mouth. Patients may demonstrate alopecia of the frontal area on the scalp, koilonychia, cutis laxa, cutis hyperelastica, mental retardation, short stature, infantilism, retarded sexual development, primary amenorrhea, numerous melanocytic nevi, and an increased risk of melanoma and thyroid disease. Coarctation of the aorta is frequently found. There may be an increased incidence of alopecia areata and halo nevi in these patients.

These patients have only 45 chromosomes rather than the normal 46. An X chromosome is missing, resulting in an XO genotype. Mosaicism, structural abnormalities of the X chromosome, or a partial deficiency of one sex chromosome may account for a number of the variations in gonadal dysgenesis. Several genetic loci have been implicated, including the short stature homeobox gene. Loss of long-arm material (Xq) can result in short stature and ovarian failure, but deletions distal to Xq21 do not appear to affect stature. Loss of the short arm (Xp) produces the full phenotype. Very distal Xp deletions usually have normal ovarian function. No specific treatment is available. Growth hormone (hGH) has been shown to be effective in treating the short stature. A review of the Cochrane Central Register of Controlled Trials determined that hGH increases short-term growth, but there are few data regarding its effects on final height.

Cave CB, et al: Recombinant growth hormone in children and adolescents with Turner syndrome. Cochrane Database Syst Rev 2003;3:CD003887.

Karnis MF, et al: Turner syndrome in adolescence. Obstet Gynecol Clin North Am 2003;30:303.

Lowenstein EJ, et al: Turner's syndrome in dermatology. J Am Acad Dermatol 2004;50:767.

Pasquino AM, et al: Adult height in sixty girls with Turner syndrome treated with growth hormone matched with an untreated group. J Endocrinol Invest 2005;38:350.

Sybert VP, et al: Turner's syndrome. N Engl J Med 2004; 351:1227.

NOONAN SYNDROME

Noonan syndrome is an autosomal-dominant disease with a webbed neck that mimics Turner syndrome. Males and females are equally affected, and the chromosome number is normal. The major features are a characteristic facies with hypertelorism, prominent ears, webbed neck, short stature, undescended testicles, low posterior neck hairline, cardiovascular abnormalities (pulmonary stenosis and hypertrophic cardiomyopathy), and cubitus valgus. Some 25% to 40% of patients have dermatologic findings: lymphedema; short, curly hair; dystrophic nails; a tendency toward keloid formation; soft, elastic skin; keratosis pilaris atrophicans (ulerythema of the eyebrows); and abnormal dermatoglyphics. The Noonan syndrome gene, PTPN11, encodes the nonreceptor protein tyrosine phosphatase SHP-2.

MULTIPLE-LENTIGINES (LEOPARD) SYNDROME

The LEOPARD (multiple lentigines, electrocardiographic-conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness) syndrome is also known as the *multiple lentigines syndrome, Gorlin syndrome II, cardiocutaneous syndrome, lentiginosis profusa syndrome*, or *progressive cardiomyopathic lentiginosis.* The lentigines are small, dark brown, polygonal, and irregularly shaped macules, usually measuring 2 to 5 mm in diameter. Individual lesions may be larger, even up to 1 to 1.5 cm. LEOPARD syndrome shares many clinical features with Noonan syndrome. They are allelic disorders, as patients with both syndromes demonstrate mutations in the Noonan syndrome gene, PTPN11. Although the "R" in LEOPARD stands for growth retardation, some individuals with the syndrome also exhibit mild mental retardation or speech difficulties. Many cases appear sporadically; however, inheritance as an autosomal-dominant genetic trait has also been reported.

Digilio MC, et al: Grouping of multiple-lentigines/LEOPARD and Noonan syndromes on the PTPN11 gene. Am J Hum Genet 2002;71:389.

Eccles D, et al: Noonan syndrome: diagnostic difficulties. A case report and literature review. J Obstet Gynaecol 2003;23:666.

Musante L, et al: Spectrum of mutations in PTPN11 and genotype–phenotype correlation in 96 patients with Noonan syndrome and five patients with cardio-facio-cutaneous syndrome. Eur J Hum Genet 2003;11:201.

Tartaglia M, et al: Noonan Syndrome and related disorders: Genetics and Pathogenesis. Annu Rev Genomics Hum Genet 2005;22:45.

Zenker M, et al: Genotype–phenotype correlations in Noonan syndrome. J Pediatr 2004;144:368.

CARDIO-FACIO-CUTANEOUS SYNDROME

Cardio-facio-cutaneous syndrome is a congenital condition manifested by numerous anomalies. Typical features include a characteristic craniofacial appearance, psychomotor and growth retardation, congenital cardiac defects, and skin and hair abnormalities. The most frequent dermatologic finding is hair that is sparse, curly, fine or thick, woolly or brittle. In more than half of the reported cases, the patient has dry, scaly, or "hyperkeratotic," ichthyotic skin.

Other cutaneous findings include sparse or absent eyebrows and eyelashes, low posterior hairline, patchy alopecia, scant body hair, follicular hyperkeratosis, keratosis pilaris, keratosis pilaris atrophicans faciei, palmoplantar keratoderma, seborrheic dermatitis, eczema, lymphedema, hemangiomas, café-au-lait spots, pigmented nevi, hyperpigmented macules or stripes, cutis marmorata, and sacral dimples. Nail dystrophy, koilonychia, and dysplastic teeth have also been reported.

The differential diagnosis includes Noonan syndrome, Turner syndrome, Pallister-Killian mosaic aneuploid syndrome (mosaic tetrasomy 12p/trisomy 12p), and Costello syndrome. The difficulty often arises in assessing the facial features,

which are similar in all of these syndromes. Exclusion of PTPN11 mutations in cardio-facio-cutaneous syndrome and Costello syndrome confirms distinct genetic etiologies. Deletion of the long arm of chromosome 12, del(12)(q21.2q22), has been associated with cardio-facio-cutaneous syndrome.

Rauen KA, et al: Cardio-facio-cutaneous syndrome phenotype in an individual with an interstitial deletion of 12q: identification of a candidate region for CFC syndrome. Am J Med Genet 2000;93:219.

Tartaglia M, et al: Exclusion of PTPN11 mutations in Costello syndrome: further evidence for distinct genetic etiologies for Noonan, cardio-facio-cutaneous and Costello syndromes. Clin Genet 2003;63:423.

PHAKOMATOSES

The phakomatoses are the various inherited disorders of the CNS that have congenital retinal tumors and cutaneous involvement. They include tuberous sclerosis, von Recklinghausen's disease (neurofibromatosis), von Hippel-Lindau disease (angiomatosis retinae), ataxia-telangiectasia, nevoid basal cell carcinoma syndrome, nevus sebaceus, and Sturge-Weber syndrome.

TUBEROUS SCLEROSIS (EPILOIA, BOURNEVILLE DISEASE)

Tuberous sclerosis, described by Desiree-Magloire Bourneville in 1880, is also called *epiloia* (*epi* = epilepsy, *loi* = low intelligence, *a* = adenoma sebaceum). This classic triad of adenoma sebaceum (Fig. 27-1), mental deficiency, and epilepsy, however, is present in only a minority of patients. Other associated features include periungual fibromas (Fig. 27-2), shagreen plaques (collagenoma), oral papillomatosis, ash-leaf hypomelanotic macules (Fig. 27-3), skin fibromas, and café-au-lait spots.

Adenoma sebaceum (angiofibromas) are 1- to 3-mm, yellowish-red, translucent, discrete, waxy papules that are distributed symmetrically, principally over the cheeks, nose, and forehead. They have also been reported in patients with multiple endocrine neoplasia (MEN 1). These lesions are present in 90% of patients older than 4 years of age, persist indefinitely, and may increase in number.

Shagreen plaque is named after a type of leather tanned to produce knobs on the surface, resembling shark skin. Patches of this type of "knobby" skin, varying from 1 to 8 cm in diameter, are found on the trunk, most commonly on the lumbosacral area. They are connective tissue nevi composed almost exclusively of collagen. They occur in 40% of patients and develop in the first decade of life.

Koenen tumors (periungual angiofibromas) (Fig. 27-4) occur in 50% of patients. The tumors are small, digitate, protruding, asymptomatic, and periungual and/or subungual. They have their onset at puberty. Similar lesions may occur on the gingiva.

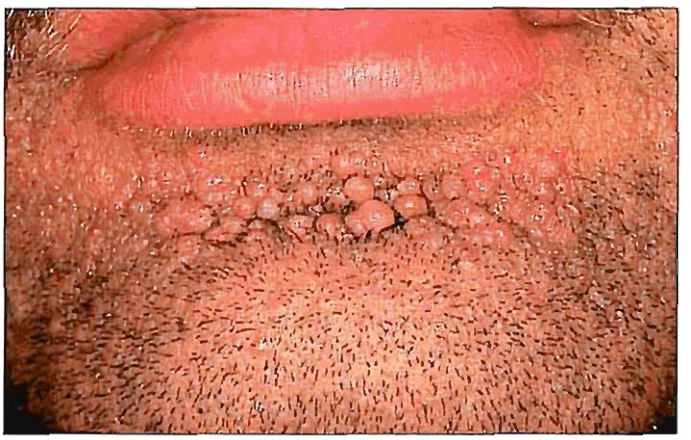

Fig. 27-1 Angiofibromas (adenoma sebaceum).

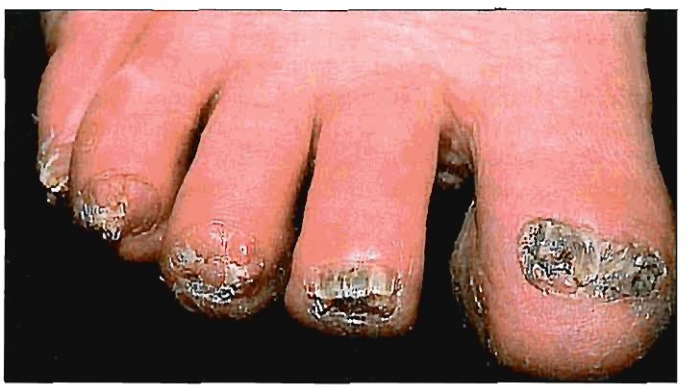

Fig. 27-2 Periungual fibromas (Koenen tumors). (Courtesy of Brooke Army Medical Center Teaching File)

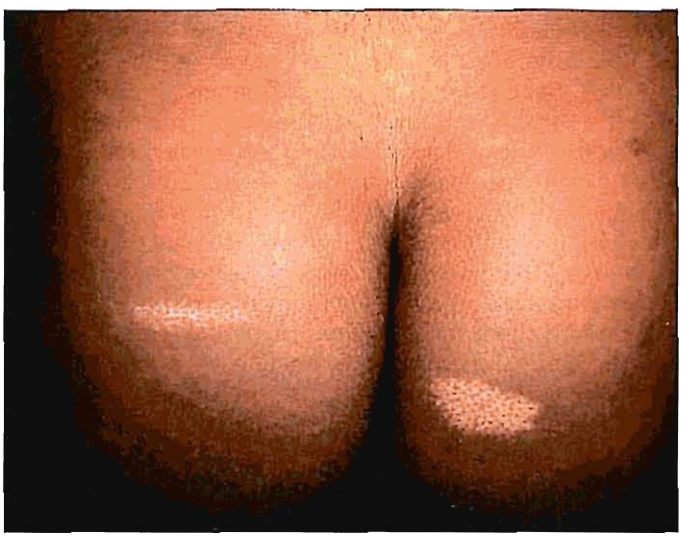

Fig. 27-3 Ash-leaf macules.

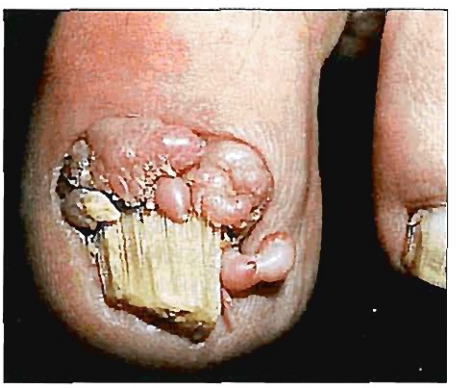

Fig. 27-4 Periungual fibromas.

Congenital white leaf-shaped macules, called *hypomelanotic macules*, are found in 85% of patients with tuberous sclerosis, their number ranging from 1 to 100. Occasional patients may not develop them until they are 6 to 8 years of age. They may be shaped like an ash leaf, but linear and confetti-type white macules may also be present. Wood's light examination should be performed when evaluating a patient for tuberous sclerosis. Focal poliosis (localized tufts of white hair) may be present at birth. Solitary ash-leaf macules are not uncommon in the general population and may be confused with other hypopigmented macules, such as nevus depigmentosus.

Mental deficiency, usually appreciated early in life, is present in 40% to 60% of patients, varying widely in its manifestations. Epilepsy also occurs, is variable in its severity, and usually also presents early in life. Eighty to 90% of patients have seizures or nonspecific electroencephalographic abnormalities. Hamartomatous proliferations of glial and neuronal tissue produce potato-like nodules in the cortex. X-ray evaluation will reveal these once they are calcified, but computed tomographic (CT) scans, cranial ultrasonography, and magnetic resonance imaging (MRI) may define these lesions as early as 6 weeks of age, and thus are useful in making an early diagnosis. These brain tumors may progress to gliomas. Subependymal nodules (candle drippings) are similar lesions in the ventricular walls. Astrocytomas may also occur.

Retinal tumors (phakomas) occur, which are optic nerve or retinal nerve hamartomas. Various ophthalmologic findings, such as pigmentary changes, nystagmus, and angioid streaks, occur in 50% of patients.

Renal hamartomas (angiomyolipomas [45%], cystic disease [18%], fibroadenomas, or mixed tumors) and cardiac tumors (rhabdomyomas [43%]) may also occur. In the familial variety of tuberous sclerosis, 80% of patients have angiomyolipomas, which are often bilateral and frequently cause renal failure. Women of childbearing age may present with pulmonary lymphangioleiomyomatosis with progressive respiratory failure or spontaneous pneumothorax. The condition is characterized by diffuse proliferation of smooth muscle cells and cystic degeneration of the pulmonary parenchyma. Nearly half of patients with epiloia have bony abnormalities such as bone cysts and sclerosis, which can be seen on x-ray evaluation. Five or more pits in the enamel of permanent teeth are a marker for this disease.

Tuberous sclerosis is a common inherited autosomal-dominant disease with highly variable penetrance. Prevalence estimates range from 1 in 5800 to 1 in 15,000. Up to 50% of cases may occur as a result of spontaneous mutations.

There are two genes, the mutations of which produce indistinguishable phenotypes—9q34 (TSC1) and 16p13.3 (TSC2). TSC1 and TSC2 are tumor suppressor genes. TSC2 encodes for tuberin, a putative GTPase-activating protein for rap1 and rab5. TSC1 encodes for hamartin, a novel protein with no significant homology to tuberin or any other vertebrate protein. Hamartin and tuberin associate physically in vivo, suggesting that they function in the same complex rather than in separate pathways. This interaction of tuberin and hamartin explains the indistinguishable phenotypes caused by mutations in either gene. Hamartomas frequently demonstrate loss of the remaining normal allele (loss of heterozygosity).

Diagnosis

The ash-leaf macules are usually present at birth and most easily seen with a Wood's light. If X-ray examination fails to show calcified intracranial nodules, ultrasonography, a CT scan or MRI should be performed. Funduscopic examination, hand and foot x-ray evaluation, and renal ultrasonography are often rewarding in a patient with few clinical findings, as up to 31% of asymptomatic parents have been identified using these tests.

Multiple periungual fibromas are highly correlated with the syndrome, but solitary fibromas may occur in unaffected individuals. Molecular analysis for TSC1 and TSC2 may be the only way to ultimately identify "mildly affected" individuals.

Treatment

Adenoma sebaceum can be treated by shaving, dermabrasion, or laser therapy. Lesions are likely to recur, requiring repeat treatment. Cranial irradiation of astrocytomas should be avoided because this may result in the subsequent development of glioblastomas.

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NEUROFIBROMATOSIS (VON RECKLINGHAUSEN'S DISEASE)

Neurofibromatosis is an autosomal-dominantly inherited syndrome manifested by developmental changes in the nervous system, bones, and skin. In type 1 neurofibromatosis (NF-1, von Recklinghausen's disease), which includes more than 85% of cases, patients have many neurofibromas, café-au-lait spots, axillary freckles (Fig. 27-5), giant pigmented hairy nevi, sacral hypertrichosis, cutis verticis gyrata, and macroglossia. Neurofibromas of the areolae occur in more than 90% of women with this disease. Lisch nodules (Fig. 27-6) are found in the irides of about one-quarter of patients under 6 years of age and in 94% of adult patients. Type 2 neurofibromatosis, central or acoustic neurofibromatosis, is distinguished by bilateral acoustic neuromas, usually in the absence of cutaneous lesions, although neurofibromas and schwannomas may occur. Type 3 (mixed) and 4 (variant) forms resemble type 2 but have cutaneous neurofibromas.

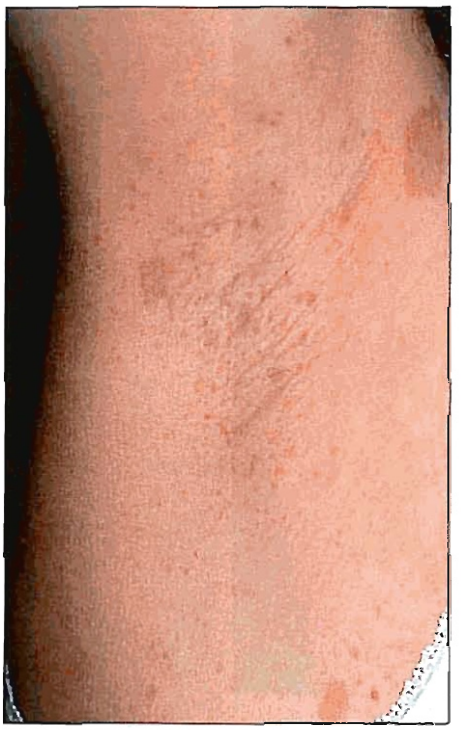

Fig. 27-5 Axillary freckling.

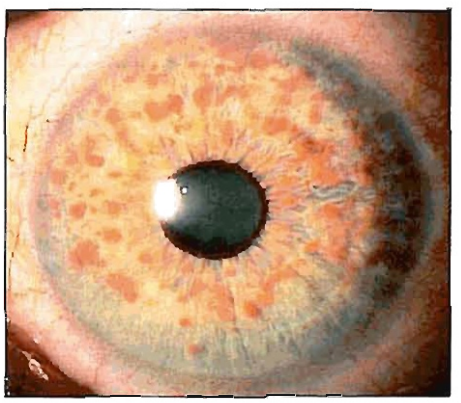

Fig. 27-6 Lisch nodules. (Courtesy of Brooke Army Medical Center Teaching File)

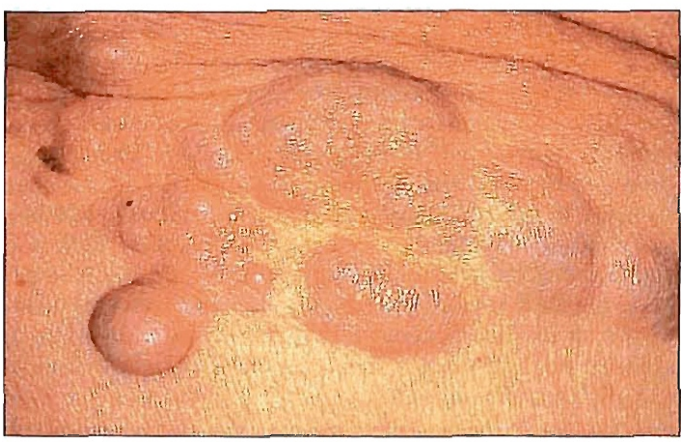

Fig. 27-7 Segmental neurofibromatosis.

Patients with these types are at greater risk for developing optic gliomas, neurilemomas, and meningiomas. These forms are inherited as autosomal-dominant traits. Segmental neurofibromatosis (Fig. 27-7) may arise from postzygotic somatic mutation or loss of heterozygosity (LOH).

Neurofibromas are soft tumors that can be pushed down into the panniculus by light pressure with the finger ("buttonholing") and spring back when released. Histologically, they are well circumscribed, but rarely encapsulated, spindle cell proliferations with a mucinous background and many mast cells. The spindle cells have a wavy appearance. Neurofibromas occur as a result of proliferation of all supporting elements of the nerve fibers. The proliferation is composed of Schwann cells, perineurial cells, endoneurial cells, mast cells, and blood vessels. Axon stains demonstrate individual axons spread randomly throughout the tumor.

Subcutaneous plexiform neurofibromas are virtually pathognomonic of NF-1 and may be a manifestation of LOH. They occur as large nodules containing multiple encapsulated neurofibromas. The overlying skin is usually hyperpigmented. On palpation, they resemble a "bag of worms." Histologically, they demonstrate numerous elongated encapsulated neurofibromas, often embedded in diffuse neurofibroma that involves the dermis and subcutaneous fat.

The café-au-lait macule is a uniformly pigmented, smooth edged, light brown macule. Most often, they are present at birth and almost always present by the time the patient is 1 year of age. The finding of six or more of these lesions at least 1.5 cm in diameter is diagnostic, usually indicating NF-1. In children, the minimum diameter for a significant lesion is 0.5 cm. Histologically, basilar hyperpigmentation is noted, and giant melanosomes may be seen. Axillary freckling (Crowe's sign) may occur, extending to the neck and involving the inguinal, genital, and perineal areas.

Many organ systems may be involved. Acromegaly, cretinism, hyperparathyroidism, myxedema, pheochromocytoma (<1%), or precocious puberty may be present. Bone changes (usually erosive) may produce lordosis, kyphosis, and pseudoarthrosis, as well as spina bifida, dislocations, and atraumatic fractures. Neuromas of spinal nerves may cause various paralyses. Patients with NF-1 are four times more likely to develop malignancies than the general population. Cutaneous neurofibromas rarely develop into neurofibrosarcomas (malignant schwannomas), but a growing or hardening lesion is an indication for biopsy. Wilms tumor, rhabdomyosarcomas, gastrointestinal malignancies, and chronic myelogenous leukemia have also been reported. Xanthogranulomas are associated with a higher incidence of chronic myelogenous leukemia. Children with NF-1 are 200 to 500 times more likely to develop malignant myeloid disorders than age-matched controls.

Mental retardation, dementia, epilepsy, and a variety of intracranial malignancies may occur. Hypertelorism heralds a severe expression of neurofibromatosis with brain involvement. Diffuse interstitial lung disease occurs in 7% of patients.

Approximately 50% of cases of NF-1 represent new mutations. The gene for NF-1 is in the pericentric region of chromosome 17q11.2 and codes for neurofibromin, a protein that negatively regulates signals transduced by Ras proteins. The gene for NF-2 is on the long arm of chromosome 22q11–q13 and encodes for merlin (schwannomin), a protein that links the actin cytoskeleton to cell-surface glycoproteins and functions as a negative growth regulator.

Diagnosis

The diagnosis of NF-1 requires two or more of the following criteria: 1) six or more café-au-lait macules of more than

5 mm in greatest diameter in prepubertal individuals, and more than 15 mm in greatest diameter in postpuberta) individuals; 2) two or more neurofibromas of any type or one plexiform neurofibroma; 3) freckling in the axillary or inguinal regions; 4) optic glioma; 5) two or more Lisch nodules; 6) a distinctive osseous lesion, such as a sphenoid dysplasia or thinning of the long bone cortex with or without pseudarthrosis; and 7) a first-degree relative (parent, sibling, or offspring) with the disease.

A diagnosis of NF-2 requires either of the following: 1) bilateral eighth nerve masses as demonstrated on CT or MRI; or 2) having a first-degree relative with NF-2 and either unilateral eighth nerve mass or two of the following: a neurofibroma, meningioma, glioma, schwannoma, and juvenile posterior subcapsular lenticular opacity.

Screening and Monitoring for Complications

In one study of 93 asymptomatic patients with NF-1 who underwent cerebral imaging, 12 optic gliomas were detected, suggesting that screening MRI or CT scans may be of value. However, this is a single study, and the results have not been validated by other authors. The National Institutes of Health (NIH) consensus panel concluded that studies should be dictated by findings on clinical evaluation. It concluded that laboratory tests in asymptomatic patients are unlikely to be of value. In the majority of patients with NF-1, imaging studies should only be performed as indicated by signs or symptoms. NF-2 patients, in contrast, often require imaging studies. Screening studies should include an audiogram and brainstem auditory evoked responses. MRI is the best imaging procedure for patients with evidence of hearing impairments or abnormal evoked responses. Tests of vestibular function may be useful, as eighth nerve tumors develop on the vestibular division. A screening MRI should be performed by puberty. Other tests should be performed as dictated by signs and symptoms. Pediatric patients with NF-2 have a worse prognosis, with 75% demonstrating hearing loss, 83% visual impairment, and 25% abnormal ambulation.

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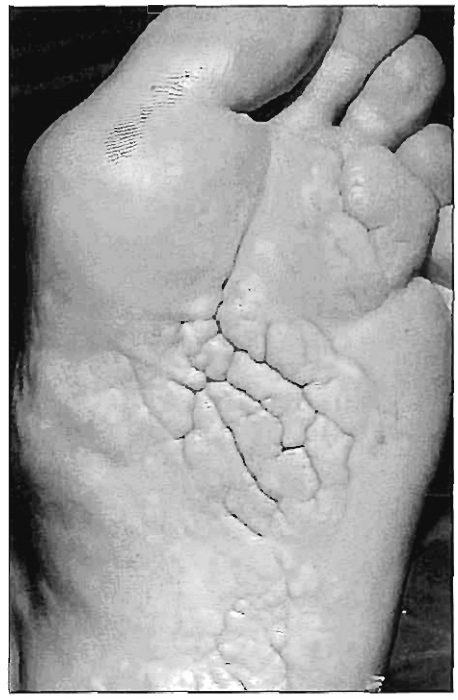

Fig. 27-8 Proteus syndrome. (Courtesy of Michelle Maroon, MD)

Ward BA, et al: Neurofibromatosis 1: from lab bench to clinic. Pediatr Neurol 2005;32:221.

PROTEUS SYNDROME

Although not a phakomatosis, Proteus syndrome may be confused with neurofibromatosis. This rare sporadic disease is named after the Greek god Proteus who could change shape. The syndrome has protean manifestations that include partial gigantism of the hands and feet, cerebriform plantar hyperplasia (Fig. 27-8), hemangiomas, lipomas, lipohypoplasia, linear verrucous epidermal nevi, patchy dermal hypoplasia, macrocephaly, hyperostosis, muscular hypoplasia, and hypertrophy of the long bones. Many investigators believe that Joseph Merrick, who was known as "the Elephant Man," had Proteus syndrome rather than neurofibromatosis. It is believed to be caused by a somatic mutation, lethal in the nonmosaic state. Those patients with a greater number of cutaneous lesions also have the most extracutaneous abnormalities. The findings of both overgrowth (pleioproteus component) and hypoplasia (elattoproteus component) in the same patient may be a manifestation of genetic twin spotting (didymosis), overexpression, and deficiency of a gene product. Although mutations in PTEN have been reported in up to 20% of patients with Proteus syndrome-like findings, no patients have been found in other studies of patients with the syndrome. Those patients with PTEN mutations are best classified as having the PTEN hamartoma-tumor syndrome. Somatic PTEN mutations also occur in sporadic primary tumors, including endometrial carcinomas and glioblastoma multiforme.

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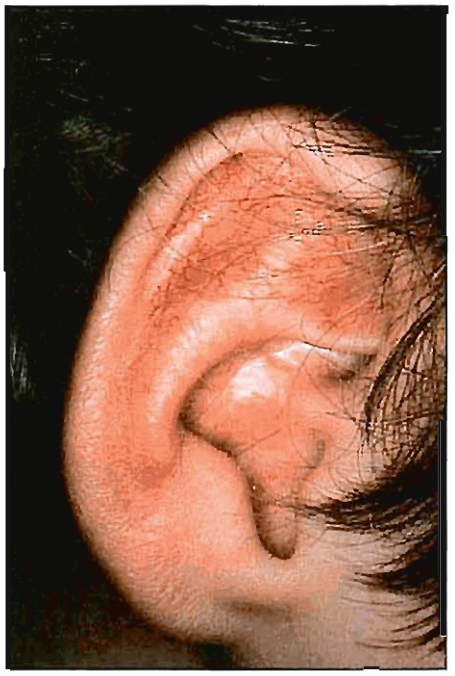

Fig. 27-9 Ataxia-telanglectasia.

VON HIPPEL-LINDAU SYNDROME

von Hippel-Lindau syndrome is an autosomal-dominant disorder consisting of retinal angiomas, cerebellar medullary angioblastic tumors, pancreatic cysts, and renal tumors and cysts. Usually the skin is not involved, although occasionally angiomas may occur in the occipitocervical region. The syndrome is associated with a germline mutation of a tumor suppressor gene on the short arm of chromosome 3.

Ten to 20% of cerebellar hemangioblastomas produce erythropoietin and are accompanied by a secondary polycythemia. Ocular lesions may lead to retinal detachment. Ten percent of hypernephromas and less than 8% of renal cysts also produce erythropoietin. Pheochromocytoma has been associated in several kindreds with von Hippel-Lindau disease.

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ATAXIA-TELANGIECTASIA

Also known as *Louis-Bar syndrome*, ataxia-telangiectasia consists of cerebellar ataxia, oculocutaneous telangiectasia, and sinopulmonary infection. It is familial and is usually first noted when the child begins to walk. There is awkwardness and a swaying gait, which by about 10 years of age results in the child needing to use a wheelchair. Choreic and athetoid movements and pseudopalsy of the eyes are other features. Fine telangiectases appear on the exposed surfaces of the conjunctiva at about age 3. Nystagmus is present. Telangiectases also appear later on the butterfly area of the face, inside the helix, and over the backs of the ears (Fig. 27-9), in the roof of the mouth, the necklace area, the flexures, and over the dorsa of the hands and feet. Other stigmata are café-au-lait patches, hypopigmented macules, seborrheic dermatitis, premature graying and sparsity of the hair, and progeroid features. The skin tends to be dry and coarse, and in time becomes tight and inelastic, as in scleroderma. Atrophic, granulomatous, scarring plaques may occur. Early death from bronchiectasis occurs in more than half of these patients, most of whom suffer from recurrent sinus and lung infections that begin when the patient is between 3 and 8 years of age.

Patients may have a marked IgA deficiency, with decreased lymphocytes and a small to absent thymus. The most common types of malignancies are lymphomas, usually of the B-cell type, and leukemias. It has been shown that homozygous patients also have a higher risk of breast cancer—100 times higher than age-matched controls. Heterozygous carriers share the defective repair of radiation-induced damage, and there is a three- to five-fold higher risk for development of neoplasms, especially breast cancer, in heterozygotes under the age of 45. The ovaries and testicles do not develop normally. There is deficient thymus development, with absence of Hassall's corpuscles, and a lack of T-helper cells. Suppressor T-cells are normal. In 80% of cases, IgA is absent or deficient, in 75% absent or deficient IgE is seen, and in 50% IgG is very low.

Ataxia-telangiectasia is transmitted as an autosomal-recessive trait, and heterozygotes, although they lack clinical findings, are cancer prone. The gene has been designated ATM (ataxia-telangiectasia mutated gene) and is a member of a family of phosphatidylinositol-3-kinase–like enzymes that are involved in cell-cycle control, meiotic recombination, telomere length monitoring, and DNA-damage response. Affected cells are hypersensitive to ionizing radiation and are defective at the G1/S check-point after radiation damage. They are abnormally resistant to inhibition of DNA synthesis by ionizing radiation. The ATM gene is located on chromosome 11q22.3. Translocations are common in these patients, particularly for chromosomes 7 and 14. A high prevalence of ATM gene mutations has also been found in a diverse array of sporadic lymphoproliferative disorders.

Early diagnosis can be difficult and the most frequent misdiagnosis is cerebral palsy. Persistently elevated levels of α-fetoprotein and carcinoembryonic antigen occur. These may be useful in early diagnosis. In culture, ataxia-telangiectasia fibroblasts are three times more sensitive to killing by ionizing radiation, but not ultraviolet light. Evaluations for elevated α-fetoprotein and radiosensitivity of fibroblasts used to be the standard for diagnosis of this disorder, but immunoblotting the ATM protein expression is now possible.

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Chun HH, et al: Improved diagnostic testing for ataxia-telangiectasia by immunoblotting of nuclear lysates for ATM protein expression. Mol Genet Metab 2003;80:437.

Goodarzi AA, et al. The role of ATM and ATR in DNA damage-induced cell cycle control. Prog Cell Cycle Res 2003;5:393.

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Meyn MS: Ataxia-telangiectasia, cancer and the pathobiology of the ATM gene. Clin Genet 1999;55:289.

EPIDERMOLYSIS BULLOSA

Epidermolysis bullosa (EB) is a group of rare genetic disorders that have in common the formation of blisters in

Box 27-1 Inherited types of epidermolysis bullosa (EB)

Intraepidermal
- EB simplex, generalized (Koebner)
- EB simplex, localized (Weber-Cockayne)
- EB herpetiformis (Dowling-Meara)
- EB simplex (Ogna)
- EB simplex with mottled pigmentation
- EB with muscular dystrophy

Junctional (intralamina lucida)
- Junction EB (JEB) atrophicans generalisata gravis (Herlitz, EB letalis)
- JEB atrophicans generalisata mitis
- JEB atrophicans localisata
- JEB atrophicans inversa
- JEB progressiva
- JEB with pyloric atresia
- Generalized atrophic benign EB (GABEB)
- Cicatricial junctional EB

Dermolytic or dystrophic (sublamina densa)

1. Dominant forms
   - Dystrophic EB, hyperplastic variant (Cockayne-Touraine)
   - Dystrophic EB, albopapuloid variant (Pasini)
   - Bart syndrome
   - Transient bullous dermolysis of the newborn
   - Acrokeratotic poikiloderma (Weary-Kindler)
2. Recessive forms
   - Generalized (gravis or mitis)
   - Localized
   - Inverse

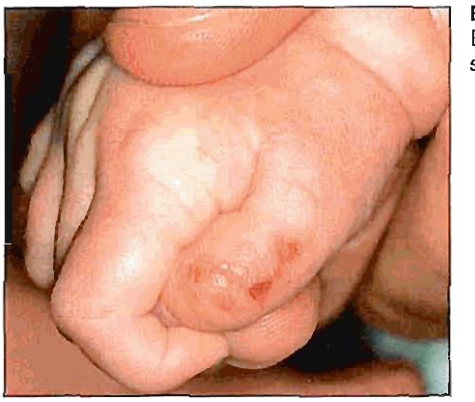

Fig. 27-10 Epidermolyis bullosa simplex.

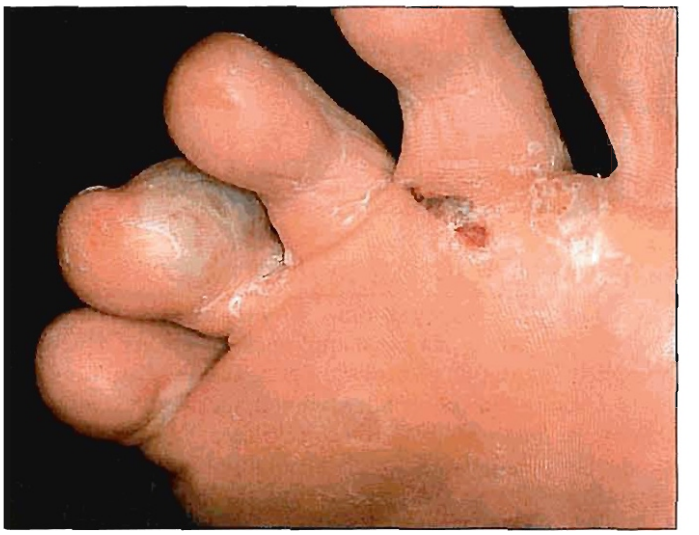

Fig. 27-11 Epidermolyis bullosa simplex.

response to minor physical injury. Treatment consists of prevention of trauma, decompression of large blisters, and treatment of infection. EB acquisita is an autoimmune disease, discussed in Chapter 21.

The inherited types of EB are classified as in Box 27-1.

Internal involvement may occur in several of these subtypes of EB. Esophageal and laryngeal complications are seen primarily in recessive dystrophic EB, but may be present in junctional EB (Herlitz). Pyloric atresia is reported to occur in junctional EB. Ocular lesions may be severe in dystrophic EB, and mild lesions have been reported in simplex and junctional disease.

Clinical findings and routine histologic features overlap, and accurate diagnosis depends on genetic mutation mapping, electron microscopic studies or immunofluorescent mapping. The latter two can identify the level of the epidermal separation, and in addition may define other defects, such as absence of anchoring fibrils or hypoplasia of hemidesmosomes. In recessive dystrophic EB, electron microscopy reveals the cleavage is below the basal lamina and that anchoring fibrils are diminished or absent.

Immunofluorescent mapping may define the level of the split without resorting to electron microscopy. By staining biopsy specimens for normal components of the basement membrane zone, such as bullous pemphigoid antigen, laminin, type IV collagen, or LDA-1 antigen, the level of the split may be determined by whether the antigen localizes at the roof or base of the blister. In simplex types, all of these components will be at the base; in dystrophic types, all will be at the roof; and in junctional types bullous pemphigoid antigen will be on the roof, while type IV collagen and LDA-1 will be at the base. KF-1 has been found to be absent or diminished in dystrophic EB. The specific keratin abnormalities along with the abnormal genes have been identified for many of these disorders. Many types of EB simplex are caused by defects in genes encoding for keratins 5 and 14. In junctional EB there are defective genes encoding for kallidin/laminin 5. Dystrophic forms result from mutations in type VII collagen gene COL7A1.

Intraepidermal Forms

Epidermolysis Bullosa Simplex (Koebner) The generalized type of EB simplex (EBS), dominantly inherited, with complete penetrance, occurs in 1 in 500,000 births. It is characterized by the development of vesicles, bullae, and milia over the joints of the hands (Fig. 27-10), elbows, knees, and feet (Fig. 27-11), and other sites subject to repeated trauma. The child is affected at birth or shortly thereafter, with improvement within the first few months, only to recur when the child begins crawling or later in childhood. The blistering is worse during the summer and improves during the winter. The lesions are sparse and do not lead to severe atrophy. The Nikolsky sign is negative. Usually the mucous membranes and nails are not involved. EBS is usually milder than other forms of EB.

Inherited as an autosomal-dominant trait, EBS is a disease in which keratin gene mutations cause the production of defective intermediate filaments, which lead to epidermal basal cell fragility and subsequent blistering. Gene mutations produce abnormalities in keratins 5 and 14, keratins expressed in the basal cell layer. Patients heterozygous for abnormal keratin 14 have blistering limited to the hands and feet, but homozygotes have more severe and widespread blistering of the skin and mucous membranes.

Separation occurs through the basal cell layer. Rubbing skin with an eraser may lead to a subclinical lesion that demonstrates the split histologically.

Localized Epidermolysis Bullosa Simplex Recurrent bullous eruption of the hands and feet (Weber-Cockayne) is autosomal-dominantly determined and appears in a chronic form in infancy or at times later in life. The lesions exacerbate during hot weather and when the patient is subjected to prolonged walking or marching, as is experienced in military service. Hyperhidrosis may be an associated finding. In localized EBS, the bullae are intraepidermal and suprabasal, and healing occurs without scarring.

Application of aluminum chloride hexahydrate in anhydrous ethanol (Drysol) on the normal skin of hands and feet twice a day has been shown to reduce blistering in this form of EB. After 2 weeks of daily therapy the patient can be switched to once or twice weekly applications.

Epidermolysis Bullosa Herpetiformis (Dowling-Meara) In this autosomal-dominant variant of EBS, active blisters with circinate configuration occur in infancy. Milia may develop, but there is no scarring. The oral mucosa is involved. Nails are shed but may regrow, sometimes with dystrophy. Blistering lessens with age. Hyperkeratosis of the palms and soles may occur. Histologically, the split is through the basal layer, and tonofilaments are clumped on electron microscopy. Point mutations have been shown in keratin 5 and 14 genes.

Epidermolysis Bullosa Simplex (Ogna) Generalized bruising and hemorrhagic blisters occur. It is transmitted as an autosomal-dominant trait. At birth there are small, acral, traumatic sanguinous blisters. The basal keratinocytes in this syndrome do not stain with antiplectin antibodies.

Epidermolysis Bullosa Simplex with Mottled Pigmentation One Swedish family has been reported with autosomal-dominant EBS with congenital scattered hyper- and hypo-pigmented macules which fade slowly after birth. The remaining features are similar to those of generalized EBS. Ultrastructural studies show vacuolization of the basal cell layer.

Epidermolysis Bullosa Simplex with Muscular Dystrophy There is a form of EBS associated with late-onset neuromuscular disease. It is inherited as an autosomal-recessive trait. There is widespread blistering at birth associated with scarring, milia, atrophy, nail dystrophy, dental anomalies, laryngeal webs, and urethral strictures. Progressive muscular dystrophy with weakness and wasting begins in childhood or later. This disease is caused by a mutation in the plectin gene, with affected patients having absent plectin in their skin and muscles.

Junctional Forms

Junctional Epidermolysis Bullosa (Epidermolysis Bullosa Letalis, Epidermolysis Bullosa Herlitz) In junctional EB, a rare type, which has autosomal-recessive transmission, severe generalized blistering may be present at birth, and extensive denudation may prove fatal within a few months. There is generalized blistering with relative sparing of the hands, and characteristic perioral and perinasal hypertrophic granulation tissue. Eventually the lesions heal without scarring or milia formation, but erosions may persist for years. Dysplastic teeth are common. Laryngeal and bronchial lesions may cause respiratory distress and even death. Additional systemic complications include gastrointestinal tract, gallbladder, corneal, and vaginal disease. In patients who survive infancy, there is growth retardation, and moderate-to-severe refractory anemia is frequent. Separation occurs in the lamina lucida, as shown by electron microscopy.

Herlitz junctional EB is caused by mutations in three genes: LAMA3, LAMB3, or LAMC2, which code for polypeptide subunits of laminin 5.

In addition to good wound care and control of infection, epidermal autographs of cultured keratinocytes, isolated from clinically uninvolved skin and grown on collagen sponges, may be useful for chronic facial erosions. Complete re-epithelialization is achieved over 7 to 10 months.

Junctional Epidermolysis Bullosa with Pyloric Atresia This rare autosomal-recessively inherited form of junctional EB presents at birth with severe mucocutaneous fragility and gastric outlet obstruction. Even if the pyloric atresia is repaired, the neonates may die because of the severity of their skin disease. If they survive the neonatal period, the blistering diminishes. Persistent scarring of the urinary tract may occur, however, with stenosis of the ureteral–vesicular junction, requiring numerous urologic procedures. This syndrome is caused by a genetic mutation in either the $\alpha 6$ or $\beta 4$ integrin genes (ITGA6 and ITGB4). This $\alpha 6$–$\beta 4$ integrin complex is uniquely expressed on epithelial surfaces.

Generalized Atrophic Benign Epidermolysis Bullosa Most cases of generalized atrophic benign EB are characterized by onset at birth, generalized blisters and atrophy, mucosal involvement, and thickened, dystrophic, or absent nails. Enamel defects in deciduous and permanent teeth and atrophic alopecia are prominent features. Multiple cutaneous squamous cell carcinomas have been reported. Cleavage is within the lamina lucida, and hemidesmosomes are reduced or absent. The basal lamina, anchoring fibrils, collagen fibers, and dermal microfibril bundles are unaltered. Inheritance is autosomal recessive. In contrast to EB Herlitz, patients often survive to adulthood. Studies have shown mutations in the COL17A1 gene encoding for type XVII collagen (BPAg2), a transmembrane component of hemidesmosomes.

Cicatricial Junctional Epidermolysis Bullosa In 1985, Haber et al described another type of junctional EB, which they named cicatricial junctional epidermolysis bullosa, because the blisters heal with scarring, which may produce syndactyly and contractures, and there is stenosis of the anterior nares. Electron microscopy reveals junctional

bullae with rudimentary hemidesmosomes. The bases of the bullae are covered by an intact basal lamina with normal anchoring fibrils.

Dermolytic or Dystrophic Forms

The cause of dystrophic EB in both autosomal-dominantly and -recessively inherited forms is mutations in the COL7A1 gene encoding for type VII collagen. The anchoring fibrils in these patients are defective or deficient.

Dominant Dystrophic Epidermolysis Bullosa On the extensor surfaces of the extremities, vesicles and bullae appear; these are most pronounced over the joints, especially over the toes (Fig. 27-12), fingers, knuckles, ankles, and elbows. Spontaneous, flesh-colored, scarlike (albopapuloid) lesions may appear on the trunk, often in adolescence, with no previous trauma. The nails may be thickened. Usually the Nikolsky sign is present, and frequently the accumulated fluid in a bulla can be moved under the skin several centimeters away from the original site. Healing usually occurs with scarring and atrophy. Milia are often present on the rims of the ears, dorsal surfaces of the hands, and extensor surfaces of the arms and legs.

The mucous membranes are frequently involved. Bullae, vesicles, and erosions are encountered on the buccal mucosa, tongue, palate, esophagus, pharynx, and larynx. The latter involvement is manifested by persistent hoarseness in some of these patients. There may be angular contractures at the gingivolabial sulcus and dysphagia from pharyngeal scarring. Scarring on the tip of the tongue is typical. The teeth are normal. Usually the conjunctiva is not involved.

Other changes include nail dystrophy, partial alopecia of the scalp, absence of body hair, dwarfism, and the formation of contractures and clawlike hands, with atrophy of the phalangeal bones and pseudosyndactylism. The albopapuloid type (Pasini) is the more severe expression of dominant dystrophic EB. The Cockayne-Touraine type is more limited in extent and severity, and no albopapuloid lesions are seen.

Histologically, a noninflammatory subepidermal bulla is generally present. On electron microscopy, cleavage occurs beneath the basal lamina, and anchoring fibrils are rudimentary and reduced in number. In blistered areas they are not demonstrable.

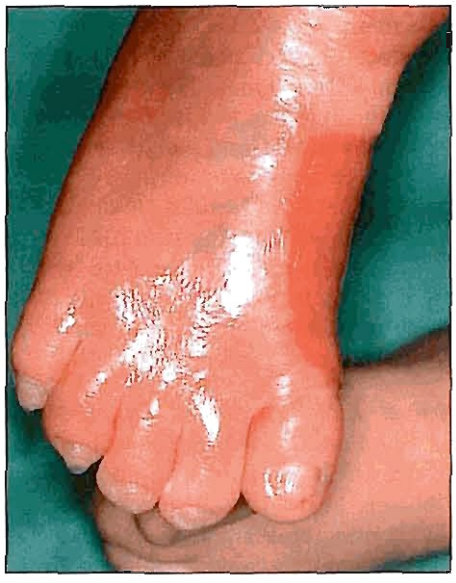

Fig. 27-12 Epidermolysis bullosa, dominant dystrophic.

Autologous meshed split-thickness skin grafts and allogeneic cultured keratinocytes may be used in treating nonhealing skin defects. In many patients with dominant dystrophic EB, blistering reduces with time and only nail dystrophy may be present in adulthood.

Bart Syndrome Bart described congenital localized defects of the skin, mechanoblisters, and nail deformities with autosomal-dominant inheritance. Although the clinical and histologic picture of this syndrome is one of a mildly scarring mechanobullous dermatosis with a favorable prognosis, associations with mandibulofacial dysostosis, renal aplasia, and congenital abnormalities of the lower extremities have been reported. Bart syndrome is a clinical variant of dominant dystrophic EB, based on identification of a defect in the COL7A1 gene (chromosome 3p) encoding for type VII collagen.

Transient Bullous Dermolysis of the Newborn In 1985, Hashimoto et al reported a newborn who developed blisters from every minor trauma. Separation was below the basal lamina, with degeneration of collagen and anchoring fibrils. There was rapid healing by 4 months of age. Nails were not damaged, and there was no scarring.

They considered as criteria for this entity: 1) vesiculobullous lesions present at birth or induced by friction; 2) spontaneous recovery at a few months of age; 3) no dystrophic scars; 4) subepidermal blisters beginning in the dermal papillae; 5) ultrastructurally observed collagenolysis and damaged anchoring fibrils; and 6) enormous dilation of rough endoplasmic reticulum, with stellate bodies of keratinocytes in their vacuoles.

The cause has been shown in one family to be a transversion mutation in the COL7A1 gene encoding for type VII collagen, and it is therefore allelic with other variants of dominant dystrophic EB. The mechanism for the transient nature of reduced amounts of type VII collagen along the dermoepidermal junction remains to be defined.

Acrokeratotic Poikiloderma (Kindler, Weary-Kindler) In 1954, Kindler reported a combination of poikiloderma congenitale and traumatic blistering of the feet from minor trauma. It shares some clinical features with dominant dystrophic EB, but in the largest reported familial cluster, inheritance followed an autosomal-recessive pattern. Characteristic features include skin fragility with blistering, congenital acral bullae, generalized poikiloderma with prominent atrophy, photosensitivity, acral keratoses, severe periodontal disease, and phimosis. Pseudoainhum and sclerotic bands were reported in one case. The principal histologic change is absence of elastic fibers in the papillary dermis and fragmented ones in the mid-dermis. Ultrastructural studies have shown replication of the lamina densa.

Recessive Dystrophic Epidermolysis Bullosa (Hallopeau-Siemens) There are three variants of recessive dystrophic EB—generalized, localized, and inverse. The generalized type has two variants: a mild or mitis form and the severe (Hallopeau-Siemens) variety. All forms result from mutations in the gene encoding type VII collagen,

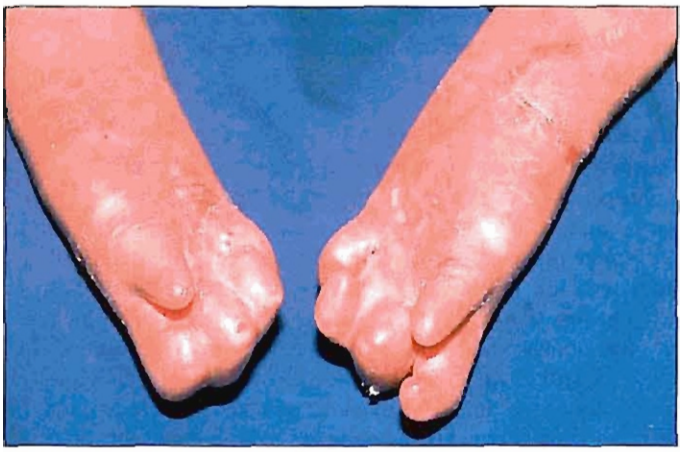

Fig. 27-13 Epidermolyis bullosa, recessive dystrophic type.

COL7A1. Generalized recessive dystrophic EB in its mild (mitis) form has blisters limited primarily to the hands, feet, elbows, and knees, and limited complications. The more severe variety characteristically begins at birth with generalized cutaneous and mucosal blistering. Digital fusion with encasement of the fingers and toes in scar tissues, forming a "mitten-like" deformity (Fig. 27-13), is characteristic of the severe form of recessive dystrophic EB, occurring in up to 90% of patients by age 25. Dental complications may be severe, such as rampant dental caries and microstomia. Esophageal stricture may be present. Anemia and growth retardation are frequently seen in the most severe cases, and progressive nutritional deficiency can result in fatal cardiomyopathy. Fatal systemic amyloidosis (AA type) has also been reported. There is a high risk of developing cutaneous squamous cell carcinomas (SCCs), with up to 50% of patients affected by age 35. These SCCs may be multiple and can metastasize and cause death.

Treatment remains primarily palliative. Debilitating oral lesions produce pain, scarring, and microstomia. Aggressive dental intervention is recommended. Nutritional support is of critical importance. Autologous meshed split-thickness skin grafts and allogeneic cultured keratinocytes have been shown to be useful in treating nonhealing cutaneous defects, or they may be used for closure after removal of large cutaneous malignancies. Family education and referral to DEBRA (Dystrophic Epidermolysis Bullosa Research Association of America, 5 West 36 th Street, Room 404, New York, NY 10018, www.debra.org) is strongly recommended.

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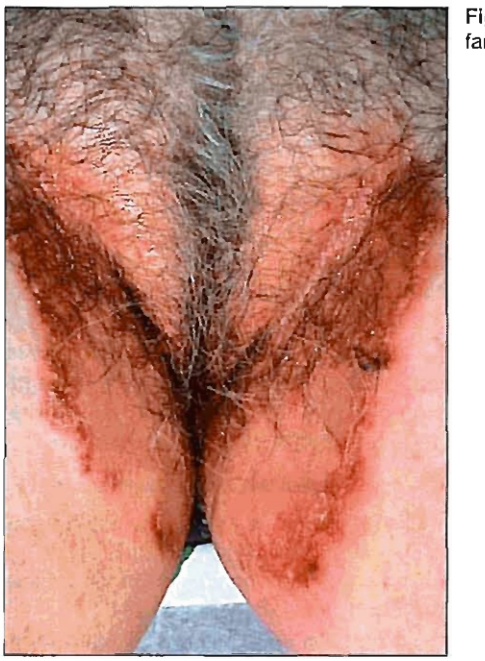

Fig. 27-14 Benign familial pemphigus.

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FAMILIAL BENIGN CHRONIC PEMPHIGUS (HAILEY-HAILEY DISEASE)

In 1939, Hailey and Hailey described a familial disease characterized by persistently recurrent bullous and vesicular dermatitis of the sides of the neck, axillae, and flexures (Fig. 27-14). The eruption may remain localized or may become widespread. Usually, intact blisters are not evident. Instead, the lesions appear as macerated plaques with a reticulated pattern of fissuring. Lesions may become thickly crusted and may resemble impetigo. Sometimes the center becomes dry and crusted and there is an actively inflammatory border that spreads peripherally, producing circinate and figurate patterns. The onset is usually in the late teens or early 20s.

The condition is typically worse during the summer. Lesions tend to recur at sites of prior involvement. A papular variant in the genital area has been described, simulating condylomata. There may be tenderness and enlargement of the regional lymph glands caused by secondary bacterial infection. Involvement of the esophagus, mouth, and labia majora is rare. Hailey-Hailey's disease is inherited in an autosomal-dominant manner. Thirty percent of patients express new mutations. The disease is due to a genetic defect in a calcium ATPase (ATP2C1) on chromosome 3q21.

In predisposed persons with Hailey-Hailey's disease, skin trauma, bacterial or fungal infection, and dermatoses may trigger lesions. Sunburn may also exacerbate the disease. Widespread bullous lesions may occur in response to drug

eruptions, and be misdiagnosed as toxic epidermal necrolysis.

The histopathologic picture is unique. There is acanthosis and full-thickness acantholysis resembling a "dilapidated brick wall." The basal cell layer remains attached to the dermis.

The treatment of Hailey-Hailey is difficult. Many cases improve with the use of systemic antibiotics effective against *Staphylococcus aureus*, topical clindamycin, antifungal agents, or mupirocin. Corticosteroids, administered topically, systemically, or both, have shown response. Cyclosporin, oral retinoids, topical calcineurin inhibitors, topical calcitriol, botulinum toxin, photodynamic therapy, and dapsone have been used in severe cases. Dermabrasion and CO_2 laser vaporization have been shown to be effective, as the epidermis heals from uninvolved adnexal structures. Grafting has been helpful in the most severe forms of the disease.

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DISORDERS OF CORNIFICATION (ICHTHYOSES AND ICHTHYOSIFORM SYNDROMES)

The term *ichthyosis* is derived from the Greek word *ichthys*, meaning "fish." Ichthyosis is not one disease but a group of diseases in which the homeostatic mechanism of epidermal cell kinetics or differentiation is altered, resulting in the clinical appearance of scale. Because these disorders manifest as abnormal differentiation of the epidermis, the term *disorders of cornification* is preferred to ichthyosis.

Treatment

Symptomatic treatment with alphahydroxy acids, such as lactic acid or 12% ammonium lactate lotion, is helpful. Patients with atopic dermatitis and ichthyosis vulgaris may find that these products sting. Other compounds with hydrating and keratolytic properties are also beneficial. Creams containing 10% urea are effective humectants. Widespread use of topical salicylic acid in children may lead to salicylism, and salicylic acid products are best reserved for localized thicker areas, when 40% urea has failed. Baths may help by hydrating the horny layer, but the water must be sealed in with an evaporation barrier such as white petrolatum. Topical calcipotriene ointment has proved effective in a variety of ichthyoses. Application of a 40% to 60% solution of propylene glycol in water under an occlusive suit removes the scales. Proplyene glycol can produce renal failure and cardiac toxicity when given systemically, but few reports of adverse effects have been noted with topical use. Many patients benefit from the use of a sauna suit even without the use of propylene glycol.

Ichthyosis Vulgaris

Ichthyosis vulgaris is autosomal-dominantly inherited and is characterized by onset in early childhood, usually between 3 and 12 months of age, with fine scales that appear "pasted-on" over the entire body. Varying degrees of dryness of the skin may be evident. The scales are coarser on the lower extremities than they are on the trunk. The extensor surfaces of the extremities are most prominently involved. The axillary and gluteal folds are usually not involved. Although the antecubital and popliteal fossae are usually spared by ichthyosis vulgaris, atopic changes may be present, as these disorders are frequently associated. Accentuated skin markings and hyperkeratosis of the palms are common features. Keratosis pilaris is frequently associated. The scalp is involved, with only slight scaling. Keratotic lesions may be found on the palmar creases (keratosis punctata). Atopy manifested as hay fever, eczema, asthma, or urticaria is frequently present. The course is favorable, with limited findings by the time the patient is an adult.

Histologically, there is a moderate degree of compact eosinophilic orthokeratosis. The granular layer is reduced or absent, and keratohyalin granules may appear spongy or fragmented on electron microscopy. The spinous layer is of normal thickness. Filaggrin is reduced in involved epidermis, and profilaggrin mRNA is unstable in keratinocytes. This is a retention hyperkeratosis, with a normal rate of epidermal turnover.

The differential diagnosis includes severe xerosis, X-linked ichthyosis, and acquired ichthyosis.

X-Linked Ichthyosis

X-linked ichthyosis is transmitted only to males by heterozygous mothers as an X-linked recessive trait. This condition results from a deficiency of steroid sulfatase (aryl sulfatase C), and occurs once in every 2000 to 5000 male births. Onset is usually before 3 months of age. The children are commonly born via cesarian section, with failure of progression of labor owing to a placental sulfatase deficiency. Scales are dark, large, and prominent on the anterior neck, extensor surfaces of the extremities (Figs 27-15 and 27-16), and the trunk. The sides of the neck are invariably involved, giving the child an unwashed look. The elbow and knee flexures are relatively spared, as are the face and scalp; the palms and soles are nearly always spared.

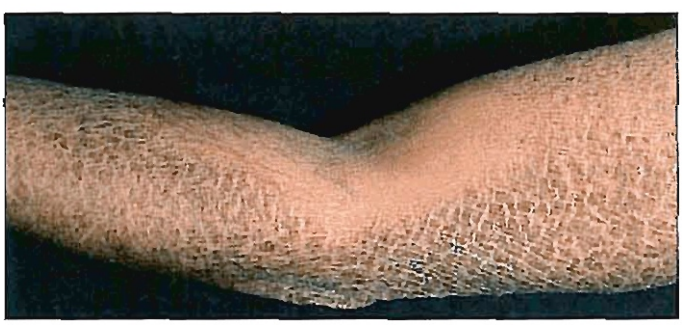

Fig. 27-15 X-linked ichthyosis.

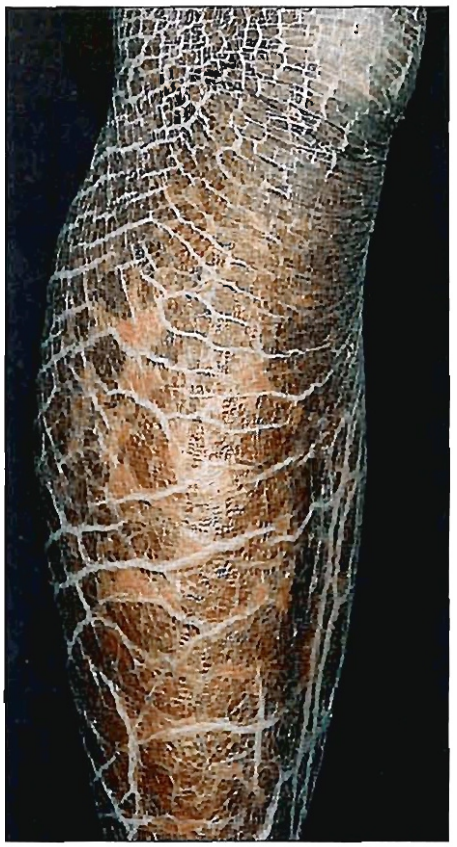

Fig. 27-16 X-linked ichthyosis.

The condition may be confused with ichthyosis vulgaris, but typically has darker scales and demonstrates dramatic clearing during the summer months. A diagnosis of X-linked ichthyosis is likely if the abdomen is more involved than the back and if the ichthyosis extends down the entire dorsum of the leg. Keratosis pilaris is not present, and the incidence of atopy is not increased. Corneal opacities (which do not affect vision) are seen by slit-lamp examination on the posterior capsule or Descemet's membrane in about 50% of affected males and female carriers. Another extracutaneous feature is a 12% to 15% incidence of cryptorchidism and an independently increased risk of testicular cancer. Unlike ichthyosis vulgaris, X-linked ichthyosis does not improve with age, but gradually worsens in both extent and severity.

There is usually a deletion at Xp22.3, and steroid sulfatase is lacking in fibroblasts, leukocytes, and keratinocytes. The diagnosis can be confirmed by lipoprotein electrophoresis, because the increase in cholesterol sulfate makes the low-density lipoproteins (LDLs) migrate much more rapidly, and cholesterol sulfate is elevated in serum, erythrocyte membranes, and keratin. The reduced enzyme activity can be assessed in fibroblasts, keratinocytes, leukocytes, and prenatally in amniocytes.

Multiple Sulfatase Deficiency

Patients with multiple sulfatase deficiency display an overlap of steroid sulfatase deficiency, mucopolysaccharidosis, and metachromatic leukodystrophy. The scaling is sometimes milder than X-linked recessive ichthyosis. There may be developmental delay, spastic quadriparesis, and coarse facial features. Histologic examination shows hyperkeratosis with a normal granular cell layer. This autosomal-recessive disorder is caused by a lack of or deficiency in all known sulfatases.

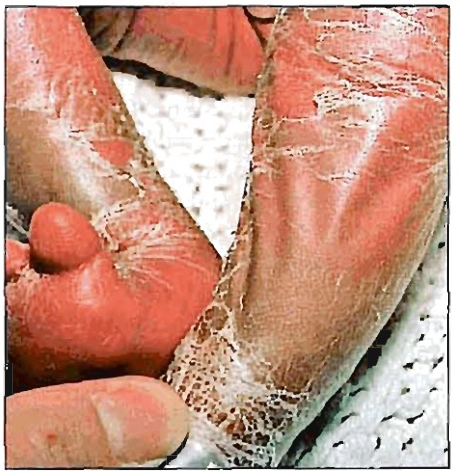

Fig. 27-17 Collodion baby.

Autosomal-Recessive Ichthyosis

Biochemical and genetic studies have helped to define the specific subtypes. Clinical features often overlap, and in the past, the severity of the disease determined the classification. Identification of specific defects, such as transglutaminase 1, and profilaggrin/filaggrin are important to define each disorder, and are the basis for classification of ichthyotic disorders.

Lamellar Ichthyosis Lamellar ichthyosis is present at birth or becomes apparent soon after, and almost always involves the entire cutaneous surface. Usually a collodion-like membrane encases the baby at birth, then desquamates over the first 2 to 3 weeks of life. The ensuing ichthyosis is characterized by large (5–15 mm), grayish-brown scales, which are strikingly quadrilateral, free at the edges and adherent in the center. In severe cases, the scales may be so thick that they are like armor plate. Moderate hyperkeratosis of the palms and soles is frequently present. The follicles in most instances have a crateriform appearance. Ectropion is almost always present and is a helpful diagnostic sign.

Lamellar ichthyosis is inherited as an autosomal-recessive trait. About half the patients have decreased or absent transglutaminase 1 (TGM1) activity. ALOXE3 and ALOX12B mutations can produce a similar appearance. Lamellar ichthyosis type 2 has been associated with mutations in the ABCA12 gene.

In addition to the topical agents recommended for the treatment of other ichthyoses, tazarotene (Tazorac) and orally administered retinoids can improve symptoms. The adverse effects of prolonged oral retinoid therapy make their use for long-term maintenance therapy difficult.

Nonbullous Congenital Ichthyosiform Erythroderma Most infants with nonbullous congenital ichthyosiform erythroderma are born enclosed in a constricting parchment- or collodion-like membrane (Fig. 27-17). They also have ectropion of the eyelids, which has led to confusion with lamellar ichthyosis, and at one time the term lamellar ichthyosis was used for almost all patients with nonbullous autosomal-recessive ichthyoses. As mutations in TGM1, ALOXE3 or ALOX12B can lead to either congenital ichthyosiform erythroderma or lamellar ichthyoses, the separation of the entities is largely on the basis of the clinical phenotype.

Within 24 h after birth, fissuring and peeling begin, and large keratinous lamellae are cast off in 10 to 14 days, coincident with rapid improvement. As the membrane is shed, underlying redness and scaling are apparent. Generalized involvement is the rule, including the face, palms, soles, and flexures. Cicatricial alopecia, nail dystrophy, and some ectropion are common. Scales may be large and platelike on the legs but are likely to be fine on the trunk, face, and scalp. The condition has been found in association with neutral lipid storage disease.

Histologically, parakeratosis and inflammation are seen more frequently in congenital ichthyosiform erythroderma than in lamellar ichthyoses. The stratum corneum is usually thicker in lamellar ichthyoses, and is usually not parakeratotic.

Harlequin Fetus Harlequin fetus is a severe disorder that affects the skin in utero, causing thick, horny, armor-like plates covering the entire surface (Fig. 27-18). The ears are rudimentary or absent, and eclabium and ectropion are severe. The child is often stillborn or dies soon after delivery; however, with aggressive management, there have been long-term survivors. These survivors develop features of congenital ichthyosiform erythroderma or lamellar ichthyosis. Absent or abnormal lamellar granules, a lack of extracellular lipid lamellae, and lipid droplets in the stratum corneum have been reported. Abnormalities of profilaggrin, and K6 and K16 expression have been reported. Recessive inheritance has been favored, and is supported by reports of consanguinity. Some reports suggest a dominant mutation with parental mosaicism.

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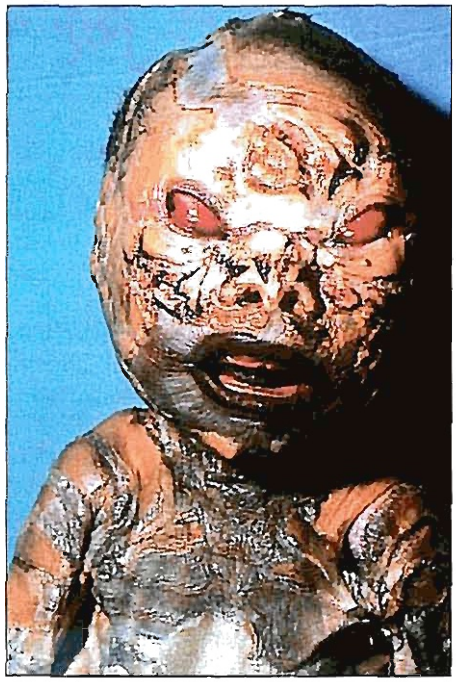

Fig. 27-18 Harlequin fetus.

Epidermolytic Hyperkeratosis (Bullous Ichthyosiform Erythroderma)

An autosomal-dominantly inherited disorder, epidermolytic hyperkeratosis (EHK), or bullous congenital ichthyosiform erythroderma, is usually manifested by blisters at or shortly after birth. Later, thickened, horny, warty or spine-like, ridged scales predominate (Fig. 27-19). They are particularly prominent at the flexures. There is remarkable heterogeneity, particularly in regard to the degree of hyperkeratosis, the extent of body surface involvement, presence or absence of erythroderma, and palm and sole involvement. Epidermal nevi of the epidermolytic type are mosaic expressions of epidermolytic hyperkeratosis.

Epidermolytic hyperkeratosis is caused by mutations in the genes for keratins K1 and K10. Keratin distribution patterns in keratinocytes are abnormal, suggesting that there is an altered assembly process of cornified cell envelopes in epidermolytic hyperkeratosis.

Histologically, the lesional skin demonstrates compact hyperkeratosis. The granular layer is markedly thickened and contains coarse keratohyaline granules. Epidermal cells detach in the granular cell layer and may appear disrupted. Electron microscopy reveals the formation of perinuclear haloes. These findings allow prenatal diagnosis by fetal skin biopsy. Epidermolytic hyperkeratosis has been described as an incidental finding in normal skin, skin adjacent to benign and malignant epidermal tumors, and normal oral mucosa. It may be more commonly seen in association with dysplastic nevi than with banal nevi.

Short intensive therapy with high-dose vitamin A (750,000 U of Aquasol A daily) for 2 weeks produces modest

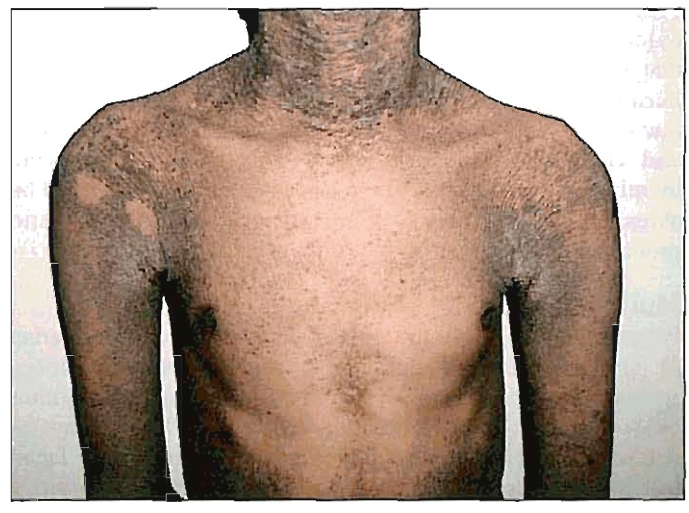

Fig. 27-19 Epidermolytic hyperkeratosis. (Courtesy of Dr Shyam Verma)

clinical improvement. Others have tried administering systemic retinoids, with similar results; however, the patient's blistering may worsen, despite clinical improvement of the scales. Decisions regarding systemic retinoid therapy must therefore be made on a case-by-case basis. Application of 0.1% retinoic acid (Retin-A cream) has been used successfully. Pyogenic infection is a common problem, and appropriate antibiotics should be administered. A water solution of 10% glycerin and 3% lactic acid applied to wet skin can result in clinical improvement. The disease tends to become less severe with age.

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Ichthyosis Bullosa of Siemens

Once classified as a subtype of epidermolytic hyperkeratosis, this condition is characterized by a lack of erythema, relatively mild hyperkeratosis usually limited to the flexures, and superficial molting or peeling of the skin (the "mauserung" phenomenon). Ichthyosis bullosa of Siemens is caused by mutations in the gene for keratin 2e.

Suga Y, et al: Hot spot mutations in keratin 2e suggest a correlation between genotype and phenotype in patients with ichthyosis bullosa of Siemens. Exp Dermatol 2000;9:11.

Restrictive Dermopathy

Restrictive dermopathy is a rare, lethal, autosomal-recessively inherited disease characterized by abnormal facies, tight skin, sparse or absent eyelashes, and secondary joint changes. Virtually all cases are associated with polyhydramnios, reduced fetal movements, and premature delivery. Infants exhibit a fixed facial expression, with blurring of groove between nose and cheek, sometimes described as an "Asiatic porcelain doll" appearance. Patients also exhibit micrognathia, mouth in the "O" position, rigid and tense skin with erosions and denudations, and multiple joint contractures. Some patients have wide cranial sutures, small pinched nose, low-set ears, microstomia, rocker-bottom feet, scaly skin, and respiratory insufficiency. Pulmonary hypoplasia, microcolon, vessel transposition, natal teeth, ectropion, submucous cleft palate, hypospadias, urethral duplication, dysplasia of clavicles, adrenal hypoplasia, and an enlarged placenta with short umbilical cord may be noted. Histopathologic features include hyperkeratosis, parakeratosis, abnormal keratohyaline granules, and effacement of the rete ridge pattern. The dermis is attenuated with collagen fibers parallel to the epidermis, resembling a scar or tendon. Elastic fibers are absent. The subcutis demonstrates hypoplastic eccrine and sebaceous glands.

Armbrust S, et al: Restrictive dermopathy associated with transposition of the great arteries and microcolon: a rare neonatal entity with new symptoms. Arch Dermatol 2005;141:611.

Nijsten TE, et al: Restrictive dermopathy: a case report and a critical review of all hypotheses of its origin. Pediatr Dermatol 2002;19:67.

Fig. 27-20 Ichthyosis linearis circumflexa.

Ichthyosis Linearis Circumflexa

Ichthyosis linearis circumflexa is an inherited autosomal-recessive disorder of cornification in which migratory annular and polycyclic patches occur (Fig. 27-20). It may first appear as severe congenital generalized exfoliative erythroderma. Later, lesions predominate on the trunk and extremities, and appear as a polycyclic serpiginous eruption characterized by constantly changing patterns. In about a week the lesions attain their maximum diameter and involute, leaving no atrophy, scarring, or pigmentation. The lesions may clear almost completely during the summer. Most patients are found to have bamboo hair (trichorrhexis invaginata). The association of ichthyosiform dermatitis, hair abnormality, and atopic diathesis is called *Netherton syndrome*. Because of coexistent atopic dermatitis, the scalp, face, and eyebrow regions are erythematous and scaly. Hairs may fracture below the surface of the scalp, so that the patient appears bald. Mutations in SPINK5, which encodes the serine protease inhibitor Kazal-type 5 protein, have been identified in Netherton syndrome.

Histologic examination shows hyperkeratosis, parakeratosis, and acanthosis. The granular layer is typically absent.

Acitretin has been effective in some patients, but should be avoided in erythrodermic neonates and long-term use is limited by toxicity. Topical tacrolimus has also been reported as effective, but in one report, three patients treated twice with 0.1% tacrolimus ointment were found to have significant tacrolimus blood levels. Although none of these patients developed signs or symptoms of toxic effects, monitoring of blood levels is advised if tacrolimus is used in this setting.

Allen A, et al: Significant absorption of topical tacrolimus in 3 patients with Netherton syndrome. Arch Dermatol 2001;137:747.

Bitoun E, et al: Netherton syndrome: disease expression and spectrum of SPINK5 mutations in 21 families. J Invest Dermatol 2002;118:352.

Suga Y, et al: A case of ichthyosis linearis circumflexa successfully treated with topical tacrolimus. J Am Acad Dermatol 2000;42:520.

Neutral Lipid Storage Disease

Dorfman-Chanarin syndrome is a rare autosomal-recessive disorder characterized by an ichthyosiform eruption, myopathy, and vacuolated leukocytes. Lipid vacuoles are present in all circulating granulocytes and monocytes, as well as dermal fibroblasts, Schwann cells, smooth muscle cells, and sweat gland cells. Other organ systems, such as the CNS, liver, muscles, ears, and eyes, may also have deposits. Associated cutaneous disorders include poikiloderma atrophicans vasculare and bullous congenital ichthyosiform erythroderma. The disorder is caused by a regulatory defect that alters the rates of synthesis and degradation of the major cellular phospholipids, particularly triacylglycerol-derived diacylglycerol. Electron microscopic findings show electron-lucent globular inclusions in lamellar structures. Dietary intervention, with modulation of dietary fats, has been shown to aid in controlling the disease.

Pena-Penabad C, et al: Dorfman-Chanarin syndrome (neutral lipid storage disease): new clinical features. Br J Dermatol 2001;144:430.

Ichthyosis Follicularis

Ichthyosis follicularis is characterized by noncicatricial universal alopecia, severe photophobia, and generalized cutaneous follicular projections that are flesh-colored and spiny. There is xerosis of nonspiny skin, and absence of sebaceous glands has been noted histologically. Hepatosplenomegaly, undescended testicles, nail dystrophy, inguinal hernia, short stature, seizures, psychomotor developmental delay, digital anomalies, and ptosis have been reported. It has also been called *ichthyosis follicularis, alopecia, and photophobia (IFAP) syndrome*. Males outnumber females 5:1. The main considerations in differential diagnosis are the keratitis-ichthyosis-deafness (KID) syndrome and keratosis follicularis spinulosa decalvans (KFSD). The disorder may be transmitted by an X-linked recessive gene, although an autosomal-dominant form has also been reported.

Alfadley A, et al: Ichthyosis follicularis: a case report and review of the literature. Pediatr Dermatol 2003;20:48.

Megarbane H, et al: Ichthyosis follicularis, alopecia, and photophobia (IFAP) syndrome: report of a new family with additional features and review. Am J Med Genet 2004;124A:323.

Sjögren-Larsson Syndrome

Sjögren-Larsson syndrome is characterized by ichthyosis, spastic paralysis, oligophrenia, mental retardation, and a degenerative retinitis. The ichthyosis is usually generalized, with little or no involvement of the scalp, hair, or nails. There is a flexural and lower abdominal accentuation. The central face is spared, ectropion is unusual, and palms and soles are involved. Beginning by the age of 2 or 3, there is spastic paralysis consisting of a stiff, awkward movement of the extremities. Electron microscopy reveals prominent Golgi apparatus and increased numbers of mitochondria in keratinocytes. Usually, a severe mental deficiency is present. The epilepsy is of the grand mal type. This syndrome is of autosomal recessive inheritance, localized to chromosome 17p11.2. These patients have a fibroblast and leukocyte deficiency in fatty aldehyde dehydrogenase.

Huag S, et al: Adeno-associated virus vectors are able to restore fatty aldehyde dehydrogenase-deficiency. Implications for gene therapy in Sjorgren-Larsson syndrome. Arch Dermatol Res 2005;296:568.

Willemsen MA, et al: Clinical, biochemical and molecular genetic characteristics of 19 patients with the Sjögren-Larsson syndrome. Brain 2001;124:1426.

Refsum Syndrome

Refsum syndrome (heredopathia atactica polyneuritiformis) is an autosomal-recessively inherited ichthyosis with atypical retinitis pigmentosa, hypertrophic peripheral neuropathy, cerebellar ataxia, nerve deafness, and various electrocardiographic changes. The ichthyosis resembles ichthyosis vulgaris. It may be generalized or localized to the palms and soles. It is of delayed onset and shows lipid vacuoles in the basal layer. The epidermal cell turnover rate is increased. Biochemically the disease is a peroxisomal disorder characterized by excessive accumulation of phytanic acid, pristanic acid, and picolenic acid in fatty tissues, myelin sheaths, heart, kidneys and retinal tissues. The disease is caused by a deficiency of phytanolyl/pristanoyl-CoA-hydroxilase. In most patients, mutations in the PHYH gene have been identified, and a second locus has been found on chromosome 6q22–24 with mutations in PEX7 (a gene also associated with rhizomelic chondrodysplasia punctata type 1). Dietary restriction of phytanic acid-containing vegetables can lead to an improvement of neurologic symptoms, but does not affect retinal changes. Unfortunately, in many patients, dietary restriction is not sufficient to prevent acute attacks or stabilize the progressive course. The acids are localized within very low-density lipoprotein (VLDL), LDL, and high-density lipoprotein (HDL) particles, and may be removed by extracorporal LDL-apheresis.

Straube R, et al: Membrane differential filtration is safe and effective for the long-term treatment of Refsum syndrome—an update of treatment modalities and pathophysiological cognition. Transfus Apheresis Sci 2003;29:85.

van den Brink DM, et al: Identification of PEX7 as the second gene involved in Refsum disease. Am J Hum Genet 2003;72:471.

Rud Syndrome

Rud syndrome is characterized by ichthyosis, hypogonadism, small stature, mental retardation, acanthosis nigricans, epilepsy, macrocytic anemia, and, rarely, retinitis pigmentosa. Most kindreds have shown autosomal-recessive inheritance and may be atypical variants of well-described disorders, such as Sjögren-Larsson syndrome or Refsum syndrome, rather than representing a distinct inherited disorder. Some patients have X-linked steroid sulfatase deficiency.

Rajagopalan B: Non-bullous ichthyosiform erythroderma associated with retinitis pigmentosa. Am J Med Genet 2001;99:181.

Stoll C, et al: A syndrome of congenital ichthyosis, hypogonadism, small stature, facial dysmorphism, scoliosis and myogenic dystrophy. Ann Genet 1999;42:45.

Keratitis-Ichthyosis-Deafness Syndrome

The KID syndrome (Senter syndrome) is characterized by vascularization of the cornea, an extensive congenital ichthyosiform eruption, neurosensory deafness, reticulated hyperkeratosis of the palms and soles, hypotrichosis, partial anhidrosis, nail dystrophy, and tight heel cords. Distinctive leathery, verrucoid plaques involve the central portion of the face and ears. These changes, with absent eyebrows and eyelashes, and furrows about the mouth and chin, give the children a unique facies. The disorder is related to missense mutations in the GJB2 gene that encodes connexin-26 (Cx26). Most cases are sporadic.

Isotretinoin treatment may exacerbate and promote corneal vascularization. Treatment with acitretin has been reported to clear the hyperkeratotic ichthyotic lesions with little effect on the cornea or hearing. Cyclosporin A eye drops have been used to treat corneal neovascularization.

Mohrenschlager M, et al: Additional aspects of keratics, ichthyosis, and deafness (KID) syndrome. Pediatr Dermatol 2004;21:518.

Sahoo B, et al: KID syndrome: response to acitretin. J Dermatol 2002;29:499.

Congenital Hemidysplasia with Ichthyosiform Erythroderma and Limb Defects Syndrome

Present at birth, congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) syndrome is characterized by unilateral inflammatory epidermal nevi and ipsilateral limb hypoplasia or limb defect. Features may vary widely, from complete absence of an extremity to defects of internal organs involving the musculoskeletal, cardiovascular, or central nervous systems. It is believed to be X-linked dominant and lethal in hemizygous males. Survival in males has been reported as a result of mosaicism. In females, Lyonization may produce cutaneous patterns following the lines of Blaschko, similar to incontinentia pigmenti or X-linked dominant chondrodysplasia. The pathogenesis is related to mutations in the gene NSDHL that is localized at Xq28 and involved in cholesterol metabolism. When unilateral epidermal nevi show features of verruciform xanthoma, CHILD syndrome should be suspected. The CHILD nevus is distinguished by ptychotropism (flexural involvement), waxy yellowish scaling, lateralization showing both diffuse and linear involvement, and the presence of foamy macrophages in the dermal papillae.

Bittar M, et al: CHILD syndrome avant la lettre. J Am Acad Dermatol 2004;50(2 Suppl):S34.

Happle R, et al: The CHILD nevus: a distinct skin disorder. Dermatology 1995;191:210.

Hashimoto K, et al: CHILD syndrome with linear eruptions, hypopigmented bands, and verruciform xanthoma. Pediatr Dermatol 1998;15:360.

Erythrokeratodermia Variabilis

Erythrokeratodermia variabilis, also called *erythrokeratodermia figurata variabilis*, *erythrokeratodermia variabilis*, and *Mendes da Costa type erythrokeratodermia*, is a rare autosomal-dominant disorder characterized by erythematous patches and hyperkeratotic plaques of sparse but generalized distribution. The erythematous patches may assume bizarre geographic configurations that are sharply demarcated. Over time, they change their shape or size or involute completely. The keratotic plaques are reddish-brown, often polycyclic, and fixed in location. The extensor surfaces of the limbs, buttocks, axillae, groins, and face are most often involved. Approximately 50% of patients display a palmoplantar keratoderma associated with peeling. Hair, nails, and mucous membranes are spared.

The onset of the condition is shortly after birth or, rarely, at birth, or in early adult life. There may be some improvement with age, particularly after menopause. Exacerbations have been seen during pregnancy. The figurate erythematous component may be accentuated by exposure to heat, cold, or wind. Emotional upsets may also be a factor.

The gene has been mapped to 1p34–p35, the gene GJB3 coding for a gap junction protein α-4 (connexin 31). Histologically, there is hyperkeratosis and parakeratosis, and a diminished granular layer. Acanthosis may occur. Ultrastructurally, epidermal keratinosomes are diminished.

Systemic retinoids such as acitretin or isotretinoin can restore the deficient keratinosomes and partially clear the hyperkeratotic plaques. The disease often relapses when therapy is discontinued. Urea, salicylic acid, and lactic acid have proved useful for the hyperkeratotic plaques

Morley SM, et al: A new, recurrent mutation of GJB3 (Cx31) in erythrokeratodermia variabilis. Br J Dermatol 2005;152:1143.

Strober BE: Erythrokeratodermia variabilis. Dermatol Online J 2003;9:5.

Progressive Symmetric Erythrokeratodermia

Progressive symmetric erythrokeratodermia (erythrokeratodermia progressiva symmetrica) is a rare, autosomal-dominantly inherited disorder that manifests soon after birth with erythematous, hyperkeratotic plaques that are symmetrically distributed on the extremities, buttocks, and face, sparing the trunk. Palmoplantar keratoderma may be present. The lesions may regress at puberty. The cause in one kindred was related to an insertion mutation in the loricrin gene. Topical treatments, including keratolytics, corticosteroids, and retinoids, have had variable success.

Khoo BP, et al: Generalized erythematous plaques. Progressive symmetric erythrokeratodermia PSEK) (erythrokeratodermia progressiva symmetrica). Arch Dermatol 2000;136:665, 668.

Gray LC, et al: Progressive symmetric erythrokeratodermia. J Am Acad Dermatol 1996;34:858.

Acquired Ichthyosis

Ichthyosis clinically similar to ichthyosis vulgaris may develop in patients with several systemic diseases. Acquired ichthyosis has been reported with Hodgkin's disease, and may be a presenting symptom. It has also occurred in non-Hodgkin lymphoma, mycosis fungoides, multiple myeloma, and carcinomatosis. In hypothyroidism, patients may develop fine scaling of the trunk and extremities, as well as carotenemia and diffuse alopecia. Characteristic ichthyosiform lesions may develop in patients with sarcoidosis, particularly over the lower extremities. Biopsy of the lesion will often show granulomas. Ichthyosiform changes have also been reported

in patients with leprosy, nutritional deficiency, acquired immune deficiency syndrome (AIDS), human T-cell lymphotropic virus infection, lupus erythematosus, and dermatomyositis. Drug-induced ichthyosis may occur with nicotinic acid, triparanol, and butyrophenones.

Okulicz JF, et al: Hereditary and acquired ichthyosis vulgaris. Int J Dermatol 2003;42:95.

PITYRIASIS ROTUNDA

Pityriasis rotunda (pityriasis circinata) manifests as perfectly circular scaly patches on the torso and proximal portions of the extremities. The scale is adherent and resembles that of ichthyosis vulgaris. There is a strong ethnic predisposition, with a preponderance of reports in black persons, Japanese, Koreans, and Italians. Some cases are associated with systemic illnesses, especially in darker skinned patients. Associated illnesses include tuberculosis, other pulmonary disorders, liver disease, malnutrition, leukemia, lymphoma, and carcinoma of the esophagus or stomach. Familial cases with autosomal-dominant transmission have also been described.

Two forms of the disease occur. Type I is found in black or Asian persons, usually has fewer than 30 hyperpigmented lesions, is nonfamilial, and may be associated with systemic disease. Type II disease occurs in white persons, has larger numbers of hypopigmented lesions, is often familial, and usually is not associated with internal disease.

The differential diagnosis includes tinea versicolor, tinea corporis, erythrasma, leprosy, fixed drug eruptions, and pityriasis alba. Some patients note a seasonal improvement during the summer, and some respond to emollients during the winter months. Topical and systemic retinoids have been used successfully, but often the condition is unresponsive unless there is an underlying systemic illness that can be treated.

Mafong EA: Pityriasis rotunda. Dermatol Online J 2002;8:15.
Pinto GM, et al: Pityriasis rotunda. Cutis 1996;58:406.

POROKERATOSIS

Porokeratosis is a heterogeneous group of disorders that are inherited in an autosomal-dominant fashion. Except for the punctate type, they are characterized by distinct clinical findings of a keratotic ridge with a central groove that corresponds to the cornoid lamella on histology. The groove may be accentuated by the application of gentian violet followed by removal with alcohol. The dye remains in the groove. Povidone iodine has been used in a similar fashion. Immunosuppression, ultraviolet exposure, and radiation therapy may exacerbate porokeratosis and promote the development of skin cancers within the lesions. The linear type has the greatest risk of malignant transformation.

Topical 5-fluorouracil (5-FU) is generally effective in destroying individual lesions. It may have to be applied under occlusion but may result in scarring. In disseminated superficial actinic porokeratosis (DSAP), where the risk of malignant transformation is very low, the risks of treatment with 5-FU must be weighed against the generally indolent course of the lesions. Sun protection, emollients, and observation for signs of malignant degeneration may be the most suitable course of action for many patients with DSAP. Other agents that have been shown to be effective for some patients with DSAP include topical vitamin D3 analogs and topical retinoids, including tazarotene. Salicylic acid and α-hydroxyl acids may make the lesions less noticeable. Topical imiquimod has been used for porokeratosis, including porokeratosis of Mibelli. Oral retinoids have shown efficacy, but the lesions commonly recur after treatment, and long-term treatment with these agents is impractical. Combinations of oral retinoids and topical 5-FU have been effective for refractory DSAP and porokeratosis plantaris, palmaris, et disseminata, but the side effects of treatment may be considerable. Destructive modalities must extend into the dermis and produce scarring. More superficial treatment is commonly followed by recurrence. Other effective modalities include cryotherapy, electrodesiccation and curettage, CO_2 laser ablation, flashlamp-pumped pulsed dye laser, frequency-doubled Nd:YAG laser, dermabrasion and Grenz ray.

Plaque-Type Porokeratosis (Mibelli)

Plaque-type porokeratosis is a chronic, progressive disease characterized by the formation of slightly atrophic patches surrounded by an elevated, warty border. The lesion begins as a small keratotic papule, which spreads peripherally and becomes depressed centrally. Eventually, it becomes a circinate or serpiginous, well-defined plaque surrounded by a keratotic wall or collar. This wall is grayish or brownish and frequently is surmounted by a tiny groove or linear ridge running along its summit. The enclosed central portion of the plaque consists of dry, smooth, atrophic skin, the lanugo hairs generally being absent when the patches occur in hairy areas. Linear or zosteriform distribution of the lesions may also occur. If the nail matrix is involved, nail dystrophy may develop. Lesions may appear during chemotherapy for malignancy, after renal transplantation, while on PUVA treatment, and in areas of chronic sun damage, or chemical exposure, such as benzylhydrochlorothiazide.

Sites of predilection are the surfaces of the hands and fingers, and the feet and ankles. The disease also occurs on the face and scalp (where it produces bald patches), on the buccal mucosa (where the ridge becomes macerated by moisture and appears as a milky white, raised cord), and on the glans penis (where it causes erosive balanitis).

Histologically, the principal diagnostic changes are in the area of the cornoid lamella. This area demonstrates a column of parakeratotic keratin extending at about a 45° angle from a focus of dyskeratotic cells in the malpighian layer. The column trails behind the focus of dyskeratosis as the focus expands peripherally. The granular cell layer is absent beneath the parakeratotic column. The central portion of the lesion may demonstrate atrophy with loss of the rete ridge pattern, lichenoid dermatitis, or psoriasiform hyperplasia.

Disseminated Superficial Actinic Porokeratosis

DSAP is characterized by numerous superficial, annular, keratotic, brownish-red macules found on sun-exposed areas. It is more common in women. The keratotic ridge is thin and thread-like, but may be accentuated by application of gentian violet followed by removal with alcohol. A surgical skin marking pen or cotton tipped applicator work equally well for dye application.

The distribution of the lesions on the sun-exposed areas indicates that actinic radiation is an important factor in its pathogenesis, and new lesions have been induced by exposure to commercial tanning salons. Exacerbations occur in up to two-thirds of patients during summer. Immunosuppression is also well documented to exacerbate the disease. It has been seen in patients with AIDS, cirrhosis, and Crohn's disease. Organ transplant patients may develop DSAP. Improvement of the immunosuppression may lead to resolution of the lesions. Gene loci for DSAP have been localized to chromosomes 12q23.2–24.1 and 15q25.1–26.1, suggesting that DSAP is a genetically heterogeneous disorder.

Linear Porokeratosis

Linear porokeratosis may be segmental or generalized. It may be identified during the newborn period, and when found in the segmental pattern, may follow the lines of Blaschko. Ulcerations and erosions involving the face or extremities may delay the correct diagnosis, and linear porokeratosis should be included in the differential diagnosis of ulcerative lesions in the neonatal period. This form of porokeratosis has the highest risk of developing cutaneous malignancies, including squamous cell carcinoma, Bowen's disease, and basal cell carcinoma.

Porokeratosis Palmaris, Plantaris, et Disseminata

In this distinctive form of porokeratosis, lesions first appear on the palms or soles, or more often both. Onset is frequently noted when patients are in their 20s. Slowly, the lesions may extend over the entire body. In porokeratotic eccrine ostial and dermal duct nevus, the presentation clinically appears like a nevus comedonicus of the palm or sole, but histologic analysis reveals multiple comedoid lamella-like parakeratotic columns. In porokeratosis punctata, palmaris et plantaris or punctate porokeratosis, lesions are limited to the hands and feet.

Harrison S, et al: Porokeratosis of Mibelli: successful treatment with topical 5% imiquimod cream. Australas J Dermatol 2003; 44:281.

Maubec E, et al: Common skin cancers in porokeratosis. Br J Dermatol 2005;152:1389.

Rongioletti F, et al: Disseminated porokeratosis with fatal metastatic squamous cell carcinoma: an additional case of "malignant disseminated porokeratosis". Am J Dermatopathol 2002;24:144.

Silver SG, et al: Fatal squamous cell carcinoma arising from transplant-associated porokeratosis. J Am Acad Dermatol 2003;49:931.

Thomas CJ, et al: Medical pearl: Gentian violet to highlight the cornoid lamella in disseminated superficial actinic porokeratosis. J Am Acad Dermatol 2005;52:513.

DARIER'S DISEASE (KERATOSIS FOLLICULARIS, DARIER-WHITE DISEASE)

Darier's disease is an autosomal-dominantly inherited skin disorder characterized by brown keratotic papules that tend to coalesce into patches in a seborrheic distribution. Early lesions are small, firm papules, almost the color of normal skin. Each papule becomes covered with a greasy, gray–brown crust that fits into a small concavity in the summit of the papule. As the lesions grow older, their color darkens (Fig. 27-21). In the course of years, the papules grow and may fuse to form malodorous, papillomatous and vegetating growths.

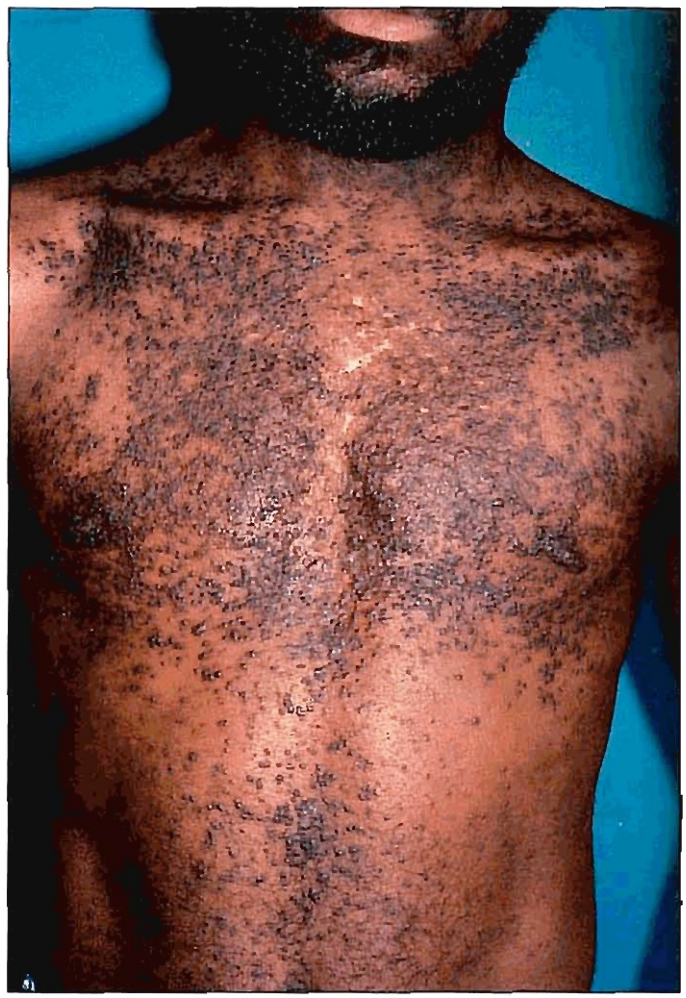

Fig. 27-21 Darier's disease. (Courtesy of Larry Lieblich, MD)

The neck and shoulders, face, extremities, front of the chest, and midline of the back are sites of predilection for the disease. A frequent site for the earliest lesions is behind the ears. As the eruption spreads, the entire trunk, buttocks, genitals, and other parts of the skin may be involved. Usually the eruption is symmetrical and widespread, but striking unilateral or segmental involvement may also occur. Cases with segmental distribution probably represent post-zygotic mutations.

Vegetations appear chiefly in the axillae, gluteal crease, groin, and behind the ears. The scalp is generally covered with greasy crusts. Lesions on the face are often prominent about the nose. The lips may be crusted, fissured, swollen, and superficially ulcerated, and there may be a patchy keratosis with superficial erosions on the dorsum of the tongue. Small white papules or pebbling may be present on the gingiva and palate. Involvement of the oropharynx, esophagus, hypopharynx, larynx, and anorectal mucosa has been reported. Punctate keratoses are frequently noted on the palms and soles. A general horny thickening of the palms and soles may be present because of innumerable closely set small papules. On the dorsa of the hands and on the shins

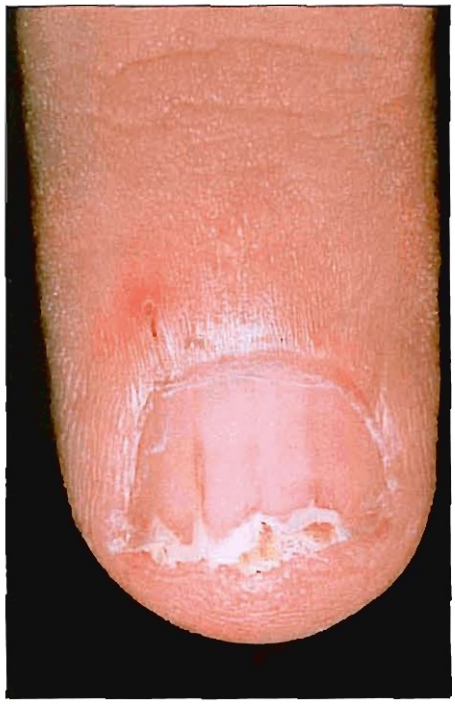

Fig. 27-22 Darier nail.

the flat verrucous papules may resemble verrucae planae. The nails show subungual hyperkeratosis, fragility, and splintering, with longitudinal alternating white and red streaks, and triangular nicking of the free edges (Fig. 27-22).

Darier's disease is usually worse in the summer. It may begin after severe sunburn, and in some patients the lesions may be reproduced with suberythema doses of UVB. Lithium carbonate has been shown to induce Darier's disease in some individuals. Disseminated cutaneous herpes simplex may be a complication of the disease.

Abnormal dissolution of desmosomal plaque proteins is seen, specifically desmoplakin I and II, plakoglobin, and desmoglein. Acantholysis occurs as a result of deficiency in the tonofilament/desmosome attachment. Ca^{2+}-dependent cell–cell adhesion molecules (epithelial cadherins) are markedly reduced on the acantholytic cells of patients with Darier's disease. The Darier gene (ATP2A2) has been localized to 12q23–24.1 and codes for the second isoform of a calcium ATPase of the sarco/endoplasmic reticulum (SERCA2) pump, which transports Ca^{2+} from the cytosol into the endoplasmic reticulum. Inhibition of SERCA impairs trafficking of desmoplakin to the cell surface, contributing to acantholysis.

Histology

Darier's disease is characterized by acantholytic dyskeratosis with overlying hyperkeratosis. Abnormally keratinizing cells appear as round eosinophilic or basophilic cells (corps ronds), which often demonstrate a pale halo surrounding the nucleus. Grains are flat, deeply basophilic, dyskeratotic cells, seen most frequently in the stratum granulosum and stratum corneum. Both grains and corps ronds are separated from the surrounding cells as a result of acantholysis. Formation of a suprabasal cleft (lacuna) is noted, and may involve hair follicles as well as the surface epidermis. Dermal papillae covered by a single layer of basal cells project as villi into the acantholytic space.

Treatment

During flares, topical antibacterial agents, oral antibiotics and short-term application of a corticosteroid may be of benefit. For localized disease, topical retinoids may be effective, but papules often occur at the periphery of the treated region. Oral retinoids are the drugs of choice for most severe cases. Cyclosporin may control severe flares, and topical sunscreens and ascorbic acid can prevent disease flares in some patients. For hypertrophic lesions, dermabrasion, laser vaporization, or excision and grafting can be considered. Photodynamic therapy using topical 5-aminolaevulinic acid produces an initial inflammatory response that lasts 2 to 3 weeks. In some patients, this is followed by sustained improvement. Because of the initial inflammatory response, it is only appropriate for patients who have failed most other options.

Cooper SM, et al: Darier's disease: epidemiology, pathophysiology, and management. Am J Clin Dermatol 2003;4:97.

Dhitavat J, et al: Mutations in the sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase isoform cause Darier's disease. J Invest Dermatol 2003;121:486.

Exadaktylou D, et al: Treatment of Darier's disease with photodynamic therapy. Br J Dermatol. 2003;149:606.

Kosann MK: Keratosis follicularis. Dermatol Online J 2003;9:35.

Sehgal VN, et al: Darier's (Darier-White) disease/keratosis follicularis. Int J Dermatol 2005;44:184.

ACROKERATOSIS VERRUCIFORMIS

This rare autosomal-dominant genodermatosis is characterized by numerous flat verrucous papules occurring on the backs of the hands, insteps, knees, and elbows. The papules are closely grouped and resemble warts except that they are flatter and more localized. The verrucous lesions are identical to those in Darier's disease, and acrokeratosis verruciformis of Hopf is allelic to Darier's disease (caused by mutations in the same gene).

Histologically, hyperkeratosis, thickening of the granular layer, acanthosis and church spire papillomatosis characterize the disease. Available treatments are liquid nitrogen therapy, shave excision, and CO_2 laser ablation. Recurrence is common.

Dhitavat J, et al: Acrokeratosis verruciformis of Hopf is caused by mutation in ATP2A2: evidence that it is allelic to Darier's disease. J Invest Dermatol 2003;120:229.

PACHYONYCHIA CONGENITA

In 1906, Jadassohn and Lewandowsky described a rare, often familial, anomaly of the nails to which they gave the name pachyonychia congenita. It is characterized by thickened nailbeds of all fingers and toes, palmar and plantar hyperkeratosis, blistering under the callosities, palmar and plantar hyperhidrosis, spiny follicular keratoses, and benign leukokeratosis of the mucous membranes. The nail plates are extremely hard and are firmly attached to the nailbeds. The nailbed is filled with yellow, horny, keratotic debris, which may cause the nail to project upward at the free edge (Fig. 27-23). Paronychial inflammation is frequently present.

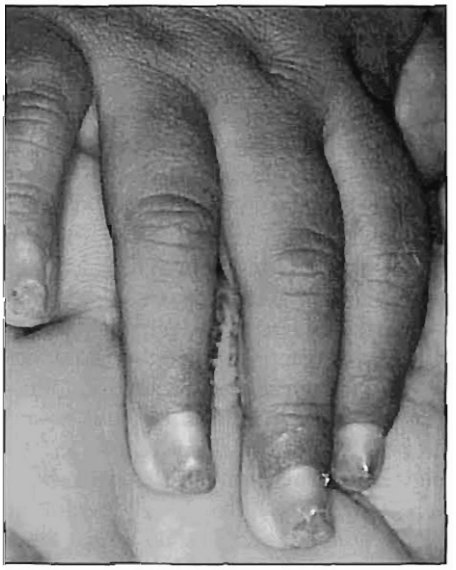

Fig. 27-23 Pachyonychia congenita.

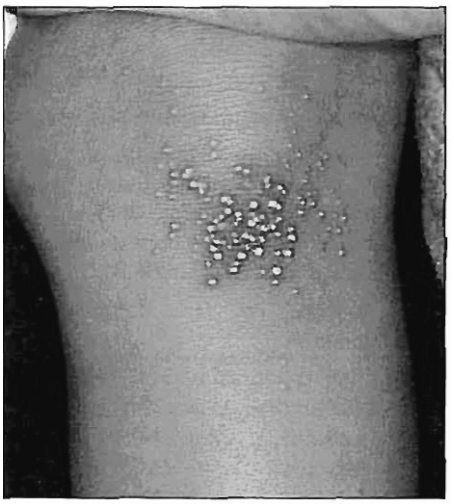

Fig. 27-24 Pachyonychia congenita.

Delayed onset of pachyonychia in young adulthood has been described.

On the extensor surfaces of the extremities (Fig. 27-24), buttocks (Fig. 27-25), and lumbar regions are spine-like follicular keratotic papules. Removal of these central cores leaves a slightly bleeding cavity. The eruption on the outer aspects of the upper and lower extremities is also follicular, resembling keratosis pilaris. This latter condition is not constant and disappears at times.

Painful friction blisters may develop on the plantar aspects of the toes or heels or along the edges of the feet, and cases have been misdiagnosed as epidermolysis bullosa. Leukokeratosis of the tongue (Fig. 27-26) and oral mucosa, as well as occasional laryngeal involvement with hoarseness, may occur. This oral leukokeratosis resembles an oral white sponge nevus histologically and is not predisposed to the development of malignancy.

Pachyonychia congenita is divided into four types. Type I (Jadassohn-Lewandowsky syndrome) is the most common and is described above. Type II (Jackson-Sertoli syndrome) has the same features as type I, with the additional features of natal teeth and steatocystoma multiplex. Patients with type II syndrome typically have less severe palmoplantar keratoderma and oral lesions may be absent. Type III (Schafter-

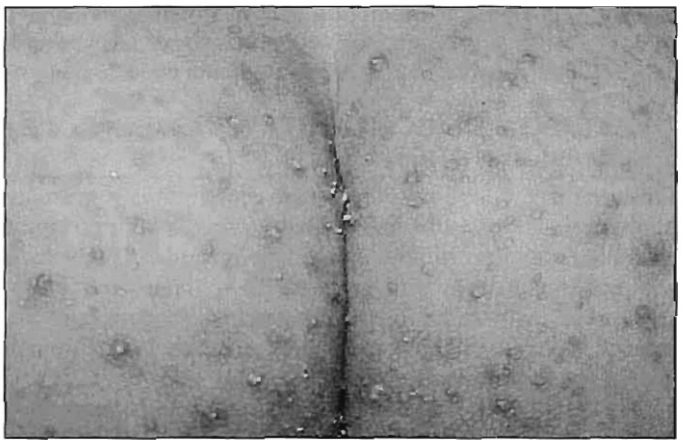

Fig. 27-25 Pachyonychia congenita.

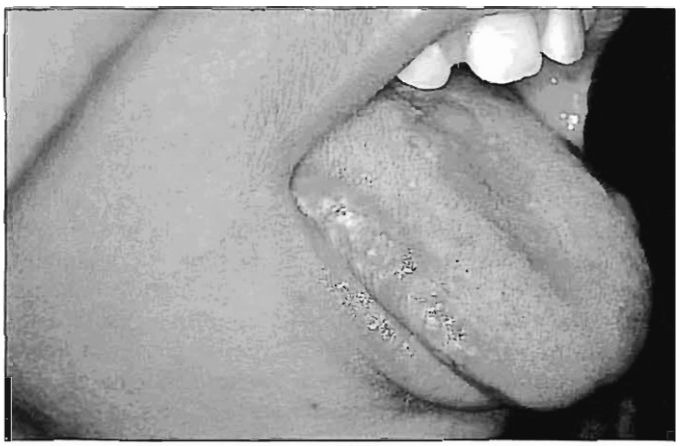

Fig. 27-26 Pachyonychia congenita.

Branauer syndrome) is like type 1 with the addition of leukokeratosis of the corneas. *Pachyonychia congenita tarda* was suggested as the name for late-onset disease (type IV). Type IV disease has been described with hyperpigmentation around the neck, waist, axillae, thighs, flexures of the knees, buttocks, and abdomen. Pigmentary incontinence and amyloid deposition are seen in biopsy specimens.

Pachyonychia congenita is usually inherited as an autosomal-dominant trait, although recessive forms have been reported. There is a genetic mutation of keratin 6a or 16 in type I and keratin 6b or 17 in type II disease.

Avulsion of the nails brings about only temporary relief. Vigorous curettage of the matrix and nailbed is the simplest and most effective therapy. Destruction of the nail matrix with phenol may be partially effective, but recurrence of nailbed hyperkeratosis is common. The keratoderma is difficult to treat, but topical lactic acid, ammonium lactate, salicylic acid, or urea may be of some benefit. Isotretinoin has been reported to clear the keratotic papules and the oral leukokeratosis but not the palms or soles. Acitretin has been shown to be effective in treating the late-onset form.

Elston DM: Pachyonychia congenita. Cutis 2003;72:104, 143.

Strober BE: Pachyonychia congenita. Dermatol Online J 2003; 9:12.

Garcia-Rio I, et al: A severe case of pachyonychia congenita type 1 due to a novel proline mutation in keratin 6a. Br J Dermatol 2005;152:800.

Ward KM, et al: Identification of a recurrent mutation in keratin 6a in a patient with overlapping clinical features of pachyonychia congenita types 1 and 2. Clin Exp Dermatol 2003;28:434.

DYSKERATOSIS CONGENITA (ZINSSER-COLE-ENGMAN SYNDROME)

Dyskeratosis congenita is a rare congenital syndrome characterized by cutaneous poikiloderma, nail dystrophy, and premalignant leukoplakia. Atrophy and telangiectasia are accompanied by tan–gray mottled hyper- and hypopigmented macules or reticulated patches. These lesions are located typically on the upper torso, neck, and face, although the extremities may also be involved.

The nails may be thin and dystrophic, although only ridging and longitudinal fissuring may be seen in mild cases. This is the first component of the syndrome to appear, becoming apparent between the ages of 5 and 15. The other cutaneous lesions generally follow within 3 to 5 years. Leukoplakia occurs mostly on the buccal mucosa, where extensive involvement with verrucous thickening may be present. The anus, vagina, conjunctiva, and urethral meatus can be involved. Malignant neoplasms of the skin, mouth, nasopharynx, esophagus, rectum, and cervix may occur in sites of leukoplakia.

Other manifestations of dyskeratosis congenita include hyperhidrosis of the palms and soles, bullous conjunctivitis, gingival disorders, dysphagia resulting from esophageal strictures and diverticula, skeletal abnormalities, aplastic anemia, mental deficiency, and hypersplenism. In many cases, a Fanconi type of anemia develops, beginning with leukopenia and thrombocytopenia, and progressing to severe pancytopenia. Pulmonary complications include interstitial fibrosis and *Pneumocystis carinii* pneumonia.

The genetic defect for the X-linked form is located on Xq28 and associated with the DKC1 gene for *dyskerin*, a protein implicated in both telomerase function and ribosomal RNA processing. Autosomal-dominant inheritance is associated with mutations in hTR (hTERC), involved in the RNA component of telomerase. Some autosomal-dominant cases have anemia and reticulated pigmentation following the lines of Blaschko. Of interest, some patients with idiopathic aplastic anemia or myelodysplastic syndrome without skin findings demonstrate hTERC mutations. Autosomal-recessive inheritance of dyskeratosis congenita has also been reported.

Granulocyte colony-stimulating factor and erythropoietin may provide short-term benefits in treating bone marrow failure. Bone marrow transplantation or hematopoietic stem cell transplantation with nonmyeloablative conditioning affords the best outcomes.

Hoyeraal-Hreidarsson syndrome is characterized by intrauterine growth retardation, cerebellar hypoplasia, mental retardation, microcephaly, progressive combined immune deficiency, and aplastic anemia. The syndrome is genetically heterogeneous. Some patients demonstrate DKC1 gene mutations and are therefore allelic to dyskeratosis congenita.

Bessler M, et al: Dyskeratosis congenita and telomerase. Curr Opin Pediatr 2004;16:23.

Sznajer Y, et al: Further delineation of the congenital form of X-linked dyskeratosis congenita (Hoyeraal-Hreidarsson syndrome). Eur J Pediatr 2003;162:863.

FANCONI SYNDROME

Also known as *familial pancytopenia* or *familial panmyelophthisis*, Fanconi syndrome may be associated with diffuse pigmentation of the skin (hypopigmentation, hyperpigmentation, and café-au-lait macules), absence of the thumbs, aplasia of the radius, severe hypoplastic anemia, thrombocytopenia, retinal hemorrhage, strabismus, generalized hyperreflexia, and testicular hypoplasia. The syndrome is associated with increased risk of myelomonocytic leukemia, squamous cell carcinoma, and hepatic tumors. No hypersensitivity to UV light, x-rays, or chemical agents is present. Human papillomavirus DNA is often found in the squamous cell carcinomas. Some patients manifest short stature, failure to thrive, absent thumbs, short palpebral fissures, and typical skin abnormalities, but no hematologic abnormalities.

The syndrome is inherited in an autosomal-recessive fashion. Complementation analysis has shown five complementation groups (FA-A, -B, -C, -D, and -E) and therefore five associated genes. The genes play an important role in hematopoiesis, and abnormal gene expression has been shown to increase apoptosis. FA-A has been localized to 16q24.3, and FA-D to 3p22.26. Chromosome patterns are frequently abnormal.

Kutler DI, et al: Human papillomavirus DNA and p53 polymorphisms in squamous cell carcinomas from Fanconi anemia patients. J Natl Cancer Inst 2003;95:1718.

Tipping AJ, et al: Molecular diagnosis of Fanconi anemia and dyskeratosis congenita. Methods Mol Med 2004;91:3.

ECTODERMAL DYSPLASIA

The ectodermal dysplasias are a clinically and genetically heterogenous group of genodermatoses in which the cardinal features are the abnormal, absent, incomplete, or delayed development during embryogenesis of one or more of the epidermal or mucosal appendages (hair, sebaceous glands, nails, teeth, or mucosal glands).

Hypohidrotic Ectodermal Dysplasia (Anhidrotic Ectodermal Dysplasia, Christ-Siemens-Touraine Syndrome)

The classic triad of this disorder consists of hypotrichosis, anodontia, and hypohidrosis or anhidrosis. Febrile seizures may occur in childhood. Biopsy confirms that eccrine glands are absent or rudimentary. Prenatal skin biopsy may be diagnostic.

Patients with the disorder have facies suggestive of congenital syphilis. The cheekbones are high and wide, whereas the lower half of the face is narrow. The supraorbital ridges are prominent and the nasal bridge is depressed, forming a saddle nose. The tip of the nose is small and upturned, and the nostrils are large and conspicuous. The eyebrows are scanty, and the eyes slant upward. The lips are thickened, with the upper lip particularly protrusive. At the buccal commissures there may be radiating furrows (pseudorhagades), and on the cheeks there may be telangiectases. Sebaceous gland hyperplasia may be noted on the cheeks and forehead. Absence of mammary glands and nipples has been reported.

Generalized hypotrichosis is present with thin, sparse hair on the scalp. The skin is soft, thin, dry, and smooth. There is partial or total anodontia, and nails may be thinned, brittle,

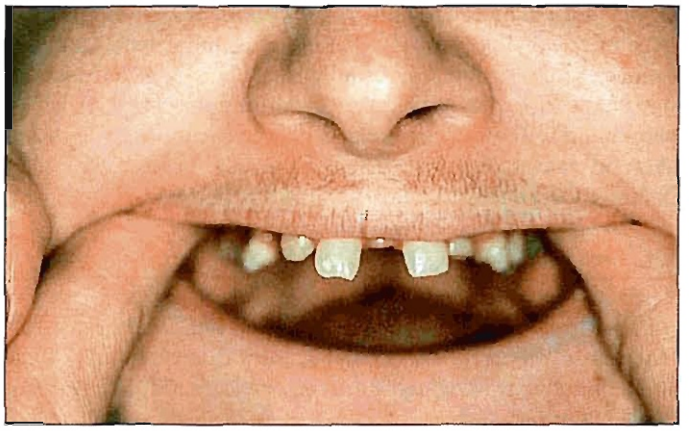

Fig. 27-27 Hypohidrotic ectodermal dysplasia. (Courtesy of James Fitzpatrick, MD)

and ridged. The teeth may be conical in shape (Fig. 27-27). Mental retardation has been reported but may be a consequence of hyperthermic episodes in childhood.

The inheritance pattern is almost always X-linked recessive. Three genes, ectodysplasin (EDA1), EDA-receptor (EDAR), and EDAR-associated death domain (EDARADD) have been described. They are all involved in nuclear factor (NF)-κB activation. Female carriers may have segmental expression that can be demonstrated with a starch iodide test for sweating. Both autosomal-recessive and -dominant modes of inheritance have been described. The gene for autosomal-dominant hypohidrotic ectodermal dysplasia has been mapped to 2q11–q13.

X-linked anhidrotic ectodermal dysplasia with immunodeficiency is caused by mutations in the gene encoding encoding NF-κB modulator, NEMO, or inhibitor of κB kinase (IKK-γ). Stop codon mutations are associated with a severe phenotype with associated osteopetrosis and lymphoedema.

Hidrotic Ectodermal Dysplasia

The hidrotic type of congenital ectodermal dysplasia is often referred to as *Clouston syndrome*. Inheritance is autosomal dominant, eccrine sweat glands function normally, and facial features are normal. Alopecia, nail dystrophy, palmoplantar hyperkeratosis, and eye changes, such as cataracts and strabismus, are seen. Some patients have features resembling pachyonychia congenita. Widespread poromas and palmoplantar syringofibroadenomas have been described. The defective gene has been identified as GJB6, encoding the gap junction protein connexin 30 on the pericentromeric region of chromosome 13q (13q11–q12.1).

AEC Syndrome (Hay-Wells Syndrome)

Ankyloblepharon, ectodermal defects, and cleft lip and/or palate constitute the AEC syndrome. It has an autosomal-dominant pattern of inheritance. Fusion or partial fusion of the lids (ankyloblepharon) may be present at birth. Sparse hair, dental defects, cleft palate and lip, dystrophic nails, hypospadias, syndactyly, short stature, absent lacrimal puncta, stenotic auditory canals, and short stature may be present. An erosive scalp dermatitis is more likely to be observed in AEC than in other ectodermal disorders and occurs at an early age. The scalp dermatitis is often extensive, difficult to treat, and persists or recurs. The syndrome is associated with mutations in the p63 gene.

EEC Syndrome

Ectodermal dysplasia, ectrodactyly, and cleft lip/palate are defining features of EEC syndrome. EEC lacks scalp dermatitis, has mild hypohidrosis, and ectrodactyly (congenital absence of all or part of a digit) is a prominent feature. Folliculitis with scarring may be noted during puberty. Like the AEC syndrome, EEC syndrome is associated with mutations in the p63 gene.

Rapp-Hodgkin Ectodermal Dysplasia Syndrome

Characteristic features of Rapp-Hodgkin ectodermal dysplasia syndrome include anomalies of hair (pili torti, pili canaliculi, alopecia, erosive folliculitis, thinning of eyebrows/lashes), cleft lip/palate, onychodysplasia, dental caries, hypodontia, craniofacial abnormality, hypohidrosis, otitis media (hearing deficits), and hypospadias. It is usually inherited in an autosomal-dominant manner. The syndrome is allelic to AEC and EEC, with mutations in the p63 gene have been demonstrated in all three.

Ectodermal Dysplasia with Corkscrew Hairs

Abramovits-Ackerman et al described this disorder in 27 patients from seven families who live on Margarita Island, northeast of Venezuela. Salient features include corkscrew hairs (exaggerated pili torti), scalp keloids, follicular plugging, keratosis pilaris, xerosis, eczema, palmoplantar keratodermia, syndactyly, onchodysplasia, and conjunctival neovascularization. Typical facies, anteverted pinnae, malar hypoplasia, cleft lip and palate, and dental abnormalities may also be found. Inheritance is autosomal recessive. Anhidrosis or hypohidrosis are not features.

Odonto-Tricho-Ungual-Digital-Palmar Syndrome

First described by Mendoza et al, the salient clinical features are natal teeth, trichodystrophy, prominent interdigital folds, simian-like hands with transverse palmar creases, and ungual digital dystrophy, inherited as an autosomal-dominant trait. Hypoplasia of the first metacarpal and metatarsal bones and distal phalanges of the toes may also occur.

Costello Syndrome

Costello syndrome is characterized by growth retardation, failure to thrive in infancy, coarse facies, redundant skin on the neck, palms, soles, and fingers, acanthosis nigricans, and nasal papillomata. Ventricular dilatation is observed in more than 40% of cases. Hydrocephalus, brain atrophy, Chiari malformation, and syringomyelia may occur. Mild-to-moderate mental deficiency is frequently discovered, and most patients exhibit a characteristic sociable and friendly personality.

Lenz-Majewski Syndrome

Lenz-Majewski syndrome is characterized by hyperostosis, craniodiaphyseal dysplasia, dwarfism, cutis laxa, proximal symphalangism, syndactyly, brachydactyly, mental retardation, enamel hypoplasia, and hypertelorism.

CHIME Syndrome

The CHIME syndrome, a rare neuroectodermal disorder, comprises colobomas of the eye, heart defects, ichthyosiform dermatosis, mental retardation, and ear defects. Other features may include facial anomalies, epidermal nevi, developmental delay, infantile macrostomia, recurrent infections, acute lymphoblastic leukemia, and duplicated renal collecting system. The inheritance is believed to be autosomal recessive.

Lelis syndrome

The Lelis syndrome is a form of ectodermal dysplasia with acanthosis nigricans, palmoplantar hyperkeratosis, hypotrichosis, hypohidrosis, nail dystrophy, early loss of adult teeth, and mental retardation.

Bougeard G, et al: The Rapp-Hodgkin syndrome results from mutations of the TP63 gene. Eur J Hum Genet 2003;11:700.

Lamartine J: Towards a new classification of ectodermal dysplasias. Clin Exp Dermatol 2003;28:351.

Majewski F: Lenz-Majewski hyperostotic dwarfism: reexamination of the original patient. Am J Med Genet 2000;93:335.

Motil KJ, et al: Growth characteristics of children with ectodermal dysplasia syndromes. Pediatrics 2005;116:229.

Steiner CE, et al: Ectodermal dysplasia with acanthosis nigricans (Lelis syndrome). Am J Med Genet 2002;113:381.

Sprecher E. Genetic hair and nail disorders. Clin Dermatol 2005;23:47.

van Steensel MA, et al: Clouston syndrome can mimic pachyonychia congenita. J Invest Dermatol 2003;121:1035.

Wisniewski SA, et al: Recent advances in understanding of the molecular basis of anhidrotic ectodermal dysplasia: discovery of a ligand, ectodysplasin A and its two receptors. J Appl Genet 2002;43:97.

PACHYDERMOPERIOSTOSIS (IDIOPATHIC HYPERTROPHIC OSTEOARTHROPATHY, TOURAINE-SOLENTE-GOLE SYNDROME)

Pachydermoperiostosis is characterized by thickening of the skin in folds and accentuation of creases on the face and scalp, clubbing of the fingers, and periostosis of the long bones. The changes are especially prominent on the forehead, where the horizontal lines are deepened and the skin becomes shiny. The eyelids, particularly the upper ones, are thickened. Likewise, there is thickening of the ears and lips, and the tongue is enlarged. The scalp may be thickened and show cutis verticis gyrata (pachydermie vorticelle). The extremities, especially the elbows, knees, and hands, are enlarged and spade shaped. The fingers become club shaped. The palms are rough, and the thenar and hypothenar eminences are enlarged. Hyperhidrosis is common. Hyperkeratotic linear lesions of the palms and soles may be present. These lines are rippled, resembling sand of the "wind-blown desert." Movements of the muscles may be painful.

There are inherited and acquired forms. The acquired form may occur with chronic pulmonary, mediastinal, and cardiac diseases that are associated with chronic hypoxia in peripheral tissues. Some cases have been associated with bronchogenic carcinoma. When such an association occurs, enlargement of the forehead, hands, and fingers may antedate the recognition of the tumor or may develop after the tumor is known to be present. Bronchogenic carcinoma-associated pachydermoperiostosis occurs almost exclusively in men over the age of 40, whereas inherited Touraine-Solente-Gole syndrome usually occurs as an autosomal-dominant disorder with onset in late adolescence. It is not associated with malignant disease. More prominent signs are seen in males. Autosomal-recessive inheritance with cleft palate and congenital heart defects has been described.

CUTIS VERTICIS GYRATA

Cutis verticis gyrata is characterized by folds and furrows on the scalp, usually in an anteroposterior direction. Most frequently the vertex is involved, but other areas may have the distinctive furrowing. There may be 2 to 20 folds. The hair itself is normal.

Cutis verticis gyrata has been reported primarily in males, with a male-to-female ratio of 6:1. Onset is usually at puberty, with more than 90% of patients developing it before age 30. The condition may be familial when it occurs as a component of pachydermoperiostosis. It has been reported to be the result of developmental anomalies, inflammation, trauma, tumors, nevi, amyloidosis, syphilis, myxedema, Ehlers-Danlos syndrome, Turner syndrome, Klinefelter syndrome, fragile X syndrome, and the insulin-resistance syndrome. Biopsy findings can be normal or show thick collagen bundles and hypertrophy of adnexal structures.

Cutis verticis gyrata is frequently found in patients with mental retardation, seizures, and schizophrenia. Rarely, a cerebriform intradermal nevus may be mistaken for this disorder. In severely involved cases, excision with grafting or scalp reduction may be indicated.

Nguyen NQ: Cutis verticis gyrata. Dermatol Online J 2003;9:32.

APLASIA CUTIS CONGENITA

Aplasia cutis congenita has a predilection for the midline of the vertex of the scalp. It presents with localized absence of skin and is rarely associated with full-thickness defects of the cranium. An association with thyroid disease and thyroid medications has been noted. Rarely, multiple symmetrical defects may occur in the skin of the lower extremities. Distal radial epiphyseal dysplasia has been associated with localized aplasia cutis congenita.

The "hair collar sign" refers to a ring of dark, long hair encircling the lesion. It is commonly seen with membranous aplasia cutis, which may represent a form fruste of a neural tube defect. Bullous aplasia cutis congenita demonstrates a fibrovascular or edematous stroma similar to that seen in encephaloceles and meningoceles, suggesting is may also be related to a neural tube defect.

Colon-Fontanez F, et al: Bullous aplasia cutis congenita. J Am Acad Dermatol 2003;48(5 Suppl):S95.

Davidson AW, et al: Radial dysplasia with localized cutis aplasia congenita. J Pediatr Orthop B 2003;12:398.

Verhelle NA, et al: Abdominal aplasia cutis congenita: case report and review of the literature. J Pediatr Surg 2004;39:237.

ADAMS-OLIVER SYNDROME

Features of Adams-Oliver syndrome include severe aplasia cutis congenita of the scalp, which may involve both skin and

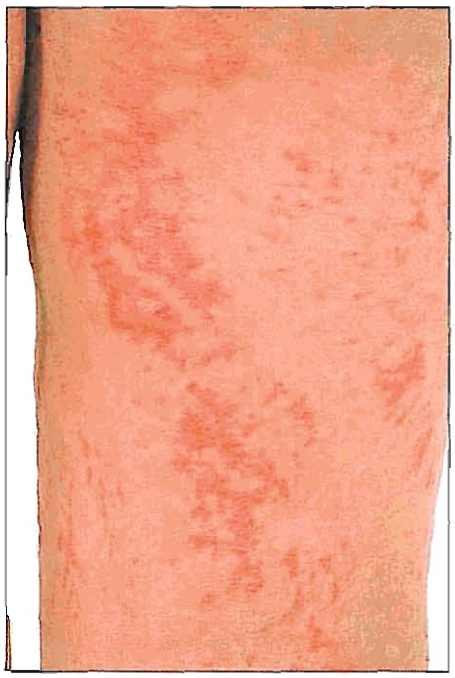

Fig. 27-28 Goltz syndrome.

skull ossification defects, limb defects (brachydactyly, syndactyly of toes 2 and 3, and hypoplastic toenails), extensive cutis marmorata telangiectatica congenita, cryptorchidism, and cardiac abnormalities. Other associations include hemangiomas, retro- and micro-gnathia, strabismus, and atrial septal defect. It is a rare autosomal-dominantly inherited neuroectodermal syndrome.

Klinger G, et al: Adams-Oliver syndrome: autosomal recessive inheritance and new phenotypic-anthropometric findings. Am J Med Genet 1998;79:197.

Mempel M, et al: The wide spectrum of clinical expression in Adams-Oliver syndrome: a report of two cases. Br J Dermatol 1999;140:1157.

FOCAL DERMAL HYPOPLASIA (GOLTZ SYNDROME)

Goltz syndrome is characterized by multiple abnormalities of mesodermal and ectodermal tissues. Reddish-tan, atrophic, often linear or cribriform patches are commonly present on the buttocks, axillae, and thighs (Fig. 27-28). Later, lipocytes accumulate in the lesions in a nevoid fashion, resulting in yellowish-brown nodules. The lesions are strikingly linear and often serpiginous, following lines of Blaschko. They are often narrower than typical Blaschko segments, suggesting that the genetic defect is lethal in many of the affected cells during development. Telangiectases are commonly present. Papillomas may occur around the orifices of the mouth, anus, and vulva (Fig. 27-29). They may be misdiagnosed as condyloma acuminata. Eighty percent of patients have skeletal defects. Bone changes most commonly involve the extremities, where there may be syndactyly, oligodactyly, and adactyly (Fig. 27-30). Scoliosis, spina bifida, and hypoplasia of the clavicle have also been reported. Forty to 50% of patients have ocular or dental abnormalities, with coloboma being the most common ocular defect. Van Allen-Myhre syndrome appears to represent a severe form of Goltz syndrome with split foot and split hand anomalies.

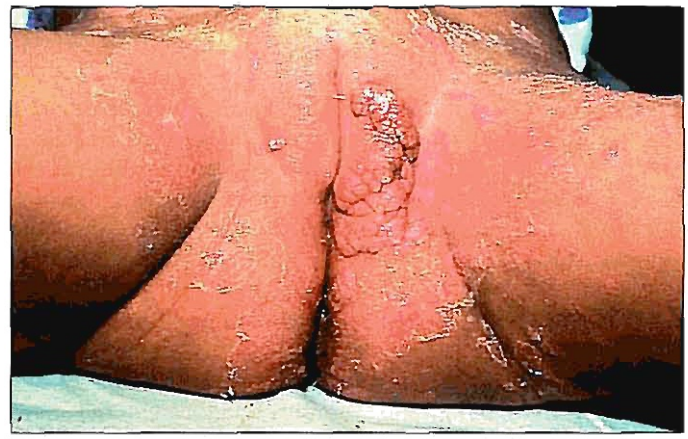

Fig. 27-29 Goltz syndrome.

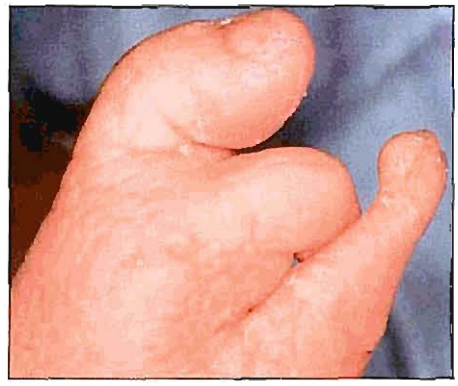

Fig. 27-30 Goltz syndrome.

The large majority of patients with Goltz syndrome have been female. X-linked dominant inheritance, with lethality in males, is likely. Females are protected by X-chromosome mosaicism, identical to the situation in incontinentia pigmenti. Treatment of atrophic erythematous patches has been successful using a flashlamp-pumped pulsed dye laser.

Hancock S, et al: Probable identity of Goltz syndrome and Van Allen-Myhre syndrome: evidence from phenotypic evolution. Am J Med Genet 2002;110:370.

WERNER SYNDROME (ADULT PROGERIA)

Werner syndrome is a premature-aging syndrome characterized by many metabolic and structural abnormalities involving the skin, hair, eyes, muscles, fatty tissues, bones, blood vessels, and carbohydrate metabolism. Cells demonstrate genomic instability. Because most of these signs are not fully manifested before the age of 30, the diagnosis is usually made in middle age. These patients usually die before the age of 50 from malignant disease or vascular accidents.

The most characteristic findings are premature aging and arrest of growth at puberty, senile cataracts developing in the late 20s and 30s, premature balding and graying, and scleroderma-like lesions of the skin. A characteristic change is the loss of subcutaneous tissue and wasting of muscles, especially the extremities, so that the legs become spindly and the trunk becomes stocky. Osteoporosis and aseptic necrosis are frequent in the small bones of the hands. The skin changes include poikiloderma, scleroderma, atrophy, hyperkeratoses, and leg ulcers. The skin has a dark gray or

blackish diffuse pigmentation. A high-pitched voice and hypogonadism in both sexes are distinctive in this syndrome.

Painful callosities with ulcerations may occur around the malleoli, Achilles tendons, heels, and toes. The hair thins on the eyebrows, axillae, and pubis. The skin over the cheek bones becomes taut to produce proptosis and beaking of the nose. Cataracts develop early, and the vocal cords become thickened so that a weak, high-pitched voice ensues. Premature arteriosclerosis and sexual impotence are frequently observed. Diabetes is frequent, and areas of calcinosis circumscripta occur. Gene expression mimics normal aging.

A high rate of malignancy is associated with Werner syndrome. Uterine sarcoma, hepatoma, carcinoma of the breast, fibrosarcoma, and thyroid adenocarcinoma have occurred. Histologic changes in the skin may include atrophy of the epidermis and fibrosis of the dermis.

Consanguinity and familial incidence are encountered, suggesting a mendelian recessive mode of transmission. Werner syndrome is molecularly heterogeneous. The Werner protein confers adhesive properties to macromolecular proteins and is required for genomic stability. It belongs to the RecQ family of DNA helicases. Mutant LMNA encoding nuclear lamin A/C is associated with atypical Werner syndrome with a more severe phenotype. Mutations in LMNA also cause Hutchinson-Gilford progeria, Emery-Dreifuss muscular dystrophy, and dilated cardiomyopathy.

PROGERIA (HUTCHINSON-GILFORD SYNDROME)

Progeria, or Hutchinson-Gilford syndrome, is characterized by accelerated aging, dwarfism, alopecia, generalized atrophy of the skin and muscles, enlarged head with prominent scalp veins, and a high incidence of generalized atherosclerosis, usually fatal by the second decade. The large bald head and lack of eyebrows and eyelashes are distinctive. The skin is wrinkled, pigmented, and atrophic. The nails are thin and atrophic. Most patients lack subcutaneous fat, which produces the appearance of premature senility. There are usually sclerodermatous plaques on the extremities. The intelligence remains intact. Arteriosclerosis, anginal attacks, and hemiplegia may occur, followed by death from coronary heart disease at an early age. Mutations in LMNA and mosaicism have been identified. Treatment is symptomatic: chiefly, control of diabetes mellitus and treatment of leg ulcerations.

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Chen L, et al: LMNA mutations in atypical Werner's syndrome. Lancet 2003;362:440.

Corso C, et al: Molecular cytogenetic insights into the ageing syndrome Hutchinson-Gilford Progeria (HGPS). Cytogenet Genome Res 2005;111:27.

Duvic M, et al: Werner's syndrome. Dermatol Clin 1995;13:163.

Fossel M: The progerias. J Anti Aging Med 2003;6:123.

Hegele RA: Drawing the line in progeria syndromes. Lancet 2003;362:416.

Pesce K, et al: The premature aging syndromes. Clin Dermatol 1996;14:161.

Wuyts W, et al: Somatic and gonadal mosaicism in Hutchinson-Gilford progeria. Am J Med Genet A 2005;15:66.

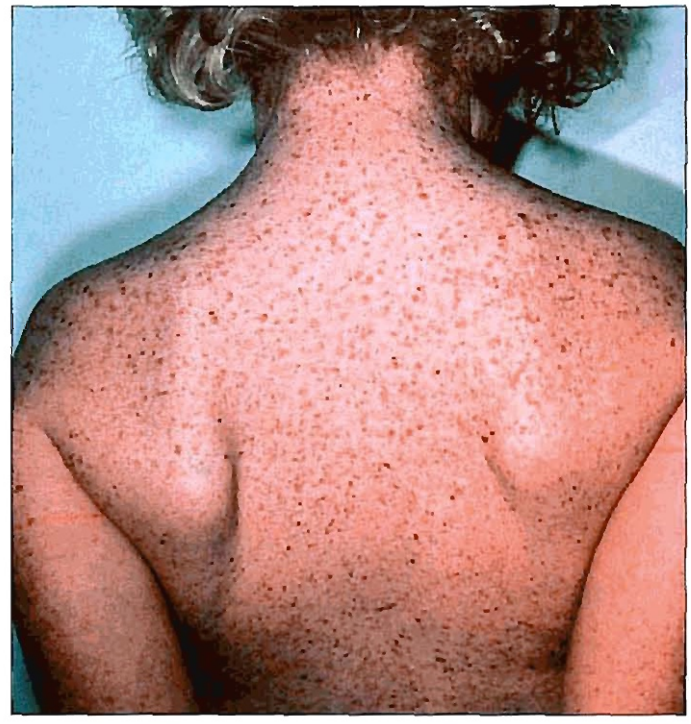

Fig. 27-31 Xeroderma pigmentosum. (Courtesy of Ken Kraemer, MD)

XERODERMA PIGMENTOSUM

Xeroderma pigmentosum is an autosomal-recessive disorder characterized by defective DNA thymidine dimer excision repair, extreme sun sensitivity, freckling, and skin cancer. Sun sensitivity and lentigines (Fig. 27-31) are early skin findings with the median onset before the age of 2. Skin cancers often appear before 10 years of age, and an increase in internal cancer has been noted as well. In a study of 830 patients, 45% had basal cell carcinoma or squamous cell carcinoma and melanoma was noted in 5%. Most of the tumors occur on the head and neck. Ocular abnormalities were found in 40% and included ectropion, corneal opacity, and neoplasms. Progressive neurologic degeneration is seen in about 20% of patients. Xeroderma pigmentosum patients in complementation group C remain free of neurologic problems. Complementation groups are defined by correction of excision repair when fibroblasts from patients in different groups are fused. A variant type with normal excision repair has also been described. Retinoids can prevent the appearance of new cancers, but side effects are significant, and a rebound in the number of cancers occurs when the drug is stopped, suggesting that the tumors are merely suppressed. Photoprotection remains essential for management. Topical application of recombinant liposomal encapsulated T4 endonuclease V repairs UV-induced cyclobutan–pyrimidine dimers and is a promising form of therapy. Gene therapy is also being pursued. Guidelines for evaluation and management from the XP Society can be found at www.xps.org. A publication from the NIH can be found at www.cc.nih.gov/ccc/patient_education/pepubs/xeroderma.pdf.

Xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy are all associated with defects in nucleotide excision repair. Skin tumors in xeroderma pigmentosum patients have sunlight-induced mutations in ras, p53, and ptch genes. Mutations in the XPG gene give rise to the comple-

mentation group G form of xeroderma pigmentosum, as well as early-onset Cockayne syndrome.

The De Sanctis-Cacchione syndrome consists of xeroderma pigmentosum with mental deficiency, dwarfism, and gonadal hypoplasia. It occurs most often in patients in complementation group D. Mutations in the ERCC6 gene which also cause Cockayne syndrome type B, have also been demonstrated

COCKAYNE SYNDROME

Cockayne syndrome is an autosomal-recessive syndrome with sun sensitivity and neurologic degeneration. It differs from xeroderma pigmentosum by the lack of freckling and skin cancer, and by the presence of dwarfism, beaked nose, loss of subcutaneous tissue, deafness, basal ganglia calcification, and retinopathy.

Cockayne described the syndrome as *dwarfism with retinal atrophy and deafness*. Dermatologic features include photodermatitis with telangiectasia, atrophy, and scarring. The hands and feet are large and cyanotic. Microcephaly, sunken eyes, severe flexion contractures, dorsal kyphosis, cryptorchidism, cataracts, growth retardation, mental retardation, hypothalamic and cerebellar dysfunction, and retinitis pigmentosa with optic atrophy may be seen. There is progressive neurologic disturbance with a shortened lifespan. Dermal fibroblasts and lymphoblastoid cell lines, as well as cultured amniotic fluid cells from an affected fetus, demonstrate impaired colony-forming ability, and decreased DNA and RNA synthesis after UV light exposure (254 nm).

DNA helicases unwind DNA and are important in DNA replication, DNA repair, and RNA transcription. Mutations in XPB or XPD DNA helicase can result in xeroderma pigmentosum, Cockayne syndrome, or trichothiodystrophy. The CSA and CSB genes responsible for Cockayne syndrome are associated with RNA polymerase. Cockayne syndrome has also been associated with mutations in XPG.

XERODERMA PIGMENTOSUM/COCKAYNE SYNDROME COMPLEX

Some patients have skin features of xeroderma pigmentosum and neurologic features of Cockayne syndrome. Patients in complementation groups B, D, and G have presented with the complex. Mutations in the associated genes may give rise to clinical manifestations of xeroderma pigmentosum, Cockayne syndrome, or the xeroderma pigmentosum/Cockayne syndrome complex.

TRICHOTHIODYSTROPHY

Trichothiodystrophy is an autosomal-recessive disorder characterized by photosensitivity, ichthyosis, brittle hair, intellectual impairment, decreased fertility, and short stature (PIBIDS). Tay syndrome is similar but lacks photosensitivity. Abnormalities in nucleotide excision repair of UV-damaged DNA are present in about 50% of those with the disorder. The UV sensitivity and defective excision repair are similar to that of xeroderma pigmentosum patients, but these patients do not experience an increased incidence of skin cancer. Two of the three described complementation groups match xeroderma pigmentosum groups B and D, with the XPD gene accounting for most photosensitive trichothiodystrophy. A combined xeroderma pigmentosum/trichothiodystrophy complex has been described. Patients with trichothiodystrophy without xeroderma pigmentosum do not have an increase in skin cancer formation.

The hair, with sulfur reduced to 50% of the normal value, has distinctive features under polarizing, light, and scanning electron microscopy. With polarizing microscopy, the hair shows alternating bright and dark regions that give a striking striped, or tiger tail, appearance, but the pattern may not be evident at birth. With light microscopy, trichoschisis (clean fractures), and trichorrhexis nodosa-like fractures may be seen. In addition, the hair is markedly flattened and folds over itself like a thick ribbon. The hair shaft outline is irregular and slightly undulating, and the melanin granules are distributed in a wavy pattern. With scanning electron microscopy, the surface shows marked ridging and fluting, and the cuticle scales may be absent or greatly reduced.

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BLOOM SYNDROME (BLOOM-TORRE-MACHACEK SYNDROME)

Bloom syndrome is transmitted as an autosomal-recessive trait, chiefly among Jewish persons of eastern European origin. It is characterized by photosensitive telangiectatic erythema in the butterfly area of the face and dwarfism. Telangiectatic erythematous patches resembling lupus erythematosus develop in the first 2 years of life. Bullous, crusted lesions may be present on the lips. Exacerbation of skin lesions occurs during the summer. Other changes that may be noted are café-au-lait spots, ichthyosis, acanthosis nigricans, syndactyly, irregular dentition, prominent ears, hypospadias, and cryptorchidism. The stunted growth is characterized by normal body proportions, no endocrine abnormalities (except diabetes mellitus), and low birth weight at full term. Dolichocephaly and narrow, delicate facies are present. Immune functions are abnormal, and gastrointestinal and respiratory infections occur frequently. Cancer of all cell types and sites are increased in frequency. Leukemia, lymphoma, adenocarcinoma of the sigmoid colon, and oral and esophageal squamous cell carcinoma, as well as other malignancies, have been associated with Bloom syndrome. About one-quarter of patients under the age of 20

develop a neoplasm. Regular use of a broad-spectrum sunscreen as well as photoprotection is recommended.

The gene mutated in Bloom syndrome, BLM, codes for a RecQ DNA-helicase. BLM is localized to the nuclear bodies and the nucleolus and is critical for genomic stability. BLM interacts with WRN, the DNA helicase mutated in Werner syndrome, and is part of a large BRCA-1-containing complex containing DNA repair factors. BLM expression is highest during the S and G2 phases of the cell cycle. BLM associates with telomeres and ribosomal DNA. BLM interacts directly with ATM (the protein product of the gene mutated in ataxia-telangiectasia) and together they recognize abnormal DNA structures.

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ROTHMUND-THOMSON SYNDROME (POIKILODERMA CONGENITALE)

Rothmund-Thomson syndrome is a rare autosomal-recessive disorder. Poikiloderma begins at 3 to 6 months of age, with tense, pink, edematous patches on the cheeks, hands, feet, and buttocks, sparing the chest, back and abdomen (acute phase). Sensitivity to sunlight may be manifested by the development of bullae or intense erythema after brief sun exposure. There follows fine reticulated or punctate atrophy associated with telangiectasia and reticulated pigmentation (chronic phase) (Fig. 27-32). Characteristically, the arms and legs are affected with sparing of the antecubital and popliteal fossae.

The skin lesions are characteristic. Otherwise, patients with Rothman-Thomson syndrome may have a broad range of noncutaneous lesions. Short stature (two-thirds of patients), small hands with radial ray defects, saddle nose, absence or sparseness of eyebrows and eyelashes (73%), alopecia of the scalp (50%), and numerous bone defects (75%) are frequently observed. Hypogonadism, dystrophic nails, and defective dentition are seen in a significant proportion of patients (25–60%). Cataracts occur in a small percentage of patients in childhood or young adult life. Squamous and basal cell carcinoma of the skin occasionally occur, but it is the risk for osteosarcoma of bone that is particularly high (>30%). Several patients with compound heterozygous mutations in RECQL4, a human helicase gene, have been reported. Thus, at least a subset of patients with Rothmund-Thomson syndrome has abnormal DNA helicase activity, as do patients with Werner and Bloom syndromes.

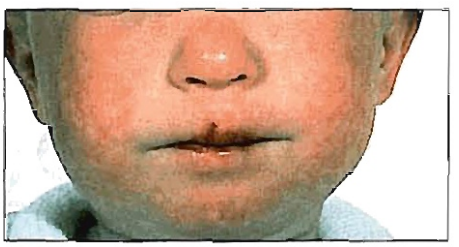

Fig. 27-32
Rothmund-Thomson syndrome.

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HEREDITARY SCLEROSING POIKILODERMA AND MANDIBULOACRAL DYSPLASIA

Hereditary sclerosing poikiloderma is an autosomal-dominant condition The skin changes consist of generalized poikiloderma appearing in childhood (but not at birth), with hyperkeratotic and sclerotic cutaneous bands extending across the antecubital spaces, axillary vaults, and popliteal fossae. In addition, the palms and soles may show sclerosis resembling shiny scotch-grain leather. Aortic stenosis, clubbing of the fingers, and localized calcinosis of the skin have also been noted. There is no treatment.

The cases reported by Weary were subsequently reported later in life as mandibuloacral dysplasia, a rare autosomal-recessive syndrome characterized by mandibular hypoplasia; delayed cranial suture closure; dysplastic clavicles; abbreviated, club-shaped terminal phalanges; acroosteolysis; atrophy of the skin of the hands and feet; and typical facial changes. Mandibuloacral dysplasia must be distinguished from progeria and Werner syndrome.

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SCLEROATROPHIC SYNDROME OF HURIEZ

Huriez syndrome, a very rare autosomal-dominant disorder, is characterized by: 1) scleroatrophy of the hands, with sclerodacyly; 2) ridging, clubbing, or hypoplasia of the nails; and 3) lamellar keratoderma of the hands and, to a lesser extent, the soles. Patients with Huriez syndrome may also have multiple telangiectasias of the lips and face, and flexion contractures of the little finger. Aggressive squamous cell

carcinomas occur in the scleroatrophic skin, including that of the palms and soles (13% lifetime risk, 5% mortality in affected persons). Affected patients have reduced Langerhans cells in affected skin, but normal dermal dendritic cells.

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FRANCESCHETTI-KLEIN SYNDROME (MANDIBULOFACIAL DYSOSTOSIS)

This syndrome includes palpebral antimongoloid fissures, hypoplasia of the facial bones, macrostomia, vaulted palate, malformations of both the external and internal ear, buccal–auricular fistula, abnormal development of the neck with stretching of the cheeks, accessory facial fissures, and skeletal deformities. Patients who have the complete syndrome usually die in infancy, but patients with the abortive type may live to an old age. The syndrome is allelic to the Treacher Collins syndrome and caused by the Treacher Collins Franceschetti (TCOF1) gene.

TREACHER COLLINS SYNDROME

This syndrome includes midface hypoplasia with micrognathia, microtia, conductive hearing loss, and cleft palate. It is inherited as an autosomal-dominant trait and caused by mutations in the TCOF1 gene which encodes a protein called treacle.

POPLITEAL PTERYGIUM SYNDROME

Pterygia or skinfolds may extend from the thigh down to the heel and thus prevent extension or rotation of the legs. Crural pterygia, cryptorchism, bifid scrotum, agenesis of the labia majora, cleft lip and palate, adhesions between the eyelids, syndactyly, and talipes equinovarus may be present. Autosomal-dominant inheritance has been described, and the syndrome is allelic to the van der Woude syndrome.

VAN DER WOUDE SYNDROME

The syndrome is an autosomal-dominant craniofacial disorder characterized by hypodontia, pits of the lower lip, and cleft palate. It is associated with mutations in the IRF6 gene. Other reported associations include natal teeth, ankyloglossia, syndactyly, equinovarus foot deformity, and congenital heart disease. Lower lip pits may be found in other congenital disorders, such as popliteal pterygium syndrome, and occasionally in orofaciodigital syndrome type I (oral frenula and clefts, hypoplasia of alae nasi, and digital asymmetry). Surgical excision is the treatment of choice.

APERT SYNDROME (ACROCEPHALOSYNDACTYLY)

Apert syndrome is autosomal-dominantly inherited and characterized by craniosynostosis and fusion of the digits (syndactyly). Patients present with synostosis of the feet, hands, carpi, tarsi, cervical vertebrae, and skull. The facial features are distorted and the second, third, and fourth fingers are fused into a bony mass with a single nail. Neurologic defects may be due in part to brain compression by the abnormal skull. Oculocutaneous albinism and severe acne vulgaris have been reported with Apert syndrome, although some of the acneiform lesions actually represent follicular hamartomas. Mutations in the fibroblast growth factor receptor (FGFR2) gene are responsible for Apert syndrome, Crouzon syndrome, and Pfeiffer syndrome.

PFEIFFER SYNDROME

The syndrome is autosomal-dominantly inherited and consists of osteochondrodysplasia and craniosynostosis. Type 1 has normal intelligence and generally good outcome. Types 2 and 3 have severe neurologic compromise, a poor prognosis, and sporadic occurrence.

CROUZON SYNDROME

The syndrome includes craniosynostosis and acanthosis nigricans. It is associated with mutations in the FGFR2 gene. The Crouzonodermoskeletal syndrome with choanal atresia and hydrocephalus is caused by mutations in the FGFR3 gene, a gene associated with achondroplastic dwarfism.

WHISTLING FACE SYNDROME

In this rare disorder, also known as *cranio-carpo-tarsal syndrome, Freeman-Sheldon syndrome, Windmill-Vane-Hand syndrome*, and *distal arthrogryposis type 2*, the child appears to be whistling all the time. This configuration is the result of microstomia, deep-set eyes, flattened mid-face, coloboma, contracted joint muscles of the fingers and hands, and alterations of the nostrils. Ulnar deviation of the fingers, kyphoscoliosis, and talipes equinovarus may be present. Brain anomalies have also been reported. Autosomal-dominant, -recessive, and sporadic variants have been reported. Prenatal diagnosis can be made on ultrasound. Surgical intervention may be required for some patients.

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SYNDROMES THAT INCLUDE ABNORMALITIES OF THE HAIR

Hallerman-Streiff Syndrome

This syndrome includes characteristic "bird facies," congenital cataracts, microphthalmia, mandibular hypoplasia, hypotrichosis, and dental abnormalities. The nose is thin,

sharp, and hooked, and the chin is absent. The hair is diffusely sparse and brittle. Baldness may occur frontally or at the scalp margins, but sutural alopecia—hair loss following the lines of the cranial sutures—is characteristic of this syndrome. The small face is in sharp contrast with a disproportionately large-appearing head. The lips are thin; some of the teeth may be absent while others are dystrophic, resulting in malocclusion. Nystagmus, strabismus, and other ocular abnormalities are present. Cleft palate and syndactyly may be present, representing overlap with oculodentodigital dysplasia associated with GJA1 gene mutation.

Polyostotic Fibrous Dysplasia (Albright's Disease)

This may present as slowly progressive lifelong unilateral hair loss: scalp, pubic, axillary, and palpebral. Sickle-cell disease is often characterized by scantiness of body and facial hair.

Cronkhite-Canada Syndrome

The Cronkhite-Canada syndrome is characterized by alopecia, skin pigmentation, onychodystrophy, malabsorption, and generalized gastrointestinal polyposis.

Marinesco-Sjögren Syndrome

This syndrome consists of cerebellar ataxia, mental retardation, congenital cataracts, inability to chew food, thin brittle fingernails, and sparse hair. The dystrophic hairs do not have the normal layers (cortex, cuticle, and medulla), and 30% of the hair shafts show narrow bands of abnormal incomplete keratinization. There is an autosomal-recessive type of inheritance in this syndrome and the gene has been mapped to chromosome 5q31.

Trichothiodystrophy

This is discussed above with xeroderma pigmentosum.

Generalized Trichoepitheliomas

Generalized trichoepitheliomas, alopecia, and myasthenia gravis may be a variant of the generalized hair follicle hamartoma syndrome. There is a report of a localized variant of this syndrome. Histologically, there is replacement of the hair follicles by trichoepithelioma-like epithelial proliferations associated with hyperplastic sebaceous glands.

Crow-Fukase (POEMS) syndrome

This syndrome is characterized by polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes such as diffuse hyperpigmentation, dependent edema, skin thickening, hyperhidrosis, and hypertrichosis.

Cartilage–Hair Hypoplasia (McKusick Type Metaphyseal Chondrodysplasia)

This encompasses short-limbed dwarfism and abnormally fine and sparse hair in children. These children are especially susceptible to viral infections and recurrent respiratory infections. A functional defect of small lymphocytes, with impaired cell-mediated immunity, may occur. Most patients are anergic to skin-test panels and have increased numbers of natural killer (NK) cells. The major mutation involves the RMRP gene, which encodes a component of mitochondrial RNA-processing endoribonuclease.

Tricho-Rhino-Phalangeal Syndrome

This is a genetic disorder consisting of fine and sparse scalp hair, thin nails, pear-shaped broad nose, and cone-shaped epiphyses of the middle phalanges of some fingers and toes. There is an autosomal-dominant and also a recessive inheritance type. The syndrome can result from either single base pair mutations or deletion of the TRPS1 gene, which encodes a zinc-finger transcription factor located on chromosomal band 8q24.1.

Papillon-Lefèvre Syndrome

This is characterized by hyperkeratosis palmaris et plantaris, periodontosis, and sparsity of the hair. Hyperhidrosis and other signs and symptoms begin early in life. Inheritance of this disease is of an autosomal-recessive type.

Klippel-Feil Syndrome

This syndrome consists of a low posterior scalp hairline extending onto the shoulders, with a short neck, limiting movement of the neck and suggestive of webbing. The cervical vertebrae are fused. This syndrome is caused by faulty segmentation of the mesodermal somites between the third and seventh weeks in utero. Strabismus, nystagmus, cleft palate, bifid uvula, and high palate are other features. This syndrome occurs mostly in girls.

McCusick Syndrome

Features of this syndrome include short-limbed dwarfism and fine, sparse, hypoplastic, and dysmorphic hair.

Atrichia with Papules

This is a rare disorder characterized by loss of hair beginning shortly after birth and the development of cutaneous cystic papules. Mutations in the hairless gene have been identified in both humans and mice, but a similar phenotype has also been reported with a normal hairless gene but with vitamin D-resistant rickets type IIA and mutations in the vitamin D receptor gene. The cyst epithelium demonstrates keratin-15 and -17, suggesting derivation from the follicular bulge and the presence of stem cells. Both the hairless gene and the vitamin D receptor gene produce zinc finger proteins and may have overlapping functions.

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KERATOSIS PILARIS

Keratosis pilaris may be limited in mild cases to the posterior upper arms, and manifests as a horny plug in each hair follicle. The thighs are the next most common site, but lesions may occur on the face, forearms, buttocks, trunk, and legs. Facial involvement may be mistaken for acne vulgaris and may leave small pitted scars, even when the condition does not scar elsewhere. Variants of keratosis pilaris with more prominent scarring are included under the heading of keratosis pilaris atrophicans.

The individual lesions are small, acuminate, follicular papules. They may or may not be erythematous. Sometimes the keratotic plugs are the most prominent feature of the eruption, whereas at other times most of the lesions are punctate erythematous papules. Occasionally, inflammatory acneiform pustules and papules may appear.

Forcible removal of one of the plugs leaves a minute cup-shaped depression at the apex of the papule, which is soon filled by new keratotic material. The lesions tend to be arranged in poorly defined groups, dotting the otherwise normal skin in a fairly regular pattern. They are prone to appear in xerotic or atopic subjects. Autosomal-dominant inheritance has been described.

Other conditions associated with keratosis pilaris are ichthyosis follicularis, atrichia with papular lesions, mucoepidermal dysplasia, cardiofacio-cutaneous syndrome, ectodermal dysplasia with corkscrew hairs, and KID syndrome.

Treatment is difficult, but some patients respond to topical retinoids. Twelve percent ammonium lactate can produce some smoothing of the lesions but seldom results in improvement of the erythema. Topical calcipotriene is effective in some patients.

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FOLLICULAR ATROPHODERMA

Follicular atrophoderma consists of follicular indentations without hairs, notably occurring on extensor surfaces of the hands, legs, and arms. Scrotal (fissured) tongue may also be found. It has been described repeatedly in association with other genetically-determined abnormalities, including X-linked dominant chondrodysplasia punctata, Bazex syndrome (follicular atrophoderma type), and keratosis palmoplantaris disseminata.

KERATOSIS PILARIS ATROPHICANS

Keratosis pilaris atrophicans is seen in three syndromes: 1) keratosis pilaris atrophicans faciei; 2) atrophodermia vermiculata; and 3) keratosis pilaris follicularis spinulosa decalvans. Keratosis pilaris atrophicans has been reported associated with woolly hair and Noonan syndrome. Overlap between the three entities may occur.

Response to therapy is often limited, but some response has been noted with keratolytics and retinoids. Pulsed dye laser has led to improvement in erythema, but not skin roughness.

Keratosis Pilaris Atrophicans Faciei and Ulerythema Ophryogenes

Keratosis pilaris atrophicans faciei is characterized by persistent erythema and small horny follicular papules with onset during childhood. On involution these leave pitted scars and atrophy with resulting alopecia. It involves the eyebrows, from which it may rarely spread to the neighboring skin and even to the scalp. The term *ulerythema ophryogenes* is used to describe cases with involvement limited to the lateral third of the eyebrows.

Lesions may also begin on the cheeks or temples, rather than the eyebrows. The follicles become reddened, then develop papules, and finally, follicular atrophy. In keratosis pilaris atrophicans faciei the follicular involvement extends to the cheeks and forehead.

Histologically, follicular hyperkeratosis of the upper third of the hair follicle is seen. A small depressed scar forms when the lesion heals. It may occur with atopy, and may be seen in Noonan syndrome and the cardio-facio-cutaneous syndrome. Transmission is autosomal dominant.

Atrophodermia Vermiculata

Atrophodermia vermiculata is also known as *atrophoderma vermiculata*, *atrophodermia ulerythematosa*, *folliculitis ulerythematosa reticulata*, and *honeycomb atrophy*. It is characterized by symmetrical involvement of the face by numerous closely crowded small areas of atrophy separated by narrow ridges, producing a cribriform or honeycomb surface. This worm-eaten (vermiculate) appearance results from atrophy of the follicles and surrounding skin. Each atrophic area is an abrupt, pitlike depression 1 to 3 mm in diameter. Among the ridges a few milia may be seen.

The skin covering the ridges is even with the normal skin and is contrasted with it by being somewhat waxy, firmer, and apparently stretched. The cause of the disease is undetermined but familial occurrence has been noted, and it may be associated with other diseases, such as congenital heart block, other cardiac anomalies, neurofibromatosis, oligophrenia, or Down syndrome.

Histologically, the epidermis is slightly atrophic with diminution in size of the interpapillary projections. In the dermis the capillaries are dilated and the vessels have a moderate lymphocytic perivascular infiltration. Follicles may be enlarged, tortuous, dilated, and hyperkeratotic.

Rombo Syndrome

Rombo syndrome is a rare disorder characterized by atrophoderma vermiculata, cyanosis of the hands and feet, milia, telangiectases, hypotrichosis, multiple basal cell carcinomas, and trichoepitheliomas. The associated vermicular atrophoderma produces a coarse, grainy skin texture. The syndrome is inherited in an autosomal-dominant fashion. It must be distinguished from Bazex syndrome, Rasmussen syndrome (milia, trichoepithelioma, and cylindroma), and multiple trichoepitheliomas.

Keratosis Follicularis Spinulosa Decalvans (Siemens-1 syndrome)

In keratosis follicularis spinulosa decalvans, keratosis pilaris begins on the face and progresses to involve the scalp, limbs, and trunk. There is hyperkeratosis of the palms and soles. Cicatricial alopecia of the scalp and eyebrows is characteristic. Atopy, photophobia, and corneal abnormalities are commonly associated. Deafness, physical and mental retardation, recurrent infections, nail abnormalities, and aminoaciduria have also been purported associations. The disorder is genetically heterogeneous. Although inheritance in large kindreds has been X-linked recessive, X-linked dominant and autosomal-dominant inheritance have also been suggested. In one X-linked form, the defective genetic site is on Xp22.13–p22.2 in the region of the gene for spermidine/spermine *N*(1)-acetyltransferase.

Baden HP, et al: Clinical findings, cutaneous pathology, and response to therapy in 21 patients with keratosis pilaris atrophicans. Arch Dermatol 1994;130:469.

Callaway SR, et al: Keratosis pilaris atrophicans: case series and review. Pediatr Dermatol 2004;21:14.

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Gimelli G, et al: Gene dosage of the spermidine/spermine *N*(1)-acetyltransferase (SSAT) gene with putrescine accumulation in a patient with a Xp21.1p22.12 duplication and keratosis follicularis spinulosa decalvans (KFSD). Hum Genet 2002; 111:235.

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CHAPTER

28 Dermal and Subcutaneous Tumors

The dermis and subcutaneous tissue contain many cellular elements, all capable of both reactive and neoplastic proliferation. In this chapter, proliferations derived from vascular endothelial cells, fibroblasts, myofibroblasts, smooth muscle cells, Schwann cells, and lipocytes are reviewed. Also discussed are several neoplasms of cells invading or aberrantly present in the dermis, such as metastatic cancer, endometriosis, and meningioma.

CUTANEOUS VASCULAR ANOMALIES

Clear differentiation between infantile hemangiomas and vascular malformations is helpful when planning therapy, as infantile hemangiomas involute spontaneously while vascular malformations are persistent. The biology of vascular lesions remains a fertile area for research. Blie et al reported six kindreds in which infantile hemangiomas and/or vascular malformations occurred in various family members in an autosomal-dominant fashion. This unexpected finding clinically links malformations and hemangiomas. The nature of underlying angiogenic etiologic factors awaits elucidation. PHACE syndrome is another instance where hemangiomas and vascular malformations segregate together. Pediatric patients with vascular abnormalities benefit from multidisciplinary evaluation by experts, as the diagnosis and management may be difficult.

Blie F, et al: Familial segregation of hemangiomas and vascular malformations as an autosomal dominant trait. Arch Dermatol 1998;134:718.

Mathes EFD, et al: Clinical characteristics and management of vascular abnormalities. Arch Dermatol 2004;140:979.

Requena L, et al: Cutaneous vascular anomalies. Part I. J Am Acad Dermatol 1997;37:523.

Requena L, et al: Cutaneous vascular neoplasms. Part II. J Am Acad Dermatol 1997;37:887.

Requena L, et al: Cutaneous vascular neoplasms. Part III. J Am Acad Dermatol 1998;38:143.

Hamartomas

Hamartomas are characterized by an abnormal arrangement of tissues normally present in a given site.

Phakomatosis Pigmentovascularis Patients with a combination of vascular malformations and melanocytic or epidermal nevi are grouped into this disorder, and are manifestations of genetic twin spotting. In the traditional classification, types I to IV have nevus flammeus. Those with a coexisting epidermal nevus have type I; if aberrant Mongolian spots are present, it is classified as type II; if a nevus spilus is seen, it is classified as type III; and when both ectopic Mongolian spots and nevus spilus are present, it is classified as type IV. The last three categories may have associated nevus anemicus. The association of extensive cutis marmorata telangiectatica congenita and aberrant Mongolian spots has been classified as type V. If cutaneous disease only is present, the patient's condition is designated subtype a; if there is associated systemic disease, subtype b is appended. A revised classification includes only 3 types: phacomatosis cesioflammea (blue spots and nevus flammeus), phacomatosis spilorosa (nevus spilus and a pale pink spot), and phacomatosis cesiomarmorata (blue spots and cutis marmorata telangiectatica congenita). Associated systemic findings may include intracranial and visceral vascular anomalies, ocular abnormalities, choroidal melanoma and hemihypertrophy of the limbs. Type II is the most common (85%). Half of patients with this type have serious manifestations, such as Klippel-Trenaunay-Parkes-Weber syndrome or Sturge-Weber syndrome. Type III has been associated with multiple granular cell tumors. Most patients are Asian.

Diociaiuti A, et al: Phakomotosis pigmentovascularis type IIIb: a case associated with Sturge-Weber and Klipper-Trenaunay syndromes. J Am Acad Dermatol 2005;53:536.

Happle R: Phacomatosis pigmentovascularis revisited and reclassified. Arch Dermatol. 2005;141:385.

Mahroughan M, et al: Phakomatosis pigmentovascularis. Pediatr Dermatol 1996;13:36.

Trans HV, et al: Primary choroidal melanoma in phakomatosis pigmentovascularis IIa. Oppthalmology 2005;112:1232.

Eccrine Angiomatous Hamartoma Eccrine angiomatous hamartoma usually appears as a solitary nodular lesion on the acral areas of the extremities, particularly the palms and soles. This lesion appears at birth or in early childhood and is often associated with pain and hyperhidrosis. The lesion is a dome-shaped, tender, bluish nodule. When stroked or pinched, drops or beaded rings of perspiration may be seen.

Histologically, there is a combination of lobules of mature eccrine glands and ducts with thin-walled blood vessels. Excision may be necessary because of pain.

Martinelli PT, et al: Eccrine angiomatous hamartoma: a case report and review of the literature. Cutis 2003;71:449.

Pelle MT, et al. Eccrine angiomatous hamartoma. J Am Acad Dermatol 2002;47:429.

Malformations

These are abnormal structures that result from an aberration in embryonic development or trauma. The abnormality may result from an anatomic malformation, or from functional

alteration (as in nevus anemicus). The former are subdivided according to the type of vessel involved: capillary, venous, arterial, lymphatic, or combined.

Nevus Anemicus Nevus anemicus is a congenital disorder characterized by macules of varying size and shape that are paler than the surrounding skin and cannot be made red by trauma, cold, or heat. The nevus resembles vitiligo, but there is a normal amount of melanin. Wood's light does not accentuate it, and diascopy causes it to merge into the surrounding blanched skin. The patches are usually well defined with irregular edges. Rarely, it may occur in neurofibromatosis, tuberous sclerosis, or as one component of phakomatosis pigmentovascularis. In nevus anemicus the triple response of Lewis lacks a flare, but outside the nevus a flare does develop after rubbing the skin. The underlying defect is an increased sensitivity of the blood vessels to catecholamines.

Ahkami RN, et al: Nevus anemicus. Dermatology 1999;198:327.

Nevus Oligemicus Nevus oligemicus presents as a patch of livid skin that is cooler than the normal skin, as a result of decreased blood flow. Vasoconstriction of deep vessels is thought to be the underlying defect.

Davies MG, et al: Nevus oligemicus. Arch Dermatol 1981; 117:111.
Plantin P, et al: Nevus oligemicus. J Am Acad Dermatol 1992; 26:268.

Cutis Marmorata Telangiectatica Congenita (Congenital Phlebectasia, Van Lohuizen Syndrome) Cutis marmorata telangiectatica congenita is characterized by the presence of a purplish, reticulated vascular network with a segmental distribution, usually involving the extremities (Fig. 28-1). The mottling is pronounced and is made more distinct by crying, vigorous activity, and cold. Lesions usually improve by 2 years of age, but may remain stable. The condition occurs sporadically, and there is a female preponderance. The segmental distribution suggests mosaicism, and occasional familial occurrence could be explained by paradominant inheritance, where heterozygous individuals are phenotypically normal, the mutation is transmitted unperceived, and only becomes manifest when a post-zygotic mutation gives rise to loss of heterozygosity.

Associated anomalies occur in more than half of patients. Common anomalies include varicosities, nevus flammeus, ulceration, macrocephaly, and hypoplasia and hypertrophy of soft tissue and bone. Unusual associations include generalized congenital fibromatosis, premature ovarian failure, Chiari I malformation, and rectal and genital anomalies. These lesions are associated with Mongolian spots as type 5 phacomatosis pigmentovascularis. They have also been reported in association with features of the Adams-Oliver syndrome (limb abnormalities, scalp defects, skull ossification defects).

The differential diagnosis includes residual vascular lesions from neonatal lupus and Bockenheimer syndrome. Bockenheimer syndrome appears in childhood and shows progressive development of large venous ectasias involving one limb. No treatment is required. Many will become less noticeable with time.

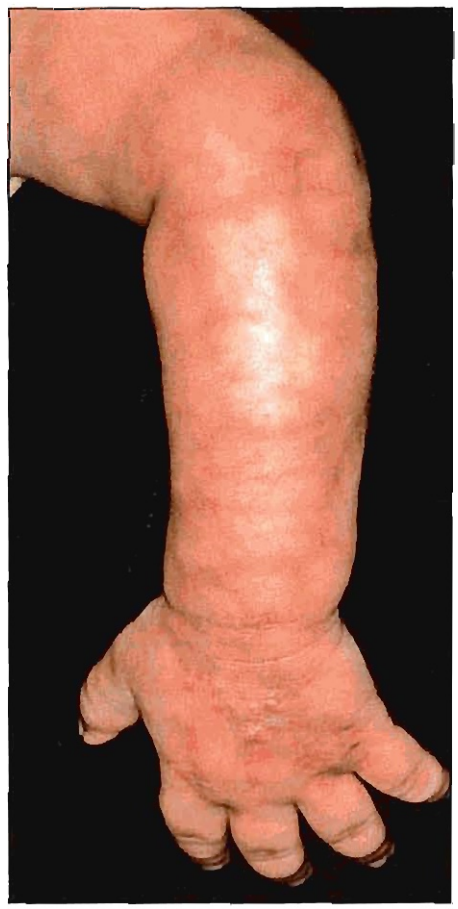

Fig. 28-1 Cutis marmorata telangiectatica congenital. (Courtesy of Brooke Army Medical Center *Teaching File*)

Danarti R, et al: Paradominant inheritance may explain familial occurrence of cutis marmorata telangiectatica congenita. Dermatology 2001;203:208.
Fujita M, et al. Cutis marmorata telangiectatica congenita with hemangiomatous histopathologic features. J Am Acad Dermatol 2003;48:950.
Stoll C: Macrocephaly-cutis marmorata telangiectatica congenita: report of a patient with a translocation. Genet Couns 2003;14:173.
Tubbs RS, et al. Cutaneous manifestations and the Chiari I malformation. Pediatr Neurol 2003;29:250.

Nevus Flammeus (Capillary Malformation, Port-Wine Stain) Nevus flammeus nuchae (stork bite) is a congenital capillary malformation present in 25% of newborns. It may persist in at least 5% of the population. It usually is a pink–red macule situated on the posterior midline between the occipital protuberance and the tip of the spine of the fifth cervical vertebra. The long axis is usually up and down. A similar appearing midline nevus flammeus (salmon patch or angel's kiss) on the glabellar region or on one upper eyelid is present in approximately 15% of newborns. They tend to fade during childhood.

Other port-wine stains occur in an estimated 3 in 1000 children. They are present at birth, and vary in color from pink to dark or bluish red. The lesions are usually unilateral

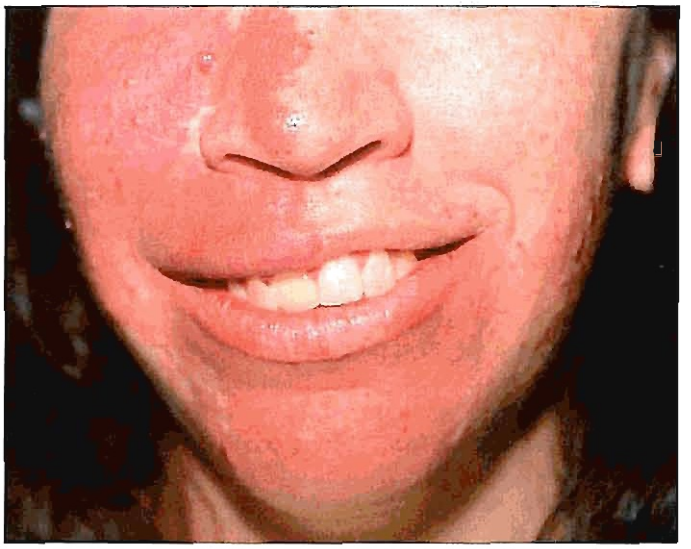

Fig. 28-2 Port-wine stain.

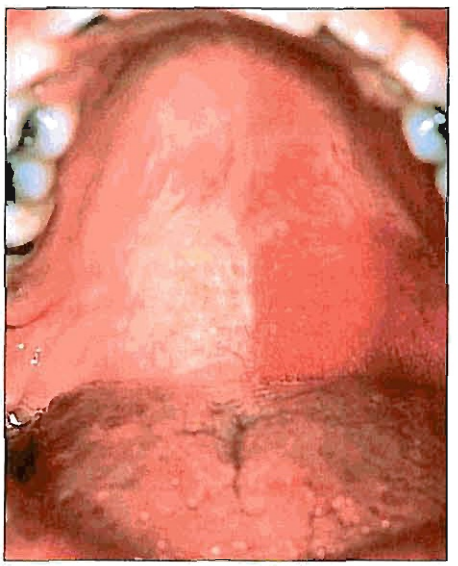

Fig. 28-3 Port-wine stain.

and located on the face and neck, although they may be widespread and involve as much as half the body. The most common site is a unilateral distribution on the face (Fig. 28-2). The mucous membrane of the mouth may be involved (Fig. 28-3). Although the surface of a nevus flammeus is usually smooth, small vascular nodular outgrowths or warty excrescences may develop over time. These lesions often become more bluish or purple with age. Several reports document multiple basal cell carcinomas occurring in adult life over sites of long-standing nevus flammeus. Rarely, nevus flammeus may appear as an acquired condition, usually with onset after trauma.

Nevus flammeus in the area supplied by the ophthalmic division of the trigeminal cranial nerve is a component of the Sturge-Weber syndrome (encephalotrigeminal angiomatosis), but the leptomeningeal component is present in only 10% of patients with all or most of the V1 branch of the trigeminal nerve involved. Leptomeningeal angiomatosis may clinically manifest as epilepsy, mental retardation, hemiplegia, hemisensory defects, and homonymous hemianopsia. Characteristic calcifications are present in the outer layers of the cerebral cortex; these consist of double-contoured "tram tracks" that follow the brain convolutions. Ocular abnormalities, such as glaucoma, buphthalmos (infantile glaucoma, related to abnormal development of the angle formed by cornea and iris), retinal detachment, and blindness affect approximately 50% of patients. These may be present without leptomeningeal involvement. The syndrome results from the persistence of the primitive embryonal vascular plexus that develops during the sixth fetal week around the cephalic neural tube and in the region destined to become facial skin. Normally, the plexus regresses during the ninth week, but in the Sturge-Weber syndrome it persists. Fibronectin gene expression is increased in lesional fibroblasts.

Overgrowth of soft tissue and underlying bone may occur in an affected extremity, giving rise to the Klippel-Trenaunay-Parkes-Weber syndrome. The Klippel-Trenaunay syndrome is characterized by port-wine malformations and the Parkes-Weber syndrome by deep arteriovenous malformations.

Port-wine stains are components of many rare congenital disorders. Occasionally, nevus flammeus may be associated with nevus anemicus, nevus spilus, atypical Mongolian spots, or epidermal nevi. Such patients have a condition called *phakomatosis pigmentovascularis*. The Beckwith-Wiedemann syndrome may comprise facial port-wine stain, macroglossia, omphalocele, visceral hyperplasia, occasionally hemihypertrophy, and hypoglycemia. Cobb syndrome (cutaneous meningospinal angiomatosis) is a nonfamilial disorder characterized by a port-wine hemangioma or other vascular malformation in a dermatome supplied by a segment of the spinal cord containing a venous or arteriovenous malformation. Kyphoscoliosis is common and multiple neurologic, gastrointestinal, urologic, and skeletal abnormalities may also be present. Proteus syndrome is characterized by vascular malformations including nevus flammeus, hemihypertrophy, macrodactyly, verrucous epidermal nevus, soft-tissue subcutaneous masses, and cerebriform overgrowth of the plantar surface. Roberts syndrome consists of a facial port-wine stain and hypomelia, hypotrichosis, growth retardation, and cleft lip. The Wyburn-Mason syndrome consists of unilateral retinal arteriovenous malformation associated with ipsilateral port-wine stain near the affected eye. This may be present in association with Sturge-Weber syndrome. The TAR syndrome is defined by congenital thrombocytopenia, bilateral absence or hypoplasia of the radius, and port-wine stain. Coats' disease manifests retinal telangiectasia and ipsilateral facial port-wine stain.

Occasional familial segregation of port-wine stains has been noted, and a large associated gene locus, CMC1, has been identified on chromosome 5q. RASA1, a gene encoding p120–RasGAP, is found within this region and heterozygous inactivating RASA1 mutations have been found in affected families.

Histologically, port-wine stains demonstrate dilation of capillaries in the subpapillary network. Laser therapy has been used with satisfactory results, but a number of treatments are required and recurrence is common. The flashlamp pulsed dye laser has the best record of safety and efficacy. Commonly, a pulse duration of 0.45 ms is used. A study of cryogen-spray cooled laser treatment at wavelengths of 585 versus 595 nm, both with 7-mm spot size in a range of 7 to 10 J/cm^2, demonstrated better blanching at 585 nm. In another study, purple lesions responded best to 585 nm at

0.5 ms, while red and pink lesions showed similar results with either 585 nm at 0.5 ms or 595 nm for 20 ms. In this study, 595 nm at 0.5 ms was less effective than the other settings. Optical–thermal models predict that for vessel diameters of 40, 80, and 120 μm, effective pulse durations should be approximately 1.5, 6, and 20 ms, respectively. Cryospray cooling and fluence can be varied to produce optimal results. For darker skinned patients, multiple pulse stacking with multiple cryogen spurts provides better epidermal protection. Intense pulsed light has been effective in some patients resistant to multiple pulsed dye laser treatments.

Ackermann G, et al: Correlations between light penetration into skin and the therapeutic outcome following laser therapy of port-wine stains. Lasers Med Sci 2002;17:70.

Aguilar G, et al: Cryogen spray cooling efficiency: improvement of port wine stain laser therapy through multiple-intermittent cryogen spurts and laser pulses. Lasers Surg Med. 2002; 31:27.

Bjerring P, et al. Intense pulsed light source for the treatment of dye laser resistant port-wine stains. J Cosmet Laser Ther 2003;5:7.

Chang CJ, et al: Comparing the effectiveness of 585-nm vs 595-nm wavelength pulsed dye laser treatment of port wine stains in conjunction with cryogen spray cooling. Lasers Surg Med 2002;31:352.

Edstrom DW, et al: Flashlamp pulsed dye laser and argon-pumped dye laser in the treatment of port-wine stains: a clinical and histological comparison. Br J Dermatol 2002; 146:285.

Eerola I, et al. Capillary malformation–arteriovenous malformation, a new clinical and genetic disorder caused by RASA1 mutations. Am J Hum Genet 2003;73:1240.

Enjolras O, et al: Vascular anomalies and the growth of limbs: a review. J Pediatr Orthop B 2004;13:349.

Greve B, et al. Prospective study of port wine stain treatment with dye laser: comparison of two wavelengths (585 nm vs. 595 nm) and two pulse durations (0.5 milliseconds vs. 20 milliseconds). Lasers Surg Med 2004;34:168.

Kauvar AN, et al: Laser treatment of cutaneous vascular anomalies. Lymphat Res Biol 2004;23:349.

Kelly KM, et al. Treatment of port-wine stain birthmarks using the 1.5-msec pulsed dye laser at high fluences in conjunction with cryogen spray cooling. Dermatol Surg 2002;28:309.

Pence B, et al: Outcomes of 532 nm frequency-doubled Nd:YAG laser use in the treatment of port-wine stains. Dermatol Surg 2005;31:509.

Tunnell JW, et al. Optimum pulse duration and radiant exposure for vascular laser therapy of dark port-wine skin: a theoretical study. Appl Opt 2003;42:1367.

Verrucous Vascular Malformation (Angiokeratoma Circumscriptum Naeviforme) This is a malformation of dermal and subcutaneous capillaries and veins. The vascular malformation is congenital. Over time, a verrucous component appears. The lesions are bluish-red, well-defined, and occur on the lower extremities mostly, but also on the chest or forearm. Linear segmental lesions have been described. Associated spinal lesions (Cobb syndrome) have been reported. Klippel-Trenaunay syndrome has also been reported in association with verrucous vascular malformation. Superficial ablative therapy is typically followed by recurrence, regardless of whether ablation is performed by excision, laser, cryotherapy, or electrocautery. Full-thickness excision is generally effective, and may be used in combination with laser therapy.

Clinton TS, et al: Cobb syndrome associated with a verrucous (angiokeratomalike) vascular malformation. Cutis 2003; 71:283.

Yang CH, et al: Successful surgical treatment of verrucous hemangioma: a combined approach. Dermatol Surg 2002;28:913.

Deep Venous Malformations Including Cavernous Venous Malformation Cavernous venous malformations present as rounded, bright red or deep purple, spongy nodules. They occur chiefly on the head and neck and may involve both the skin and the mucous membranes. There is usually a deep component with a connection to the venous circulation. Calcified phleboliths and localized hyperhidrosis may occasionally be present, but the lesions are generally asymptomatic. The deep components are not amenable to laser therapy. Results of surgical resection are generally poor. Compression may be helpful. Customized, snug-fitting garments are preferable to elastic bandages.

Several syndromes are associated with venous malformations. The Bannayan-Riley-Ruvalcaba syndrome is described in Chapter 30. Maffucci syndrome, also known as *dyschondroplasia with hemangiomata*, is characterized by multiple vascular malformations with dyschondroplasia. The dyschondroplasia is manifested by uneven bone growth as a result of the defects of ossification, with enchondromatosis that results in multiple and frequent fractures in the period of bone growth. During the prepubertal years, 1- to 2-cm nodules appear on the small bones of the hand or foot. Later, larger nodules, the enchondromas, appear on the long bones. Much later, similar lesions appear on the trunk. Sarcomatous degeneration occurs in 50% of patients. The distribution of the lesions is mostly unilateral. Multiple venous malformations of the skin and mucous membranes are present in this nonhereditary mesodermal dysplasia disorder. Lymphangiomas may also occur. Pigmentary changes, such as vitiligo and café-au-lait macules, have been noted. In Ollier disease, the enchondromatosis is present without the cutaneous abnormalities. Human enchondromatosis has been associated with abnormalities in parathyroid hormone-related protein (PTHrP), its receptor, and the Indian hedgehog (IHH) gene. PTHrP delays differentiation of proliferating chondrocytes, whereas IHH promotes proliferation.

The blue rubber bleb nevus syndrome is characterized by cutaneous and gastrointestinal venous malformations. The skin lesions have a cyanotic, bluish appearance with a soft, elevated, nipple-like center, but deeper lesions may also occur. They can be emptied by firm pressure, leaving them flaccid. They are located predominantly on the trunk and arms. Nocturnal pain may occur and is a characteristic symptom. Gastrointestinal hemangiomas are found throughout the gastrointestinal tract, but are numerous in the small intestines. Rupture of a lesion may produce melena. Occasionally, other organs may express venous malformations and symptomatic central nervous system (CNS) lesions have been described. This syndrome generally occurs as a sporadic

condition. It may be present as an autosomal-dominant familial trait. Treatment of bleeding or painful lesions is destruction or excision. Minimally invasive surgical techniques are well suited to the treatment of numerous lesions. For patients who continue to have bleeding episodes that require blood transfusions, octreotide, a somatostatin analog known to decrease splanchnic blood flow, may be effective. Epsilonaminocaproic acid has also been used.

Gorham's disease (Gorham's sign) is characterized by cutaneous and osseus venous and lymphatic malformations associated with massive osteolysis or "disappearing bones." Although multiple areas of the skeletal system may be involved, usually only a single bone is destroyed. There is complete or partial replacement of the bone with fibrous tissue. The cutaneous malformation may be the initial sign of the disease, which appears commonly in young children, usually in areas adjacent to involved bones.

Sinusoidal hemangioma is a vascular malformation that usually presents in adults as a bluish-purple nodule, less than 4 cm in diameter, on the trunk or breasts. Multiple lesions may occur and a facial location has also been reported. Histologically, it appears as a lobular, circumscribed mass with dilated interconnected vascular channels filled with blood.

A familial condition of multiple cutaneous and mucosal venous malformations that show abnormal venous channels with decreased or absent smooth muscle has been shown to be the result of an activating mutation in the receptor tyrosine kinase TIE-2 endothelial gene. It is located on chromosome 9p and is the result of a single amino acid substitution in the kinase domain of the TIE-2 receptor.

Cerebral cavernomas are vascular malformations that may be inherited in an autosomal-dominant fashion. The gene, CCM1, has been mapped to chromosome 7. Cutaneous malformations are sometimes present, including hyperkeratotic cutaneous capillary venous malformations.

Venous malformations (VM) should be distinguished from glomuvenous malformations (GM, gomangioma). VM are usually sporadic, while GM are frequently inherited. VM is linked to chromosome 9p21, while GM is linked to 1p21 and loss of function mutations in glomulin. GM can be pink at initial presentation, but evolves to blue–black with a cobblestone appearance with minimal hyperkeratosis. Involvement of an extremity is typical and the lesions are often painful if compressed. VM is an isolated mucosal or subcutaneous blue lesion that may involve muscle. The lesion often shrinks with external pressure and is typically painful in the morning due to congestion. Increased pain may be noted at puberty, during menstruation, with pregnancy or with oral contraceptives. VM may be associated with intravascular coagulopathy. Sclerotherapy is more effective in VM than in GM.

Bertucci V, et al: What syndrome is this? Ollier disease + vascular lesions: Maffucci syndrome. Pediatr Dermatol 1995;12:55.

Boon LM, et al: Glomuvenous malformation and venous malformation. Arch Dermatol 2004;140:971.

Gonzalez D, et al: Chronic subcutaneous octreotide decreases gastrointestinal blood loss in blue rubber-bleb nevus syndrome. J Pediatr Gastroenterol Nutr 2001;33:183.

Hopyan S, et al: A mutant PTH/PTHrP type I receptor in enchondromatosis. Nat Genet 2002;30:306.

Labauge P, et al. An association between autosomal dominant cerebral cavernomas and a distinctive hyperkeratotic cutaneous vascular malformation in 4 families. Ann Neurol 1999;45:250.

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Velez A, et al: Gorham's syndrome. Int J Dermatol 1993;32:884.

Vikkula M, et al: Vascular dysmorphogenesis caused by activating mutation in the receptor tyrosine kinase TIE-2. Cell 1996;87:1181

Watanabe Y, et al. Multiendoscope-assisted treatment for blue rubber bleb nevus syndrome. Surg Endosc 2000;14:595.

Klippel-Trenaunay Syndrome (Hemangiectatic Hypertrophy, Angioosteohypertrophy Syndrome)

Klippel-Trenaunay syndrome (KTS) is characterized as a triad of nevus flammeus, venous and lymphatic malformations, and soft-tissue hypertrophy of the affected extremity. The lower limb is affected in approximately 95% of patients. When there is an associated arteriovenous fistula, *Parkes-Weber* is appended to the diagnosis.

The earliest and most common presenting sign is a nevus flammeus that is confined to the skin of an extremity. The port-wine stain often stops abruptly at the midline with a sharp, linear border, but it may be patchy and extend over the buttocks and trunk, and may occasionally be seen with a bilateral or generalized distribution. Varicose veins may be present. The deeper venous malformation in this sporadic syndrome may be confined to the skin; however, it is common for the malformation to extend to muscle and bone. Venous thromboembolism has been reported with an incidence as high as 22%. In other patients, the deep venous system is hypoplastic.

The involved limb is usually larger and longer than normal. Other less frequent features include intermittent claudication, venous ulcers, increased skin temperature, diffuse hair loss, hypertrichosis, lymphedema, altered sweating, lacrimation, or salivation. Gait abnormalities are common. Hemihypertrophy of the face; cutaneous lymphangioma; varicose pulmonary, bladder, and colonic veins; and recurrent pulmonary emboli have been reported. Intradural spinal cord arteriovenous malformations, epidural hemangioma, and epidural angiomyolipoma have been reported to occur at the same segmental level as cutaneous lesions of KTS syndrome. Clinical evaluation consists of color duplex ultrasonography to evaluate the patency of the deep venous system, magnetic resonance imaging (MRI) for visualization of hypertrophic muscle and bone, arteriography when an arteriovenous fistula is suspected, and conventional radiography of both extremities. Early venography may be performed, if the deep venous system is not hypoplastic, to determine whether there are defects that might be amenable to surgical correction. Thick-slice dynamic magnetic resonance projection angiography (MRPA) and intra-arterial digital subtraction angiography can be used to detect arteriovenous shunting in Parkes-Weber syndrome.

Mutations associated with the angiogenic factor, VG5Q, have been described in KTS. A balanced translocation involving chromosomes 8q22.3 and 14q13 has also been reported.

Flashlamp pumped pulsed dye laser treatments may be used for the nevus flammeus component. The varicosities and

edema may be managed with elevation, graded compression pumps, fitted garments, and diuretics. Surgery may be performed to correct the inequality in limb length, to relieve deep venous obstruction, or to correct an associated arteriovenous fistula. The Klippel-Trenaunay Support Group website can be found at www.k-t.org.

Baraldini V, et al: Early surgical management of Klippel-Trenaunay syndrome in childhood can prevent long-term hemodynamic effects of distal venous hypertension. J Pediatr Surg 2002;37:232.

Capraro PA, et al: Klippel-Trenaunay syndrome. Plast Reconstr Surg 2002;109:2052.

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Timur AA, et al: Biomedicine and diseases: the Klippel-Trenaunay syndrome, vascular anomalies and vascular morphogenesis. Cell Mol Lif Sci 2005;62:1434.

Arteriovenous Fistulas The arteriovenous (AV) fistula is a route from artery to vein, bypassing the capillary bed. AV fistulas may be congenital or acquired. Congenital AV fistulas occur mostly on the extremities and may be recognized, or at least suspected, in the presence of varicose veins, ulcerations, hemangiomas, and nevus flammeus. They may occur internally as a component of Osler-Weber-Rendu disease (hereditary hemorrhagic telangiectasia). Acquired fistulas are usually the result of trauma, but may be created intentionally for hemodialysis access.

The skin over these fistulas is warmer, hair may grow faster, and the affected limb may be larger than the other; thrills and bruits may be discerned in some cases. There may be changes resulting from stasis, edema, a vascular mass, increased sweating, or paresthesias. At times, reddish-purple nodules or a plaque may be present that clinically resembles Kaposi sarcoma; this has been called *pseudo-Kaposi sarcoma* (Stewart-Bluefarb syndrome). It may occur because of congenital malformations, in which case a unilateral purplish discoloration of the skin over or distal to the AV anomaly begins to appear in the second or third decade of life. This type accounts for 80% of cases; the remainder are secondary to fistulas caused by trauma. Iatrogenic AV fistulas, such as those produced to facilitate hemodialysis, may also bring about skin changes, including reactive angioendotheliomatosis. Histologically, there is an increase in thick-walled vessels lined by plump endothelial cells, extravasated erythrocytes, and deposits of hemosiderin. Proliferating endothelial cells may occlude the lumen.

Cirsoid aneurysms (angioma arteriale racemosum) are uncommon congenital AV fistulas of the scalp or face. They may appear on the skin as a pulsating mass that may extend over the neck and scalp, and may penetrate into the cranium, or they may simply manifest as a solitary blue or red papule in the mid-adult period.

Diagnosis of an AV fistula is established by plethysmography, thermography, determination of oxygen saturation of venous blood, or arteriography.

Treatment of traumatically-induced AV fistulas by excision is curative. Because the congenital malformation variety consists of multiple small distal lesions, surgical intervention is not feasible in most cases. Color echo-Doppler ultrasonography-guided sclerotherapy with polidocanol microfoam has been used successfully in this setting. Pressure and elevation as supportive measures may limit ulceration, infection, and other secondary complications. Cirsoid aneurysms of the scalp have been treated by embolization and injection of sodium tetradecyl sulfate.

Cabrera J, et al: Treatment of venous malformations with sclerosant in microfoam form. Arch Dermatol 2003;139:1409.

Requena L, et al: Intravascular and diffuse dermal reactive angioendotheliomatosis secondary to iatrogenic arteriovenous fistulas. J Cutan Pathol 1999;26:159.

Prominent Inferior Labial Artery The arteries supplying the lips are normally tortuous to accommodate the movements of the mouth. Howell and Freeman reported a potentially troublesome arterial anomaly of the lower lip characterized by the appearance of a pulsating papule in the lower vermilion, a centimeter or two from the oral commissure, formed by an especially tortuous segment of the inferior labial artery. A similar anomaly may involve the upper lip. Caliber-persistent labial artery may be misdiagnosed as squamous cell carcinoma, and the biopsy may produce significant bleeding. On the lip, it is best to "palpate for pulsation prior to puncture."

Howell JB, Freeman RG: The potential peril from caliber-persistent arteries of the lips. J Am Acad Dermatol 2002;46:256.

Lovas JG, et al: Caliber-persistent labial artery. A common vascular anomaly. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;86:308.

Acral Arteriolar Ectasia Paslin and Heaton reported a man with purple serpiginous ectatic arterioles on the backs of his fingers, which appeared in the fifth decade of life.

Paslin DA, Heaton CL: Acral arteriolar ectasia. Arch Dermatol 1972;106:906.

Superficial Lymphatic Malformation (lymphangioma circumscriptum) The old term for superficial lymphatic malformation was *lymphangioma circumscriptum*; however, this is not a tumor but rather a congenital malformation of the superficial lymphatics. A superficial lymphatic malformation presents as groups of deep-seated, vesicle-like papules, resembling frog spawn, at birth or shortly thereafter. The lesions are usually yellowish but may be pink, red, or dark. When the papules are punctured, they exude clear, colorless lymph. The papules are arranged irregularly in groups that may be interconnected by sparsely scattered lymph cysts. The entire process, however, is as a rule localized to one region. The sites of predilection are the abdomen, axillae, genitalia, and mouth, particularly the tongue. The scrotum is subject to multifocal lymphatic malformations presenting as clear, thick-walled, vesicle-like lesions. At times the surface is verrucous, in which instance the color may be brownish,

and the lesions may be mistaken for warts. Lesions resembling molluscum contagiosum have also been described.

Frequently, the lesions consist of a combination of blood and lymph element so that purple areas are sometimes seen scattered within the vesicle-like papules. The lesions are also frequently associated with a deep component that occupies the subcutaneous tissues and muscles. In the course of time, these lymphatic malformations show only slight changes.

Excision and grafting, fulguration, or coagulation are frequently unsatisfactory because of recurrences resulting from vascular connections between the surface lesions and deep-seated lymphatic cisterns. The deeper component should be evaluated by MRI or other suitable radiologic imaging procedure to delineate the extent of deep involvement before planned procedures. Vaporization with the CO_2 laser may be successful if deeper components are not present. Pulsed dye laser has also been reported as effective. Keloid formation has been described after laser vaporization of genital lymphangiomas. Sclerotherapy may be successful.

Bikowski JB, et al: Lymphangioma circumscriptum: treatment with hypertonic saline sclerotherapy. J Am Acad Dermatol 2005;53:442.

Gupta S, et al: Lymphangioma circumscriptum of the penis mimicking venereal lesions. J Eur Acad Dermatol Venereol 2003;17:598.

Huilgol SC, et al: CO_2 laser therapy of vulval lymphangiectasia and lymphangioma circumscriptum. Dermatol Surg 2002; 28:575.

Lai CH, et al: Lymphangioma circumscriptum treated with pulsed dye laser. Pediatr Dermatol 2001;18:509.

Tawfik HA, et al: Lack of response to systemic corticosteroids in patients with lymphangioma. Ophthal Plast Reconstr Surg 2005;21:302.

Vlastos AT, et al: Lymphangioma circumscriptum of the vulva: a review of the literature. Obstet Gynecol 2003;101(5 Pt 1):946.

Cystic Lymphatic Malformation Cystic lymphatic malformations are deep-seated, typically multilocular, ill-defined soft-tissue masses that are painless and covered by normal skin. They are most common in the oral cavity and on the extremities, and have been described in Maffucci syndrome. Cystic hygromas are clinically better circumscribed, occurring usually in the neck, axilla, or groin. The posterior neck lesions may be associated with Turner syndrome, other chromosomal aneuploidy conditions, hydrops fetalis, or other congenital abnormalities. Cytogenic analysis of children born with cystic hygromas is indicated as aneuploidy may recur in subsequent pregnancies. Transabdominal or transvaginal sonography can visualize these lesions in utero. Usually these lesions will recur after surgical treatments because of their depth, but injection sclerotherapy with agents such as OK-432 may result in regression.

Fujino A, et al. A role of cytokines in OK-432 injection therapy for cystic lymphangioma: an approach to the mechanism. J Pediatr Surg 2003;38:1806.

Lille ST, et al: The surgical management of giant cervicofacial lymphatic malformations. J Pediatr Surg 1996;31:1648.

Paoloni-Giacobino A, et al: Pregnancy outcome of 30 fetuses with cystic hygroma diagnosed during the first 15 weeks of gestation. Genet Couns 2003;14:413.

Requena L, et al: Cutaneous vascular anomalies. J Am Acad Dermatol 1997;37:523.

Taipale P, et al: Increased nuchal translucency as a marker for fetal chromosomal defects. N Engl J Med 1997;337:1654.

Lymphangiomatosis Diffuse or multifocal dilated lymphatic channels involving the skin, soft tissues, bone, and parenchymal organs are a rare congenital condition. If an extremity is affected, the prognosis is good; however, when vital internal organs are involved, the prognosis is poor. Skin lesions are a presenting sign in 7% of patients with thoracic lymphangiomatosis. These patients have a high incidence of complications, including chylothorax (49%), pulmonary infiltrates (45%), bone lesions (39%), splenic lesions (19%), cervical involvement (15%), and disseminated intravascular coagulation (9%).

Alvarez OA, et al: Thoracic lymphangiomatosis in a child. J Pediatr Hematol Oncol 2004;26:136.

Moerman P, et al: Lymphangiomatosis of the body wall. Pediatr Pathol Lab Med 1997;17:617.

Singh Gomez C, et al: Lymphangiomatosis of the limbs. Am J Surg Pathol 1995;19:125.

Dilation of Preexisting Vessels

Spider Angioma (Vascular Spider, Spider Nevus, Nevus Araneus) The lesion of spider angioma is suggestive of a red spider; hence its name. The ascending central arteriole represents the "body" of the spider, and the radiating fine vessels are suggestive of the multiple legs. These small telangiectases occur singly or severally, most frequently on the face and neck, with decreasing frequency on the upper trunk and upper extremities. In young children, the sites of predilection are the backs of the hands and forearms, and the face.

Young children and pregnant women show these lesions most frequently. In pregnant women palmar erythema is usually present with the vascular spiders. The presence of vascular spiders in otherwise healthy children is common.

The vascular spiders of childhood usually involute without treatment; however, several years may elapse before that happens. In pregnant women, most lesions will involute soon after delivery.

Vascular spiders also occur in patients with cirrhosis, hepatitis C, malignant disease of the liver, and other hepatic dysfunctions. The common denominator has been shown to be an elevated blood estrogen level. Elevations in vascular endothelial growth factor and basic fibroblastic growth factor are also significant predictors for spider angiomas in cirrhotic patients. When vascular spiders occur with palmar erythema and pallid nails with distal hyperemic bands, cirrhosis of the liver should be considered. Arteriovenous hemangioma has also been reported to be associated with chronic liver disease.

If active therapy is to be performed, either obliteration by electrodesiccation of the central punctum or laser treatment produces excellent results.

Akiyama M, et al: Arteriovenous haemangioma in chronic liver disease: clinical and histopathological features of four cases. Br J Dermatol 2001;144:604.

Gupta G, et al: A prospective study of the impact of laser treatment on vascular lesions. Br J Dermatol 2000;143:356.
Li CP, et al: Spider angiomas in patients with liver cirrhosis: role of vascular endothelial growth factor and basic fibroblast growth factor. World J Gastroenterol 2003;9:2832.

Venous Lakes Venous lakes (phlebectases) are small, dark blue, slightly elevated blebs (Fig. 28-4). These are easily compressed (Fig. 28-5), and are located on the face, ears, lips, neck, forearms, and backs of the hands. These manifestations of chronic sun damage are markedly dilated, blood-filled spaces that are lined with thin, elongated endothelial cells, and are usually surrounded by prominent solar elastosis.

Venous lakes may be treated by light electrocautery, laser ablation, fulguration, infrared coagulation, intralesional injection of 1% polidocanol, and cryotherapy. Sometimes they must be treated because of traumatic bleeding.

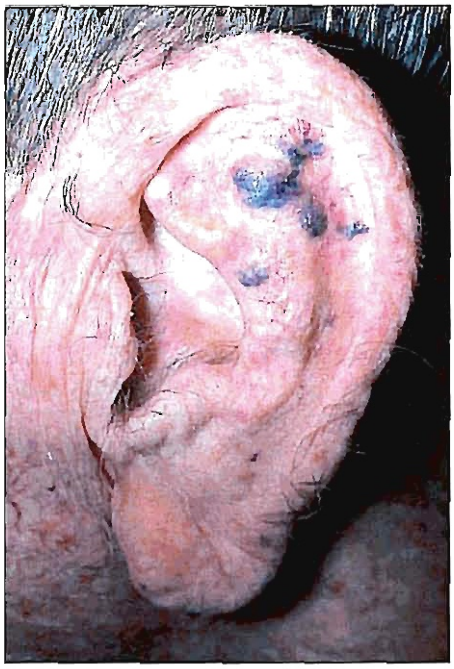

Fig. 28-4 Venous lake.

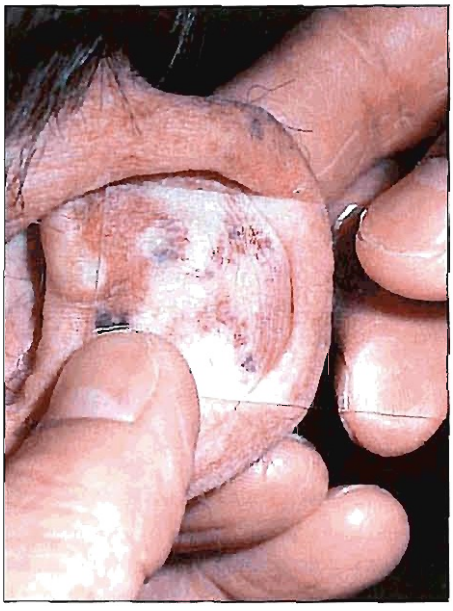

Fig. 28-5 Venous lake.

Kuo HW, et al: Venous lake of the lip treated with a sclerosing agent: report of two cases. Dermatol Surg 2003;29:425.
Majamaa H, et al: Treatment of venous-lake angiomas with a carbon dioxide laser. J Eur Acad Dermatol Venereol 2003; 17:352.

Capillary Aneurysms These flesh-colored solitary lesions, resembling an intradermal nevus, may suddenly grow larger and darker and become blue–black or black as a result of thrombosis. They are surrounded by a zone of erythema. The lesions may be clinically indistinguishable from malignant melanoma. Histologically, these are thrombotic, dilated capillaries lying just below the epidermis. Shave excision in stages will expose the clot and eliminate the uncertainty.

Requena L, et al: Cutaneous vascular anomalies. J Am Acad Dermatol 1997;37:523.

Telangiectasia A telangiectasis is a dilated cutaneous blood vessel—venule, capillary, or arteriole. Telangiectases are fine, linear vessels coursing on the surface of the skin; the name given to them collectively is *telangiectasia*. Telangiectasia may occur in normal skin at any age, in both sexes, and anywhere on the skin and mucous membranes. Fine telangiectases may be seen on the alae nasi of most adults.

They are prominent in areas of chronic actinic damage seen in fair-skinned persons. Persons long exposed to wind, cold, or heat are also subject to telangiectasia.

Telangiectases can be found in such conditions as radiodermatitis, xeroderma pigmentosum, lupus erythematosus, dermatomyositis, scleroderma and the CREST syndrome, rosacea, cirrhosis of the liver, acquired immunodeficiency syndrome (AIDS), poikiloderma, basal cell carcinoma, necrobiosis lipoidica diabeticorum, sarcoid, lupus vulgaris, adenoma sebaceum, keloid, angioma serpiginosum, angiokeratoma corporis diffusum, ataxia-telangiectasia, pregnancy, Osler-Weber-Rendu disease, and Bloom syndrome. These entities are discussed in other sections with the disease states in which they occur.

Altered capillary patterns on the fingernail folds (cuticular telangiectases) are indicative of collagen vascular disease, such as lupus erythematosus, scleroderma, or dermatomyositis. Tortuous glomeruloid loops are characteristic of lupus erythematosus, whereas dilated loops and avascular areas are typical for scleroderma and dermatomyositis. Reticular telangiectatic erythema may occur overlying implantable cardioverter defibrillators.

Electrodessication and laser ablation can be effective. Pulsed dye laser and other vascular lasers, such as the 532-nm Nd:YAG laser, are usually well tolerated and associated with a low risk of scarring. Larger vessels require a longer pulse duration. Contact or cryospray cooling can reduce the incidence of complications. Pulse stacking (multiple pulses of low fluencies) has been used to reduce the incidence of side effects, such as purpura, hyperpigmentation, hypopigmentation, and scar formation.

Ferringer T, et al: Telangiectatic erythematous cutaneous reaction to an implantable cardioverter defibrillator. Am J Contact Dermat 2003;14:37.

Jasim ZF, et al: Long-pulsed (6-ms) pulsed dye laser treatment of rosacea-associated telangiectasia using subpurpuric clinical threshold. Dermatol Surg 2004;30:37.
Rohrer TE, et al: Does pulse stacking improve the results of treatment with variable-pulse pulsed-dye lasers? Dermatol Surg 2004;30(2 Pt 1):163.
Ross V, et al: Laser leg vein treatment: a brief overview. J Cosmet Laser Ther 2003;5:192.
Woo WK, et al: 532-nm Nd:YAG and 595-nm pulsed dye laser treatment of leg telangiectasia using ultralong pulse duration. Dermatol Surg 2003;29:1176.

Generalized Essential Telangiectasia Generalized essential telangiectasia (GET) is characterized by the dilation of veins and capillaries over a large segment of the body without preceding or coexisting skin lesions. The telangiectases may be distributed over the entire body or be localized to some large area such as the legs, arms, and trunk. They may be discrete or confluent. Distribution along the course of the cutaneous nerves may occur. This type of telangiectasia is not associated with systemic disease, although patients with a similar appearance may have autoimmune disease. One report documented gastrointestinal bleeding from a watermelon stomach in a woman with GET.

GET develops most frequently in women in their 40s and 50s. The initial onset is on the lower legs and then spreads to the upper legs, abdomen, and arms. The dilations persist indefinitely. Generally, this is a sporadic condition, although it has been described in families as an autosomal-dominant condition. In the latter case it has been termed *hereditary benign telangiectasia*.

It has been reported that GET may be differentiated from telangiectasia associated with systemic disease by the presence of alkaline phosphatase activity. Telangiectatic vessels in GET do not have alkaline phosphatase activity in the endothelium of the terminal arteriole and the arterial portion of the capillary loops.

Individual areas may be treated with laser ablation. High-energy, high-frequency, long-pulse Nd:YAG laser and the 585-nm flashlamp-pumped pulsed dye laser have been reported to produce good results. Tetracycline, ketoconazole, and the treatment of a chronic sinus infection have led to involution in individual reports.

Blume JE. Generalised essential telangiectasia: a case report and review of the literature. Cutis 2005;75:223.
Buscaglia DA, et al: Successful treatment of generalized essential telangiectasia with the 585-nm flashlamp-pumped pulsed dye laser. Cutis 2001;67:107.
Gambichler T, et al: Generalized essential telangiectasia successfully treated with high-energy, long-pulse, frequency-doubled Nd:YAG laser. Dermatol Surg 2001;27:355.
Long D, et al: Generalized essential telangiectasia. Australas J Dermatol 2004;45:67.

Universal Angiomatosis Universal angiomatosis, called *generalized telangiectasia* by Bean, is a bleeding disease that affects the blood vessels of the skin and mucous membranes as well as other parts of the body. Bean and Rather reported a 13-year-old boy who had frequent nose bleeds, and ear and upper respiratory infections. He had mottled skin with redness that blanched on pressure. Finely dilated blood vessels were universal, suggesting the term "pink man." Some irregular white patches were also present. Continual bleeding into the skin was evident despite normal coagulation of the blood. This type of angiomatosis differs from generalized telangiectasia because of its hemorrhagic tendency, especially epistaxis.

Bean WB, Rathe J: Universal angiomatosis. Arch Intern Med 1963;112:869.

Unilateral Nevoid Telangiectasia In unilateral nevoid telangiectasia, fine, threadlike telangiectases develop in a unilateral, sometimes dermatomal, distribution. The areas most often involved are the trigeminal and C3 and C4 or adjacent areas, with the right side involved slightly more often than the left. In some cases the condition is congenital, but more often it is acquired. Increased estrogen appears to play a role in the onset of acquired cases, e.g. pregnancy, puberty in women, adrenarche in men, and hepatitis/alcohol related cases have all been reported.

Sardana K, et al: Unilateral nevoid telangiectasia syndrome. J Dermatol 2001;28:453.
Hynes LR, et al: Unilateral nevoid telangiectasia. J Am Acad Dermatol 1997;36:819.

Angiokeratomas Angiokeratomas are essentially telangiectases that have an overlying hyperkeratotic surface (Fig. 28-6). These are dilations of preexisting papillary dermal vessels. Angiokeratoma circumscriptum is discussed in the malformations section above. Angiokeratoma corporis diffusum is discussed in Chapter 26.

Angiokeratoma of Mibelli The lesions of angiokeratoma of Mibelli consist of 1- to 5-mm red vascular papules, the surfaces of which become hyperkeratotic in the course of time. The papules are dull red or purplish-black, verrucous, and rounded, and are usually situated on the dorsum of the fingers and toes, the elbows, and knees. Frequently, these are called *telangiectatic warts*. The patient often has cold, cyanotic hands and feet.

This is a rare genodermatosis with an autosomal-dominant trait for vascular lesions located over bony prominences

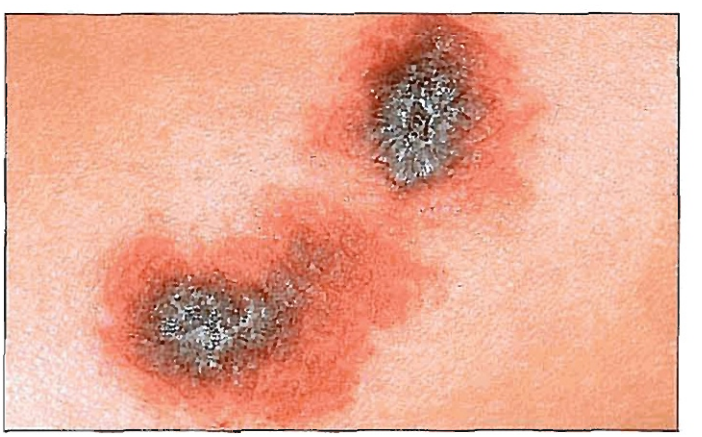

Fig. 28-6 Angiokeratoma.

and a family history of chilblains. The condition is most frequently discovered in prepubertal children.

Histologically, hyperkeratosis, increased thickness of the granular layer, and dilation of the subpapillary vessels to form lacunae are the chief features.

In the differential diagnosis of angiokeratomas of the dorsal hands in children is acral pseudolymphomatous angiokeratoma in children (APACHE). However, APACHE is unilateral, sporadic in nature, has no associated cold sensitivity, and on histologic examination there is a dense, nodular, lymphohistiocytic infiltrate with occasional plasma cells, eosinophils, and multinucleated giant cells. It is a variant of pseudolymphoma and not primarily a vascular lesion. Similar lesions may occur in adolescents and adults, and the term acral angiokeratoma-like pseudolymphoma has been proposed for these lesions in all age groups.

Angiokeratoma may be treated with electrocautery, fulguration, CO_2 laser ablation, long-pulse vascular laser therapy, or cryotherapy with fairly good results.

Angiokeratoma of the Scrotum (Fordyce) The angiomas are multiple small vascular papules that stud the scrotum (Fig. 28-7) and sometimes the vulva in middle-aged and elderly individuals. There is often a diffuse redness of the involved area that may be a source of concern to the patient. Urethral or clitoral lesions may be seen also. Infrequently, the keratotic part may be involuntarily scratched off to produce considerable bleeding. Rarely, they may bleed spontaneously.

Histologically, the many communicating lacunae in the subpapillary layer are lined with endothelium and connected underneath by dilated veins.

Treatment is best accomplished by shave excision, cautery, laser ablation, or fulguration of troublesome lesions. The primary therapy is reassurance.

Solitary Angiokeratoma Described by Imperial and Helwig in 1967, solitary angiokeratoma is a single small, bluish-black, warty papule that occurs predominantly on the lower extremities. It is not a hereditary lesion and probably follows trauma, with subsequent telangiectasia before the formation of the angiokeratoma. The mode of acquiring this lesion, and its small size, solitary nature, and location distinguish it from other forms of angiokeratoma.

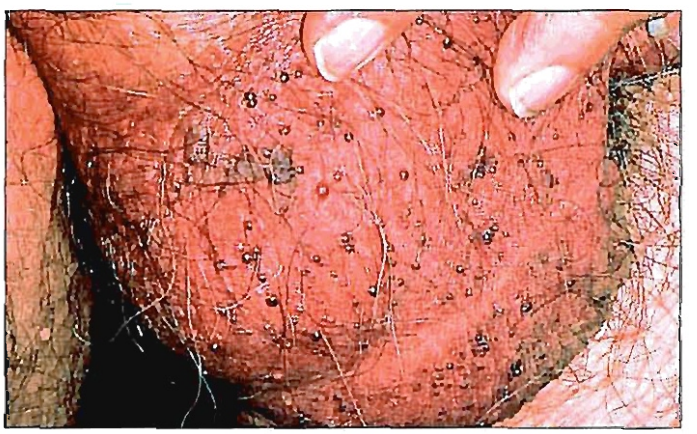

Fig. 28-7 Fordyce angiokeratomas.

Solitary angiokeratoma is to be considered in the differential diagnosis of seborrheic keratosis, melanoma, pigmented basal cell carcinoma, and ordinary hemangioma. Treatment is by electrosurgery, laser ablation, or excision.

Bechara FG, et al: Unilateral angiokeratoma scroti: a rare manifestation of a vascular tumor. J Dermatol 2004;31:39.

Gorse SJ, et al: Successful treatment of angiokeratoma with potassium tritanyl phosphate laser. Br J Dermatol 2004; 150:620.

Karthikeyan K, et al: Angiokeratoma of the oral cavity and scrotum. J Dermatol 2000;27:131.

Okada M, et al: Acral angiokeratoma-like pseudolymphoma: one adolescent and two adults. J Am Acad Dermatol 2001;45(6 Suppl):S209.

Schiller PI, et al: Angiokeratomas: an update. Dermatology 1996;193:275.

Sommer S, et al: Severe predominantly acral variant of angiokeratoma of Mibelli: response to long-pulse Nd:YAG (1064 nm) laser treatment. J Am Acad Dermatol 2001;45:764.

Lymphangiectasis (Lymphangioma) Lymphangiectases are acquired dilations of lymph vessels. Some forms are discussed under malformations (above). Solitary lymphangiomas have an appearance resembling frog's eggs. Like angiokeratomas, they may be seen adjacent to café-au-lait macules (Fig. 28-8). This may represent a twin spotting phenomenon. Acquired lesions occur on the arms, axillae, chest, and back of women after lymph node dissection and irradiation for breast cancer, and on the scrotum, penis, thighs, and pubic region of men treated aggressively for prostate cancer. Other cancers treated similarly, such as cervical carcinoma, may result in similar lesions. If cancers obstruct outflow from an extremity, lymphangiectases may occur and may be the presenting sign of disease. At times, benign disease, such as scrofuloderma or recurrent erysipelas, which leads to progressive scarring of the lymphatic

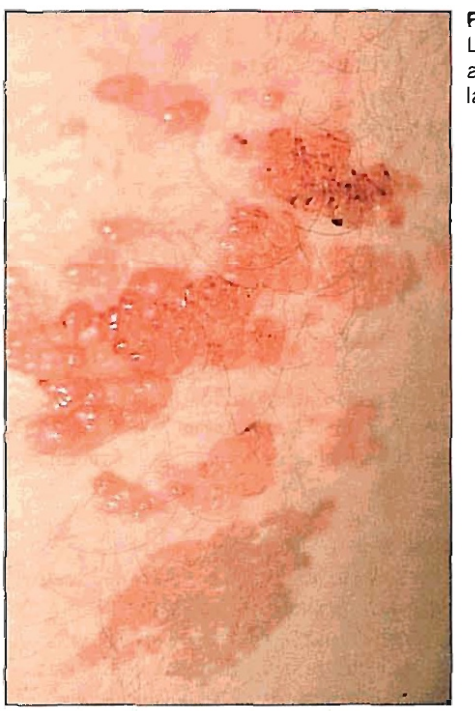

Fig. 28-8 Lymphangioma adjacent to café-au-lait macule.

vessels, may induce lymphangiectasia. Rarely, degenerative changes to the supporting connective tissue may allow lymphangiectasia to develop. A peculiar penicillamine-induced dermopathy may result from damage to the underlying supporting structures of the dermis and allow dilation of lymph vessels within areas of trauma, such as the dorsal hands and knees. Central facial involvement may be seen in variegate porphyria, and sites of chronic high potency steroid application may develop lymphangiectasia.

The lesions are thick-walled, translucent, 2- to 5-mm white vesicles. They are multiple and when present on the penis may mimic condylomata. Spontaneous drainage of a straw-colored to milky white fluid may occur. Such chylous discharge may induce surface irritation and erythema of the site. At times, recurrent erysipelas may complicate the moist, superficially eroded flexural skin. In penicillamine-induced dermopathy there is a hemorrhagic macular stain that is often surmounted by milia.

The method of treatment depends on the cause. If lymphangiectasis results from cancer infiltration and pressure, treatment of the primary process may reopen the lymphatic drainage and lead to resolution. If the condition results from penicillamine or topical steroid application, decreasing the dose or discontinuance may result in improvement. If the underlying process is fibrosis and scarring, and the involved part is amenable to pressure dressings or a pump, the chylous discharge may be improved. If recurrent erysipelas is a recurrent complication, long-term oral antibiotic prophylaxis may prevent this.

Pena JM, et al: Cutaneous lymphangiectases associated with severe photoaging and topical corticosteroid application. J Cutan Pathol 1996;23:175.

Stone MS: Central-facial papular lymphangiectases. J Am Acad Dermatol 1997;36:493.

Hyperplasias

Angiolymphoid Hyperplasia with Eosinophilia

Patients with angiolymphoid hyperplasia with eosinophilia (AHLE) usually present with pink to red–brown, dome-shaped, dermal papules or nodules of the head or neck, especially about the ears and on the scalp (Fig. 28-9). AHLE may also occur in the mouth, trunk and extremities, penis, and vulva. Grouped lesions merge to form plaques or grapelike clusters. There is a female preponderance, and the average age of onset is 32 years. Symptoms can be pain or pruritus; these may occur after trauma. An underlying arteriovenous shunt is present as a result of damage to and repair of an artery or vein.

Histologically, central thick-walled vessels with hobnail endothelium are noted. Surrounding hyperplasia of smaller vessels and nodular lymphoid aggregates with eosinophils are present.

Lesions do not spontaneously regress. Treatment with surgical excision is successful in 65% of cases. The lesions may recur if the underlying arteriovenous shunt is not excised. Intralesional corticosteroids, pulsed dye laser therapy, cryotherapy, pentoxifylline, indomethacin, and electrodesiccation have been successful in some cases. Difficult cases have been controlled with interferon (IFN)-α 2b or vinblastine, and partial responses to intralesional cytotoxic agents have been reported.

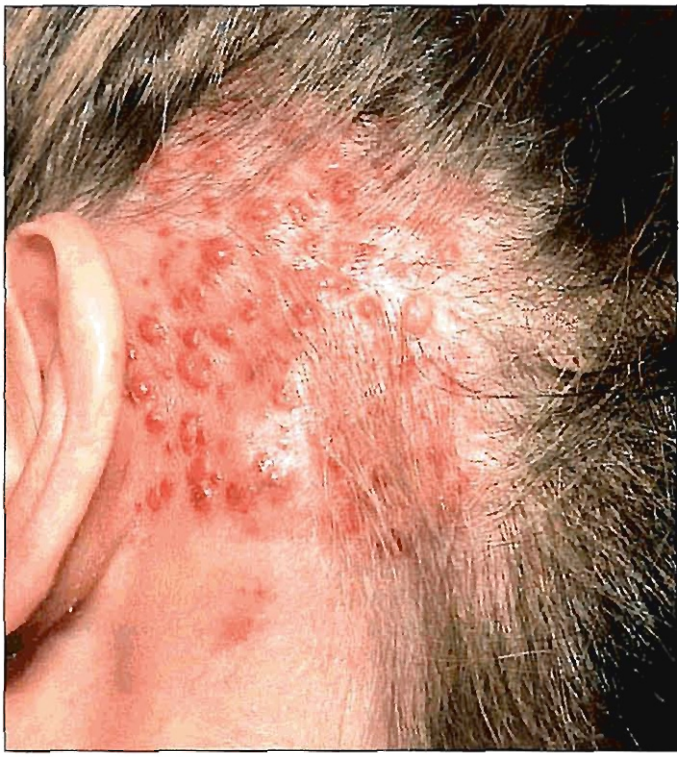

Fig. 28-9 Angiolymphoid hyperplasia with eosinophilia. (Courtesy of Brooke Army Medical Center Teaching File)

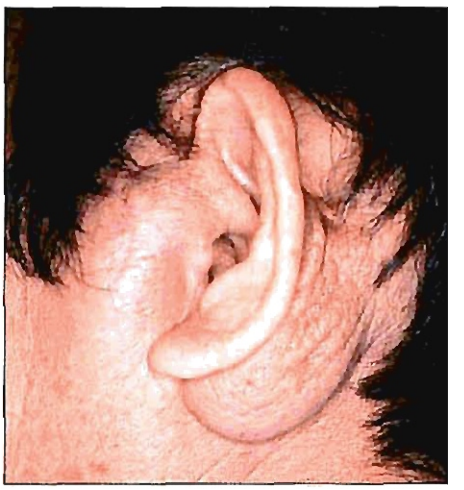

Fig. 28-10 Kimura's disease. (Courtesy of Department of Dermatology, Keio University School of Medicine)

Much confusion in the literature has centered on distinguishing AHLE from Kimura's disease (Fig. 28-10). The latter is an inflammatory disorder that presents as massive subcutaneous swelling in the periauricular and submandibular region in young Asian men. Histologically, prominent germinal centers with eosinophils are present in the subcutaneous tissue. Although blood vessels are abundant, changes are less prominent than in AHLE. Additionally, Kimura's disease is associated with allergic conditions such as asthma, rhinitis, and eczema, and is frequently accompanied by lymphadenopathy, peripheral blood eosinophilia, and an elevated IgE level. Although clonal T-cell gene rearrangement has been reported in both ALHE and Kimura's disease, heteroduplex-PCR has disproved clonality in some cases positive by conventional polymerase chain reaction (PCR).

Abrahamson TG, et al: Angiolymphoid hyperplasia with eosinophilia responsive to pulsed dye laser. J Am Acad Dermatol 2003;49(2 Suppl Case Reports):S195.
Chim CS, et al. Analysis of clonality in Kimura's disease. Am J Surg Pathol 2002;26:1083.
Fosko SW, et al. Eradication of angiolymphoid hyperplasia with eosinophilia by copper vapor laser. Arch Dermatol 2001; 137:863.
Jang KA, et al: Polymerase chain reaction (PCR) for human herpesvirus 8 and heteroduplex PCR for clonality assessment in angiolymphoid hyperplasia with eosinophilia and Kimura's disease. J Cutan Pathol 2001;28:363.
Kempf W, et al: Angiolymphoid hyperplasia with eosinophilia: evidence for a T-cell lymphoproliferative origin. Hum Pathol 2002;33:1023.
Khoo BP, et al: Kimura disease: 2 case reports and a literature review. Cutis 2002;70:57.
Kimura Y, et al: Angiolymphoid hyperplasia with eosinophilia arising from the facial artery. J Laryngol Otol 2003;117:570.
Nomura T, et al: Rapid remission of severe pruritus from angiolymphoid hyperplasia with eosinophilia by pulsed dye laser therapy. Clin Exp Dermatol 2003;28:595.
Zhang GY, et al: Disseminated angiolymphoid hyperplasia with eosinophilia: a case report. Cutis 2003;72:323.

Pyogenic Granuloma A pyogenic granuloma is a small, eruptive, usually solitary, sessile or pedunculated, friable papule (Fig. 28-11). The lesion is common in children, but may occur at any age. It occurs most often on an exposed surface: on the hands, forearms, or face, or at sites of trauma. The lesion also occurs in the mouth, especially on the gingiva, most often in pregnant women (granuloma gravidarum). On the sole of the foot or nailbed, it may be mistaken for a melanoma. Pyogenic granulomas bleed easily on the slightest trauma and, if cut off superficially, promptly recur. Recurring lesions may have one or many satellite lesions.

Pyogenic granulomas may be seen in patients treated with isotretinoin, capecitabine, or indinavir. Isotretinoin treatment of acne vulgaris can be complicated by numerous exuberant pyogenic granuloma-like lesions of the trunk, or periungual lesions. Some data suggest that patients with pyogenic granuloma have a statistically higher prevalence of Bartonella seropositivity compared with controls, but a definite etiologic role has not been established.

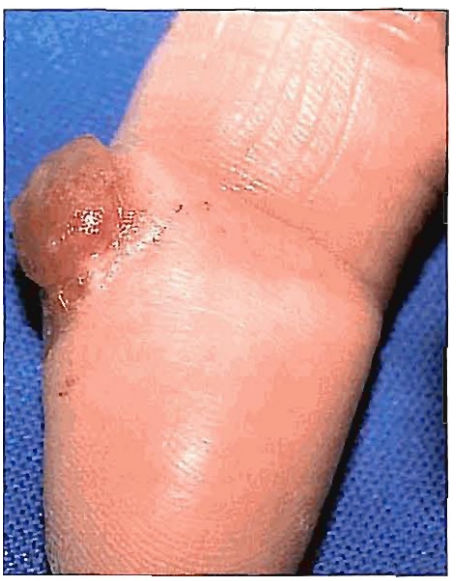

Fig. 28-11 Pyogenic granuloma.

Histologically, pyogenic granuloma is a lobular capillary hemangioma, with lobules separated by connective tissue septae. With time, the epidermis becomes thinned, then eroded. Heavy secondary staphylococcal colonization is common. Intravascular pyogenic granuloma appears as a lobular capillary proliferation within a vein.

Treatment is by curettage or shave excision, followed by destruction of the base by fulguration or silver nitrate. Silver nitrate alone may be sufficient to treat smaller lesions. Sclerotherapy with monoethanolamine oleate has also been used successfully. At times, a recalcitrant lesion may require excision or laser ablation. The drug-induced variety will regress after lowering of the dose or discontinuation of the medication. Systemic steroids have been used to treat recurrent giant pyogenic granulomas.

Demir Y, et al. Cutaneous lobular capillary hemangioma induced by pregnancy. J Cutan Pathol 2004;31:77.
Kocer U, et al: Intravenous pyogenic granuloma of the hand. Dermatol Surg 2003;29:974.
Lee J, et al: Pyogenic granuloma: pyogenic again? Association between pyogenic granuloma and Bartonella. J Cutan Med Surg 2001;5:467.
Matsumoto K, et al: Treatment of pyogenic granuloma with a sclerosing agent. Dermatol Surg 2001;27:521.
Pagliai KA, et al: Pyogenic granuloma in children. Pediatr Dermatol 2004;21:10.
Piguet V, et al: Pyogenic granuloma-like lesions during capecitabine therapy. Br J Dermatol 2002;147:1270.
Quitkin HM, et al: The efficacy of silver nitrate cauterization for pyogenic granuloma of the hand. J Hand Surg [Am] 2003; 28:435.
Tursen U, et al: Giant recurrent pyogenic granuloma on the face with satellitosis responsive to systemic steroids. Clin Exp Dermatol 2004;29:40.

Intravascular Papillary Endothelial Hyperplasia Masson described this intravascular papillary proliferation that may mimic angiosarcoma. The lesions appear as red or purplish 5-mm to 5-cm papules or deep nodules on the head, neck, or upper extremities. The condition represents recanalization of a thrombosed vessel. Histologic examination reveals intravascular papillary projections lined by endothelial cells. Thrombi may still be present, and the papillary projections may have a fibrinous or hyaline core. Excision is curative.

Stewart M, et al: Multiple lesions of intravascular papillary endothelial hyperplasia (Masson's lesions). Arch Pathol Lab Med 1994;118:315.
Yamamoto T, et al: Recurrent intravascular papillary endothelial hyperplasia of the toes. Dermatology 2000;200:72.

Angioma Serpiginosum Angioma serpiginosum, first described by Hutchinson in 1889, is characterized by minute, copper-colored to bright red angiomatous puncta that have a tendency to become papular. These puncta occur in groups, which enlarge through the constant formulation of new points at the periphery, whereas those at the center fade. In this manner small rings or serpiginous patterns

are formed. No purpura is present, but a netlike or diffuse erythema forms the background. In the areas undergoing involution, a delicate tracery of rings and lines, a fine desquamation, and, at times, a semblance of atrophy are seen. Slight lichenification and scaling may be evident in the papular lesions. The eruption predominates on the lower extremities. Although it affects both sexes at all ages, 90% of cases occur in girls under 16. It is usually slowly progressive and chronic, and although involution may occur it is probably never complete. Treatment with a pulsed dye laser will improve or eliminate such lesions.

Angioma serpiginosum must be differentiated from the progressive pigmentary disease of Schamberg. In the latter, pinpoint areas of purpura, the so-called cayenne pepper spots, form macules that tend to coalesce and form diffusely pigmented patches. The pigment is hemosiderin. Purpura annularis telangiectodes (Majocchi) is often bilateral and is characterized by acute outbreaks of telangiectatic points that spread peripherally and form small rings. In lichenoid purpuric and pigmentary dermatosis of Gougerot and Blum, the primary lesion is a minute, lichenoid, reddish-brown papule that is sometimes hemorrhagic. It has a tendency toward central involution and residual pigmentation.

In angioma serpiginosum, the most important histologic finding is dilated and tortuous capillaries in the dermal papillae and the upper dermis. No inflammatory infiltrate or extravasation of red cells is observed. The dilated capillaries show no alkaline phosphatase activity, in contrast to normal capillaries.

Katta R, et al: Angioma serpiginosum with extensive cutaneous involvement. J Am Acad Dermatol 2000;42(2 Pt 2):384.

Long CC, et al: Treatment of angioma serpiginosum using a pulsed tunable dye laser. Br J Dermatol 1997;136:631.

Namazi MR, et al: Angioma serpiginosum. Dermatol Online J 2003;9:19.

Benign Neoplasms

Infantile Hemangioma (Strawberry Hemangioma)

Strawberry (capillary) hemangiomas, the most common benign tumor of childhood, is present at birth in one-third of cases. The remainder appear shortly thereafter. Sixty percent are on the head and neck, but they may occur anywhere. The dome-shaped lesion is dull to bright red, and when involution begins, streaks or islands of white appear in the lesion as it flattens. The lesions have sharp borders; they are soft and easily compressed (Fig. 28-12).

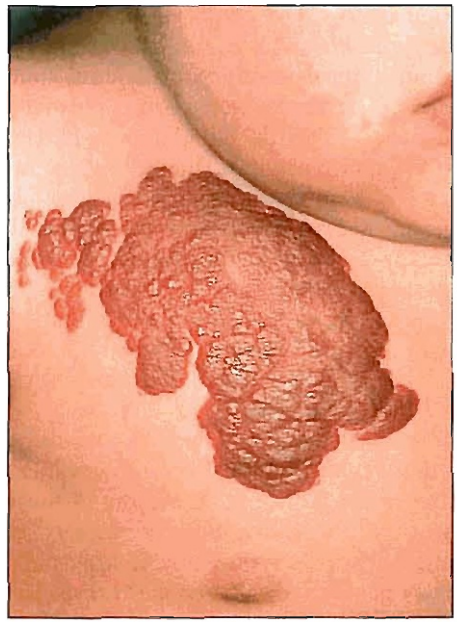

Fig. 28-12 Infantile hemangioma.

Generally, they tend to grow over the first year or so, remain stable for a period of months, and then slowly involute spontaneously. Approximately 30% resolve by the third year, 50% by age 5, and 70% by the time the patient is 7 years of age. The skin may appear normal after involution, but more commonly, atrophy, telangiectasia, or anetoderma-type redundancy is present.

The majority of these lesions occur sporadically, but kindreds with autosomal-dominant inheritance of infantile hemangiomas and/or vascular malformations have been described. Approximately 7% of hemangiomas may occur in association with structural malformations. One grouping of associated abnormalities is the PHACE syndrome. This acronym, proposed by Frieden et al in 1996, denotes the association of posterior fossa brain malformations (primarily the Dandy-Walker malformation), hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities. When sternal clefting and abdominal raphae are present, the designation PHACES is used. The hemangiomas tend to be large, plaquelike, and facial in location, frequently involving more than one dermatome. They recommended that brain imaging studies be performed in all infants with such hemangiomas. Solitary segmental hemangiomas of the skin are also associated with visceral hemangiomatosis involving the liver, gastrointestinal tract, lung, brain, and mediastinum: 40% have PHACE(S) syndrome.

Multiple hemangiomas, usually 1 to 10 mm in size, may appear in the first few weeks to months of life and can be large in number. If they are purely cutaneous, generally they involute without sequelae, and the term *benign neonatal hemangiomatosis* is applied. However, visceral lesions may be present in the CNS, lungs, liver, or other organs. When internal lesions are present, complications may occur, such as gastrointestinal or CNS bleeding, high-output cardiac failure, obstructive jaundice, or respiratory failure; this results in a high mortality rate among untreated patients. This more ominous variant is called *diffuse neonatal hemangiomatosis.* Flat lumbar hemangiomas are often associated with occult spinal dysraphism.

Rapidly involuting congenital hemangioma (RICH) and non-involuting congenital hemangioma (NICH) are rare vascular tumors that present fully grown at birth and either involute rapidly or fail to involute. Whereas smooth muscle actin (αSMA)-positive cells are common in the walls of infantile hemangiomas, they are rare in RICH. Children with RICH or NICH coexisting with infantile hemangioma have been described, as have children with RICH showing rapid but incomplete regression. In these cases, the residuum was NICH. Gorham's Sign (Gorham Stout Syndrome) is massive osteolysis (disappearing bone) associated with a proliferation of hemangioma-like tissue. Response to bishopsphonates has been noted.

Histologically, strawberry marks are composed of primitive endothelial cells similar to those found before

the embryonic development of true venous channels. Ultrastructurally, they lack typical Weibel-Palade bodies but do have crystalloid inclusions typical of embryonic endothelium and stain for GLUT-1 (a glucose transporter normally restricted to endothelial cells with blood–tissue barrier function, such as in brain and placenta). They also stain for FcγRII, Lewis Y antigen (LeY), and merosin. Some subgroups, such as rapidly involuting hemangiomas and noninvoluting hemangiomas lack GLUT-1 staining. Young hemangiomas show evidence of endothelial progenitor cells that stain with CD133 and CD34. In late stages the endothelium flattens and the lumina are more apparent because of increased blood flow. In time, fibrosis becomes pronounced as involution progresses.

In most cases, intervention produces a cosmetic result no better or worse than that achieved with simple observation. Proponents of early treatment point out that many of these hemangiomas remain significant body image factors to children when they enter school. Cryotherapy or laser ablation of early lesions has generally not been successful. The pulsed dye laser can improve the appearance of residual involuted lesions with prominent telangiectasia; however, the depth of the hemangiomas does not allow the lasers to be effective in growing or stable childhood hemangiomas. Vascular lasers have been used to treat ulcerated hemangiomas, but have also caused ulceration.

The so-called Cyrano defect, a hemangioma that causes the end of the nose to become bulbous, may be successfully approached surgically in many cases before beginning school. Additionally, surgical intervention in small pedunculated hemangiomas and eyelid tumors may also be excellent options. Finally, compressive wraps may improve extremity hemangiomas.

Specific circumstances necessitate treatment. Indications for intervention include severe hemorrhage, thrombocytopenia, threatened cardiovascular compromise from high-output cardiac failure, nasal or auditory canal obstruction, hepatic hemangiomatosis, skin ulceration, or threatened interference with vital functions, such as feeding, respiration, passage of urine or stool, limb function, tissue destruction, or vision. There is a risk of occlusion amblyopia, astigmatism, and myopia from periorbital hemangiomas. Additionally, strong consideration should be given to treatment of those hemangiomas that may lead to permanent disfigurement or long-term psychological consequences, such as large hemangiomas of the ear, nose, glabellar area, or lips.

Oral prednisone or intralesional steroids have been employed, but intralesional treatment carries some risk of embolization and occlusion of ocular vessels. Injection regularly produces pressures exceeding the systemic arterial pressure, leading to the possibility of embolization. SubTenon steroid infusion with a blunt cannula may be useful for the treatment of orbital hemangiomas in children and may be safer than direct intralesional injection.

Oral treatment with prednisone requires a dose of 2 to 4 mg/kg/day. In the 30% of patients who respond well to treatment, the enlarging hemangioma stops growing in 3 to 21 days. Ulcerations will heal within 2 weeks. The lesion will usually shrink if treatment is continued for 30 to 90 days. Laryngeal involvement and stridor, if present, are usually dramatically relieved by treatment. Repeated courses of treatment may be undertaken if rebound of growth occurs on discontinuation of the steroidal agent. Some experts recommend prolonged low-dose oral steroids over a 12-month period to prevent this rebound phenomenon. In another 40%, the clinical situation will stabilize with this treatment; however, the remaining 30% do not respond to treatment with prednisone. Treatment with recombinant IFN-α 2a or 2b may result in a good response in 80% of patients. The dose is usually 1 to 3 MU/m^2/day. Many patients require prolonged therapy for 6 to 10 months or more. Thyroid dysfunction and neurotoxicity in the form of spastic diplegia may occur. In a meta-analysis, 11 of 441 children treated for vascular lesions developed spastic diplegia and 16 developed a motor developmental disturbance. Of interest, all of these children were under 1 year of age when the therapy was started. Topical imiquimod and selective arterial embolization have also been used. Both Nd:YAG and KTP lasers have been used to deliver intralesional laser therapy.

Berenguer B, et al: Rapidly involuting congenital hemangioma: clinical and histopathologic features. Pediatr Dev Pathol 2003; 6:495.

Bava GL, et al: Life-threatening hemorrhage from a vulvar hemangioma. J Pediatr Surg 2002;37:E6.

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Bischoff J: Monoclonal expansion of endothelial cells in hemangioma: an intrinsic defect with extrinsic consequences? Trends Cardiovasc Med 2002;12:220.

Burstein FD, et al: Intralesional laser therapy of extensive hemangiomas in 100 consecutive pediatric patients. Ann Plast Surg 2000;44:188.

Egbert JE, et al: High injection pressure during intralesional injection of corticosteroids into capillary hemangiomas. Arch Ophthalmol 2001;119:677.

Frischer JS, et al: Biomolecular markers and involution of hemangiomas. J Pediatr Surg 2004;39:400.

Hammer F, et al: Gorham-Stout disease-stabilization during bisphosphonate treatment. J Bone Miner Res 2005;20:350.

Leon-Villapalos J, et al: GLUT-1: an extra diagnostic tool to differentiate between haemangiomas and vascular malformations. Br J Plast Surg 2005;58:348.

Li Q, et al: Differential expression of CD146 in tissues and endothelial cells derived from infantile haemangioma and normal human skin. J Pathol 2003;201:296.

Loo WJ, et al: Recent advances in laser therapy for the treatment of cutaneous vascular disorders. Lasers Med Sci 2002;17:9.

Marler JJ, et al: Successful antiangiogenic therapy of giant cell angioblastoma with interferon alfa 2b: report of 2 cases. Pediatrics 2002;109:E37.

Martinez MI, et al: Infantile hemangioma: clinical resolution with 5% imiquimod cream. Arch Dermatol 2002;138:881.

Metry DW, et al: Association of solitary segmental hemangiomas of the skin with visceral hemangiomatosis. Arch Dermatol 2004;140:591.

Michaud AP, et al: Spastic diplegia and other motor disturbances in infants receiving interferon-alpha. Laryngoscope 2004; 114:1231.

Miller T, et al: Hemanglomas: new insights and classification. Pediatr Ann 2005;34:179.

Mulliken JB, et al: Congenital hemangiomas and infantile hemangioma: missing links. J Am Acad Dermatol 2004; 50:875.

North PE, et al: A unique microvascular phenotype shared by juvenile hemangiomas and human placenta. Arch Dermatol 2001;137:559.
North PE, et al: Congenital nonprogressive hemangioma: a distinct clinicopathologic entity unlike infantile hemangioma. Arch Dermatol 2001;137:1607.
North PE, et al: GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. Hum Pathol 2000; 31:11.
Patel DV: Gorham's Disease or massive osteolysis. Clin Med Res 2005;3:65.
Ranchod TM, et al: Corticosteroid treatment of periorbital haemangioma of infancy: a review of the evidence. Br J Ophthalmol 2005;89:1134.
Reischle S, et al: Treatment of capillary hemangiomas of early childhood with a new method of cryosurgery. J Am Acad Dermatol 2000;42(5 Pt 1):809.
Spring MA, et al: Cutaneous vascular lesions. Clin Plast Surg 2005;32:171.
Tubbs RS, et al: Isolated flat capillary midline lumbosacral hemangiomas as indicators of occult spinal dysraphism. J Neurosurg 2004;100(2 Suppl):86.
Welsh O, et al: Treatment of infantile hemangiomas with short-term application of imiquimod 5% cream. J Am Acad Dermatol 2004;51:639.
Yu Y, et al: Endothelial progenitor cells in infantile hemangioma. Blood 2004;103:1373.

Cherry Angiomas (Senile Angiomas, De Morgan Spots) These round, slightly elevated, 0.5 to 6 mm in diameter, ruby-red papules are the most common vascular anomalies. It is a rare 30-year-old person who does not have a few, and the number increases with age. Probably every 70-year-old person has some. Most are on the trunk; they are rarely seen on the hands, feet, or face. Early lesions may mimic petechiae. When lesions are surrounded by a purpuric halo, amyloidosis should be suspected.

They are easily obliterated without scarring by light electrodesiccation or laser ablation. Shave excision can also be performed, but most patients accept reassurance and do not request their removal.

Aghassi D, et al: Time-sequence histologic imaging of laser-treated cherry angiomas with in vivo confocal microscopy. J Am Acad Dermatol 2000;43(1 Pt 1):37.
Dawn G, et al: Comparison of potassium titanyl phosphate vascular laser and hyfrecator in the treatment of vascular spiders and cherry angiomas. Clin Exp Dermatol 2003; 28:581.

Targetoid Hemosiderotic Hemangioma In 1988, Santa Cruz and Aronberg described a lesion characterized by a central brown or violaceous papule that is surrounded by an ecchymotic halo (Fig. 28-13). The term hobnail hemangioma has been proposed, as many lesions are not targetoid. These acquired hemangiomas occur in the young to middle aged and are present on the trunk or extremities. They likely represent trauma to a preexisting hemangioma with thrombosis and subsequent recanalization. Histologically, a biphasic growth pattern is seen, with central superficial dilated vascular structures lined by prominent hobnail endothelial cells, and collagen-dissecting, narrow vessels in deeper parts of the lesion. The endothelial cells commonly stain for CD31, but not CD34. Carlson et al studied 33 cases and concluded that targetoid hemosiderotic hamangiomas are variants of solitary angiokeratomas. They found episodic changes of swelling, darkening, and/or involution in three patients.

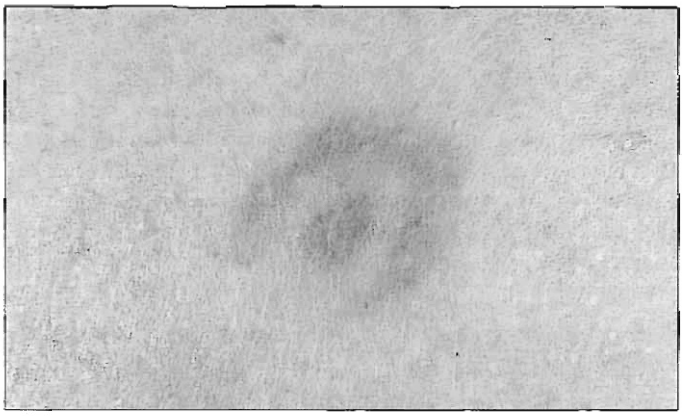

Fig. 28-13 Targetoid hemosiderotic hemangioma.

Christenson LJ, et al: Trauma-induced simulator of targetoid hemosiderotic hemangioma. Am J Dermatopathol 2001; 23:221.
Mentzel T, et al: Hobnail hemangioma ("targetoid hemosiderotic hemangioma"): clinicopathologic and immunohistochemical analysis of 62 cases. J Cutan Pathol 1999;26:279.

Glomeruloid Hemangioma This distinctive benign vascular neoplasm was described in 1990 and has been reported in patients with POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome (Crow-Fukase syndrome) and Castleman's disease.

POEMS syndrome consists of polyneuropathy (severe sensorimotor), organomegaly (heart, spleen, kidneys), endocrinopathy, M protein, and skin changes (hyperpigmentation, hypertrichosis, thickening, sweating, clubbed nails, leukonychia, and angiomas). Small, firm, red to violaceous papules appear on the trunk and proximal extremities in approximately one-third of patients. Histologically, they may be microvenular hemangiomas, cherry angiomas, multinucleated cell angiohistiocytomas or glomeruloid hemangiomas. The latter consist of ectatic vascular structures containing aggregates of capillary loops within a dilated lumin, simulating the appearance of a renal glomerulus. Sequestered degenerating red blood cells are a characteristic finding. Two types of endothelial cells have been noted within the lesions, a capillary-type endothelium with large vesicular nuclei, open chromatin pattern, and large amount of cytoplasm, and sinusoidal endothelium with small basal nuclei with dense chromatin and scant cytoplasm.

Kishimoto S, et al: Glomeruloid hemangioma in POEMS syndrome shows two different immunophenotypic endothelial cells. J Cutan Pathol 2000;27:87.
Yang SG, et al: A case of glomeruloid hemangioma associated with multicentric Castleman's disease. Am J Dermatopathol 1998;20:266.

Microvenular Hemangioma This recently described acquired benign vascular neoplasm presents as an asymptomatic, slowly growing, 0.5- to 2.0-cm reddish lesion on the forearms or other sites of young to middle-aged adults. Monomorphous, elongated blood vessels with small lumina involve the entire reticular dermis. In many areas, the endothelial cells are surrounded by pericytes. The main differential diagnosis is that of Kaposi sarcoma. Along with glomeruloid hemangioma, they may sometimes be present in POEMS syndrome.

Hudnall SD, et al: Human herpesvirus-8-positive microvenular hemangioma in POEMS syndrome. Arch Pathol Lab Med 2003;127:1034.

Stefanaki C, et al: Microvenular hemangioma: a rare vascular lesions. J Dermatol 2005;32:402.

Tufted Angioma (Angioblastoma) This lesion usually develops in infancy or early childhood on the neck and upper trunk. These angiomas are ill-defined, dull red macules with a mottled appearance; they vary from 2 to 5 cm in diameter. Some show clusters of smaller angiomatous papules superimposed on the main macular area, and associated hypertrichosis has been noted. The lesions are usually sporadic, although familial cases have been reported. Histologic examination reveals small, circumscribed angiomatous tufts and lobules scattered in the dermis in a so-called cannonball pattern. Tumors with features of both tufted angioma and kaposiform hemangioendothelioma (KHE) have been described, and transformation between the tumors has also been noted. Immunostaining can be helpful in distinguishing these tumors. Tufted angioma is characterized by a proliferation CD34+ endothelial cells with few actin-positive cells. KHE shows CD34 staining only in the luminal endothelial cells. In infantile hemangiomas, actin-positive cells outnumber CD34+ cells.

Most lesions slowly extend with time, being progressive but benign in nature. Occasional spontaneous regression is documented; however, treatment with pulsed dye laser, excision, high-dose steroids, and IFN-α has been successful in individual cases.

The term angioblastoma has also been used for a rare pediatric tumor often associated with destruction of regional structures including bone. Basic fibroblast growth factor has been reported to be elevated, and some patients have responded to treatment with IFN-α 2b.

Chu CY, et al: Transformation between Kaposiform hemangioendothelioma and tufted angioma. Dermatology 2003;206:334.

Herron MD, et al: Tufted angiomas: variability of the clinical morphology. Pediatr Dermatol 2002;19:394.

Mahendran R, et al: Response of childhood tufted angioma to the pulsed-dye laser. J Am Acad Dermatol 2002;47:620.

Tille JC, et al: Familial predisposition to tufted angioma: identification of blood and lymphatic vascular components. Clin Genet 2003;63:393.

Kaposiform Hemangioendothelioma KHE is an uncommon vascular tumor that affects infants and young children. Rare cases have been reported in adults. It was first designated KHE in 1993. Although it frequently occurs in the retroperitoneum, they may present as multinodular soft-tissue masses, purpuric macules, plaques, and multiple telangiectatic papules. The lesions extend locally and usually involve the skin, soft tissues, and even bone. The cutaneous variant may be associated with lymphangiomatosis. KHE is locally aggressive and may be complicated by platelet trapping and consumptive coagulopathy (Kasabach-Merritt syndrome), but distant metastases have not yet been reported. It has also been reported in association with Milroy-Nonne disease (primary hereditary lymphedema).

Histologically, there are combined features of cellular infantile hemangioma and Kaposi sarcoma. Additionally, in some tumors, lymphangiomatosis is seen sharply separated from the vascular lesion. There is a multilobular appearance that closely resembles that of tufted angioma, but in KHE they are larger, less circumscribed, and involve the deep soft tissue and even bone. Transition between these tumors has been described.

The prognosis depends on the depth and location of the lesion. Significant morbidity and mortality may occur as a result of the compression and invasion of surrounding structures. If localized to the skin, they may be successfully excised. However, because of their tendency for deep and infiltrative growth this is usually not possible. Prednisone may shrink the tumor or limit tumor expansion. If Kasabach-Merritt phenomenon occurs, prognosis is linked to this complication.

Brasanac D, et al: Retroperitoneal kaposiform hemangioendothelioma with tufted angioma-like features in an infant with Kasabach-Merritt syndrome. Pathol Int 2003;53:627.

Cooper JG, et al: Kaposiform haemangioendothelioma: case report and review of the literature. Br J Plast Surg 2002; 55:163.

Enjolras O, et al: Residual lesions after Kasabach-Merritt phenomenon in 41 patients. J Am Acad Dermatol 2000;42(2 Pt 1): 225.

Hardisson D, et al: Kaposiform hemangioendothelioma of the external auditory canal in an adult. Head Neck 2002;24:614.

Mendez R, et al: Kaposiform hemangioendothelioma associated with Milroy's disease (primary hereditary lymphedema). J Pediatr Surg 2003;38:E9.

Metry DW, et al: Benign cutaneous vascular tumors of infancy: when to worry, what to do. Arch Dermatol 2000;136:905.

Multifocal Lymphangioendotheliomatosis Patients with multifocal lymphangioendotheliomatosis present at birth with hundreds of red–brown plaques as large as several centimeters. Similar lesions may occur in the gastrointestinal tract and are associated with severe bleeding. Severe thrombocytopenic coagulopathy (Kasabach-Merritt syndrome) occurs in affected children. Corticosteroids and/or IFN-α results in little to no improvement. The histology is distinctive with delicate thin-walled vessels lined by hobnailed endothelium with papillary tufting. The endothelial cells demonstrate a high proliferative fraction with Ki-67 staining, and are reactive with LYVE-1, suggesting lymphatic differentiation.

North PE, et al: Multifocal lymphangioendotheliomatosis with thrombocytopenia. Arch Dermatol 2004;140:599.

Kasabach-Merritt Syndrome (Hemangioma with Thrombocytopenia) This syndrome is seen in infants at an average age of 7 weeks. Before the onset of the acute event, the infant will often have a reddish or bluish plaque or tumor on the limb or trunk, or in rare instances no visible lesion at all. The lesions usually have an associated lymphatic component and most are KHEs. Kasabach-Merrit syndrome (KMS) also occurs in tufted angiomas and multifocal lymphangioendotheliomatosis, lesions that both demonstrate lymphatic differentiation. It is rarely reported in association with capillary hemangiomas. Some patients with venous malformations will have a chronic low-grade consumptive coagulopathy that occurs throughout life, and this is not to be confused with KMS.

Infants with KMS suddenly develop a painful violaceous mass in association with purpura and thrombocytopenia. The most striking sign is the bleeding tendency, especially in the hemangioma itself or into the chest or abdominal cavities. The spleen may be enlarged. Hemoglobin, platelets, fibrinogen, and factors II, V, and VIII are all reduced. Prothrombin time and partial thromboplastin time are prolonged, and fibrin split products may be elevated. Cases of microangiopathic hemolytic anemia have also been described. Repeated episodes of bleeding may occur, and although these may be spontaneous, it is not uncommon for bleeding to be precipitated by surgery, directed either at the hemangioma or elsewhere. The mortality may be as high as 30%, with most deaths being secondary to bleeding complications.

As KMS may be a self-limited disorder, expectant observation may be the best approach initially. Systemic steroids, IFN-α 2a, vincristine, vinblastine, cyclophosphamide, actinomycin D, embolization, ε-aminocaproic acid, antiplatelet agents, irradiation, excision, and compression therapy have been utilized alone or in combination, but treatment is often difficult and some patients responds poorly to all attempted treatment.

Blei F, et al: Successful multimodal therapy for kaposiform hemangioendothelioma complicated by Kasabach-Merritt phenomenon: case report and review of the literature. Pediatr Hematol Oncol 1998;15:295.

Haisley-Royster C, et al: Kasabach-Merritt phenomenon: a retrospective study of treatment with vincristine. J Pediatr Hematol Oncol 2002;24:459.

Hesselmann S, et al: Case report: Kasabach-Merritt syndrome: a review of the therapeutic options and a case report of successful treatment with radiotherapy and interferon alpha. Br J Radiol 2002;75:180.

Hu B, et al: Kasabach-Merritt syndrome-associated kaposiform hemangioendothelioma successfully treated with cyclophosphamide, vincristine, and actinomycin D. J Pediatr Hematol Oncol 1998;20:567.

Maguiness S, et al: Kasabach-Merritt syndrome. J Cutan Med Surg 2002;6:335.

Ozsoylu S: Megadose methylprednisolone for Kasabach-Merritt syndrome. Pediatr Hematol Oncol 1999;16:373.

Wananukul S, et al: Treatment of Kasabach-Merritt syndrome: a stepwise regimen of prednisolone, dipyridamole, and interferon. Int J Dermatol 2003;42:741.

Acquired Progressive Lymphangioma (Benign Lymphangioendothelioma) The term *acquired progressive lymphangioma* was introduced by Wilson-Jones in 1976 to designate a group of lymphangiomas that occur anywhere in young individuals, grow slowly, and present as bruise-like lesions or erythematous macules. Rarely, the lesion is yellow or alopecic. The histologic appearance is that of delicate endothelium-lined spaces dissecting between collagen bundles. A similarity to the plaque stage of Kaposi sarcoma may be striking. Simple excision is curative. Prednisolone has caused some extensive lesions to regress.

Guillou L, et al. Benign lymphangioendothelioma (acquired progressive lymphangioma): a lesion not to be confused with well-differentiated angiosarcoma and patch stage Kaposi's sarcoma: clinicopathologic analysis of a series. Am J Surg Pathol 2000;24:1047.

Hwang LY, et al: Acquired progressive lymphangioma. J Am Acad Dermatol 2003;49(5 Suppl):S250.

Glomus Tumor (Glomangioma) The solitary glomus or neuromyoarterial tumor is most frequently a skin-colored or slightly dusky blue firm nodule 1 to 20 mm in diameter. Subungual tumors show a bluish tinge through the translucent nail plate. The tumor is usually extremely tender and paroxysmal pain occurs frequently. Sensitivity is likely to be present constantly, and when touched the tumor responds with severe radiating pain. However, nontender glomus tumors are encountered. The characteristic location is subungual, but it may occur on the fingers and arms, or elsewhere. Digital lesions are more common in women, and there is a male predominance of nondigital lesions. High-resolution MRI, high-resolution ultrasonography (5–9 MHz) and color duplex sonography may be used to define the limits of the tumor before surgery is undertaken. Progressive growth may lead to ulceration.

Multiple glomangiomas are usually nontender and are generally widely distributed over the body. These may be inherited as an autosomal-dominant trait and can be congenital. Clinically, they may resemble lesions of blue rubber bleb nevus. When grouped in one area they may appear as a confluent mass. Hereditary multiple glomus tumors may represent an autosomal-dominant mosaic trait and may be congenital. The glomus coccygeum is a normal structure that may be seen in pilonidal sinus excision specimens.

Histologically, glomus tumors contain numerous vascular lumina lined by a single layer of flattened endothelial cells. Peripheral to the endothelial cells are layers of glomus cells. Generally these are round and arranged in distinct rows resembling strings of black pearls. Rarely, the cells have a somewhat spindled morphology. Multiple glomangiomas tend to have only one or two layers of glomus cells. Glomangiomyomas have a prominent muscularis media in addition to one or two layers of glomus cells. Both solitary and multiple glomus tumors are related to the arterial segment of the cutaneous glomus, the Sucquet-Hoyer canal. The glomus cells are modified vascular smooth muscle cells and stain with vimentin rather than desmin. Smooth muscle actin is often positive.

Treatment of solitary glomus tumors is best carried out by complete excision, which immediately produces relief from pain. The subungual tumors are most difficult to locate and eradicate since they are usually small, seldom more than a few millimeters in diameter.

Rare reports of glomangiosarcomas describe large, deeply located extremity lesions that consist of sarcomatous areas intermingled with areas of benign glomus tumor.

Allombert-Blaise CJ, et al: Type 2 segmental manifestation of congenital multiple glomangiomas. Dermatology 2003;206:321.
Antony FC, et al: Complete pain relief following treatment of a glomangiomyoma with the pulsed dye laser. Clin Exp Dermatol 2003;28:617.
Chen SH, et al: The use of ultrasonography in preoperative localization of digital glomus tumors. Plast Reconstr Surg 2003; 112:115.
Calduch L, et al: Familial generalized multiple glomangiomyoma: report of a new family, with immunohistochemical and ultrastructural studies and review of the literature. Pediatr Dermatol 2002;19:402.
Santos LD, et al: Glomus coccygeum may mimic glomus tumour. Pathology 2002;34:339.

Hemangiopericytoma A hemangiopericytoma is a nontender, bluish red tumor that occurs on the skin or in the subcutaneous tissues on any part of the body. The firm, usually solitary nodule may be up to 10 cm in diameter.

Histologically, the tumor is composed of endothelium-lined vessels that are filled with blood and surrounded by cells with oval or spindle-shaped nuclei (pericytes). The pericytes often form a concentric perivascular pattern. Staghorn-like ecstatic spaces are often encountered. Wide local excision is the treatment of choice, but radiation therapy may produce excellent palliation.

It is difficult to distinguish between benign and malignant forms of hemangiopericytoma, although large lesions and those with numerous mitoses are more likely to metastasize. Nearly half of the malignant hemangiopericytomas of deep soft tissues metastasize. The rate of metastases from lesions of the skin is closer to 20%. The most common cause of death is pulmonary metastasis. Infantile tumors are almost always cutaneous or subcutaneous, and do not metastasize.

Constantinides H, et al: Haemangiopericytoma of the submental region. J Laryngol Otol 2002;116:969.
Espat NJ, et al: Conventional hemangiopericytoma: modern analysis of outcome. Cancer 2002;95:1746.

Proliferating Angioendotheliomatosis Diseases designated *angioendotheliomatosis* have historically been divided into two groups: a reactive, involuting type and a malignant, rapidly fatal type. "Malignant angioendotheliomatosis" has been shown to be *intravascular (angiotropic) lymphoma*, rather than a true vascular lesion.

The reactive type of angioendotheliomatosis is uncommon. It occurs in patients who have subacute bacterial endocarditis, Chagas' disease, pulmonary tuberculosis, cryoproteinemia, severe atherosclerotic disease, and antiphospholipid antibodies, as well as in patients with no identifiable underlying process. They present with red-purple patches, plaques, nodules, petechiae, and ecchymoses, usually of the lower extremities. Some patients may present with a livedoid pattern or lesions resembling atrophie blanche. Diffuse dermal angiomatosis is a variant associated with atherosclerosis. The lesion occurs most often on the thigh in areas of vascular insufficiency and clears with revascularization. It has also been described in association with an arteriovenous fistula and with anticardiolipin antibodies.

Histologically, the vessels in benign reactive angioendotheliomatosis are dilated and are filled with proliferating endothelial cells, usually without atypia. Some cases demonstrate a proliferation of capillaries in the dermis, with diffuse, lobular, or mixed patterns. Fibrin microthrombi are common, and some cases show amyloid deposits or positive immunohistochemical staining for human herpesvirus (HHV)-8 in lesional endothelial cell nuclei. The course in this type is characterized by involution over 1 to 2 years. Therapy for the underlying condition has been considered to hasten involution.

The malignant type of "angioendotheliomatosis" is actually a large-cell intravascular lymphoma. It is a rapidly progressive disease: usually death ensues within 10 months of diagnosis. The mean age at onset is 55 years. Reddish-purple plaques, nodules, or patches develop in the skin. Multisystem involvement is characteristic, with the CNS often involved. There may be progressive dementia or focal signs that reflect ischemic infarcts. Kidney, heart, lung, and gastrointestinal lesions may occur. Biopsy will show a proliferation of atypical cells that fill the lumen of cutaneous vessels. Immunochemical stains for leukocyte/common antigen have confirmed the lymphomatous nature of these cells. Angioendotheliomatosis is usually B-cell in phenotype, but cases of T-cell lineage have been reported. Some organs may show diffuse large-cell lymphoma.

Doxorubicin alone, as well as in combination with *vincristine*, *prednisone*, and cyclophosphamide, has been effective in isolated cases. Rituximab has also been useful in CD20+ B-cell intravascular lymphoma.

Creamer D, et al: Reactive angioendotheliomatosis in association with the antiphospholipid syndrome. J Am Acad Dermatol 2000;42(5 Pt 2):903.
Eros N, et al: Intravascular B-cell lymphoma. J Am Acad Dermatol 2002;47(5 Suppl):S260.
Han K, et al: Regression of cutaneous intravascular lymphoma with rituximab. Cutis 2003;72:137.
Kim S, et al: Diffuse dermal angiomatosis: a variant of reactive angioendotheliomatosis associated with peripheral vascular atherosclerosis. Arch Dermatol 2002;138:456.
McMenamin ME, et al: Reactive angioendotheliomatosis: a study of 15 cases demonstrating a wide clinicopathologic spectrum. Am J Surg Pathol 2002;26:685.
Ortonne N, et al: Reactive angioendotheliomatosis secondary to dermal amyloid angiopathy. Am J Dermatopathol 2001; 23:315.
Pichardo RO, et al: What is your diagnosis? Diffuse dermal angiomatosis secondary to anitcardiolipin antibodies. Am J Dermatopathol 2002;24:502.
Requena L, et al: Intravascular and diffuse dermal reactive angioendotheliomatosis secondary to iatrogenic arteriovenous fistulas. J Cutan Pathol 1999;26:159.
Rongioletti F, et al: Cutaneous reactive angiomatoses: patterns and classification of reactive vascular proliferation. J Am Acad Dermatol 2003;49:887.
Sommer S, et al: Diffuse dermal angiomatosis due to an iatrogenic arteriovenous fistula. Acta Derm Venereol 2004;84:251.
Yegappan S, et al: Angiotropic lymphoma: an immunophenotypically and clinically heterogeneous lymphoma. Mod Pathol 2001;14:1147.

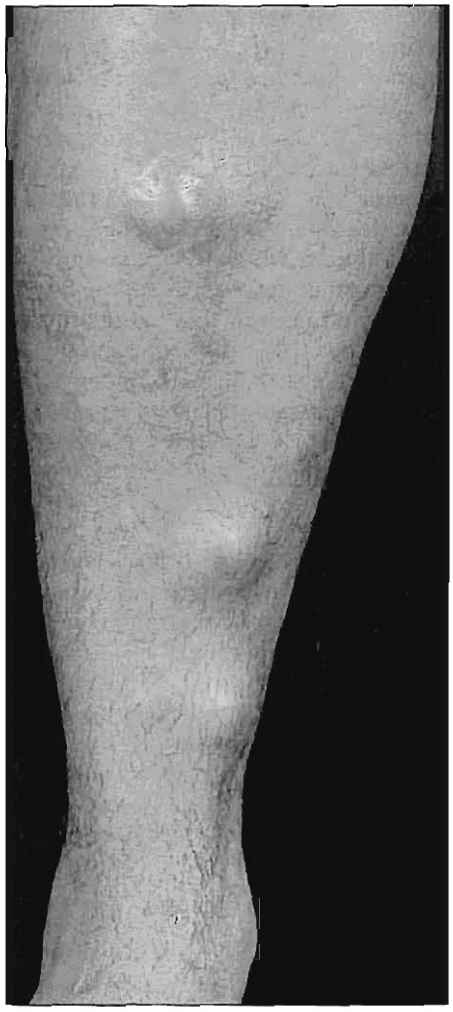

Fig. 28-14 Spindle cell hemangioendothelioma. (Courtesy of Timothy Gardner, MD)

Spindle-Cell Hemangioendothelioma Spindle-cell hemangioendothelioma is a vascular tumor that was first described in 1986. The condition commonly presents in a child or young adult who develops blue nodules of firm consistency on a distal extremity (Fig. 28-14). Usually, multifocal lesions occur within an anatomic region. Histologically, a well-circumscribed dermal nodule will contain dilated vascular spaces with fascicles of spindle cells between them. Areas of the tumor will have an open alveolar pattern resembling hemorrhagic lung tissue. Phleboliths are common. A thrombosed large adjacent vessel with recanalization may be identified. The lesions appear to represent benign vascular proliferations in response to trauma to a larger vessel. They may repeatedly recur focally after excision.

Garzon MC, et al: Vascular tumors and vascular malformations: evidence for an association. J Am Acad Dermatol 2000;42(2 Pt 1):275.

Harrison CA, et al: Spindle cell haemangioendothelioma in an arteriovenous fistula of the ring finger after blunt trauma. Br J Plast Surg 2003;56:822.

Pellegrini AE, et al: Spindle cell hemangioendothelioma. J Cutan Pathol 1995;22:173.

Tomasini C, et al: Spindle cell hemangioma. Dermatology 1999;199:274.

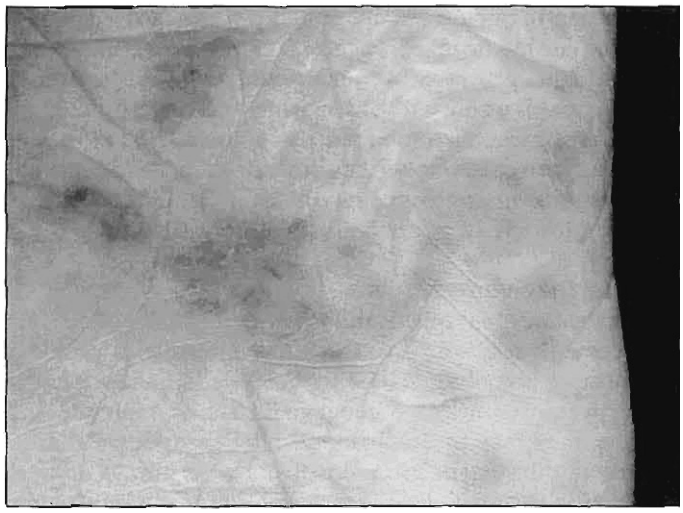

Fig. 28-15 Kaposi sarcoma.

Malignant Neoplasms

Kaposi Sarcoma Moritz Kaposi described this vascular neoplasm in 1872 and called it multiple benign pigmented idiopathic hemorrhagic sarcoma. Since his description, the disease has been reported in five separate clinical settings, with different presentations, epidemiology, and prognoses. The five subtypes are: 1) classic Karposi sarcoma (KS), an indolent disease seen chiefly in middle-aged men of Southern and Eastern European origin; 2) African cutaneous KS, a locally aggressive process affecting middle-aged Africans in tropical Africa; 3) African lymphadenopathic KS, an aggressive disease of young patients, chiefly children under age 10; 4) KS in patients immunosuppressed by AIDS; or by 5) lymphoma or immunosuppressive therapy.

Clinical Features

Classic Kaposi Sarcoma. The early lesions appear most commonly on the toes or soles as reddish, violaceous, or bluish-black macules and patches that spread and coalesce to form nodules or plaques (Fig. 28-15). These have a rubbery consistency. There may be brawny edema of the affected leg. Macules or nodules may appear, usually much later, on the arms and hands, and rarely may extend to the face, ears, trunk, genitalia, or buccal cavity, especially the soft palate. The course is slowly progressive and may lead to great enlargement of the lower extremities as a result of lymphedema.

However, there may be periods of remission, particularly in the early stages of the disease, when nodules may undergo spontaneous involution. After involution there may be an atrophic and hyperpigmented scar.

African Cutaneous Kaposi Sarcoma. Nodular, infiltrating, vascular masses occur on the extremities, mostly of men between the ages of 20 and 50. This form of KS is endemic in tropical Africa, and has a locally aggressive but systemically indolent course.

African Lymphadenopathic Kaposi Sarcoma. Lymph node involvement, with or without skin lesions, may occur in children under 10 years of age. The course is aggressive, often terminating fatally within 2 years of onset.

AIDS-Associated Kaposi Sarcoma. Cutaneous lesions begin as one or several red to purple-red macules, rapidly

progressing to papules, nodules, and plaques. There is a predilection for the head, neck, trunk, and mucous membranes. A fulminant, progressive course with nodal and systemic involvement is expected. This may be the presenting manifestation of human immunodeficiency virus (HIV) infection.

Immunosuppression-Associated Kaposi Sarcoma. The lesion's morphology resembles that of classic KS; however, the site of presentation is more variable.

Internal Involvement

The gastrointestinal tract is the most frequent site of internal involvement in classic KS. The small intestine is probably the most commonly involved viscus. In addition, the lungs, heart, liver, conjunctiva, adrenal glands, and lymph nodes of the abdomen may be involved. Skeletal changes are characteristic and diagnostic. Bone involvement is always an indication of widespread disease. Changes noted are rarefaction, cysts, and cortical erosion.

African cutaneous KS is frequently accompanied by massive edema of the legs and frequent bone involvement.

African lymphadenopathic KS has been reported among Bantu children, who develop massive involvement of the lymph nodes, especially the cervical nodes, preceding the appearance of skin lesions. The children also develop lesions on the eyelids and conjunctiva from which masses of hemorrhagic tissue hang down. Eye involvement is often associated with swelling of the lacrimal, parotid, and submandibular glands with a picture similar to Mikulicz syndrome.

In AIDS-associated KS, 25% of patients have cutaneous involvement alone, whereas 29% have visceral lesions only. The most frequent sites of visceral involvement are the lungs (37%), gastrointestinal tract (50%), and lymph nodes (50%). Visceral involvement ultimately occurs in more than 70% of patients with AIDS-associated KS.

Other immunosuppressed patients with KS may have visceral involvement in a variable percentage of cases.

Epidemiology

KS is worldwide in distribution. In Europe there are foci of classic KS in Galicia, near the Polish–Russian border, and extending southward to Austria and Italy. In New York City, KS has occurred mostly in elderly male Galician Jewish and southern Italian persons. In Africa, KS occurs largely south of the Sahara. Northeast Congo and Rwanda–Burundi areas have the highest prevalence, and to a lesser extent, West and South Africa.

The prevalence of AIDS-related KS has decreased since the 1980s. Most cases are in male homosexuals. Very few reports have documented the exceptional occurrence of KS in patients with AIDS who acquired their infection from intravenous drug use, or in Haitians, children, or people with hemophilia.

Patients at risk for developing KS associated with other causes of immunosuppression include those with iatrogenic suppression from oral prednisone or other chronic immunosuppressive therapies, as may be given to transplant patients.

KS is associated with an increased risk of developing second malignancies, such as malignant lymphomas (Hodgkin's disease, T-cell lymphoma, non-Hodgkin lymphoma), leukemia, and myeloma. The risk of lymphoreticular malignancy is about 20 times greater in KS patients than in the normal population.

Etiopathogenesis

KS is formed by proliferation of abnormal vascular endothelial cells. HHV-8 was first found in tissue of a patient with KS and was reported in 1994. Now it has been found in KS lesional tissue irrespective of clinical type. Detection of HHV-8 in HIV-infected individuals who do not have KS is predictive of the development of KS, usually within 2 to 4 years. It is considered at this time that sexual or fecal–oral transmission is the most likely means of acquiring this infection. The HHV-8 genome has many open reading frames that encode products that produce growth dysregulation or evasion of immune surveillance. How these orchestrate the formation and proliferation of spindle cells is under active investigation. Primary effusion lymphoma, solid lymphoma, and Castleman's disease are other confirmed associations with HHV-8 infection.

Histology

There is considerable variation in the histopathology according to the stage of the disease. Early lesions demonstrate irregularly shaped ecstatic vessels with scattered lymphocytes and plasma cells. The endothelial cells of the capillaries are large and protrude into the lumen, like buds. Later lesions show proliferation of vessels around preexisiting vessels and adnexal structures. The preexisting structure may jut into the vascular space forming a promontory sign. Dull pink globules, extravasated erythrocytes, and hemosiderin are present. Nodular lesions are composed of spindle cells with erythrocytes that appear to line up between spindle cells with no apparent vascular space.

Treatment

All types of KS are radiosensitive. Radiation therapy has been used with considerable success, either by small fractionated doses, larger single doses to limited or extended fields, or by electron beam radiation. Local excision, cryotherapy, alitretinoin gel (Panretin), locally injected chemotherapy or IFN, and laser ablation have been used for troublesome, localized lesions.

Vincristine solution 0.1 mg/mL injected intralesionally, not more than 3 mL at one time and at intervals of 2 weeks, produces involution of tumors, some for as long as 8 months. These studies indicate that adequate control of the lesions may be had, at least for periods of 6 to 12 months. The development of resistance to medication seems to be inevitable.

Many other agents have been found to be effective; among the best are IFN, vinblastine, and actinomycin D. The response rate initially is high, but recurrent lesions, which are common, are generally less responsive. Systemic therapy is usually needed if more than 10 new KS lesions develop in 1 month, or if there is symptomatic lymphedema, symptomatic pulmonary disease, or symptomatic visceral involvement.

In the setting of HIV, protease inhibitors have been shown to have antiangiogenic effects; however, the results of nonnucleoside reverse transcriptase inhibitor-based regimens are not inferior to protease inhibitor-based therapy in the prevention of KS. This suggests regression of KS is mediated by an overall improvement in immune function and not by the effects of specific antiretrovirals. Liposomal anthracyclines and paclitaxel have been approved by the US Food and Drug Administration (FDA) as first- and second-line monotherapy, respectively, for advanced KS.

Course

Classic KS progresses slowly, with rare lymph node or visceral involvement. Death usually occurs years later from unrelated causes. African cutaneous KS is aggressive, with early nodal involvement, and death from KS is expected within 1 to 2 years. AIDS-related KS, although widespread, is almost never fatal; nearly all patients die of intercurrent infection. The course of the disease is variable in patients who develop immunosuppression-related KS from causes other than AIDS. Removal of the immunosuppression may result in resolution of the KS without therapy.

Bower M, et al: Immune reconstitution inflammatory syndrome associated with Kaposi's sarcoma. J Clin Oncol 2005;23:5224.

Cathomas G: Kaposi's sarcoma-associated herpesvirus (KSHV)/human herpesvirus 8 (HHV-8) as a tumour virus. Herpes 2003;10:72.

Geraminejad P, et al: Kaposi's sarcoma and other manifestations of human herpesvirus 8. J Am Acad Dermatol 2002;47:641.

Krown SE: Therapy of AIDS-associated Kaposi's sarcoma: targeting pathogenetic mechanisms. Hematol Oncol Clin North Am 2003 Jun;17:763.

Mohammed AZ, et al: Changing patterns of Kaposi's sarcoma in Nigerians. Trop Doct 2005;35:168.

Noy A. Update in Kaposi sarcoma. Curr Opin Oncol 2003; 15:379.

Stebbing J, et al: The efficacy of ritonavir in the prevention of AIDS-related Kaposi's sarcoma. Int J Cancer 2004;108:631.

Epithelioid Hemangioendothelioma In 1982, Weiss et al described this rare tumor that both clinically and histologically is intermediate between angiosarcoma and hemangioma. It is usually a solitary, slowly growing papule or nodule on a distal area of an extremity. There is a male preponderance, and onset is frequently before the individual is 25 years of age. Histologically, there are two components: dilated vascular channels and solid epithelioid and spindle cell elements with intracytoplasmic lumens. Some may have cellular pleomorphism and mitotic activity. Wide excision is recommended with evaluation of regional lymph nodes. This is the usual site of metastases, and if they occur here, further surgery may be curative. In the minority of cases in which distant metastatic lesions develop, chemotherapy, radiation, or both may be employed. Of the 31 patients from the original series who had follow-up at an average of 18 months, 20 were alive and well.

Epithelioid sarcoma-like hemangioendothelioma demonstrates round to slightly spindled cells in sheets and nests. The cells demonstrate immunohistochemical evidence of endothelial differentiation. Local recurrence and regional soft-tissue metastases may occur.

Fernandez-Flores A, et al: Cutaneous epithelioid angiomatous nodule of the external ear. Am J Dermatopathol 2005;27:175.

Forschner A, et al: Ulcerated epithelioid hemangioendothelioma of the foot in childhood. J Am Acad Dermatol 2003;49:113.

Retiform Hemangioendothelioma Retiform hemangioendothelioma is a low-grade angiosarcoma, first described in 1994. It presents as a slow-growing exophytic mass, dermal plaque, or subcutaneous nodule. It most commonly occurs on the upper or lower extremities of young adults. Histologically, there are arborizing blood vessels reminiscent of normal rete testis architecture. HHV-8 DNA sequences have been reported in this tumor. Wide excision is recommended, although local recurrences are common. To date, no widespread metastases have occurred, although regional lymph nodes may develop tumor infiltrates.

Schommer M, et al: Retiform hemangioendothelioma: another tumor associated with human herpesvirus type 8? J Am Acad Dermatol 2000;42(2 Pt 1):290.

Composite Hemangioendothelioma This low-grade angiosarcoma typically occurs in adults, although it has been described in infancy. The tumor exhibits a mix of retiform hemangioendothelioma-like, spindle cell hemangioma-like, cavernous hemangioma-like, epithelioid hemangioendothelioma -like, and angiosarcoma-like patterns. Local recurrences and regional lymph node metastasis have been noted.

Nayler SJ, et al: Composite hemangioendothelioma: a complex, low-grade vascular lesion mimicking angiosarcoma. Am J Surg Pathol 2000;24:352.

Reis-Filho JS, et al: Congenital composite hemangioendothelioma: case report and reappraisal of the hemangioendothelioma spectrum. J Cutan Pathol 2002;29:226.

Endovascular Papillary Angioendothelioma (Dabska Tumor) Endovascular papillary angioendothelioma, a rare low-grade angiosarcoma, presents as a slow-growing tumor on the head, neck, or extremity of infants or young children. It shows multiple vascular channels with papillary plugs of endothelial cells surrounding central hyalinized cores that project into the lumina, sometimes forming a glomeruloid pattern. The entity is controversial, as similar histologic features have been observed in other vascular tumors, such as angiosarcoma, retiform hemangioendothelioma, and glomeruloid hemangioma. The tumor may be a distinct entity, or a histologic pattern seen in other vascular tumors. One patient with this histologic pattern developed KMS, and others have developed regional metastasis. Wide excision and, in cases where they are involved, regional lymph node excision is usually curative.

Fukunaga M: Endovascular papillary angioendothelioma (Dabska tumor). Pathol Int 1998;48:840.

Quecedo E, et al: Dabska tumor developing within a preexisting vascular malformation. Am J Dermatopathol 1996;18:302.

Schwartz RA, et al: The Dabska tumor: a thirty-year retrospect. Dermatology 2000;201:1.

Angiosarcoma Angiosarcomas of the skin occur in four clinical settings. First and most common are those that occur in the head and neck of elderly people. The male-to-female ratio is 2:1. The lesion often begins as an ill-defined bluish macule that may be mistaken for a bruise. Distinguishing features are the frequent occurrence of a peripheral erythematous ring, satellite nodules, the presence of intratumoral hemorrhage, and the tendency for the lesion to bleed spon-

taneously, or after minimal trauma. The tumor progressively enlarges asymmetrically, often becomes multicentric, and develops indurated bluish nodules and plaques. The sudden development of thrombocytopenia may herald metastatic disease or an enlarging primary tumor.

Histologically, anaplastic pleomorphic endothelial cells are present, with new vascular channels among them. Solid sheets of epithelioid cells may be present, but more commonly, the pattern is that of subtle infiltration in the dermis, producing the appearance of cracks between collagen bundles. The spaces are lined by hyperchromatic nuclei. Immunoperoxidase staining for endothelial markers such as CD31, CD34, and *Ulex europeus* lectin aids in the diagnosis.

Early diagnosis and complete surgical excision followed by moderate dose, very wide field radiotherapy offer the best prognosis for limited disease. Chemotherapy and radiation therapy for extensive disease are often only palliative, especially when dealing with scalp lesions. Doxorubicin–ifosfamide chemotherapy produces a modest response rate. Paclitaxel and interferon have shown some response for scalp and facial angiosarcomas. Because of the multicentricity of lesions, the frequent occurrence on the face or scalp, and the rapid growth with early metastasis, death occurs in most patients within 2 years. Spieth et al reported a dramatic response in a 77-year-old man with recurrent angiosarcoma of the face and scalp after combination treatment with IFN-α 2a and 13-*cis*-retinoic acid.

The second classic clinical situation in which angiosarcoma develops is in chronic lymphedematous areas, such as that which occurs in the upper arm after mastectomy, the so-called Stewart-Treves syndrome (Fig. 28-16). This tumor appears approximately 11 to 12 years after surgery in an estimated 0.45% of patients. The prognosis is poor for these patients, with a mean survival of 19 to 31 months, and a 5-year survival rate of 6% to 14%. Metastases to the lungs are the most frequent cause of death. Early amputation offers the best hope.

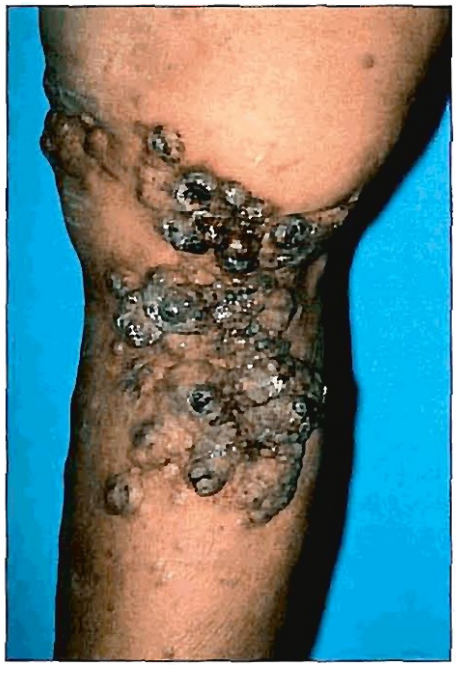

Fig. 28-16 Stewart-Treves syndrome.

A third setting includes tumors that develop in previously irradiated sites. If the condition for which radiation therapy was given was a benign one, the average interval between radiation and development of angiosarcoma is 23 years. If the preceding illness was a malignant condition, the interval is shortened to 12 years. Again, the prognosis is poor, with survival time generally between 6 months and 2 years after diagnosis. Many patients with the Stewart-Treves syndrome received radiation, and radiation may play a pathogenic role.

Angiosarcomas develop in settings other than those previously described, and this small miscellaneous subset comprises the fourth category. An angiosarcoma producing granulocyte colony-stimulating factor was associated with prominent peripheral leukocytosis.

Benbenisty KM, et al: Extensive angiosarcoma on chronically sun-damaged skin. Am J Clin Dermatol 2004;5:53.

Budd GT: Management of angiosarcoma. Curr Oncol Rep 2002; 4:515.

Nara T, et al: Granulocyte colony-stimulating factor-producing cutaneous angiosarcoma with leukaemoid reaction arising on a burn scar. Br J Dermatol 2003;149:1273.

Ohguri T, et al: Angiosarcoma of the scalp treated with curative radiotherapy plus recombinant interleukin-2 immunotherapy. Int J Radiat Oncol Biol Phys 2005;61:1446.

Pawlik TM, et al: Cutaneous angiosarcoma of the scalp: a multidisciplinary approach. Cancer 2003;98:1716.

Rao J, et al: Cutaneous angiosarcoma as a delayed complication of radiation therapy for carcinoma of the breast. J Am Acad Dermatol 2003;49:532.

Ward JR, et al: Radiation therapy for angiosarcoma. Head Neck 2003;25:873.

FIBROUS TISSUE ABNORMALITIES

Keloid

A keloid is a firm, irregularly shaped, fibrous, hyperpigmented, pink or red excrescence. The growth usually arises as the result of a cut, laceration, or burn—or, less often, an acne pustule on the chest or upper back—and spreads beyond the limits of the original injury, often sending out clawlike (cheloid) prolongations. The overlying epidermis is smooth, glossy, and thinned from pressure. The early, growing lesion is red and tender, and has the consistency of rubber. It is often surrounded by an erythematous halo, and the keloid may be telangiectatic. Lesions may be tender, painful, pruritic, and may rarely ulcerate or develop draining sinus tracts.

Keloids are often multiple. They may be as tiny as pinheads or as large as an orange. Those that follow burns and scalds are large. Lesions are often linear, often with bulbous expansions at each end. The surface may be larger than the base, so that the edges are overhanging. The most common location is the sternal region, but keloids also occur frequently on the neck, ears (Fig. 28-17), extremities, or trunk, and rarely on the face, palms, or soles. The earlobes are frequently involved as a result of ear piercing, but involvement of the central face is rare. They are much more common, and grow to larger dimensions, in black persons than in other races.

Why certain individuals develop keloids still remains unsolved. Trauma is usually the immediate causative factor, but

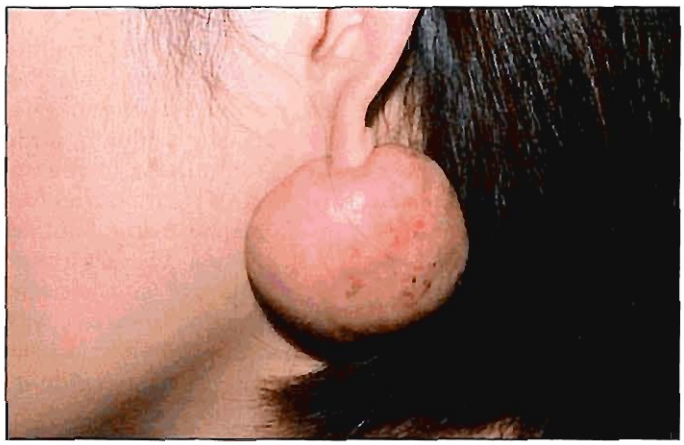

Fig. 28-17 Keloid.

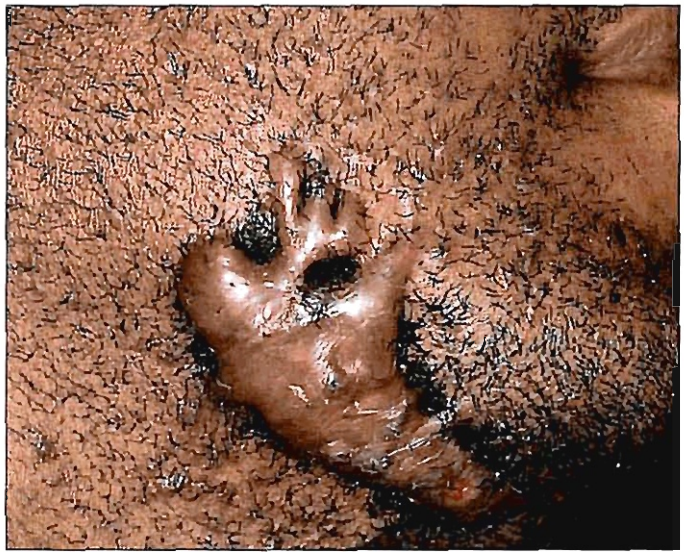

Fig. 28-18 Keloid.

this induces keloids only in those with a predisposition for their development. There is also a regional predisposition.

Histologically, a keloid is a dense and sharply defined nodular growth of myofibroblasts and collagen with a whorl-like arrangement resembling hypertrophic scar. Centrally, thick hyalinized bundles of collagen are present, and distinguish keloids from hypertrophic scars. There is a paucity of elastic tissue, just as in a scar. By pressure, the tumor causes thinning of the normal papillary dermis and atrophy of adjacent appendages, which it pushes aside. Mucopolysaccharides are increased, and often there are numerous mast cells.

Keloids are usually distinctive. They may be distinguished from hypertrophic scars by their clawlike projections (Fig. 28-18), which are absent in the hypertrophic scar, the extension of the lesion beyond the confines of the original injury, and the presence of thick hyalinized collagen bundles histologically. Frequently there is a spontaneous improvement of the hypertrophic scar over a period of months, whereas in the keloid this does not occur. Atypical lesions should be biopsied, as carcinoma en cuirasse may mimic keloid.

Initial treatment is usually by means of intralesional injection of triamcinolone suspension. Using a 30-gauge needle on a 1-mL tuberculin Luer syringe, triamcinolone suspension is injected into various parts of the lesion; 40 mg/mL is generally used for initial treatment and, as the lesion softens, 10 to 20 mg/mL may be sufficient to produce involution with less risk of surrounding hypopigmentation and atrophy related to lymphatic spread of the corticosteroid. Injections are repeated at intervals of 6 to 8 weeks, as required. Flattening and cessation of itching are reliably achieved by this approach, and may sometimes even be achieved with topical corticosteroids. The lesions are never made narrower, however, and hyperpigmentation generally persists. Transforming growth factor (TGF)-β is known to be involved in keloid formation, and triamcinolone acetonide-induced decreases in cellular proliferation and collagen production are associated with a statistically significant decrease in the level of TGF-β1 in both normal and keloid fibroblast cell lines.

Other approaches to treatment include flashlamp pulsed dye laser treatment, which is also associated with reduced expression of TGF-β1. Cryosurgery (including contact, intralesional needle cryoprobe, and spray cryosurgery), intralesional 5-fluorouracil, and calcium-channel blockers have some demonstrated efficacy in the treatment of keloids. Fibroblasts derived from the central part of keloids grow faster than peripheral keloid and nonkeloid fibroblasts. Verapamil has been shown to decrease interleukin (IL)-6 and vascular endothelial growth factor in these cultured cells, and to inhibit cell growth.

If surgical removal by excision is feasible, and if narrowing of the keloid is a vitally important goal, the keloid may be excised. After the excision, intralesional injection of triamcinolone or IFN-α 2b may be combined with postoperative x-ray irradiation or topical application of imiquimod. Silicone sheeting and pressure are other adjunctive methods used to limit recurrences. Results with these modalities have been mixed. Silicone gel-sheet treatment has been shown to reduce lesional mast cell numbers and decrease itching.

Pierced-ear keloids occur with considerable frequency. When the keloid is young, intralesional injection of triamcinolone is frequently sufficient to control the problem. In old keloids, excision of the lesion using lidocaine with triamcinolone, followed by injections at 2-week intervals, produces good results. CO_2 laser excision has also been successful in old mature keloids in this site.

Alster TS, et al: Hypertrophic scars and keloids: etiology and management. Am J Clin Dermatol 2003;4:235.

Bayat A, et al: Description of site-specific morphology of keloid phenotypes in an Afrocaribbean population. Br J Plast Surg 2004;57:122.

Bayat A, et al: Genetic susceptibility to keloid disease: transforming growth factor beta receptor gene polymorphisms are not associated with keloid disease. Exp Dermatol 2004;13:120.

Berman B, et al: Imiquimod 5% cream for keloid management. Dermatol Surg 2003;29:1050.

Carroll LA, et al: Triamcinolone stimulates βFGF production and inhibits TGF-beta1 production by human dermal fibroblasts. Dermatol Surg 2002;28:704.

D'Andrea F, et al: Prevention and treatment of keloids with intralesional verapamil. Dermatology 2002;204:60.

Eishi K, et al: Silicone gel sheets relieve pain and pruritus with clinical improvement of keloid: possible target of mast cells. J Dermatolog Treat 2003;14:248.

Giugliano G, et al: Verapamil inhibits interleukin-6 and vascular endothelial growth factor production in primary cultures of keloid fibroblasts. Br J Plast Surg 2003;56:804.

Hanasono MM, et al: The effect of silicone gel on basic fibroblast growth factor levels in fibroblast cell culture. Arch Facial Plast Surg 2004;6:88.

Har-Shai Y, et al: Intralesional cryotherapy for enhancing the involution of hypertrophic scars and keloids. Plast Reconstr Surg 2003;111:1841.

Hasegawa T, et al: IFN-gamma fails to antagonize fibrotic effect of TGF-beta on keloid-derived dermal fibroblasts. J Dermatol Sci 2003;32:19.

Kuo YR, et al: Flashlamp pulsed dye laser (PDL) suppression of keloid proliferation through down-regulation of TGF-beta1 expression and extracellular matrix expression. Lasers Surg Med 2004;34:104.

Manuskiatti W, et al: Treatment response of keloidal and hypertrophic sternotomy scars: comparison among intralesional corticosteroid, 5-fluorouracil, and 585-nm flashlamp-pumped pulsed-dye laser treatments. Arch Dermatol 2002;138:1149.

Mullinax K, et al: Carcinoma en cuirasse presenting as keloids of the chest. Dermatol Surg 2004;30(2 Pt 1):226.

Nanda S, et al: Intralesional 5-fluorouracil as a treatment modality of keloids. Dermatol Surg. 2004;30:54.

Ragoowansi R, et al: Treatment of keloids by surgical excision and immediate postoperative single-fraction radiotherapy. Plast Reconstr Surg 2003;111:1853.

Shaffer JJ, et al: Keloidal scars: a review with a critical look at therapeutic options. J Am Acad Dermatol 2002;46(2 Suppl): S63.

Dupuytren Contracture

Dupuytren contracture is a fibromatosis of the palmar aponeurosis. The lesion arises most commonly in men between the ages of 30 and 50 as multiple firm nodules in the palm. Usually three to five nodules about 1 cm in diameter develop, proximal to the fourth finger. Later the fibromatosis produces contractures, which may be disabling. It occurs at times with alcoholic cirrhosis, diabetes mellitus, and chronic epilepsy. It is also associated with Peyronie's disease, plantar fibromatosis, and knuckle pads. In some cases there is a familial predisposition. The fibrous nodules are composed of myofibroblasts that express androgen receptors. 5-α-Dihydrotestosterone induces an increase in Dupuytren fibroblast proliferation. In contrast to deep fibromatoses which behave more aggressively, superficial fibromatoses lack β-catenin and adenomatous polyposis coli (APC) gene mutations.

Early intralesional triamcinolone may help, but surgical excision of the involved palmar fascia may be the only way to liberate severely contracted fingers. Androgen blockade represents a potential avenue of pharmacologic therapy.

Montgomery E, et al: Superficial fibromatoses are genetically distinct from deep fibromatoses. Mod Pathol 2001;14:695.

Pagnotta A, et al. Responsiveness of Dupuytren's disease fibroblasts to 5 alpha-dihydrotestosterone. J Hand Surg [Am] 2003;28:1029.

Saar JD, et al: Dupuytren's disease: an overview. Plast Reconstr Surg 2000;106:125.

Skoff HD: The surgical treatment of Dupuytren's contracture: a synthesis of techniques. Plast Reconstr Surg 2004;113:540.

Plantar Fibromatosis

The plantar analog of Dupuytren contracture, plantar fibromatosis (Ledderhose's disease) occurs as slowly enlarging nodules on the soles that ultimately cause difficulty in walking or even weight-bearing. The diagnosis is usually made clinically, but both biopsy and MRI can be used to confirm the diagnosis. The usual treatment, as for Dupuytren contracture, is wide excision of the plantar fascia. Subtotal excision is associated with a high rate of recurrence. Although adjuvant radiotherapy is effective in decreasing the recurrence rate, it has a significant complication rate with functional impairment. Improvement by the intralesional injection of triamcinolone acetonide, 30 mg/mL monthly for 5 months, has been reported. The triamcinolone can be diluted with lidocaine solution.

de Bree E, et al: Incidence and treatment of recurrent plantar fibromatosis by surgery and postoperative radiotherapy. Am J Surg 2004;187:33.

Watson-Ramirez L, et al: Plantar fibromatosis: use of magnetic resonance imaging in diagnosis. Cutis 2001;68:219.

Knuckle Pads

Knuckle pads (heloderma) are well-defined, round, plaque-like, fibrous thickenings that develop on the extensor aspects of the proximal interphalangeal joints (Fig. 28-19) of the toes and fingers, including the thumbs. They develop at any age and grow to be some 10 to 15 mm in diameter in the course of a few weeks or months, then persist permanently. They are flesh colored or somewhat brown, with normal or slightly hyperkeratotic epidermis overlying and adherent to them. They are a part of the skin and are freely movable over underlying structures.

Knuckle pads are sometimes associated with Dupuytren contracture and camptodactylia (irreducible flexion contracture of one or more fingers). Some cases are familial and some are related to trauma or frequent knuckle cracking. An autosomal-dominant association of knuckle pads, mixed

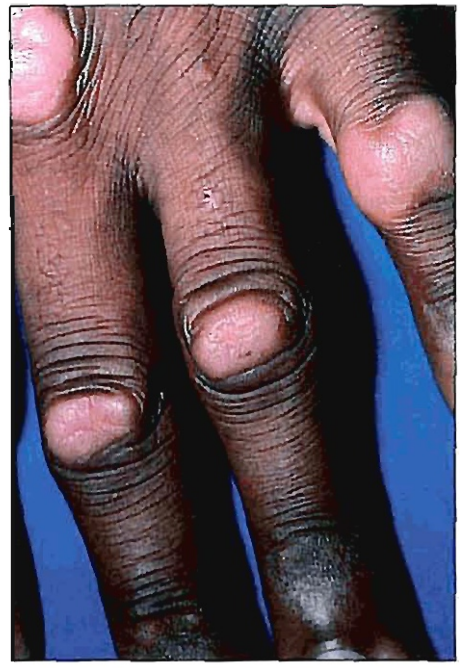

Fig. 28-19 Knuckle pads.

hearing loss (sensorineural and conductive), and total leukonychia has been reported. Knuckle pads have also be associated with autosomal-dominant epidermolytic palmoplantar keratoderma with a mutation in keratin 9.

Histologically, the lesions are fibromas. They are to be differentiated clinically from the nodular type of neurodermatitis and from the small hemispherical pitted papules that may develop over the knuckles after frostbite or in acrocyanosis, and from rheumatic nodules. Treatment with intralesional injection of corticosteroids may be beneficial.

Guberman D, et al: Knuckle pads—a forgotten skin condition: report of a case and review of the literature. Cutis 1996;57:241.
Lu Y, et al: A novel mutation of keratin 9 in epidermolytic palmoplantar keratoderma combined with knuckle pads. Am J Med Genet 2003;120A:345.
Peterson CM, et al: Knuckle pads: does knuckle cracking play an etiologic role? Pediatr Dermatol 2000;17:450.

Pachydermodactyly

Pachydermodactyly represents a benign fibromatosis of the fingers. There is a fullness of the medial and lateral digit just proximal to the proximal interphalangeal joint. This asymptomatic process is most often first noted in adolescence and usually involves multiple fingers. Five types have been described: classic pachydermodactyly localized pachydermodactyly, transgrediens pachydermodactyly in which the abnormality extends to the metacarpophalangeal areas, familial pachydermodactyly, and pachydermodactyly associated with tuberous sclerosis. Increased collagen or mucin account for the swelling. No treatment is required.

Bardazzi F, et al: Pachydermodactyly: seven new cases. Ann Dermatol Venereol 1998;125:247.
Yebenes M, et al: Acquired fusiform swelling of the fingers. Arch Dermatol 2005;141:1035.

Peyronie's Disease

Plastic induration of the penis is a fibrous infiltration of the intercavernous septum of the penis. This fibrosis results in the formation of nodules or plaques. As a result of these plaques, a fibrous chordee is produced, and curvature of the penis occurs on erection, sometimes so severe as to make intromission difficult or impossible. Sometimes pain may be severe. The association of this disease with Dupuytren contracture has been recognized. Intralesional triamcinolone suspension injected or iontophoresed into the plaques and nodules may be curative. Injection of IFN has also been used.

Surgical correction tailored to the degree of deformity is often successful. Extracorporeal shock wave therapy may reduce penile pain and improve sexual function, although objective changes in plaque size and curvature have not been demonstrated.

Hauck EW, et al: Extracorporeal shock wave therapy for Peyronie's disease: exploratory meta-analysis of clinical trials. J Urol 2004;171(2 Pt 1):740.
Ralph DJ, et al: The management of Peyronie's disease. Br J Urol Int 2004;93:208.

Desmoid Tumor

Desmoid tumors occur as large, deep-seated, well-circumscribed masses arising from the muscular aponeurosis. They most commonly occurs on the abdominal wall, especially in women during or soon after pregnancy. Desmoid tumors have been divided into five types: abdominal wall, extra-abdominal, intra-abdominal, multiple, and those occurring in Gardner syndrome/familial adenomatous polyposis. They recur locally and can kill if they invade, surround, or compress vital structures. The most dangerous, then, are those at the root of the neck and the intra-abdominal type. MRI will aid in the evaluation of soft-tissue extension and recurrence following treatment.

Treatment may be with wide local excision, radiotherapy, or hormonal manipulation. High-dose tamoxifen in combination with sulindac has been effective. Mesenteric desmoid tumors have been treated with antiangiogenic therapy with toremifene and IFN-α 2b.

Biermann JS: Desmoid tumors. Curr Treat Options Oncol 2000; 1:262.
Hansmann A, et al: High-dose tamoxifen and sulindac as first-line treatment for desmoid tumors. Cancer 2004;100:612.
Pereyo NG, et al: Extraabdominal desmoid tumor. J Am Acad Dermatol 1996;34:352.

Collagenous Fibroma (Desmoplastic Fibroblastoma)

This slow-growing, deep-set, benign fibrous tumor is usually located in the deep subcutis, fascia, aponeurosis, or skeletal muscle of the extremities, limb girdles, or head and neck regions. It is characterized by hypocellularity and dense bands of hyalinized collagen that may infiltrate into skeletal muscle. Despite this, no tumors have been reported to metastasize or recur after excision. Chromosomal translocation (2;11)(q31;q12) has been reported.

Bernal K, et al: Translocation (2;11)(q31;q12) is recurrent in collagenous fibroma (desmoplastic fibroblastoma). Cancer Genet Cytogenet 2004;149:161.
Weisberg NK, et al: Collagenous fibroma. J Am Acad Dermatol 1999;41:292.

Aponeurotic Fibroma

Aponeurotic fibroma has also been called *juvenile aponeurotic fibroma* (calcifying fibroma). It is a tumor-like proliferation characterized by the appearance of slow-growing, cystlike masses that occur on the limbs, especially the hands and feet.

Histologically, the distinctive lesions are sharply demarcated and composed of collagenous stroma showing acid mucopolysaccharides infiltrated by plump mesenchymal cells with oval nuclei. Hyalinized areas are also present, suggesting chondroid or osteoid metaplasia.

An aid to the diagnosis is stippled calcification, readily seen on roentgenograms. Surgical excision is the treatment.

Murphy BA, et al: Extra-acral calcifying aponeurotic fibroma. J Cutan Pathol 1996;23:369.

Infantile Myofibromatosis

Infantile myofibromatosis is the most common fibrous tumor of infancy. Eighty percent of patients have solitary lesions with half of these occurring on the head and neck. About 60% are present at or soon after birth.

Congenital generalized fibromatosis is an uncommon condition that presents at birth or soon after. It is characterized by multiple firm dermal and subcutaneous nodules. Skeletal lesions, primarily of the metaphyseal regions of the long bones, occur in 50% of patients. If only the skin and bones develop fibromas, the prognosis is excellent, with spontaneous resolution of the lesions without complications expected within the first 1 to 2 years of life. Some refer to this limited disease as *congenital multiple fibromatosis*. Females more commonly get the generalized disease.

The fibromas may involve the viscera, including the gastrointestinal tract, breast, lungs, liver, pancreas, tongue, serosal surfaces, lymph nodes, or kidney. Autosomal-dominant inheritance has been reported. Histologically, fascicles of spindle cells occur in a whorled pattern. These nodules are composed of myofibroblasts.

Mortality in this more widespread subset is high. Eighty percent of affected individuals die from obstruction or compression of vital organs. Those who survive past 4 months have spontaneous regression of their disease. Some life-threatening cases have responded to low-dose chemotherapy.

Gandhi MM, et al: Successful treatment of life-threatening generalized infantile myofibromatosis using low-dose chemotherapy. J Pediatr Hematol Oncol 2003;25:750.

Ikediobi NI, et al: Infantile myofibromatosis: support for autosomal dominant inheritance. J Am Acad Dermatol 2003;49(2 Suppl):S148.

Stanford D, et al: Dermatological presentations of infantile myofibromatosis: a review of 27 cases. Australas J Dermatol 2000;41:156.

Zand DJ, et al: Autosomal dominant inheritance of infantile myofibromatosis. Am J Med Genet 2004;126A:261.

Juvenile Hyaline Fibromatosis and Infantile Systemic Hyalinosis

Juvenile hyaline fibromatosis and infantile systemic hyalinosis are allelic autosomal-recessive conditions characterized by multiple subcutaneous skin nodules, hyaline deposition, gingival hypertrophy, osteolytic bone lesions, and joint contractures. Nodular tumors of the scalp, face, and extremities usually appear in early childhood. Pink confluent papules may occur on the paranasal folds, and periauricular and perianal regions. The gene has been mapped to chromosome 4q21 with at least 15 different mutations in the gene encoding capillary morphogenesis protein 2, a transmembrane protein that is induced during capillary morphogenesis and that binds laminin and collagen IV.

Histologically, there are fibroblasts with fine intracytoplasmic eosinophilic granules, embedded in a homogeneous eosinophilic dermal ground substance. Ultrastructurally, the fibroblasts demonstrate defective synthesis of collagen, deposited as fibrillogranular material.

Haleem A, et al: Juvenile hyaline fibromatosis: morphologic, immunohistochemical, and ultrastructural study of three siblings. Am J Dermatopathol 2002;24:218.

Hanks S, et al: Mutations in the gene encoding capillary morphogenesis protein 2 cause juvenile hyaline fibromatosis and infantile systemic hyalinosis. Am J Hum Genet 2003;73:791.

Larralde M, et al: Juvenile hyaline fibromatosis. Pediatr Dermatol 2001;18:400.

Infantile Digital Fibromatosis (Infantile Digital Myofibroblastoma, Inclusion Body Fibroma)

Infantile digital fibromatosis is a rare neoplasm of infancy and childhood that usually occurs on the dorsal or lateral aspects of the distal phalanges of the toes and fingers. The thumb and great toe are usually spared. These asymptomatic, firm, red, smooth nodules occur during the first year of life, 47% in the first month. Rare congenital lesions have been noted. The lesions do not metastasize, but may infiltrate deeply.

Histologically, the epidermis is normal, but the dermis is infiltrated with proliferating myofibroblasts and collagen bundles. Eosinophilic cytoplasmic inclusions in many of the fibroblasts are characteristic. Treatment by surgical excision has a high risk of recurrence, and conservative, nonsurgical management is often appropriate. Spontaneous regression is generally noted, but the lesion may cause functional impairment and may infiltrate deeply before regression occurs. Mohs micrographic surgery has been performed successfully using both trichrome staining and smooth muscle actin staining to demonstrate the inclusion bodies within tumor cells.

Albertini JG, et al: Infantile digital fibroma treated with Mohs micrographic surgery. Dermatol Surg 2002;28:959.

Kanwar AJ, et al: Congenital infantile digital fibromatosis. Pediatr Dermatol 2002;19:370.

Fibrous Hamatoma of Infancy

Fibrous hamartoma of infancy is a single dermal or subcutaneous firm nodule of the upper trunk that is present at birth or shortly thereafter. Overlying skin changes are uncommon, but may include increased hair, alteration in pigmentation, and eccrine gland hyperplasia. Most cases are solitary, but multiple tumors have been reported. Ninety-one percent are noted within the first year of life and 23% are congenital. The male-to-female ratio is 2.4:1. Most lesions occur in the axillary region, upper arm, upper trunk, inguinal region, and external genital area. Biopsy shows an organoid pattern with different types of tissue organized in whorls or bands. In early lesions, lobules of mature fat are interspersed between myxoid and fibrous areas. Myxoid zones have primitive mesenchymal cells with stellate nuclei. Fibrosing areas demonstrate delicate collagen bundles and many elongated fibroblast nuclei. Over time, both the myxoid and fibrosing areas develop into cell-poor fibrous areas with thick collagen bundles. There is no recurrence after excision.

Dickey GE, et al: Fibrous hamartoma of infancy: current review. Pediatr Dev Pathol 1999;2:236.

Scott DM, et al: Fibrous hamartoma of infancy. J Am Acad Dermatol 1999;41(5 Pt 2):857.

Fibromatosis Colli

In fibromatosis colli there is a fibrous tissue proliferation infiltrating the lower third of the sternocleidomastoid muscle at birth. Fine needle aspiration is useful to confirm the diag-

nosis. Spontaneous remission occurs within a few months. Occasionally, some patients are left with a wryneck deformity; however, this complication is amenable to surgery.

Kurtycz DF, et al: Diagnosis of fibromatosis colli by fine-needle aspiration. Diagn Cytopathol 2000;23:338.

Diffuse Infantile Fibromatosis

This process occurs within the first 3 years of life and is usually confined to the muscles of the arms, neck, and shoulder area. There is a multicentric infiltration of muscle fibers with fibroblasts resembling those seen in aponeurotic fibromas. Calcification does not occur. Recurrence after excision occurs in about a third of cases.

Ahn JM, et al: Infantile fibromatosis in childhood: findings on MR imaging and pathologic correlation. Clin Radiol 2000 Jan; 55:19.

Allen PW: The fibromatoses. Am J Surg Pathol 1977;1:255, 305.

Aggressive Infantile Fibromatosis

The clinical presentation of this locally recurring, nonmetastasizing lesion involves single or multiple fast-growing masses that are present at birth or occur within the first year of life. Infantile fibromatosis may be seen in any location, although the arms, legs, and trunk are the usual sites. Histologically, it is hypercellular and mimics malignancy.

Amoric JC, et al: Infantile aggressive fibromatosis. Ann Dermatol Venereol 1993;120:762.

Giant Cell Tumor of the Tendon Sheath

This tumor, which is most commonly attached to the tendons of the fingers, hands, and wrists, has a predilection for the flexor surfaces. It is firm, measures from 1 to 3 cm in diameter, and does not spontaneously involute. It recurs after excision in approximately 25% of cases. Another tumor of the tendon sheath, fibroma of the tendon sheath, may represent a variant of the giant cell tumor. It also affects the flexural tendons of the fingers and hands, and morphologically, it and the giant cell tumor are identical. The condition tends to occur in younger men (the average age at onset is 30) than the giant cell variety. When a proliferation similar to giant cell tumor of the tendon sheath occurs in deeper tissues, it is referred to as pigmented villo-nodular tenosynovitis. The pigment is hemosiderin.

Histologically, the giant cell tumor consists of lobules of densely hyalinized collagen. The characteristic osteoclast-like giant cells have deeply eosinophilic cytoplasm that moulds to adjacent cells. A variable number of randomly distributed nuclei are present. Lipophages and siderophages may be numerous, and hemosiderin deposition may impart a brown color to the lesions on gross examination. The fibroma of the tendon sheath generally lacks lipophages, siderophages, and giant cells, with the lobules being composed of dense fibrocollagenous tissue.

The rate of recurrence depends on the presence or absence of a pseudocapsule, lobulation of the tumor, extra-articular location, and the presence of satellite lesions. Local recurrence has been treated with more extensive surgery. Radiation therapy has been reported anecdotally.

Al-Qattan MM: Giant cell tumours of tendon sheath: classification and recurrence rate. J Hand Surg [Br] 2001;26:72.

Scott SJ, et al: Giant-cell tumour of the tendon sheath. J Bone Joint Surg Br 2000;82:1206.

Ainhum

Ainhum is also known as *dactylolysis spontanea, banko-kerend*, and *sukhapakla*. Ainhum is a disease affecting the toes, especially the fifth toe, characterized by a linear constriction around the affected digit, which leads ultimately to the spontaneous amputation of the distal part. It occurs chiefly among black men in Africa. Usually it is unilateral, but it may be bilateral.

The disease begins with a transverse groove in the skin on the flexor surface of the toe, usually beneath the first interphalangeal articulation. The furrow is produced by a ringlike fibrosis and an induration of the dermis. It deepens and extends laterally around the toe until the two ends meet, so that the digit becomes constricted as if in a ligature. The constricted part becomes swollen and soft and after a time greatly distended. Ulceration may result in a malodorous discharge, with pain and gangrene. The course of the disease is slow, but in 5 to 10 years spontaneous amputation occurs, generally at a joint.

The cause is unknown. The condition may result from chronic trauma and exposure to the elements by walking barefoot in the tropics. Fissuring followed by chronic inflammation and fibrosis may then result.

Treatment in early cases by cutting the constricting band is unsuccessful; in advanced cases amputation of the affected member is advisable. Surgical correction by Z-plasty has produced good results. Intralesional injection of betamethasone (total, 15 injections) has also been successful.

Pseudo-Ainhum

Pseudo-ainhum has been a term used in connection with certain hereditary and nonhereditary diseases in which annular constriction of digits occurs. Hereditary disorders include hereditary palmoplantar keratodermas, especially Vohwinkel syndrome and mal de Meleda, pachyonychia congenita, Ehlers-Danlos syndrome, erythropoietic protoporphyria, and congenital ectodermal defect. Nonhereditary disorders associated with constriction of digits are ainhum, leprosy, cholera, ancyclostomiasis, scleroderma, Raynaud syndrome, pityriasis rubra pilaris, psoriasis, Olmstead syndrome, Reynold syndrome (scleroderma and primary biliary cirrhosis with antimitochondrial antibodies), syringomyelia, ergot poisoning, and tumors of the spinal cord. Factitial pseudo-ainhum may be produced by self-application of a rubber band, string, or other ligature.

Congenital cases have been reported that may affect digits or limbs. It may occur as a familial condition or may result secondary to amniotic bands.

Treatment may be with surgery or intralesional injection of corticosteroids, as in ainhum. Retinoids may be used in diseases responsive to them.

Almond SL, et al: Pseudoainhum in chronic psoriasis. Br J Dermatol 2003;149:1064.

Daccarett M, et al: Ainhum (dactylolysis spontanea): a radiological survey of 6000 patients. J Foot Ankle Surg 2002;41:372.

Wollina U, et al: Pseudoainhum of all fingers associated with Reynolds' syndrome and breast cancer: report of a case and review of the literature. J Am Acad Dermatol 2001;44(2 Suppl): 381.

Connective Tissue Nevi

These uncommon lesions may present as acquired isolated plaques, as multiple lesions either acquired or congenital, or as one finding in a more generalized disease. Biopsy findings in many cases do not appear very different from normal skin, although in some cases altered amounts of collagen or elastin may be identified.

These lesions characteristically occur on the trunk, most often in the lumbosacral area. They may be solitary, but are often multiple, in which case they may show a zosteriform arrangement. Individual lesions are slightly elevated plaques 1 to 15 cm in diameter, varying in color from light yellow to orange, with a surface texture resembling shagreen leather. In Proteus syndrome, the connective tissue nevi are present as plantar, or occasionally, palmar masses with a cerebriform surface.

Connective tissue nevi of the acquired type have been classified as eruptive collagenomas, isolated collagenomas, or isolated elastomas, depending on the number of lesions and the predominant dermal fibers present. They cannot be differentiated clinically.

Hereditary types of connective tissue nevi include dermatofibrosis lenticularis disseminata in the Buschke-Ollendorff syndrome, familial cutaneous collagenoma, and the shagreen patches seen in tuberous sclerosis.

Buschke-Ollendorff syndrome is an autosomal-dominantly inherited disorder in which widespread dermal papules and plaques develop asymmetrically over the trunk and limbs. Elastic fiber thickening, highly variable fiber diameter, and desmosine increases three- to seven-fold above normal have been described in these patients. The associated feature of osteopoikilosis is asymptomatic, but it is diagnostic in x-ray evaluation. Focal sclerotic densities are seen, primarily in the long bones, pelvis, and hands. The syndrome is highly variable, and familial inheritance of elastic tissue naevi without evidence of osteopoikilosis has been reported.

Papular elastorrhexis is characterized by multiple white evenly scattered papules usually occurring on the trunk. There is a decrease of elastic fibers, which may appear thin and fragmented. Most reported cases are sporadic but familial occurrence has been described.

Patients with familial cutaneous collagenomas may present with numerous symmetric asymptomatic dermal nodules on the back. The age of onset is usually in the mid to late teens. In patients with the inherited disease, multiple endocrine neoplasia type I multiple collagenomas were reported in 23 of 32 patients. These were less than 3 mm in diameter and were on the upper torso, neck, and shoulders. They occurred in association with numerous other cutaneous findings such as angiofibromas, café-au-lait macules, and lipomas.

The collagenomas of tuberous sclerosis are associated with adenoma sebaceum, periungual fibromas, and ash-leaf macules. Because at least half the cases of tuberous sclerosis result from new mutations, all patients with connective tissue nevi should be carefully studied for evidence of tuberous sclerosis, even in the absence of a family history of the disease. Isolated plantar collagenoma may exhibit a cerebriform appearance and resemble plantar fibromas of Proteus syndrome.

Eruptive collagenomas may be widespread or localized. They have rarely been associated with infectious diseases such as syphilis.

Mucinous nevus is a form of connective tissue nevus characterized by increased ground substance without increases in collagen or elastin. Histologically, collagen bundles are widely separated by mucin and may be attenuated. Overlying follicular induction similar to that seen in dermatofibromas may be present.

Amaya M, et al: A case of eruptive collagenoma localized on the neck and shoulders. J Dermatol 2002;29:79.

Chang SE, et al: A case of congenital mucinous nevus: a connective tissue nevus of the proteoglycan type. Pediatr Dermatol 2003;20:229.

Choi JC, et al: Isolated plantar collagenoma. Br J Dermatol 2002;146:164.

Choonhakarn C, et al: Papular elastorrhexis: a distinct variant of connective tissue nevi or an incomplete form of Buschke-Ollendorff syndrome? Clin Exp Dermatol 2002;27:454.

Woodrow SL, et al: The Buschke-Ollendorff syndrome presenting as familial elastic tissue naevi. Br J Dermatol 2001; 144:890.

Elastofibroma Dorsi

Elastofibroma dorsi is a rare benign tumor usually located in the deep soft tissues in the subscapular region, but sometimes at other sites. The tumor is firm, unencapsulated, and measures up to several centimeters in diameter. It is believed to represent an unusual response to repeated trauma. Histologically, the tumor consists of abundant compact sclerotic collagen mixed with large, swollen, irregular elastic fibers, often appearing as globules of elastic tissue. Computed tomography (CT) and MRI can define the extent of the lesion, and excision is curative.

Kudo S: Elastofibroma dorsi: CT and MR imaging findings. Semin Musculoskelet Radiol 2001;5:103.

Abe S, et al. Elastofibroma dorsi: CT, MRI, and pathologic findings. Plast Reconstr Surg 1999;104:2121.

Angiofibromas

These skin-colored to reddish papules, which show fibroplasia and varying degrees of vascular proliferation in the upper dermis, may occur as a solitary nonhereditary form, the fibrous papule of the nose, as multiple nonhereditary lesions, pearly penile papules, or as multiple hereditary forms as in tuberous sclerosis, Birt-Hogg-Dube Syndrome (in combination with the specific lesion, the fibrofilliculoma) and multiple endocrine neoplasia type I. There have been reports of agminated or segmental angiofibromas that may represent a segmental form of tuberous sclerosis. The multiple hereditary types are discussed in other chapters.

Cellular angiofibroma of the vulva is a well circumscribed but not truly encapsulated lesion that occurs in older women. It is composed of small spindle cells arranged in short fascicles and relatively abundant small rounded vessels. They may express estrogen and progesterone receptors, and also CD34.

Dargent JL, et al: Cellular angiofibroma of the vulva. J Cutan Pathol 2003;30:405.
Schaffer JV, et al: Multiple facial angiofibromas. J Am Acad Dermatol 2005;53:S108.
Trauner MA, et al: Segmental tuberous sclerosis presenting as unilateral facial angiofibromas. J Am Acad Dermatol 2003; 49(2 Suppl):S164.

Fibrous Papule of the Nose (Fibrous Papule of the Face, Benign Solitary Fibrous Papule) These lesions occur in adults as dome-shaped, sessile, skin-colored, white, or reddish papules 3 to 6 mm in diameter on or near the nose (Fig. 28-20). Fibrous papule is usually solitary, but it is not uncommon for a few lesions to occur. It may be confused with a nevocytic nevus, neurofibroma, granuloma pyogenicum, or a basal cell carcinoma. Like other angiofibromas, fibrous papules demonstrate concentric fibrosis surrounding vessels and adnexal structures. Stellate dermal dendrocytes are often prominent. They stain for factor XIIIa. Large pyramidal junctional melanocytes are often noted overlying the lesion, and a superficial shave biopsy may be mistaken for a melanocytic lesion. Conservative excision is curative; recurrence is rare. Multiple lesions should prompt a search for other stigmata of tuberous sclerosis.

Cerio R, et al: An immunohistochemical study of fibrous papule of the nose: 25 cases. J Cutan Pathol 1989;16:194.

Pearly Penile Papules This is the term given to pearly white, dome-shaped papules occurring circumferentially on the coronal margin and sulcus of the glans penis. The lesions may be firm or soft and filliform. Occasionally, lesions are also present on the penile shaft. Pearly penile papules are not uncommon. Patients usually present around the age of 20 to 30 years concerned these are condylomata or are referred as treatment-resistant venereal warts.

These lesions should be distinguished from papillomas, hypertrophic sebaceous glands, and condyloma acuminatum.

No treatment is necessary, only reassurance. If treatment is desired, laser ablation or shave excision is effective.

Agrawal SK, et al: Pearly penile papules: a review. Int J Dermatol 2004;43:199.
Hogewoning CJ, et al: Pearly penile papules: still no reason for uneasiness. J Am Acad Dermatol 2003;49:50.

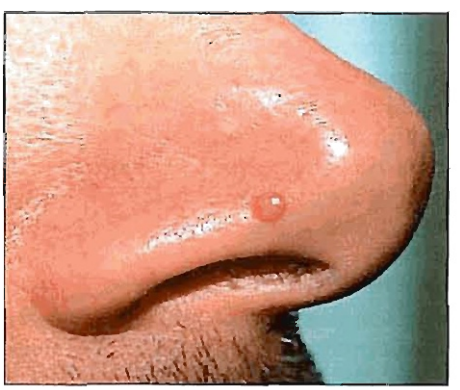

Fig. 28-20 Fibrous papule.

Lane JE, et al: Treatment of pearly penile papules with CO_2 laser. Dermatol Surg 2002;28:617.

Acral Fibrokeratoma

Acral fibrokeratoma, often called *acquired digital fibrokeratoma*, is characterized by a pinkish, hyperkeratotic, hornlike projection occurring on a finger, toe, or palm. The projection usually emerges from a collarette of elevated skin. The average age of the patient is 40. The lesion resembles a rudimentary supernumerary digit, cutaneous horn, or a neuroma.

Histologic sections show a central core of thick collagen bundles interwoven closely in a vertical position. This is surrounded by capillaries and a fine network of reticulum fibers. Stellate dermal dendrocytes may be present, as in fibrous papule.

Simple surgical excision or laser ablation at the level of the skin surface is effective.

Kakurai M, et al: Giant acquired digital fibrokeratoma. J Am Acad Dermatol 2003;48(5 Suppl):S67.

Familial Myxovascular Fibromas

Multiple verrucous papules on the palms and fingers, which on biopsy show focal neovascularization and mucin-like changes in the papillary dermis, have been described. Clinically, these lesions closely resemble warts. They have been reported from several family members, with a probable autosomal-dominant inheritance.

Coskey RJ, et al: Multiple vascular fibromas and myxoid fibromas of the fingers. J Am Acad Dermatol 1980;2:425.
Moulin G, et al: Familial multiple acral mucinous fibrokeratomas. J Am Acad Dermatol 1998;38:1998.
Peterson JL, et al: Familial myxovascular fibromas. J Am Acad Dermatol 1982;6:470.

Subungual Exostosis

Subungual exostosis is a solitary osteochondroma protruding from beneath the distal edge of the nail, most commonly of the great toe. Rarely, the terminal phalanges of other toes, particularly the little toe or even the fingers, may be involved. The exostosis is seen chiefly in women between the ages of 12 and 30. The first appearance is a small pinkish growth projecting slightly beyond the inner free edge of the nail. The overlying nail becomes brittle and either breaks or is removed, after which the tumor, being released, mushrooms upward and distally above the level of the nail. It grows slowly to a maximum diameter of about 8 mm. Pressure of the shoe on the lesion causes great pain.

Subungual exostosis must be differentiated from pyogenic granuloma, verruca vulgaris, pterygium inverum unguis, ingrowing nail, and glomus tumor. If subungual exostosis is suspected, the diagnosis can be confirmed by radiographic examination. Complete excision or curettage is the proper method of treatment.

Dumontier CA, et al: Nail unit enchondromas and osteochondromas: a surgical approach. Dermatol Surg 2001;27:274.
Ilyas W, et al: Subungual exostosis of the third toe. J Am Acad Dermatol 2001;45(6 Suppl):S200.

Chondrodermatitis Nodularis Chronica Helicis

This is a small, nodular, tender, chronic inflammatory lesion occurring on the helix of the ear. Most patients are men. The lesions are not uncommon and sometimes as many as 12 nodules may arrange themselves along the edge of the upper helix. The lesions are 2 to 4 mm in diameter, well defined, slightly reddish, and extremely tender. At times the surface is covered by an adherent scale or a shallow ulcer. After the masses have reached a certain size, growth ceases, but the lesions persist unchanged for years. There is no tendency to malignant change. Similar lesions may occur on the anthelix, predominantly in women.

The lesion is produced by ischemic necrosis of the dermis, and generally occurs on the side the patient favors during sleep. There may be a history of frostbite, chronic trauma, or chronic actinic exposure with concomitant actinically induced lesions of the face and dorsal hands.

Histologically, a zone of eosinophilic necrosis of collagen is flanked by granulation tissue. Overlying acanthosis and hyperkeratosis and central ulceration may be present. The histologic changes resemble those of a decubitus ulcer, but on a smaller scale. Occasionally, bizarre reactive fibroblasts are noted, as in atypical decubital fibroplasia.

The lesions may be excised. The underlying cartilage may be excised or fenestrated to reduce pressure on the overlying skin during sleep. The patient may be encouraged to change sleeping positions, but many find this difficult. Pillows with an ear slot are also available.

Long D, et al: Surgical pearl: surgical planning in the treatment of chondrodermatitis nodularis chronica helicis of the antihelix. J Am Acad Dermatol 1996;35(5 Pt 1):761.

Oelzner S, et al: Bilateral chondrodermatitis nodularis chronica helicis on the free border of the helix in a woman. J Am Acad Dermatol 2003;49:720.

Oral Submucous Fibrosis

A distinctive fibrosis of the oral mucosa occurs in the western Pacific basin and south Asia among persons whose diet is heavily seasoned with chili or who chew betel, a compound of the nut of the areca palm, the leaf of the betel pepper, and lime. The irritation produced causes first a thickening of the palate, tonsillar pillars, and fauces secondary to dermal and muscular fibrosis. As the disease progresses, opening of the mouth and protrusion of the tongue develops such that eating, swallowing, and speech are impaired. Later ulceration and leukoplakic areas occur and finally, in approximately 7% of patients, malignant transformation to squamous cell carcinoma develops. Treatment consists of the intralesional injection of dexamethasone and hyaluronidase, and in advanced cases surgical excision and grafting. Discontinuance of the offending substance and physical therapy are also needed.

Chiu CJ, et al: A scoring system for the early detection of oral submucous fibrosis based on a self-administered questionnaire. J Public Health Dent 2002;62:28.

Thomas G, et al: Risk factors for multiple oral premalignant lesions. Int J Cancer 2003;107:285.

Fascial Hernia

Evanescent herniations in the form of nodules appear in the skin where the deep and superficial veins meet going through the fascia. These herniated nodules, seen most frequently on the lower extremities, become prominent when the underlying muscles contract, and pain may occur with prolonged exertion. Treatment is not indicated unless the area is chronically painful. Light compression may be effective.

Harrington AC, et al: Hernias of the anterior tibialis muscle. J Am Acad Dermatol 1990;22:123.

Acrochordon (Cutaneous Tag, Papilloma Colli, Fibroma Pendulum, Cutaneous Papilloma, Fibroma Molluscum, Templeton Skin Tags, Skin Tags)

Small, flesh-colored to dark brown, pinhead-sized and larger, sessile and pedunculated papillomas commonly occur on the neck, often in association with small seborrheic keratoses. These tags are also seen frequently in the axillae and on the eyelids, less often on the trunk and groins, where the soft, pedunculated growths often hang on thin stalks. These flesh-colored, teardrop-shaped tags feel like small bags. Occasionally, as a result of twisting of the pedicle, one will become inflamed, tender, and even gangrenous. Both sexes have the same incidence, with nearly 60% of individuals acquiring them by the age of 69. They often increase in number when the patient is gaining weight or during pregnancy and may be related to the growth hormone-like activity of insulin. They may be associated with diabetes mellitus. In patients preselected for gastrointestinal complaints, skin tags appear to be more prevalent in those with colonic polyps. This association has not been proved for the general population.

Histologically, acrochordons are characterized by epidermis enclosing a dermal fibrovascular stalk. The baglike papillomas generally show a flattened epidermis. Smaller lesions often demonstrate seborrheic keratosis-like acanthosis and horn cysts.

Small lesions can be clipped off at the base with little or no anesthesia. Aluminum chloride may be applied for hemostasis if needed. Light electrodesiccation can also be effective. For larger lesions, anesthesia and snip excision are preferred.

An entity that is frequently reported as perianal acrochordons or skinfolds has now been named *infantile perianal pyramidal protrusions*. This occurs in young children, usually girls, in the midline anterior to the anus. This reduces with time and no treatment is necessary. Child abuse, genital warts, hemorrhoids, granulomatous lesions of inflammatory bowel disease, or rectal prolapse must be considered in the differential diagnosis of these lesions.

Tag-like basal cell carcinomas in childhood should suggest a diagnosis of nevoid basal cell carcinoma syndrome (NBCCS). Biopsy should be performed on acrochordons in children because the lesions are uncommon in this age group, and they may be the presenting sign of NBCCS.

Chiritescu E, et al: Acrochordons as a presenting sign of nevoid basal cell carcinoma syndrome. J Am Acad Dermatol 2001;44:789.

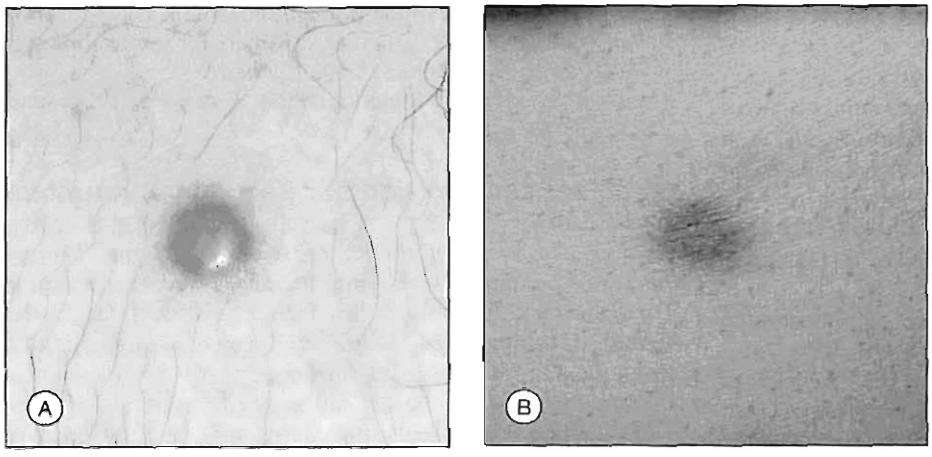

Fig. 28-21 *A* and *B*, Dermatofibroma. (Courtesy Lawrence Lieblich MD)

De la Torre C, et al: Acrochordons are not a component of the Birt-Hogg-Dube syndrome: does this syndrome exist? Case reports and review of the literature. Am J Dermatopathol 1999;21:369.

Demir S, et al: Acrochordon and impaired carbohydrate metabolism. Acta Diabetol 2002;39:57.

Dermatofibroma (Fibrous Histiocytoma)

This common skin lesion's appearance is usually sufficiently characteristic to permit clinical diagnosis. It is generally a single round or ovoid papule or nodule about 0.5 to 1 cm in diameter that is reddish-brown, sometimes with a yellowish hue (Fig. 28-21A).The sharply circumscribed nodule is more evident on palpation than expected from inspection. The larger lesions may present an abrupt elevation at the border to form an exteriorized tumor resting on a sessile base.

It may be elevated or slightly depressed. The hard lesion is adherent to the overlying epidermis, which may be thinner from pressure or even indented, so that there is a dell-like depression over the nodule (Fig. 28-21B). In such cases only the depression is seen, but on palpation the true nature of the lesion is found. Fitzpatrick proposed the term *dimple sign* for the depression created over a dermatofibroma when it is grasped gently between thumb and forefinger.

Dermatofibromas seldom occur in children; they are encountered mostly in middle-aged adults. Their size generally varies from 4 to 20 mm, although giant lesions greater than 5 cm occur. After reaching this size, growth ceases and the harmless lump remains stationary. The principal locations are on the lower extremities, above the elbows, or on the sides of the trunk. Systemic lupus erythematosus, treatment with prednisone or immunosuppressive drugs, chronic myelogenous leukemia and HIV infection have been associated with the development of multiple dermatofibromas.

It is suspected that many dermatofibromas are initiated by injuries to the skin, such as insect bites or blunt trauma.

On histologic examination there is a dermal mass composed of close whorls of fibrous tissue in which are numerous spindle or histiocytic cells. The cells have features of fibroblasts and myofibroblasts, but are probably of primitive mesenchymal origin. Immunohistochemical studies show most cells are positive for factor XIIIa, and negative for MAC387, S-100, and CD34. The tumor is not well circumscribed and may extend into adjacent structures and surround individual collagen bundles at the periphery (collagen trapping). Overlying acanthosis is typical, and induction of primitive epithelial germs or mature follicular structures may be noted. Basal cell carcinoma-like changes commonly overlie dermatofibromas, but true basal cell carcinoma is quite rare.

At times, large histiocytic cells within the lesion are strikingly atypical (monster cells). Occasionally, granular cytoplasm may predominate.

Hemosiderin, may be present, and foam cells and lipid deposits may be seen. The presence of Touton giant cells containing hemosiderin is pathognomonic of dermatofibroma. There is a great variation in the vascular components. Rarely, the vascularization is pronounced and suggests a kind of hemangioma (sclerosing hemangioma). Deep penetrating dermatofibromas may grow into the subcutaneous tissue via the fibrous septa or with a pushing front of tumor. They lack the extensive lacy and lamellar infiltrative growth pattern of dermatofibrosarcoma protuberans. Deep fascial fibrous histiocytomas may involve the fat or muscle at times.

The clinical appearance of the lesion and its location, chiefly on the lower extremities, are distinctive. Clinically, granular cell tumor, dermatofibrosis lenticularis disseminata, clear-cell acanthoma, and melanoma are some of the lesions to be considered. At times only a biopsy can differentiate these.

Progressive enlargement beyond 2 or 3 cm in diameter suggests a malignant fibrous histiocytoma or dermatofibrosarcoma protuberans, and excisional biopsy is indicated.

These lesions usually are asymptomatic and do not require treatment. Involution may occur after many years if the lesion is left alone. Simple reassurance is suggested.

Alexandrescu DT, et al: Multiple eruptive dermatofibromas occurring in a patient with chronic myelogenous leukemia. Arch Dermatol 2005;141:397.

Chan I, et al: Multiple dermatofibromas associated with lupus profundus. Clin Exp Dermatol 2005;30:128.

Mentzel T, et al: Benign fibrous histiocytoma (dermatofibroma) of the face. Am J Dermatopathol 2001;23:419.

Requena L, et al: The atrophic dermatofibroma. J Dermatol 1995;22:334.

Wick MR, et al: The pathological distinction between "deep penetrating" dermatofibroma and dermatofibromasarcoma protuberans. Semin Cutan Med Surg 1999;18:91.

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) is characterized by bulky, protuberant, neoplastic masses. Fifty to 60% occur on the trunk, with less common involvement of the proximal extremities and the head and neck. The disease begins with one or multiple elevated, erythematous, firm, nodules or plaques associated often with a purulent exudate or with ulceration. Patients, usually middle-aged, complain of a firm, painless lump in the skin that has been slowly increasing in size for several years.

The course is slowly progressive, with pain becoming prominent as the lesion grows, and frequent recurrence after initial conservative surgical intervention (Fig. 28-22). In untreated patients, severe pain and contractures may result. There is little tendency to metastasize, although wide dissemination has been reported.

Histologically, the tumor shows a subepidermal fibrotic plaque with uniform spindle cells and variable vascular spaces. In many instances there is a pronounced matlike woven pattern of spindle cells. Giant cells may be present in small numbers. Pigmented DFSP, in which the cells contain melanin, predominantly affect persons of color, and are called *Bednar tumors*. CD34 and stromelysin 3 positivity are characteristic and serve as markers to discern DFSP from dermatofibroma. S-100 is negative and may be used to separate spindle cell melanoma from a Bednar tumor. Recurrent DFSP can be myxoid and resembles the diffuse type of neurofibroma histologically. A juvenile variant, called *giant cell fibroblastoma*, is characterized by a loose arrangement of spindle cells, and by multinucleated giant cells adjacent to dilated spaces that resemble dilated lymphatic vessels.

The differential diagnosis, especially in the early stage, is that of keloid and a large dermatofibroma.

Mohs surgical excision technique is the treatment of choice. In a series of 50 patients the recurrence rate was 2%, with wide local excision recurrence is 11% to 50%. A preoperative MRI may assist in planning successful clearance.

Allan AE, et al: Clonal origin of DFSP. J Invest Dermatol 1993; 100:99.

Bouyssou-Gauthier ML, et al: DFSP in childhood. Pediatr Dermatol 1997;14:463.

Cribier B, et al: Stomelysin 3 expression. J Am Acad Dermatol 2002;46:408.

Elgart GW, et al: Bednar tumor occurring in a site of prior immunization. J Am Acad Dermatol 1999;40:315.

Gloster HM Jr: DFSP. J Am Acad Dermatol 1996;35:355.

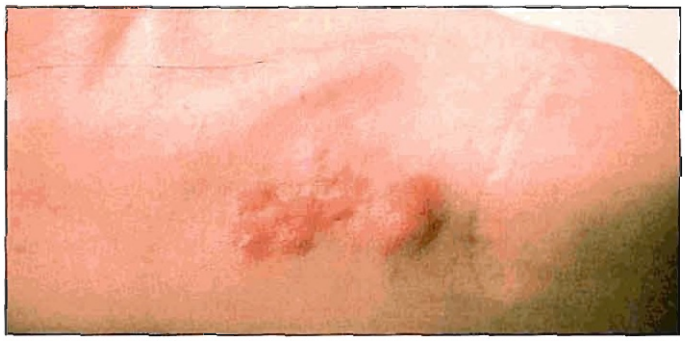

Fig. 28-22 Recurrent dermatofibromasarcoma protuberans.

Menderhall WM, et al: DFSP, Cancer 2004;100:2503.

Ratner D, et al: Mohs micrographic surgery for the treatment of DFSP. J Am Acad Dermatol 1997;37:600.

Thornton S, et al: Childhood DFSP. J Am Acad Dermatol 2005;53:76.

Nodular Fasciitis (Nodular Pseudosarcomatous Fasciitis)

Also known as *subcutaneous pseudosarcomatous fibromatosis*, this benign mesenchymal neoplasm occurs most often on the arms. Clinically, a firm, solitary, sometimes tender nodule develops in the deep fascia, and often extends into the subcutaneous tissue. It measures usually 1 to 4 cm in diameter. The lesion appears suddenly over a period of a few weeks, without apparent cause, in normal, healthy persons. Sex distribution is equal, and the average age at onset is 40.

Microscopic findings consist of well-defined, loose nodules of stellate and spindled cells that may have a myxoid appearance. Capillary proliferation is typical, and erythrocyte extravasation between spindle cells is common. Nodular lymphoid infiltrates are often noted within the lesion. On electron microscopic examination, the component cells in the neoplasm have proved to be myofibroblasts.

Dermal, intravascular, and proliferating variants (proliferative fasciitis) have been described. These are designated when the nodular masses arise in the dermis, in intimate association with blood vessels, or show ganglion-like giant cells and infiltration of collagen. The proper treatment is complete excision. Recurrence is rare and the prognosis is excellent. A rapid response to intralesional corticosteroids has been reported in one case.

Cranial fasciitis of childhood is an uncommon variant of nodular fasciitis, manifesting as a rapidly enlarging mass in the subcutaneous tissue of the scalp, which may invade the cranium. It occurs in infants and children, resembles nodular fasciitis histologically, and usually does not recur after surgical excision.

Graham BS, et al: Nodular fasciitis. J Am Acad Dermatol 1999; 40:490.

Kang SK, et al: Intradermal nodular fasciitis of the face. J Dermatol 2002;29:310.

Leung LY, et al: Nodular fasciitis. Skeletal Radiol 2002;31:9.

Patterson JW, et al: Nodular fasciitis. Arch Dermatol 1989; 125:674.

Silva P, et al: Nodular fasciitis of the head and neck. J Laryngol Otol 2005;119:8.

Plexiform Fibrohistiocytic Tumor

This rare tumor arises primarily on the upper extremities of children and young adults. There is a strong female predisposition. It presents as a slowly growing painless growth in the subcutaneous tissue. There is usually extension into the dermis or the underlying skeletal muscle. Histologically, it is a distinctly biphasic tumor, with a fibroblastic component mixed with aggregates of mononuclear histiocyte-like cells and multinucleated osteoclast-like cells. The multinucleated cells react to CD68, while the spindle cells express smooth muscle actin but not factor XIIIa. While most patients are cured with excisional surgery, some tumors will recur locally, and uncommonly regional and systemic metastases will occur.

Morio O, et al: Plexiform fibrohistiocytic tumor. Eur J Dermatol 2004;14:118.

Atypical Fibroxanthoma

Atypical fibroxanthoma (AFX) of the skin is a low-grade malignancy related to malignant fibrous histiocytoma, which it resembles histologically. Its smaller size and more superficial location account largely for its more favorable prognosis. The lesion occurs chiefly on the sun-exposed parts of the head or neck in white persons over age 50. The tumor begins as a small, firm nodule often with an eroded or crusted surface without characteristic morphologic features (Fig. 28-23). A clinical variant presents as a slowly enlarging tumor on a covered area, in patients with an average age of 39. This variant accounts for 25% of cases.

The lesion develops in the dermis and is separated from the epidermis by a thin band of collagen. The tumor consists of bizarre spindle cells mingled with atypical histiocytes. Some spindle cells have a vesicular nucleus. The cytoplasm may be vacuolated and resembles the xanthoma cell. Mitotic figures, prominent eosinophilic nucleoli, and the presence of a biphasic tumor cell population are characteristic findings. S-100 staining is sparse when compared with melanoma, and prekeratin staining is negative: this helps to distinguish AFX from squamous cell carcinoma. Variants with clear cells, granular cells and osteoclast-type cells have been described.

The treatment of choice is complete surgical excision. Mohs microsurgery results in fewer recurrences and smaller defects than in wide excision. Although the prognosis is excellent, local recurrence after inadequate excision is usual, and cases of metastasizing AFX have been reported.

Anderson PJ, et al: AFX of the scalp. Head Neck 2001;23:399.
Cooper JZ, et al: Metastasizing AFX. Dermatol Surg 2005; 31:221.
Crowson AN, et al: Clear cell AFX. J Cutan Pathol 2002;29:374.
Diaz-Cascajo C, et al: Pigmented AFX. Am J Dermatopathol 2003;25:1.
Dilek FH, et al: AFX of the skin and lower lip in seroderma pigmentosum. Br J Dermatol 2000;143:618.
Guillen DR, et al: Cutaneous and subcutaneous sarcomas. Clin Dematol 2001;19:262.
Hafner J, et al: Malignant fibrous histiocytoma and AFX in renal transplant recipients. Dermatology 1999;198:29.

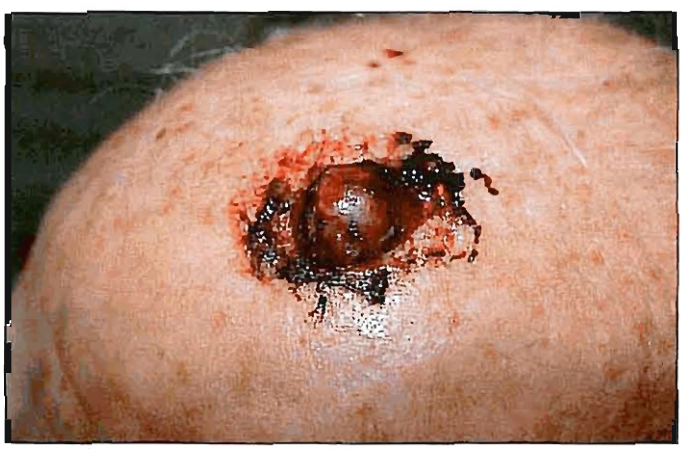

Fig. 28-23 Atypical fibroxanthoma. (Courtesy of Daniel Lao, MD)

Huether MJ, et al: Mohs micrographic surgery for the treatment of spindle cell tumors of the skin. J Am Acad Dermatol 2001; 44:656.
Kaddu S, et al: AFX of the skin. Am J Surg Pathol 2002;26:35.

Malignant Fibrous Histiocytoma

Malignant fibrous histiocytoma (MFH) is the most common soft-tissue sarcoma of middle and late adulthood. It arises deeply and is more likely to appear in deep fascial planes than in subcutaneous tissue. One-third occur on the thigh or buttock. Peak incidence is in the seventh decade. They sometimes arise in an area of radiodermatitis or in a chronic ulceration.

Several histologic variants of MFH have been described, including myxoid, inflammatory, and giant cell types. Cell staining is positive for vimentin. Pleomorphic cellular elements and bizarre mitotic figures are characteristic. AFXs are smaller and more superficial tumors of the dermis, compared with the deeper location of MFH. Epithelioid sarcoma lacks the large, bizarre, multinucleated cells often seen in MFH.

The prognosis in MFH is related to the site; deeper and more proximally located tumors have a poorer prognosis. The myxoid variant is less likely to metastasize. An especially poor prognosis attends tumors arising in sites of radiodermatitis. Local recurrence after excision occurs in 25%, 35% metastasize, and the overall survival rate is 50%. Mohs surgical removal may result in fewer recurrences.

A tumor that presents on the extremities of children as a slowly growing dermal or subcutaneous mass may be the angiomatoid type. It has been separated from the term malignant as it has a relatively good prognosis.

Alconchel MD, et al: Squamous cell carcinoma, malignant melanoma and MFH arising in burn scars. Br J Dermatol 1997;137:793.
Biederman TM, et al: Subcutaneous nodule of the lower extremity. Arch Dermatol 1999;135:1113.
Kamino H, et al: Histopathologic and immunohistochemical diagnosis of benign and malignant fibrous and fibrohistiocytic tumors of the skin. Dermatol Clin 1999;7:487.
Lew W, et al: Cutaneous metastatic malignant fibrous histiocytoma. J Am Acad Dermatol 2003;48:S39.
Pezzi CM, et al: Prognostic factors in 227 patients with malignant fibrous histiocytoma. Cancer 1992;69:2098.
Rothman AE, et al: Pediatric cutaneous malignant fibrous histiocytoma. J Am Acad Dermatol 2000, 42: 371.

Dermal Dendrocyte Hamartoma

Three female patients who were born with a rounded, medallion-like lesion on the upper trunk were found to have a proliferation of fusiform CD34, factor XIIIa-positive cells in the mid and reticular dermis. The lesions were asymptomatic, brown or erythematous in color, and had a slightly atrophic, wrinkled surface (Fig. 28-24).

Rodriguez-Jurado R, et al: Medallion-like dermal dendrocyte hamartoma: a new clinically and histopathologically distinct lesion. J Am Acad Dermatol 2004;51:359.

Epithelioid Sarcoma

Epithelioid sarcoma occurs chiefly in young adults, with onset usually being from 20 to 40 years of age. Two-thirds of

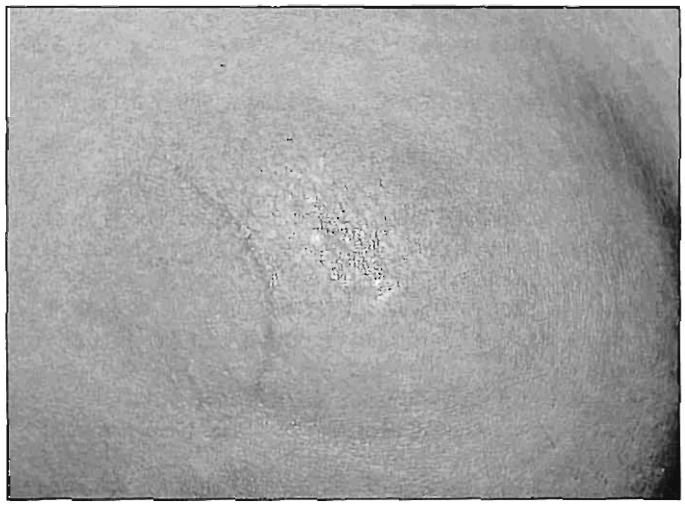

Fig. 28-24 Dermal dendrocyte hamartoma.

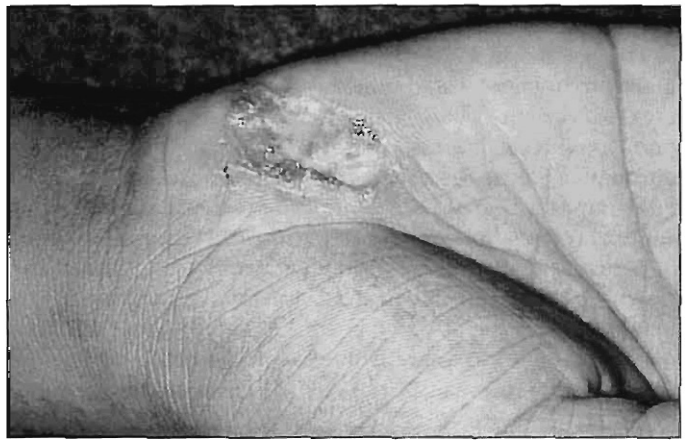

Fig. 28-25 Epithelial sarcoma.

cases are in men. Nearly all lesions are on the extremities, half of them on the hands or wrists (Fig. 28-25). It has, however, been reported from a wide variety of locations, including the genital region, the "proximal type".

The tumor grows slowly among fascial structures and tendons, often with central necrosis of the tumor nodules and ulceration of the overlying skin. Initial clinical diagnoses may include granuloma annulare, rheumatoid nodule, or ganglion cyst. Histologically, irregular nodular masses of large, deeply acidophilic polygonal cells merge with spindle cells in a biphasic pattern. Central necrosis within masses of epithelioid cells may give the impression of a palisaded granuloma. Absence of staining for CD68 (KP-1) and coexpression of keratins and vimentin confirm the diagnosis.

Wide local excision of small, early lesions may achieve a cure. Recurrence after attempted excision occurs in three of four cases, and late metastasis in 45% of patients. There is a propensity for lymph node and lung metastases and in one series of eight patients, 25% 5- and 10-year survival rates were reported. Women have a more favorable prognosis; the proximal lesions have a worse prognosis.

Billngs SD, et al: Epithelioid sarcoma arising on the nose of a child. J Cutan Pathol 2000;27:186.

Gambini C, et al: "Proximal type" epithelioid sarcoma in a girl. Pediatr Dermatol 2004;21:117.

Matsushita Y, et al: Epithelioid sarcoma of the extremities. J Orthop Sci 2002;7:462.

Ross HM, et al: Epithelioid sarcoma. Ann Surg Oncol 1997; 4:491.

Zanolli MD, et al: Epithelioid sarcoma. J Am Acad Dermatol 1992;26:302.

Myxomas

Cutaneous myxomas may be solitary, and appear as flesh-colored nodules on the face, trunk, or extremities. They may also occur as part of Carney complex. This has also been reported under the eponyms *NAME (nevi, atrial myxoma, myxoid neurofibromas, and ephelides)* and *LAMB (lentignes, atrial myxoma, mucocutaneous myxomas, blue nevi)*, and simply as *cutaneous lentiginosis with atrial myxoma.*

The Carney complex consists of patients who have two or more of the following: 1) cardiac myxomas (79%); 2) cutaneous myxomas (not myxoid neurofibromas) (45%); 3) mammary myxoid fibromas (30%); 4) spotty mucocutaneous pigmentation, including lentiginoses (not ephelides) and blue nevi often of a distinctive epithelioid variety (65%); 5) primary pigmented nodular adrenocortical disease (45%), which results in Cushing syndrome; 6) testicular tumors (56% of male patients); and 7) pituitary growth hormone-secreting tumors (10%). A peculiar type of schwannoma featuring melanin and psammoma bodies may also be present.

The cutaneous myxomas occur as small (<1 cm), multiple, skin-colored papules having a predilection for development by a mean age of 18 years, and a tendency to occur on the ears, eyelids, and nipples. The lentigines are prominent on the face, lips, conjunctival mucosa, rectal mucosa, and genital mucosa. Cardiac myxomas may occur in any of the four chamber of the heart and are recurrent in 20%. They may embolize to the skin, producing acral necrotic lesions.

Recognition of this syndrome, with diagnosis and removal of the atrial myxomas, can be lifesaving. The first-degree family members should be examined as this is an autosomal-dominantly inherited condition. The disease has been mapped to two loci and a third is likely. Mutations in the gene coding for the protein kinase A type I-a regulatory subunit (PPKAR1A) on chromosome 17 have been documented in about half of the families.

A malignant counterpart, the myxosarcoma, is a tumor that arises in the subcutaneous fat and underlying soft tissues. There is a tendency for local recurrence after wide and deep excision. Metastases are rare.

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MASTOCYTOSIS

Mastocytosis is a general term applied to local and systemic accumulations of mast cells. Mast cells are bone-marrow–derived CD34+ cells. These cells carry preformed mediators, such as histamine, heparin, and various cytokines, which, when released, may cause symptoms such as flushing, urticaria, diarrhea, abdominal pain, headache, dyspnea, syncope, and palpitations.

Mastocytosis is divided into childhood- and adult-onset disease. The condition varies in these two age groups, in clinical presentation, prognosis, and pathogenic factors. Studies have revealed mutations in the c-KIT protooncogene in many adult-onset cases. Its protein product is the transmembrane tyrosine kinase KIT receptor (CD117) whose ligand is stem cell factor (also known as *mast cell growth factor*). Both clonality studies and mutational analysis indicate that many adult cases of mastocytosis result from a neoplastic proliferation of mast cells, with a mutation at codon 816 in the c-kit gene This mutation is activating, resulting in the proliferation of mast cells. A second mutation, a chromosomal deletion on 4q12 results in the juxtaposition of platelet-derived growth factor receptor-α and FIP1L1. This fusion gene activates hematopoetic cells and is pathogenic in a subset of patients with systemic mastocytosis and eosinophilia. This subset of patients has also been considered a type of "hypereosinophilic syndrome." Thus, the vast majority of adults with mastocytosis have systemic disease which may be viewed as a fundamentally myelodysplastic disorder.

Children often do not express any c-KIT mutation, nor do the uncommon familial cases. The latter is usually transmitted by autosomal-dominant inheritance with reduced expressivity, although other patterns may occur. The mutations leading to familial disease have not been defined. It appears spontaneous childhood disease may occur from either cytokine-derived hyperplasias, from mutations other than the activating 816 type, or from mutations yet to be described. Some pediatric cases, however, are known to have inactivating mutations of c-KIT and a few have the adult-type activating mutations. Childhood disease is defined as occurring before age 15. The majority of children develop their disease before the age of 2, and in most of them the condition spontaneously involutes.

Clinical Classification

Mast cell disease is divided into two broad categories—cutaneous and systemic. Cutaneous mastocytosis describes those cases with involvement of the skin only, and includes most cases of childhood mastocytosis and infrequent adult cases. Childhood cases usually fall into one of three categories of cutaneous mastocytosis: the most common (60–80% of patients) have urticaria pigmentosa or so-called maculopapular cutaneous mastocytosis; fewer (10–35%) patients present with solitary mastocytosis; the remainder have the rare forms of diffuse cutaneous mastocytosis or the telangiectastic type.

A classification has been proposed by Akin and Metcalfe which incorporates the World Health Organization (WHO) criteria (Box 28-1).

The vast majority of adult patients with mastocytosis are classified as systemic mastocytosis, since they typically have clonal proliferation of the bone-marrow derived mast cells.

Box 28-1 Classification of mastocytosis

Cutaneous Mastocytosis
Systemic Mastocytosis

1. Indolent systemic mastocytosis (ISM)
   - Isolated bone marrow mastocytosis
   - Smouldering systemic mastocytosis (SSM)
2. Systemic mastocytosis with associated hematopoetic disease (SM-AHD, AHNMD [associated hematologic disorder mast cell disease]): systemic mastocytosis with leukaemia, myelodysplastic syndrome/disease, or non-Hodgkin lymphoma.
3. Aggressive systemic mastocytosis (ASM)
4. Mast cell leukemia
5. Mast cell sarcoma
6. Extracutaneous mastocytoma

Of adult patients with systemic mastocytosis not associated with hematopoetic disease, 60% have indolent mastocytosis and 40% have aggressive mastocytosis. Patients with aggressive systemic mastocytosis usually lack skin lesions. Mast cell leukemia and sarcoma are very rare. Many patients who present to the dermatologist with only skin lesions will have the indolent variety. Symptoms and signs of systemic disease are classified as those related to organ infiltration by mast cells, and those due to mediator release from mast cells. Direct organ involvement is most frequently bone pain from lytic bone lesions, hepatosplenomegaly, lymphadenopathy, or cytopenia from bone marrow involvement. For the dermatologists, the most important symptoms are those related to mediator release, usually acting on the gastrointestinal tract, respiratory tree, or blood vessels. These include pruritus, flushing, urticaria, angioedema, headache, nausea, vomiting, abdominal cramps, diarrhea, gastric and/or duodenal ulcer, malabsorption, asthma-like symptoms, presyncope, syncope, and anaphylaxis. These may occur spontaneously or be the result of massive histamine release after ingestion of known mast cell degranlators such as alcohol, morphine, codeine or extended rubbing of the skin. *Hymenoptera* stings may induce anaphylaxis. Mast cells also produce heparin, which may result in hematemesis, epistaxis, melena, and ecchymoses. Osteoporosis may also occur from chronic heparin release, resulting in fractures.

Cutaneous Mastocytosis

Cutaneous mastocytosis is relatively common, representing about 1 in 500 initial consultations to pediatric dermatologists.

Solitary Mastocytoma About 10% to 40% of childhood mastocytosis presents in this way. The solitary lesion may be present at birth or may develop during the first weeks of life. It originates as a brown macule that urticates on stroking. It may develop into a papule, a raised round or oval plaque, or a tumor. The size is usually less than 1 cm, but occasionally may reach two or three times this diameter. The surface is usually smooth, but may have a peau d'orange appearance. Although the mastocytoma may occur anywhere on the body, its favorite location is on the dorsum of the hand near the wrist. Edema, urtication, vesiculation, and even bulla

formation may be observed in the lesion. Even a solitary lesion may produce systemic symptoms, usually flushing.

Although the generalized form may begin with a single lesion, dissemination usually occurs within 3 months of its appearance. Most solitary mastocytomas involute spontaneously by the age of 10 or earlier. They also respond favorably to excision, or the application of a hydrocolloid dressing to prevent the rubbing which triggers mediator release and symptomatology. Progression to malignant disease does not occur.

Generalized Eruption, Childhood Type (Urticaria Pigmentosa) This form of cutaneous mastocytosis represents 60% to 90% of childhood cases. In this type, the eruption usually begins during the first weeks of life, presenting with rose-colored, pruritic, urticarial, slightly pigmented macules, papules, or nodules. The lesions are oval or round, and vary in diameter between 5 and 15 mm and may coalesce. The color varies from yellowish-brown to yellowish-red. Occasionally the lesions are a pale yellow color and this has been called xanthelasmoidea. Vesicle and bulla formation is a frequent prominent feature early in the disease (Fig. 28-26). Indeed, vesicles and bullae may be the initial presenting signs, but they usually persist no longer than 3 years. In the older age groups vesiculation rarely occurs.

At their onset, lesions are similar to urticaria except that they are not evanescent. The lesions persist and gradually become chamois- or slate-colored (Fig. 28-27). When they are firmly stroked or vigorously rubbed, urticaria with a surrounding erythematous flare (Darier's sign) usually develops. Dermographism of clinically uninvolved skin is present in a third to a half of patients. For many years the brown, waxy skin lesions may persist before they begin to involute. Pigmentation and all evidence of the disease commonly disappear within a few years, generally before puberty. The eruption, however, may uncommonly persist into adult life. Although systemic involvement is possible, malignant systemic disease is extremely rare.

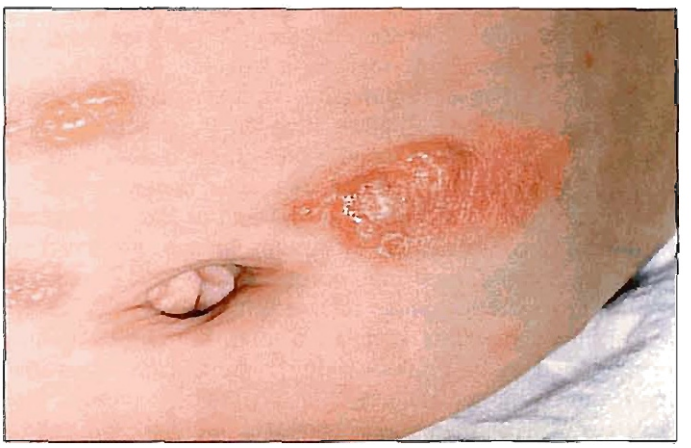

Fig. 28-26 Bullous mastocytosis.

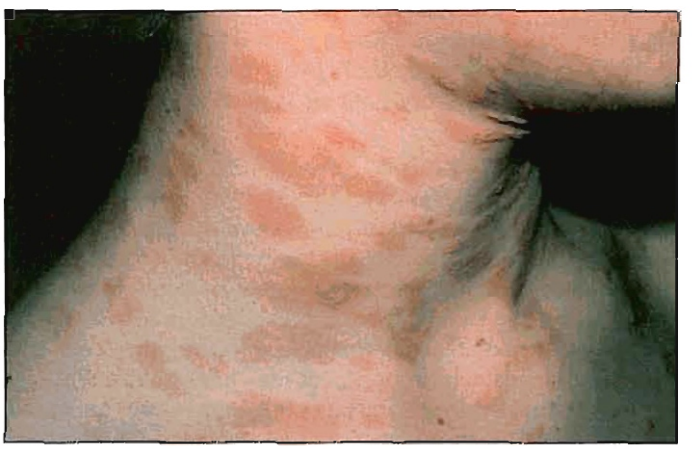

Fig. 28-27 Urticaria pigmentosa.

Diffuse Cutaneous Mastocytosis In this rare form, with diffuse involvement, the entire integument may be thickened and infiltrated with mast cells to produce a peculiar orange color, giving rise to the term *homme orange*. There is an infiltrated doughy or boggy consistency to the skin, and lichenification may be present. In the neonatal period diffuse cutaneous blistering may occur, leading to the diagnosis of epidermolysis bullosa or some other primary bullous disorder. This is termed "bullous mastocytosis."

Systemic Mastocytosis

Systemic mastocytosis is diagnosed by fulfilling the one major criterion and one minor criteria, or three minor criteria. The major criterion is the finding of dense infiltrates of mast cells (aggregates of 15 or more) in bone marrow or other extracutaneous tissues. The four minor crtiteria are: 1) atypical mast cell morphology; 2) aberrant mast cell surface phenotype (CD25 or CD2); 3) serum/plasma tryptase greater than 20 ng/mL; and 4) a codon 816 c-KIT mutation in peripheral blood, bone marrow or lesional tissue.

The most common type of systemic mastocytosis in adults is indolent systemic mastocytosis. These patients lack evidence of an associated nonmast cell hematologic disorder; lack end-organ dysfunction such as ascites, malabsorption, cytopenias, and pathologic fractures; and lack mast cell leukemia. The disorder is then diagnosed through physical and histopathologic examination of skin lesions. Several different patterns of cutaneous involvement have been described.

Generalized Eruption, Adult Type This is the most common pattern of mastocytosis presenting to the dermatologist. The most common lesions are macules, papules or nodules disseminated over most of the body but especially on the upper arms, legs, and trunk (Fig. 28-28). The upper arms and upper inner thighs may be the only areas involved on presentation. These may be reddish-purple (Fig. 28-29), rust colored, or brown. In the latter case they may closely resemble common nevi. They may urticate upon rubbing, as is seen in children with urticaria pigmentosa.

Erythrodermic Mastocytosis There is generalized erythroderma and the skin has a leather-grain appearance. Urtication can be produced over the entire surface.

Telangiectasia Macularis Eruptiva Perstans This is a persistent, pigmented, asymptomatic eruption of macules usually less than 0.5 cm in diameter with a slightly reddish-brown tinge. Despite the name, little or no telangiectasia may evident. Darier's sign may not be demonstrable, as the number of mast cells in the skin may not be greatly increased.

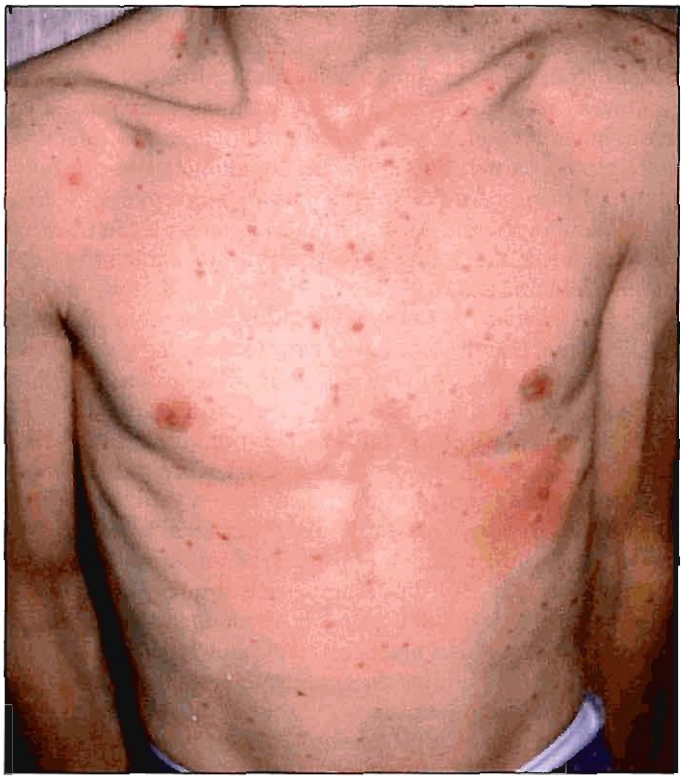

Fig. 28-28 Adult generalized mastocytosis.

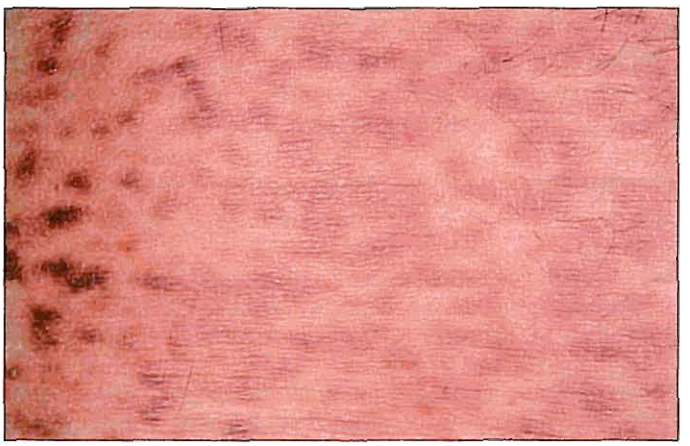

Fig. 28-29 Adult generalized mastocytosis.

Classification and Prognosis in Adult Systemic Mastocytosis

Patients with systemic mastocytosis and associated hematologic disorder (AHDMD/SM-AHD) are typically older adults with signs and symptoms of systemic disease. A variety of associated nonmast cell hematologic conditions, including polycythemia vera, hypereosinophilic syndrome, chronic myelogenous or monocytic leukemia, lymphocytic leukemia, primary myelofibrosis, and Hodgkin's disease may be seen. Typically this type does not have skin lesions. The prognosis in these patients is that of their underlying hematologic condition. Smouldering systemic mastocytosis is characterized by a slow progression and lack of end-organ dysfunction due to mast cell infiltration. It describes patients with 30% or more infiltration of the bone marrow cavity by mast cells, a serum typtase of greater than 200 ng/mL and hepatosplenomegaly. Adult systemic mastocytosis has a more fulminant course and describes those patients with end-organ dysfunction due to mast cell infiltration (bone marrow failure, liver dysfunction, splenomegaly with hypersplenism, pathologic fractures, and gastro-intestinal involvement with malabsorption and weight loss). This group of patients has a poor prognosis. Mast cell leukemia occurs when the atypical mast cells (multilobular or multiple nuclei) represent 10% of circulating cells or 20% of bone marrow cells. The prognosis is poor.

Mast Cell Sarcoma and Extracutaneous Mastocytoma

These are rare findings of isolated tumors of either atypical mast cells in mast cell sarcoma, or benign appearing mast cells in extracutaneous mastocytoma. They occur in sites other than the skin or bone marrow. Mast cell sarcomas are aggressive locally destructive lesions as opposed to the benign mastocyomas which carry a good prognosis.

Biochemical Studies

Mast cells produce tryptase. It has become the preferred laboratory test to demonstrate evidence of increased mast cell burden, replacing urinary histamine and urinary histamine metabolites. It is of prognostic significance in some cases. Tryptase is measured as a total serum tryptase level. This should be obtained when the patient is in his/her normal state of health as anaphylaxis will increase it transiently. Mastocytosis patients may have a persistently and significantly elevated level. Results above 20 ng/mL are a minor criterion for the diagnosis of systemic mastocytosis.

Histopathology

The typical skin lesion shows a dense dermal aggregate of mononuclear cells with abundant basophilic cytoplasm. When these large mononuclear cells are stained with Giemsa or toluidine blue, the metachromatic granules are observed. When blisters are present, the roof of the vesicle or bulla is subepidermal. The mast cells collect in a band below the vesicle. Infiltration of local anesthetic adjacent to the lesion rather than directly into it and the use of anesthetic without epinephrine may help to avoid mast cell degranulation. Monoclonal antibodies against tryptase and CD117 (KIT) are available and sensitive when done well. They are rarely required, however.

Diagnosis

The typical case of cutaneous mastocytosis is easily diagnosed by the presence of solitary or multiple pigmented macules, papules or nodules that urticate when irritated by stroking or scratching. The diagnosis is confirmed by biopsy of the lesion with the demonstration of increased numbers of mast cells. The bullous and vesicular lesions may be more difficult to diagnose clinically; however, scrapings from the base of the bulla when stained with Giemsa or Wright stain will show mast cells in profusion.

Once the diagnosis of skin lesions of mastocytosis is made, the decision to assess for bone marrow involvement is key. While therapy to reduce the disease burden of proliferating clonal mast cells is not effective, bone marrow examination will provide information about the extent of the disease and the presence or absence of a nonmast-cell hematologic

disorder, and will assist in the counseling concerning prognosis. All adult patients and children with the unexplained presence of an abnormal complete blood count (CBC), hepatomegaly, splenomegaly, lymphadenopathy or a serum baseline tryptase of greater than 20 ng/mL should be offered a bone marrow examination. In asymptomatic adults with their only sign or symptom of mastocytosis being skin lesions, and who do not desire a bone marrow examination, serum tryptase and CBC should be repeated at least yearly during a complete history and physical examination. Elevation of the tryptase level, a drop in the platelet count or hemoglobin or a rise in the monocytes, or the onset of organomegaly should trigger a bone marrow examination. In children with early-onset disease, the prognosis is good; usually tryptase evaluations or mutational analysis is reserved for those with the above findings, or with persistent localized bone pain, severe gastrointestinal symptoms or biochemical evidence of hepatic insufficiency.

Differential Diagnosis

Clinically, a small solitary mastocytoma most frequently resembles a pigmented nevus or juvenile xanthogranuloma. Urtication establishes the diagnosis. The disseminated lesions are also distinctive enough to give little or no difficulty in the diagnosis. The nodular form may resemble xanthomas; however, the presence of urtication is distinctive. The vesicular and bullous lesions are to be distinguished from various hereditary and nonhereditary bullous diseases. The main histologic similarity is to Langerhans cell histiocytosis.

Prognosis

Most cases of early-onset, skin-limited disease in children clear completely. The solitary mastocytoma involutes spontaneously, usually within 3 years of onset. In those children and adults with indolent systemic mastocytosis the prognosis is also good. This is the most common category of patients presenting for diagnosis in the dermatology clinic. Patients with AHNMD have the prognosis of the associated disease. In the newly described patients with smouldering systemic mastocytosis, the prognosis is intermediate and not yet well defined. Aggressive systemic mastocytosis, mast cell leukemia, and mast cell sarcoma patients have a poor prognosis.

Treatment

Symptomatic relief of histamine-mediated symptoms may be achieved in many cases by the use of antihistamines. Both H_1 and H_2 blockers and antiserotonin drugs, such as cyproheptadine may alleviate urtication, pruritus, and flushing. Nifedipine, 10 mg three times a day, may also be effective in isolated cases. Psoralen with ultraviolet A (PUVA) or medium-dose UVA1 alone produce excellent clearing of the skin in most cases. Most patients will have sustained benefit for at least 6 months following treatment. Approximately 25% will have a remission lasting longer than 5 years and in others the frequency of phototherapy may be tapered to once or twice a month and still remain clear. Intralesional triamcinolone or potent topical steroids under occlusion may also clear cutaneous lesions; however, the lesions do recur after discontinuance. Also, concern about local atrophy, striae, and systemic absorption limit the utility of this treatment.

It cannot be overemphasized that avoidance of physical stimuli, such as extremes of temperature, pressure/friction, and chemical degranulators of mast cells, is important. The application of a hydrocolloid dressing over an isolated mastocytoma in an infant may reduce the flushing it produces. The chemicals patients with mastocytosis must avoid include opiates, aspirin, alcohol, quinine, scopolamine, gallamine decamethonium, reserpine, amphotericin B, polymyxin B, and D-tubocurarine. *Hymenoptera* stings may induce anaphylaxis; the patient (and parents, if the affected individual is a child) should be taught to recognize the signs of anaphylactic shock, given a premeasured dose of epinephrine (Epipen) for emergency use, and taught about its use. After such an event it is prudent to treat for several days with 20 to 40 mg of prednisone to avoid recurrent attacks.

Control of diarrhea in systemic mastocytosis may be achieved by orally administered disodium cromoglycate. Gastrointestinal ulcers may be treated with proton-pump inhibitors and H_2 antagonists. The treatment of the systemic mast cells disease is of limited efficacy. For patients with indolent systemic mastocytosis and severe osteoporosis, IFN-α may be considered. In patients with smoldering systemic mastocytosis, watchful waiting is recommended, although IFN-α with or without glucocorticoids may be considered for progressive "B" findings. In aggressive systemic mastocytosis, IFN-α may also be used with or without glucocorticoids. 2-Chlorodeoxyadenosine (as used in Langerhans cell histiocytosis) can also be effective in aggressive systemic mastocytosis. Patients with systemic mastocytosis with or without eosinophilia who have the FIP1L1–PDGFRA translocation or lack the 816 c-KIT mutation may respond to imatinib mesylate. Patients with the 816 c-KIT mutation do not respond to this treatment. Bone marrow transplantation for the most severely affected patients with systemic mastocytosis is being investigated.

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ABNORMALITIES OF NEURAL TISSUE

Solitary Neurofibroma

The ordinary solitary cutaneous neurofibroma may be 2 to 20 mm in diameter. It is soft, flaccid, and pinkish-white. Frequently the soft small tumor can be invaginated, as if through a ring in the skin, by pressure with the finger (this is called "button-holing").

Neurofibroma is either solitary or multiple. When only one or two lesions are present, they are typically spontaneous tumors without any internal manifestations. When three or more are present, a diagnosis of neurofibromatosis should be considered. Uncommonly, large pendulous masses occur in which numerous, tortuous, thickened nerves can be felt; this has been likened to a "bag of worms." These plexiform neurofibromas, which often have overlying pigmentation, usually occur in neurofibromatosis. Neurofibromatosis is discussed in Chapter 27.

Histologically, the lesion demonstrates wavy spindled nuclei and fine collagen fibers. The stroma is often myxoid and contains many mast cells. Cholinesterase activity is markedly positive in the neurofibromas. Immunochemical staining shows positivity for S-100, vimentin, and myelin basic protein, markers for schwannian tissue.

Treatment of those lesions that are particularly objectionable is by surgical excision.

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Granular Cell Tumor

About one-third of reported cases occur on the tongue (Fig. 28-30), one-third involve the skin (Fig. 28-31), and one-third occur in the internal organs. The tumor is usually a well-circumscribed, solitary, firm nodule ranging from 5 to 30 mm with a brownish-red or flesh tint, depending on nearness to the surface. Its surface may be smooth, rough or verrucous. Rarely, the lesions may ulcerate. They are multiple in 10% to 15% of cases.

The solitary lesion may be located anywhere on the body, but nearly half of all tumors appear on the head or neck. Usually the patients are in their third to fifth decade. About two-thirds of patients are black, and two-thirds are women. In most cases it grows very slowly, and when completely removed does not usually recur. However, local or multicentric recurrence may at times cause confusion in determining if a granular cell tumor is malignant.

The histologic picture is distinctive. The cells are large, pale, and irregularly polygonal, with a poorly defined cellular

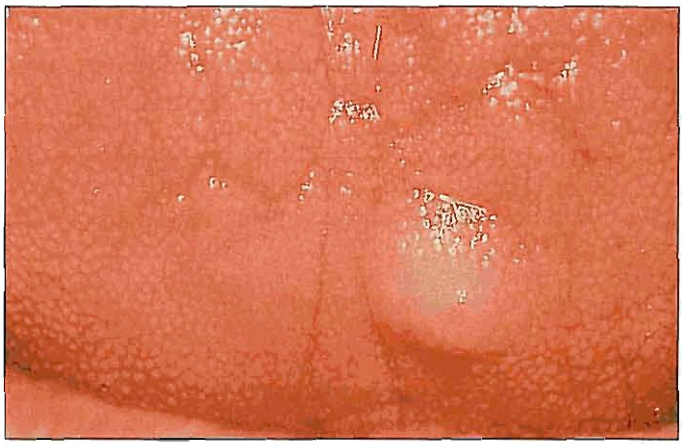

Fig. 28-30 Granular cell tumor of the tongue.

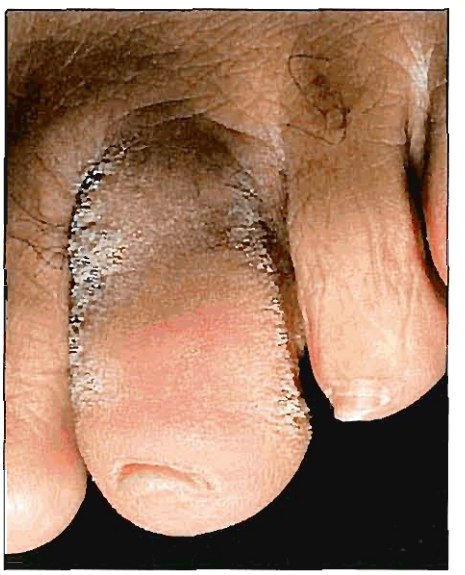

Fig. 28-31 Granular cell tumor.

membrane, and contain coarsely granular cytoplasm. Some of the cells are multinucleated or contain vacuoles or small pyknotic or eosinophilic inclusions. At times the arrangement is in cords or sheets, in irregular alveolar masses, or even organoid. Pseudo-epitheliomatous hyperplasia is a regular feature. The cells stain positively with vimentin, neuron-specific enolase, S-100, and myelin protein.

Malignant granular cell tumor is uncommon. Most are much larger than the benign granular cell tumors, with an average diameter of 9 cm; benign lesions average less than 2 cm. Most malignant granular cell tumors demonstrate cytologic atypia, but some are quite bland cytologically. Other factors that correlate with malignant behavior are an infiltrative growth pattern, history of local recurrence, older patient age, presence of necrosis, increased mitotic activity, spindling of tumor cells, and nuclear staining with the proliferation marker Ki67 (MIB 1) in greater than 10% of tumor nuclei. Mutant p53 protein has been identified in more thana half of malignant granular cell tumors studied. About one-third are aneuploid, one-third hyperdiploid, and one-third diploid. In contrast, almost all benign tumors are diploid.

Because of the difficulties in distinguishing benign from some malignant granular cell tumors, complete excision is advisable whenever possible. Malignant granular cell tumors often have an infiltrative growth pattern and perineural extension. Mohs micrographic surgery may be helpful in ensuring complete excision.

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Neuroma Cutis

Cutaneous neuromas are uncommon. Three true neuromas exist in the skin and mucous membranes: traumatic neuromas, multiple mucosal neuromas, and solitary palisaded encapsulated neuromas.

Traumatic neuromas (Fig. 28-32) result from the overgrowth of nerve fibers in the severed ends of peripheral nerves. The lesion may be tender or painful, and when scarring has occurred or the distal stump has been removed, a phantom limb syndrome may result. These often occur on the fingers, at sites of amputation of supernumerary digits, or on the sole, usually at the third metatarsal space.

Multiple mucosal neuromas (Fig. 28-33) occur as part of the autosomal-dominantly inherited multiple mucosal neuroma syndrome (multiple endocrine neoplasia, type 2b). These patients have a marfanoid habitus, thickened protruding lips, and multiple neuromas of the oral mucosa (lips, tongue, and gingiva), conjunctiva, and sometimes sclera. A few have multiple cutaneous neuromas, usually limited to the face. There is a strong association with medullary carcinoma of the thyroid, bilateral pheochromocytomas, and diffuse gastrointestinal tract ganglioneuromatosis. It is caused by a mutation in the RET proto-oncogene. Infants at risk should be screened for this mutation, and total thyroidectomy performed if positive.

The palisaded, encapsulated neuroma of the skin is a solitary, large, encapsulated tumor, usually of the face. It is a slow-growing, flesh-colored, dome-shaped, firm lesion usually appearing around the mouth or nose. It closely resembles a basal cell carcinoma or an intradermal nevus.

Kim KJ, et al: A freely movable subcutaneous nodule on the dorsum of the hand. Arch Dermatol 2004;140:1003.

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Lee NC, et al: Multiple endocrine neoplasia type 2B—genetic basis and clinical expression. Surg Oncol 2000;9:111.

Navarro M, et al: Palisaded encapsulated neuroma of the glans penis. Br J Dermatol 2000;142:1061.

Zhang M, et al: Traumatic neuroma in the lower lip arising following laser/cryosurgery to treat a mucocele. Oral Dis 2003;9:160.

Neurothekeoma (Nerve Sheath Myxoma)

Neurothekeoma, meaning a tumor of the nerve sheath, is composed of cords and nests of large cells packed among collagen bundles in close proximity to small nerves. Mitotic figures and nuclear atypia are sometimes seen, but the tumor is benign. These benign intradermal or subcutaneous tumors histologically are divided into two distinct subtypes, the classic or myxoid variant and the cellular type. An intermediate or mixed variety is also recognized. The myxoid variant (nerve sheath myxoma) is characterized by large islands of stellate and spindled cells in a mucinous matrix. The cells stain strongly for S-100 protein. Myxoid neuro-

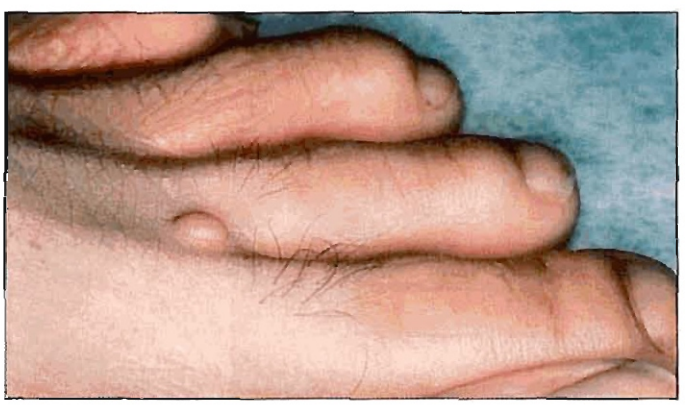

Fig. 28-32 Traumatic neuroma.

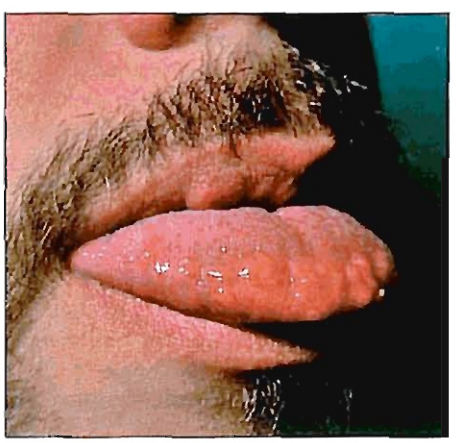

Fig. 28-33 Multiple mucosal neuromas.

thekeoma occurs in middle-aged adults, primarily on the head, neck, and upper extremities. It is twice as common in women. The cellular type occurs in childhood, with a high female preponderance, and has a predilection for the head, neck, or shoulders. The cellular type does not stain for S-100 protein, but does stain for S-100A6, PGP9.5, and NK1C3.

Fullen DR, et al: Antibody to S100a6 protein is a sensitive immunohistochemical marker for neurothekeoma. J Cutan Pathol 2003;30:118.
Papadopoulos EJ, et al: Neurothekeoma. J Am Acad Dermatol 2004;50:129.
Watanabe K, et al: Subcutaneous cellular neurothekeoma. Br J Dermatol 2001;144:1273.

Schwannoma (Neurilemmoma)

Peripheral schwannomas are usually solitary nerve sheath tumors, most often seen in women. They occur almost exclusively in deep tissues, along the main nerve trunks of the extremities, especially the flexor surface of the arms, wrists, and knees. They are also seen on the scalp, sides of the neck, and tongue. The solitary tumor is a nodule of 3 to 30 mm in diameter (Fig. 28-34). It is soft or firm, pale pink or yellowish; it may or may not be painful. Schwannomas occur in many other organs, and brain tumors such as meningiomas, gliomas, and astrocytomas may occur.

Sometimes the tumors are multiple. When this occurs, they may be seen with neurofibromatosis type 1 (NF-1) or, more commonly type 2, or as an entity independent of neurofibromatosis. The independent type may be congenital or have a delayed onset. It may be sporadic or familial. Three clinical patterns are described: elevated dome-shaped nodules; pale brown indurated macules; and multiple papules coalescing into plaques from 2 to 100 mm in diameter, with a predilection for the trunk. Cases have occurred that appeared to be unassociated with NF-2, but on further investigation of the individual or family revealed other signs of NF-2 and the gene abnormality on chromosome 22.

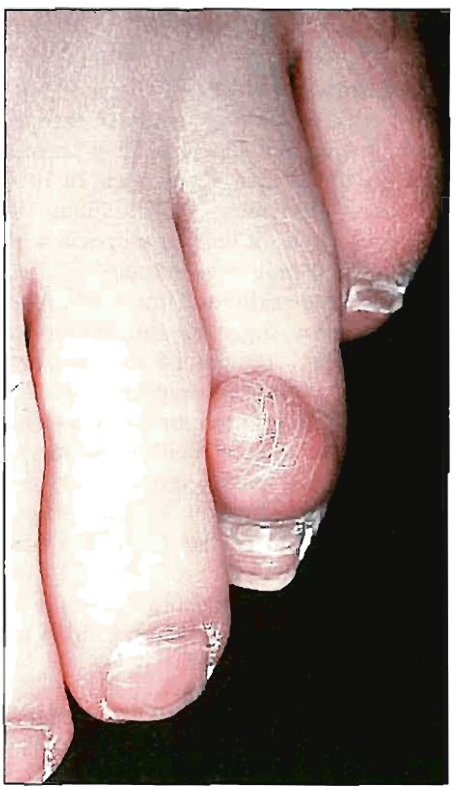

Fig. 28-34
Neurilemmoma.

Plexiform schwannomas may occur as single or multiple lesions, localized to a single anatomic site or more generalized, and arise in the dermis or subcutaneous tissue. They may occur as a solitary lesion, or be associated with NF-1, NF-2, or multiple schwannomas. Another subtype of schwannoma is the melanotic psammomatous type that is seen in association with Carney syndrome of spotty pigmentation, myxomas, and endocrine overactivity.

Histologically, the classic types are well encapsulated and composed of two types of tissue, referred to as *Antoni types A* and *B*. Hard schwannomas are firm on gross examination, and are composed of Antoni A tissue—palisades of basophilic Schwann cell nuclei separated by brightly eosinophilic zones (Verocay bodies). Soft schwannomas are edematous. They are composed mostly or entirely of Antoni B tissue, a degenerative change characterized by loose, edematous connective tissue and ectatic blood vessels. S-100, vimentin, and myelin basic protein stains are positive in hard schwannomas. Staining is variable in soft schwannomas. A Bodian or neurofilament stain reveals very few or no nerve fibers within the bulk of the tumor, although a compressed nerve may be present at one edge of the mass in a subcapsular location. Ancient schwannomas may demonstrate remarkable nuclear atypia, which represents a benign degenerative change. Mitoses are absent. Ancient schwannomas should not be confused with malignant schwannoma (neurofibrosarcoma), a tumor that generally arises in long-standing neurofibromas in the setting of NF-1. Excision is almost invariably curative, except in the malignant variety where combined wide resection and radiotherapy is needed.

Classens N, et al: Cutaneous psammomatous melanotic schwannoma. Am J Clin Dermatol 2003;4:799.
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Kurtkaya-Yapicier O, et al: The pathobiologic spectrum of Schwannomas. Histol Histopathol 2003;18:925.
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Ritter SE, et al: Cutaneous schwannoma of the foot. Cutis 2001;67:127.
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Infantile Neuroblastoma

Neuroblastoma is the most common malignant tumor of early childhood. Cutaneous nodules are most often seen in younger patients, being present in 32% of infants with the disease. These occur as multiple 2- to 20-mm, firm, blue nodules that, when rubbed, blanch and form a halo of erythema. The blanching persists for 1 to 2 h and is followed by a refractory period of several hours. Biopsy shows clusters of basophilic cells with a high nuclear-to-cytoplasmic ratio,

surrounded by eosinophilic fine fibrillar material. Two other findings that may be present are periorbital ecchymoses (the so-called raccoon eyes) and heterochromia of the irises.

For infants with skin involvement the prognosis is good, with either spontaneous remission or spontaneous transformation into benign ganglioneuromas expected. Prognostic factors other than age, based upon molecular genetic characteristics such as the status of the oncogene MYCN and chromosome 1p deletion, are helping to stratify prognosis and therapeutic recommendations.

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Ganglioneuroma

Ganglioneuroma has only rarely been described in the skin as an isolated entity. These tumors are composed of mature ganglion cells comingled with fascicles of spindle cells. They arise most often in von Recklinghausen neurofibromatosis or with neuroblastomas, and usually occur in childhood. The tissue stains positively for both argyrophilic and argentaffin granules.

Gambini C, et al: Primary congenital cutaneous ganglioneuroma. J Am Acad Dermatol 1996;35:353.
Parkham DM: Neuroectodermal and neuroendocrine tumors principally seen in children Am J Clin Pathol 2001;115(Suppl): S113.

Nasal Glioma (Cephalic Brainlike Heterotopias)

Nasal gliomas are rare, benign, congenital tumors. When they occur extranasally, they are easily confused with hemangiomas. The tumor is usually a firm, incompressible (unlike a hemangioma and encephalocele), reddish-blue to purple lesion occurring on the nasal bridge or midline near the root. It does not transilluminate or enlarge with crying, unlike some encephaloceles. They may also occur intranasally.

Nasal gliomas differ from encephaloceles in that the latter are connected to the subarachnoid space by a sinus tract, while the former usually lose this connection before birth. Clinically, these cannot be absolutely differentiated, so a biopsy should not be performed. Skull radiographs, MRI, ultrasound, and Doppler flow studies may be performed; these will help define the lesion and detect possible skull involvement. Neurosurgical consultation is advisable.

Histologically, the nodule consists of glial tissue associated with glial giant cells, fibrous tissue, and numerous blood vessels. It is unencapsulated. The lesion does not involute spontaneously.

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Cutaneous Meningioma

Primary cutaneous meningioma, also known as *rudimentary meningocele*, is a developmental defect. It results from the presence of meningocytes outside the calvarium. If actual brain remnants are present, the lesion is called a *rudimentary cephalocele*. Small, hard, fibrous, calcified nodules occur along the spine, in the scalp, on the forehead, or rarely in the external ear canal. Most occur over the scalp, some have an underlying connection to the CNS or an underlying bony abnormality, and usually come to medical attention in the first year of life. On the scalp they may present with a dark tuft of hair or an alopecic area surrounded by a dark collar of hair (hair collar sign).

Cutaneous meningiomas may develop in the scalp secondary to an intracranial meningioma, either by means of erosion of the skull, or by extension through an operative defect of the skull. Finally, they may also arise from cranial or spinal nerves. Clinically, these lesions have no distinctive appearance. They are firm subcutaneous nodules adherent to the skin.

Diagnosis is made by histologic examination. The tumors consist of strands of cells with large oval vesicular nuclei and granular cytoplasm. Lamellar, calcified psammoma bodies are commonly present. Psammoma bodies are not specific for meningiomas, and may also be found in intradermal nevi, juvenile xanthogranuloma, the pituitary of the fetus and newborn, schwannomas associated with Carney syndrome, meninges, choroid plexus, pineal gland, papillary carcinoma of the thyroid, ovarian neoplasms, and mammary intraductal papilloma.

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Fung MA, et al: Intracranial malignant meningioma mimicking frontalis-associated lipoma of the forehead. J Am Acad Dermatol 1996;34:306.
Penas PF, et al: Cutaneous meningioma underlying congenital localized hypertrichosis. J Am Acad Dermatol 1994;30:363.
Stone MS, et al: Rudimentary meningocele presenting with a scalp hair tuft. Arch Dermatol 1994;130:775.

Encephalocele and Meningocele

Primary defects in the neural tube may lead to encephaloceles, meningoceles, or meningomyeloceles. They present in infancy along the midline of the face, scalp, neck, or back as soft, compressible masses that may transilluminate or enlarge with crying. Tufts of long, dark hair, or alopecia with a surrounding collar of dark hair may overlie them.

Many cutaneous lesions of the midline of the back, most commonly at the base of the spine, suggest malformations of the spinal cord and associated structures are present. Cutaneous manifestations of spinal dysraphism include depressed or polypoid lesions; dyschromic or hairy lesions; dermal or subcutaneous lesions; vascular malformations; or neoplasms of many types. Midline masses require intensive radiologic and neurosurgical evaluation before biopsy because of the possible connection to the CNS. The MRI is the imaging modality of choice. Approximately 10% of patients with one lesion will have occult spinal dysraphism, whereas the majority with two or more different lesions are affected.

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Wiss K: Midline developmental defects in children. Adv Dermatol 2000;15:109.

Chordomas

These slow-growing, locally invasive neoplasms present as firm, smooth nodules in the sacrococcygeal region or at the base of the skull in middle-aged patients. They arise from notochord remnants. The pathologic appearance is that of incompletely encapsulated sheets, nests, and cords of large epithelioid cells with fibrous trabeculae present. They may metastasize late in their course to various sites, including the skin.

Wide excision with postoperative radiation therapy is the treatment of choice.

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ABNORMALITIES OF FAT TISSUE

Lipomas

Lipomas, subcutaneous tumors composed of fat tissue, may occur as a solitary sporadic lesion or as multiple lesions with or without a familial component. There are multiple histologic subtypes, and these frequently have an associated clinical correlation. Most have specific chromosomal alterations that help in their identification in difficult cases. Protease inhibitors given for HIV disease may induce lipomas, angiolipomas, or benign symmetric lipomatosis, as well as lipodystrophy.

Lipomas are most commonly found on the trunk. They also occur frequently on the neck, forearms, and axillae. They are soft, single or multiple, small or large, lobulated, compressible growths, over which the skin on traction often becomes dimpled, although otherwise unchanged. They usually stop growing after attaining a certain size, then remain stationary indefinitely. Frontalis-associated lipomas of the forehead are relatively large lesions arising either within or deep to the frontalis muscle (Fig. 28-35).

A lipoma located in the midline of the sacral region may be a marker for spinal dysraphism or other embryologic malformation. Other midline lesions, such as tufts of hair ("fawn's tail"), hemangiomas (Cobb syndrome), skin tags, sinuses, or pigmented lesions should also raise suspicion for occult embryologic malformations. An MRI is the most sensitive imaging modality. If spinal dysraphism is diagnosed, early treatment may be possible before irreversible damage has occurred. Do not attempt to biopsy a sacrococcygeal lipoma; call a neurosurgeon into consultation. It may be a lipomeningocele with communicating sinuses to the dura.

Histologically, the lipoma is an encapsulated, lobulated tumor containing normal fat cells held together by strands of connective tissue. Occasionally, eccrine sweat glands may be associated and then they are called *adenolipomas*. Alterations in chromosomes 12q13–15 and chromosome 13q12–22 may be detected in benign lipomas.

In the differential diagnosis, the epidermoid cyst should always be considered. At times it is difficult to distinguish the two. Many soft, deep, single, nongrowing lesions of the skin do not require biopsy. The appearance of multiple lesions or progressive growth indicates the need for biopsy. Large solitary lesions should be investigated for malignancy, especially when they occur on the upper thigh.

Lipomas may be left untreated unless they are large enough to be objectionable. They may be excised, removed with liposuction, extruded through a 3-mm incision after being freed with a cutting curette, or segmentally extracted through a stab incision. More advanced surgical technique is necessary to remove the deep lesions on the forehead, which may lie below the fascial plane.

Multiple lipomas may occur in groups of two to hundreds of confluent painless tumors of various sizes over any part of the body (Fig. 28-36). These lesions are sometimes painful when growing rapidly. When present in certain patterns, special designations are applied. Madelung's disease (benign symmetric lipomatosis or multiple symmetric lipomatosis)

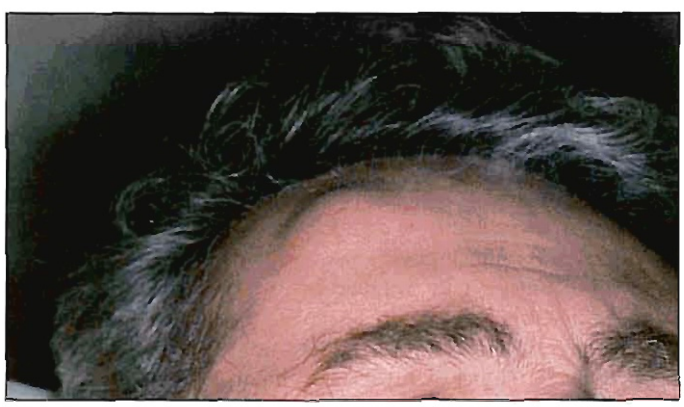

Fig. 28-35 Frontalis-associated lipoma of the forehead.

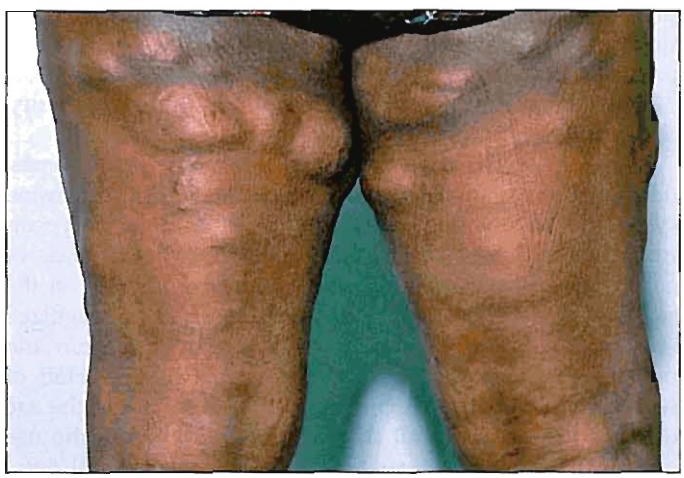

Fig. 28-36 Multiple lipomas.

occurs most commonly in middle-aged men, who may develop multiple, large, painless, coalescent lipomas around the neck, shoulders, and upper arms. Familial multiple lipomatosis is a dominantly-inherited syndrome in which multiple asymptomatic lipomas of the forearms and thighs appear in the third decade of life. The shoulders and neck are spared, and the lipomas are encapsulated and movable. Diffuse lipomatosis is characterized by an early age of onset, usually before the age of 2; diffuse infiltration of muscle by an unencapsulated mass of histologically mature lipocytes: and progressive enlargement and extension of the tumor mass. It usually involves a large portion of the trunk or an extremity. Some cases are associated with distant lipomas or hemangiomas or with hypertrophy of underlying bone.

Dercum's disease (adiposis dolorosa) is seen most often in obese or corpulent menopausal women who develop symmetrical, tender, circumscribed fatty lesions. They are often accompanied by weakness and psychiatric disturbances. Relief of pain lasting for weeks after intravenous infusions of lidocaine, 1.3 g/day for 4 days, has been reported.

Several other conditions are characterized by multiple abnormalities including lipomas. Encephalocraniocutaneous lipomatosis is a rare neurocutaneous syndrome characterized by unilateral porencephalic cysts with cortical atrophy, ipsilateral facial and scalp lesions, ocular abnormalities, cranial asymmetry, and neurologic complications. The skin changes consist of unilateral lipomatous scalp tumors with overlying alopecia and connective tissue nevi. Ipsilateral lipodermoids, choristomas, and calcifications are the eye findings. CNS abnormalities are unilateral cerebral atrophy, dilated ventricles, porencephaly, cerebral calcifications, and lipomas of the leptomeninges. Seizures and mental retardation may occur. Some cases may have overlapping features of Proteus syndrome—multiple lipomas, epidermal nevi, cerebriform lesions of the plantar surfaces, vascular malformations, macrodactyly, hemihypertrophy, exostoses, and scoliosis.

Bannayan-Riley-Ruvalcaba syndrome is characterized by multiple subcutaneous lipomas and vascular malformations, lentigines of the penis and vulva, verrucae, and acanthosis nigricans. There is overlap in some of these cases with Cowden syndrome. Both have been found to have allelic mutations of the PTEN gene.

Multiple endocrine neoplasia type 1 has been found to have skin lesions consisting of multiple facial angiofibromas, collagenomas, café-au-lait spots, lipomas, confetti-like hypopigmented macules, and multiple gingival papules in addition to the tumors of the parathyroid glands, endocrine pancreas, and anterior pituitary.

Fröhlich syndrome consists of multiple lipomas, obesity, and sexual infantilism.

Gardner syndrome consists of multiple osteomas, fibromas, desmoid tumors, lipomas, fibrosarcomas, epidermal inclusion cysts, and leiomyomas, associated with intestinal polyposis exclusively in the colon and rectum. The coexistence of cutaneous cysts, leiomyomas, and osteomas (mostly on the skull) with intestinal polyposis is frequently not recognized until malignant degeneration of one of the polyps occurs and operative removal brings the syndrome to notice. Half of such patients develop carcinoma of the colon before the age of 30, and practically all these patients die before the age of 50 unless they have surgical treatment. In general, total colectomy is advised. Bony exostoses occur in 50% of patients and usually involve the membranous bones of the face and head. Cysts occur in 63% of patients, and again occur most commonly on the face and in the scalp. These are epidermal inclusion cysts; two-thirds have within them foci of pilomatrical differentiation. Pigmented lesions of the ocular fundus occurred in 90% of 41 patients with Gardner syndrome and 46% of 43 first-degree relatives. They are usually multiple and bilateral, and, having been seen in a 3-month-old infant, are probably congenital. Gardner syndrome is transmitted as an autosomal-dominant disease. The defect is a mutation in the APC gene located at chromosome 5q21. In some families polyposis and carcinoma may occur without the skin and bone tumors.

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Subtypes

The *angiolipoma* is a painful subcutaneous nodule, having all the other features of a typical lipoma. It is seen in young adults who have multiple painful lumps in the skin. Multiple subcutaneous angiolipomas have no invasive or metastatic potential. They may be induced by protease inhibitor therapy of HIV disease.

The *angiolipoleiomyoma* affects the acral skin of middle-aged men. No signs of tuberous sclerosis or renal angiomyolipoma are present. Mature adipocytes, thick-walled blood vessels, and smooth muscle cells in facicles around blood vessels are present.

Neural fibrolipoma is an overgrowth of fibro-fatty tissue along a nerve trunk that often leads to nerve compression. Patients are usually aged 30 or younger and note a slowly enlarging subcutaneous mass with associated tenderness, decreased sensation, or parasthesia. The median nerve is most commonly involved. At times macrodactyly appears, with elongation and splaying of the phalanges. MRI will provide the diagnosis, but unfortunately there is no effective treatment.

Chondroid lipomas are deep-seated, firm, yellow tumors that characteristically occur on the legs of women. Histologically there is a thin capsule around mature lipocytes that have a single large vacuole and multivacuolated S-100, vimentin-positive cells within a chondromyxoid matrix.

The *spindle-cell lipoma* is an asymptomatic, slow-growing subcutaneous tumor that has a predilection for the posterior back, neck and shoulders of older men. It is usually solitary, although multiple lesions may occur. Some patients have been described who have a familial background of these. The neoplasm consists of lobulated masses of mature adipose tissue with areas of spindle-cell proliferation. The spindle-cells stain positively for CD34. Abnormalities of chromosome 16 and 13 have been reported. The spindled component of young spindle-cell lipomas may be myxoid or cellular. The nuclei may be wavy and accompanied by mast cells, as in a neurofibroma. In old spindle-cell lipomas (fibrolipomas), the spindle cell component has matured into dense collagen bundles.

Pleomorphic lipomas, like spindle-cell lipomas, occur for the most part on the backs or necks of elderly men. There are floret giant cells with overlapping nuclei. Occasional lipoblast-like cells and atypical nuclei may be present and require differentiation from a liposarcoma. There is loss of chromosome 16q material. Despite this alarming appearance, the lesions behave in a perfectly benign manner. Pleomorphic lipomas lack the size, depth, infiltrative growth, and arborizing vascular pattern of liposarcoma.

The *intradermal spindle cell/pleomorphic lipoma* is distinct in that it most commonly affects women, and has a wide distribution, occurring with relatively equal frequency on the head and neck, trunk, and the upper and lower extremities. Histologically they are unencapsulated and have infiltrative margins. Again the spindle cells stain positively with CD34

Hibernoma (lipoma of brown fat) is a form of lipoma composed of finely vacuolated fat cells of embryonic type. Hibernomas have a distinctive brownish color and a firm consistency, and usually occur singly. These tumors are benign. They occur chiefly in the mediastinum and the interscapular region of the back, but they also occur on the scalp, sternal region, and legs. They are usually about 3 to 12 cm in breadth and the onset is most often in adult life. Abnormalities of chromosomes 10 and 11 have been reported in the lesions. Epidural lipomatosis, collections of fat in the epidural space, may cause acute chord compression in the course of systemic corticosteroid treatment. A case of this distinctive, uncommon side effect proved to be the result of deposits of brown fat.

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Nevus Lipomatosus Superficialis

Soft, yellowish papules or cerebriform plaques, usually of the buttock or thigh, less often of the ear or scalp, with a wrinkled rather than warty surface, characterize this tumor. The distribution may be either zonal (as in the multiple lesions reported by Hoffmann and Zurhelle) or solitary. Solitary lesions appear as a fatty acrochordon. Onset before the age of 20 is the rule.

Lane JE, et al: Nevus lipomatosus cutaneous superficialis. Pediatr Dermatol 2003;20:313.

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Folded Skin with Scarring (Michelin Tire Baby Syndrome)

In this rare syndrome, there are numerous deep, conspicuous, symmetrical, ringed creases around the extremities (Fig. 28-37). The underlying skin may manifest a smooth

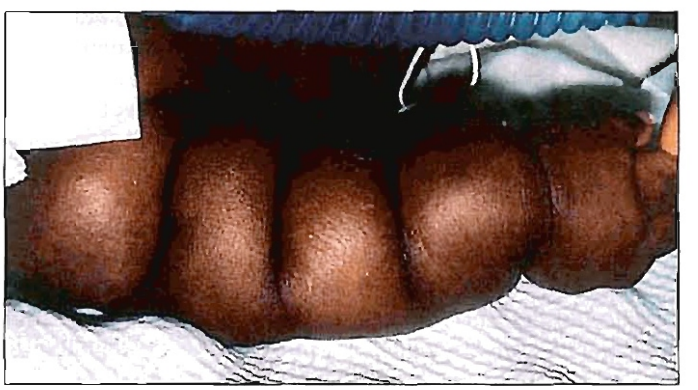

Fig. 28-37 Michelin tire baby.

muscle hamartoma, a nevus lipomatosis, or elastic tissue abnormalities. It may occur as an autosomal-dominant trait, a sporadic condition, an isolated finding, or associated with congenital facial and limb abnormalities, or with severe neurologic defects.

Kharfi M, et al: Michelin tire syndrome: a report of two siblings. Pediatr Dermatol 2005;22:245.
Sardana K, et al: Spontaneously improving Michelin tire baby syndrome. Pediatr Dermatol 2003;20:150.
Schnur RE, et al: Variability in the Michelin tire syndrome. J Am Acad Dermatol 1993;28:364.

Benign Lipoblastomatosis

This tumor, frequently confused with a liposarcoma, affects exclusively infants and young children, with approximately 90% occurring before 3 years of age. It involves most commonly the soft tissues of the upper and lower extremities. A circumscribed and a diffuse form can be distinguished. The circumscribed form is superficially located and clinically comparable to a lipoma. The diffuse form is more deeply situated and is analogous to diffuse lipomatosis. Microscopically, both forms consist of lobulated immature adipose tissue composed of lipoblasts, a plexiform capillary pattern, and a richly myxoid stroma. Rearrangements of chromosome 8q11–q13 are present and help to distinguish this tumor from liposarcoma, a distinction that can be difficult histologically. Complete local excision is the treatment of choice; however, recurrences may occur in as many as one-quarter of patients.

Dilley AV, et al: Lipoblastoma. J Pediatr Surg 2001;36:229.
Harrer J, et al: Lipoblastoma and lipoblastomatosis. Eur J Pediatr Surg 2001;11:342.

Liposarcoma

Liposarcomas are the most common soft-tissue sarcoma. They usually arise from the intermuscular fascia, and only rarely from the subcutaneous fat. They do not arise from preexisting lipomas. The usual course is an inconspicuous swelling of the soft tissue that undergoes an imperceptibly gradual enlargement. When a fatty tumor becomes larger than 10 cm in diameter liposarcoma should be seriously considered. The upper thigh is the most common site. Other frequent sites are the buttocks, groin, and upper extremities. Adult males are affected mostly.

Liposarcomas may be well-differentiated; subtypes include the adipocytic, sclerosing, inflammatory, spindle cell, and dedifferentiate variants. In this category there are aberrations of chromosome 12. Myxoid and round-cell variant liposarcoma often shows poorly differentiated histology. In most cases there is a reciprocal translocation t(12;16)(q13;q11). The third major class is pleomorphic liposarcoma.

Treatment is adequate radical excision of the lesion. In well-differentiated superficial lesions the prognosis is good; for deeper, high-grade lesions, the extension between fascial planes and presence of small satellite nodules require carefully planned surgery, which may be assisted by MRI guidance. For metastatic liposarcomas, radiation therapy may be effective.

Dei Tos AP: Liposarcoma. Ann Diagn Pathol 2000;4:252.
Bal-Bernal JF, et al: Primary purely intradermal pleomorphic liposacrcoma. J Cutan Pathol 2003;30:516.

ABNORMALITIES OF SMOOTH MUSCLE

Leiomyoma

Cutaneous leiomyomas are smooth muscle tumors characterized by painful nodules that occur singly or multiply. They may be separated conveniently into solitary and multiple cutaneous leiomyomas arising from arrectores pilorum muscles (piloleiomyomas); solitary genital leiomyomas arising from the dartoic, vulvar, or mammillary muscle; and solitary angioleiomyomas arising from the muscles of veins.

Solitary Cutaneous Leiomyoma The typical lesion is a deeply circumscribed, rounded nodule ranging from 2 to 15 mm in diameter. It is freely movable. The overlying skin may have a reddish or violaceous tint. Although the lesion is insensitive at first, painful paroxysms may occur. Once pain commences, the tendency is for it to intensify.

Multiple Cutaneous Leiomyomas These brownish, grouped, papular lesions vary from 2 to 23 mm in diameter and are the most common variety of leiomyomas (Fig. 28-38). Two or more sites of the skin surface may be involved. The firm, smooth, superficial, sometimes translucent, and freely movable nodules are located most frequently on the trunk and extremities. They often form linear or dermatomal patterns, either alone or with scattered isolated nonsegmental lesions elsewhere. These leiomyomas may occur on the tongue or, less often, elsewhere in the mouth as well. The usual age at onset is in the teens to the fourth decade. Eruptive lesions have been described in chronic lymphocytic leukemia.

Multiple leiomyomas are inherited in an autosomal-dominance fashion. Women with this inherited type often have uterine leiomyomas as well. This is part of an inherited syndrome where some patients also have a predisposition to type II papillary renal carcinomas or renal collecting duct cancer. Mutations in the fumaratae hydratase gene are present in 75% of patients with this syndrome. Fumarate hydratase gene mutations may also be inherited in an autosomal-recessive manner. Fully affected children have severe neurologic impairment. The adult carriers may develop leiomyomas. Sporadic leiomyoma, leiomyosarcomas, renal cancers, and

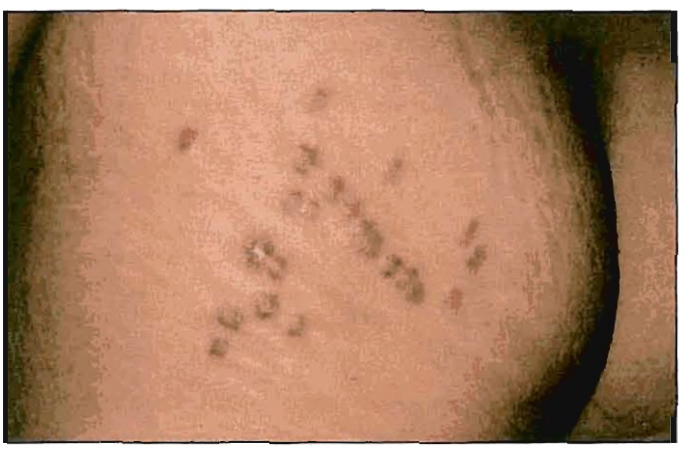

Fig. 28-38 Multiple leiomyomas.

uterine leiomyomas have a very low frequency of fumarate hydratase mutations.

Genital Leiomyomas These lesions are located on the scrotum, on the labia majora, or rarely, on the nipples. They may be intra- or sub-cutaneous in location. Most genital leiomyomas are painless and solitary. Alport syndrome is an X-linked dominant syndrome consisting of hematuric nephropathy, deafness, and maculopathy due to mutations in type IV collagen. Some of these patients will have diffuse leiomyomatosis, which may affect the esophagus, tracheobronchial tree, perirectal area, and genital tract and vulva.

Angioleiomyoma (Vascular Leiomyoma) This variety of leiomyoma arises from the muscle of veins. Pain, either spontaneous or provoked by pressure or cold, occurs in roughly half the cases. It is found mostly on the lower leg in middle-aged women. Solid tumors occur three times more frequently in women, and cavernous tumors occur four times more frequently in men. Solid lesions on the extremities are commonly painful; tumors of the head are rarely painful. In AIDS, multiple skin and visceral antioleiomyomas may occur. These tumors cells possess the Epstein-Barr virus genome.

Histologically, the leiomyoma is made up of bundles and masses of smooth muscle fibers. Varying amounts of collagen are intermingled. The smooth muscle cells are finely fibrillated and contain a glycogen vacuole adjacent to the nucleus. The nuclei are typically long, thin, and cigar shaped.

Angiolipoleiomyoma Fitzpatrick et al reported eight patients with acquired, solitary, asymptomatic acral nodules. Seven were men and all were adults. Histologically, they were well-circumscribed subcutaneous tumors composed of smooth muscle cells, blood vessels, connective tissue, and fat.

Treatment

Leiomyomas are benign. Solitary painful lesions may be excised. When multiple and familial, monitoring for renal cell or collecting duct carcinoma is important. When multiple lesions are present and painful, as they may be especially in the winter, relief of pain may be achieved by giving doxazosin, an oral α-1 adrenoceptor antagonist. This is better tolerated than phenoxybenzamine, an α-adrenergic blocker, which also has been reported to provide pain relief. Nifedipine, 10 mg three times a day, gabapentin, oral nitroglycerin, and β-blockers have also had variable success. An ice cube applied over the lesions often induces pain, and the effectiveness of therapy may be assessed by the length of time it takes the ice cube to cause pain.

Alam M, et al: Gabapentin treatment of multiple piloleiomyoma-related pain. J Am Acad Dermatol 2002;46:S27.

Alam NA, et al: Clinical features of multiple cutaneous and uterine leiomyomatosis. Arch Dermatol 2005;141:199.

Albares MP, et al: Digital angioleiomyoma. Int J Dermatol 2002; 41:527.

Barker KT, et al: Low frequency of somatic mutations in the FH/multiple cutaneous leiomyomatosis gene in sporadic leiomyosarcoms and uterine leiomyomas. Br J Cancer 2002;87:446.

Batchelor RJ, et al: Successful treatment of pain in two patients with cutaneous leiomyomata and the oral alpha-1 adrenoceptor antagonist, doxazosin. Br J Dermatol 2004;150:775.

Bergani R, et al: Eruptive multiple sporadic cutaneous piloleiomomas in a patient with chronic lymphocytic leukaemia. Br J Dermatol 2000;143:907.

Chang JY, et al: Multiple Epstein-Barr virus-associated subcutaneous antioleiomyomas in a patient with AIDS. Br J Dermatol 2002;147:563.

Fitzpatrick JE, et al: Cutaneous angiolipoleiomyoma. J Am Acad Dermatol 1990;23:1093.

Konig A, et al: Two cases of type 2 segmental manifestation in a family with cutaneous leiomyomatosis. Eur J Dermatol 2000; 10:590.

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Martínez-Mir A, et al: Germline fumarate hydratase mutations in families with multiple cutaneous and uterine leiomyomata. J Invest Dermatol 2003;121:741.

Mothes H, et al: Alport syndrome associated with diffuse leiomyomatosis. Nephrol Dial Transplant 2002;17:70.

Pournaras CC, et al: Multiple painful cutaneous nodules. Arch Dermatol 2005;141:633.

Toro JR, et al: Mutations in the fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in families in North America. Am J Hum Genet 2003;73:95.

Congenital Smooth Muscle Hamartoma

Congenital smooth muscle hamartoma is typically a skin-colored or lightly pigmented patch or plaque with hypertrichosis (Fig. 28-39). It is often present at birth, usually on the trunk, with the lumbosacral area involved in two-thirds of patients. Older patients may have perifollicular papules. They vary in size from 2 × 3 to 10 × 10 cm. The Michelin tire baby syndrome may result from a diffuse smooth muscle hamartoma. One patient presented with a linear reddish-purple plaque. The incidence is approximately 1 in 2600 newborns. Transient elevation on rubbing may be seen (pseudo-Darier's sign) in 80%.

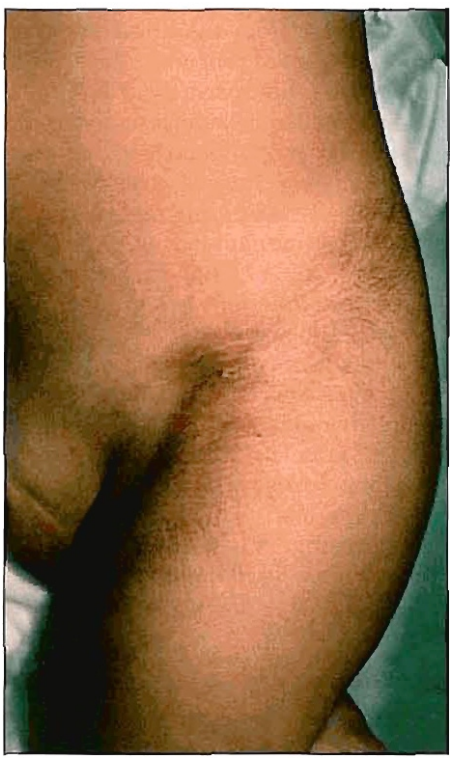

Fig. 28-39 Smooth muscle hamartomas.

Histologically, numerous thick, long, well-defined bundles of smooth muscle are seen in the dermis at various angles of orientation. There may be an increase in hair follicles.

In some cases there is clinical and histologic overlap with Becker nevus. Classically, Becker nevus is a unilateral (rarely bilateral) acquired hyperpigmentation, usually beginning as a tan macule on the shoulder or pectoral area of a teenage male. Over time hypertrichosis develops within it. Biopsy of such lesions shows acanthosis, papillomatosis, and increased basal cell pigmentation. Occasional congenital lesions manifesting hyperpigmentation and hypertrichosis have shown biopsy findings consistent with those of a Becker nevus (no smooth muscle proliferation), and lesions with a typical late-onset history compatible with Becker nevus have occasionally shown smooth muscle-hamartoma–like changes in the dermis. Other cases of late-onset smooth muscle hamartomas are occasionally reported that are not hyperpigmented or hypertrichotic.

No treatment is necessary.

Darling TN, et al: Acquired cutaneous smooth muscle hamartoma. J Am Acad Dermatol 1993;28:844.

Gagne EJ, et al: Congenital smooth muscle hamartoma of the skin. Pediatr Dermatol 1993;10:142.

Gualandri L, et al: Multiple familial smooth muscle hamartomas. Pediatr Dermatol 2001;18:17.

Holst VA, et al: Cutaneous smooth muscle neoplasms. J Am Acad Dermatol 2002;46:477.

Pearson IC, et al: A lesion present at birth. Clin Exp Dermatol 2004;29:693.

Leiomyosarcoma

Superficial leiomyosarcomas (those originating in the dermis or subcutaneous tissue) comprise approximately 2% of all soft-tissue sarcomas. Occasionally, a lesion may present in the skin that is a metastasis from an internal source. The cutaneous leiomyosarcoma appears in the dermis as a solitary nodule. It may originate from the arrector pili or genital dartoic muscle. This has a good prognosis. Recurrence rates with Mohs surgery are approximately 15%, with metastases a rare event. Subcutaneous leiomyosarcomas, on the contrary, have a guarded prognosis, since hematogenous metastases occur in approximately 35% of patients. These prove fatal in about one-third of cases. Lung metastases are frequent so chest imaging is an important part of monitoring these patients.

The clinical appearance of these lesions is not distinctive, so that the diagnosis is established by the histopathologic findings. These differ from the leiomyoma by dense cellularity, nuclear pleomorphism, numerous mitotic figures, and disarray of the smooth muscle bundles. Collagen is found only in the septa. Desmin, smooth muscle actin, and h-Caldesmon are helpful in differentiating leiomyosarcoma from other spindle cell or pleomorphic tumors.

The preferred method of treatment is wide local excision. The Mohs surgical approach is useful in limiting recurrences and sparing tissue. Radiation therapy and chemotherapy are generally not effective.

Bellezza G, et al: Primary cutaneous leiomyosarcoma. Int J Surg Pathol 2004;12:39.

Haffner AC, et al: Complete remission of advanced cutaneous leiomyosarcoma following isolated limb perfusion with high-dose tumour necrosis factor-alpha and melphalan. Br J Dermatol 1999;141:935.

Holst VA, et al: Cutaneous smooth muscle neoplasms. J Am Acad Dermatol 2002;46:477.

Humphreys TR, et al: Superficial leiomyosarcoma treated with Mohs micrographic surgery. Dermatol Surg 2004;30:108.

Jensen ML, et al: Intradermal and subcutaneous leiomyosarcoma. J Cutan Pathol 1996;23:458.

Kuflik JH, et al: Dermal leiomyosarcoma. J Am Acad Dermatol 2003;48:S51.

Miyajima K, et al: Clinicopathological prognostic factors in soft tissue leiomyosarcoma. Histopathology 2002;40:353.

MISCELLANEOUS TUMORS AND TUMOR-ASSOCIATED CONDITIONS

Cutaneous Endometriosis

Endometriosis of the skin is characterized by the appearance of brownish papules at the umbilicus or in lower abdominal scars after gynecologic surgery in middle-aged women. The usually solitary tumor ranges from a few to 60 mm (average, 5 mm) in diameter. The tender or painful lesion is bluish-black from the bleeding that occurs cyclically in many patients.

Histopathologic findings are glandular structures with a decidualized stroma typically containing extravasated red blood cells and hemosiderin. Treatment of choice is surgical excision. Preoperative treatment with danazol or leuprolide may reduce its size.

Albrecht LE, et al: Cutaneous endometriosis. Int J Dermatol 1995;34:261.

Choi SW, et al: A case of cutaneous endometriosis developed in postmenopausal women receiving hormonal replacement. J Am Acad Dermatol 1999;41:327.

Munoz H, et al: An ulcerated umbilical nodule. Arch Dermatol 1999;135:1113.

Teratoma

Teratomas may develop in the skin but are most common in the ovaries or testes. They have no characteristic clinical features, but on microscopic examination many types of tissue, representative of all three germ layers, are present. Hair, teeth, and functioning thyroid tissue are examples of fully differentiated tissues that may develop. Occasionally, malignancy may occur.

Boughton RS, et al: Malignant melanoma arising in an ovarian cystic teratoma in pregnancy. J Am Acad Dermatol 1987; 17:871.

Tsai TF, et al: A cystic teratoma of the skin. Histopathology 1996;29:384.

Metastatic Carcinoma

Malignant tumors are able to grow at sites distant from the primary site of origin; thus, dissemination to the skin may occur with any malignant neoplasm. These infiltrates may result from direct invasion of the skin from underlying tumors, may extend by lymphatic or hematogenous spread, or may be introduced by therapeutic procedures.

Five to 10% of patients with cancer develop skin metastases. The reported incidence figures vary widely according to the type of study undertaken and the site of primary tumor studied. The frequency of involvement of the skin is low when other sites are considered, such as the lung, liver, lymph nodes, and brain.

Usually, metastases occur as numerous firm, hard, or rubbery masses, with a predilection for the chest, abdomen, or scalp, in an adult over the age of 40 who has had a previously diagnosed carcinoma. Many variations in morphology, number of lesions, site of growth, age at onset, and timing of metastases exist, however. They are most commonly intradermal papules, nodules, or tumors that are firm, skin-colored to reddish, purplish, black or brown; may be fixed to underlying tissues; and rarely ulcerate.

Several unusual morphologic patterns occur. Carcinoma en cuirasse is a diffuse infiltration of the skin that imparts an indurated and hidebound leathery quality to it. This sclerodermoid change, also referred to as scirrhous carcinoma, is produced by fibrosis and single rows of tumor cells. This type primarily occurs with breast carcinoma. Carcinoma telangiectaticum is another unusual type of cutaneous metastasis from breast carcinoma that presents as small pink to purplish papules, pseudovesicles, and telangiectases.

Inflammatory carcinoma (carcinoma erysipelatoides) is characterized by erythema, edema, warmth, and a well-defined leading edge, similar to erysipelas in appearance (Fig. 28-40). This is usually caused by breast carcinoma, but has been reported with many other primary tumors. Histologically, there is little to no inflammation, but rather neoplastic cells within dilated superficial dermal vessels.

Alopecia neoplastica (Fig. 28-41) may present as a cicatricial localized area of hair loss, which on biopsy is usually caused by breast metastases in women, and lung or kidney carcinoma in men. Metastatic breast cancer may be darkly pigmented, as may Paget's disease of the breast.

The so-called Sister Mary Joseph nodule is formed by localization of metastatic tumors to the umbilicus (Fig. 28-42). The most common primary sites are the stomach, large bowel, ovary, and pancreas. Zosteriform, linear, or chancroidal ulcerations of the genitalia, and verrucous nodules of the legs, are other rarely reported clinical presentations.

The primary tumor is usually diagnosed before the appearance of metastases, and dissemination to the skin is often a late finding. Metastases to other more commonly involved organs such as the lung and liver have usually occurred. A poor prognosis is thus the rule. Skin infiltrates may, however, be the first harbinger of a malignant visceral neoplasm and is often the first clinically apparent metastatic site.

The principal anatomic sites to which metastases localize are the chest, abdomen, and scalp, with the back and extremities being relatively uncommon areas. Involvement of the skin is likely to be near the area of the primary tumor. Thus, chest lesions are usually caused by breast carcinoma in women and lung carcinoma in men, abdominal or perineal lesions to colonic carcinoma, and the face to squamous cell carcinoma of the oral cavity. Extremity lesions, when they occur, are most commonly caused by melanoma.

Because of its overall high prevalence, breast cancer is the type most commonly metastatic to the skin in women, and melanoma, followed by lung cancer, are the types seen most commonly in men. Colon carcinoma is also common because of its high incidence in both sexes. Renal cell carcinoma, while less common, has a predilection for scalp metastases. Metastatic lesions are uncommon in children, but when they do occur, neuroblastoma and leukemia are the most frequent causes.

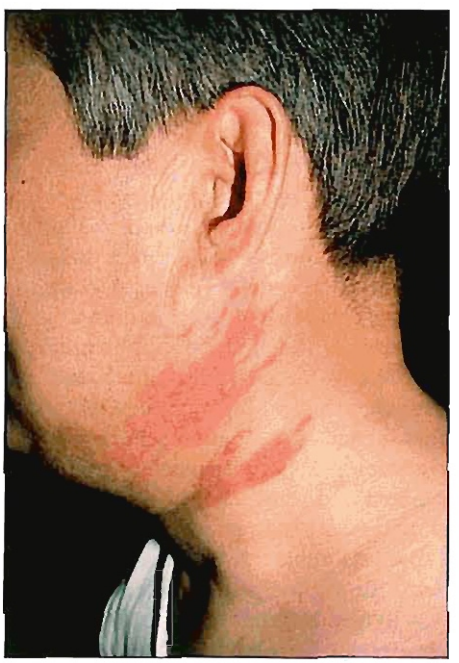

Fig. 28-40 Metastatic rectal cancer presenting as inflammatory carcinoma.

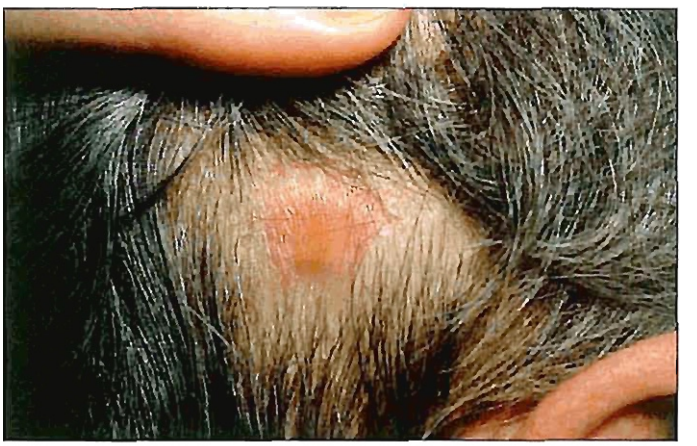

Fig. 28-41 Alopecia neoplastica secondary to breast carcinoma.

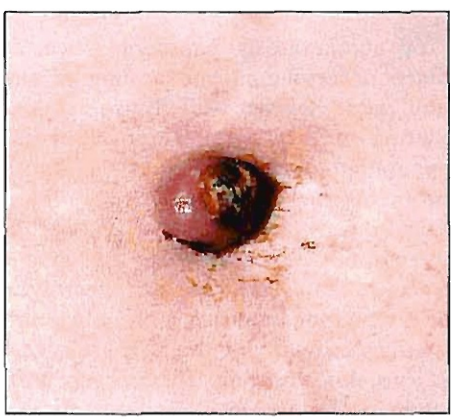

Fig. 28-42 Sister Mary Joseph nodule.

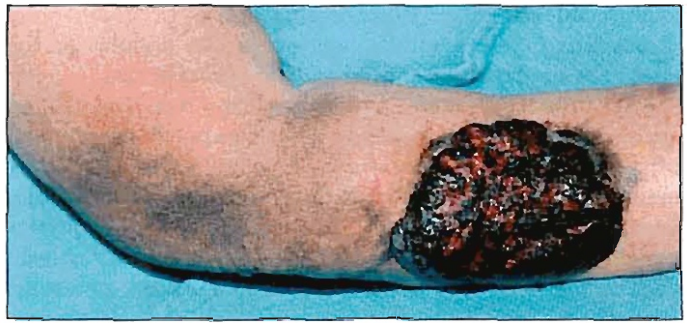

Fig. 28-43 Stewart-Treves tumor.

Lymphangiosarcoma (Stewart-Treves syndrome) develops in a site of chronic lymphedema, such as in breast cancer patients who have had lymph node resection (Fig. 28-43). Antikeratin antibodies are useful in identifying metastatic breast carcinoma, while CD34, CD31 and *Ulex europeus* lectin are positive in Stewart-Treves angiosarcoma.

Alwaheeb S, et al: Cutaneous manifestation of thyroid cancer. J Clin Pathol 2004;57:435.

Cormio G, et al: Skin metastases in ovarian carcinoma. Gynecol Oncol 2003;90:682.

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Powell FC, et al: Sister Mary Joseph's nodule. J Am Acad Dermatol 1984;10:610.

Requena L, et al: Pigmented mammary Paget disease and pigmented epidermotropic metastases from breast carcinoma. *Am J Dermatopathol 2002;24:189.*

Shonmann R, et al: Inflammatory skin metastases from ovarian carcinoma. Gynecol Oncol 2003;90:670.

Paraneoplastic Syndromes

Some cancers produce findings in the skin that indicate that an underlying internal malignancy may be present. These may range from a specific eruption characteristic of a particular type of cancer, such as necrolytic migratory erythema, to a nonspecific cutaneous reaction pattern, among the causes of which may be an internal malignancy. Although many of these syndromes are discussed in other sections of the book, a few are mentioned here as illustrative examples of this phenomenon.

Bazex syndrome, or acrokeratosis paraneoplastica, is characterized by violaceous erythema and scaling of the fingers, toes, nose, and aural helices. Nail dystrophy and palmoplantar keratoderma may be seen. These cases are secondary to primary malignant neoplasms of the upper aerodigestive tract or metastatic cancer to lymph nodes, often in the cervical region.

The glucagonoma syndrome is characterized by weight loss, glucose intolerance, anemia, glossitis, and necrolytic migratory erythema. Erythematous patches with bullae and light brown papules with scales involving the face, groin, and abdomen characterize the skin eruption. This is seen with glucagon-secreting tumors of the pancreas.

Fig. 28-44 Erythema *gyratum repans* secondary to ovarian cancer.

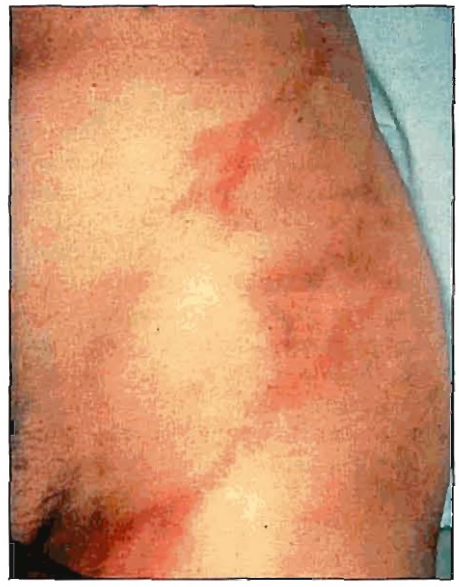

Fig. 28-45 Superficial migratory thrombophlebitis secondary to breast cancer.

Erythema gyratum repens is a gyrate serpiginous erythema with characteristic wood-grain–pattern scales; it is nearly always associated with an underlying malignancy (Fig. 28-44). Hypertrichosis lanuginosa acquisita, or malignant down, is the sudden growth of profuse, soft, nonmedullated, nonpigmented, downy hair in an adult. The most common sites of associated carcinoma were the lung and colon.

The sign of Leser-Trelat is the sudden appearance of multiple pruritic seborrheic keratoses, associated with an internal malignancy. Trousseau's sign, or migratory thrombophlebitis, is usually associated with pancreatic carcinoma (Fig. 28-45). A form of pemphigus, paraneoplastic pemphigus, is most commonly associated with lymphoma, chronic lymphocytic leukemia, and Castleman's disease.

Several cutaneous diseases that are not associated with internal malignancy with the frequency of the above conditions, but that may be a sign of internal malignancy in some cases, are exfoliative erythroderma (lymphoproliferative

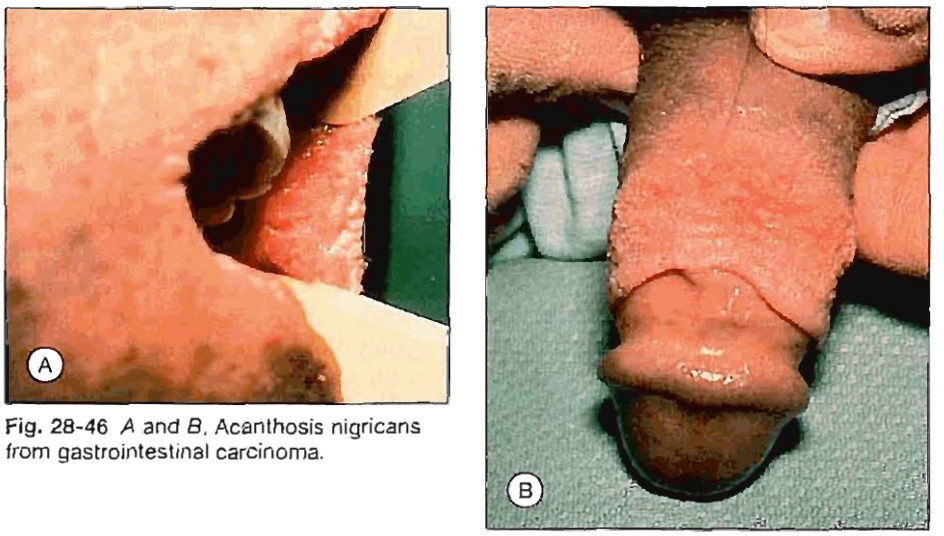

Fig. 28-46 *A* and *B*, Acanthosis nigricans from gastrointestinal carcinoma.

disease), acanthosis nigricans (adenocarcinoma) (Fig. 28-46), multicentric reticulohistiocytosis, Sweet syndrome (acute myelogenous leukemia), nodular fat necrosis (pancreatic carcinoma), Paget's disease (underlying adnexal or breast carcinoma, or adenocarcinoma of the genitourinary tract or colon), dermatomyositis in patients over the age of 40, palmar fasciitis and polyarthritis syndrome, and acquired ichthyosis (lymphoproliferative).

A variant of acquired ichthyosis, pityriasis rotunda, manifests circular, brown, scaly patches from 1 to 28 cm in diameter and varying in number from 1 to 20. They may occur on the trunk or extremities. These symptomless patches may be a clue to the diagnosis of hepatocellular carcinoma in South African black patients. Tripe palms, considered by some to be acanthosis nigricans of the palms, are associated with carcinoma in more than 90% of cases. Filiform hyperkeratosis of the palms may present in patients who develop cancer.

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Kaddu S, et al: Palmar filiform hyperkeratosis. J Am Acad Dermatol 1995;33:337.

Khachemoune A, et al: Bazex syndrome. Cutis 2004;74:289.

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Perez-Losada E, et al: Hypertrichosis lanuginose acquisita preceding extraskeletal Ewing's sarcoma. Clin Exp Dermatol 2001;26:182.

Rizos E, et al: Acquired ichthyosis. Lancet Oncol 2002;3:727.

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Carcinoid

Carcinoid involves the lungs, heart, gastrointestinal tract, as well as the skin. The outstanding feature of the skin is flushing, usually lasting 5 to 10 min. It involves most prominently the head and neck, but also produces a diffuse, scarlet color, with mottled red patches on the thorax and abdomen. Striking color changes may occur, with salmon red, bluish-white, and other colors appearing simultaneously on various portions of the skin. Cyanosis may also be present. As the episodic flushing continues over months to years, telangiectases and plethora appear, as though the patient has polycythemia vera. Gyrate and serpiginous patches of erythema and cyanosis flare up and subside, not only on the face but on all parts of the body and extremities.

Pellagroid changes may appear as a result of shunting of dietary tryptophan away from the kynurenine–niacin pathway and into the 5-hydroxyindole pathway. Periorbital swelling, edema of the face, neck, and feet, and sclerodermatous changes may occur. Disseminated deep dermal and subcutaneous metastatic nodules from a primary bronchial carcinoid tumor have been documented.

The clinical features of the carcinoid syndrome become evident only after hepatic metastases have occurred, or when the primary tumor is a bronchial carcinoid, or if the carcinoid arises in an ovarian teratoma, where the venous drainage bypasses the hepatic circulation.

The release of excessive amounts of serotonin and bradykinin into the circulation produces attacks of flushing of the skin, weakness, abdominal pain, nausea, vomiting, sweating, bronhoconstiction, palpitation, diarrhea, and collapse. These attacks may last a few hours. Right-sided cardiac valvular fibrosis occurs in 60% of chronically affected patients. Symptoms may be induced in these patients by the injection of epinephrine, at which time kinin peptide is released. Alcohol,

hot beverages, exercise, and certain foods, among others, may induce flushing. The patient will provide the relevant triggers by history.

Etiologic Factors

Carcinoid, also called *argentaffinoma*, is a tumor that arises from the argentaffin Kulchitsky chromaffin cells in the appendix or terminal ileum, but also in other parts of the gastrointestinal tract, from the lungs as bronchial adenomas, and rarely from ovarian or testicular teratomas. Some of these produce large amounts of serotonin (5-hydroxytryptamine), a derivative of tryptophan, and others do not. The primary lesion is more active in the production of serotonin than are the metastases. The tumor frequently metastasizes to the draining lymph glands or to neighboring organs, especially the liver, rarely to more distal sites.

Laboratory Findings

The diagnosis may be established by finding a high level of 5-hydroxyindolacetic acid (5-HIAA) in the urine. The normal urinary excretion of 5-HIAA is 3 to 8 mg/day, but in the presence of carcinoid it may reach 300 mg. Urinary values greater than 25 mg/day are diagnostic of carcinoid. Any value above the normal output is considered suspicious. The ingestion of bananas may cause significant elevations of 5-HIAA in the urine within a few hours, because banana pulp contains serotonin (4 mg/banana) and catecholamines. Tomatoes, red plums, pineapples, avocados, and eggplants also contain serotonin, but in much smaller amounts.

A screening test for 5-HIAA is the addition of nitrosonaphthol to the urine. A purple color is produced when there 40 mg/day of 5-HIAA is excreted. Other serotonin metabolites besides 5-HIAA are found in the urine. The blood also contains serotonin in amounts of 0.2 to 0.4 mg%. In the presence of carcinoid the amount may be 10 times normal.

Treatment

In the rare cases where there is only a primary tumor without metastases, this should be removed. Excision of metastatic lesions in the liver may also be considered. If this is impossible, long-acting somatostatin analogs provide good long-term symptomatic control of the flushing and diarrhea. Injections are given monthly. Vitamin supplementation with niacin and avoidance of known trigger factors to flushing is recommended. Restriction of tryptophan-containing foods for short periods may limit serotonin production.

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Garland J, et al: Sandostatin LAR (long-acting octreotide acetate) for malignant carcinoid. Aliment Pharmacol 2003; 17:437.

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CHAPTER

29 Epidermal Nevi, Neoplasms, and Cysts

EPIDERMAL NEVI

Keratinizing epidermal nevi are described by a great variety of terms, such as *hard nevus of Unna*, *soft epidermal nevus*, *nevus verrucosus (verrucous nevus)*, *nevus unius lateris*, *linear epidermal nevus*, and *ichthyosis hystrix*. Hyperkeratosis without cellular atypia characterizes them all: melanocytic nevus cells do not occur. In some cases the primary constituent is hyperplasia of an adnexal component (nevus comedonicus, nevus sebaceous). These lesions are all considered to represent somatic mosaicism in the affected region. The histologic features are apparently a consequence of the genetic mutation affecting that region. These lesions follow the lines of Blascko rather than dermatomes, suggesting they represent mutations that occurred at some postzygotic time during fetal development. Epidermal nevi are relatively common, with a prevalence of about 1 in 1000.

Linear Verrucous Epidermal Nevus

The individual lesions are verrucous skin-colored, dirty-gray or brown papules, which coalesce to form a serpiginous plaque (Figs 29-1 and 29-2). Interspersed in the localized patch may be horny excrescences and, rarely, comedones. The age of onset of epidermal nevi is generally at birth, but they may also develop within the first 10 years of life. They follow the lines of Blaschko. The term *ichthyosis hystrix* had been used to describe cases with extensive bilateral involvement.

The histologic changes in the epidermis are hyperplastic and affect chiefly the stratum corneum and stratum malpighii. There is variable hyperkeratosis, acanthosis, and papillomatosis. Up to 62% of biopsies of epidermal nevi have this pattern. About 16% show epidermolytic hyperkeratosis. At times, other histologic patterns may be found, including a psoriatic type, an acrokeratosis verruciformis-like type, and a Darier's disease-like type.

Rarely keratinocytic and adnexal malignancies occur in epidermal nevi. Any newly appearing lesion within a stable epidermal nevus should be biopsied to exclude this possibility. Management of epidermal nevi is difficult, since unless the treatment also affects the dermis (and hence may cause scarring), the lesion recurs. The combination of 5% 5-fluorouracil (5-FU) plus 0.1% tretinoin creams once a day may

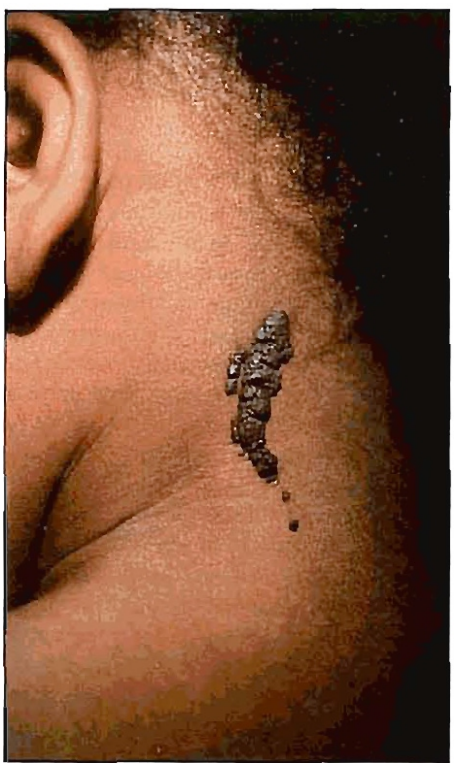

Fig. 29-1 Verrucous linear epidermal nevus, note the superficial resemblance to seborrheic keratosis.

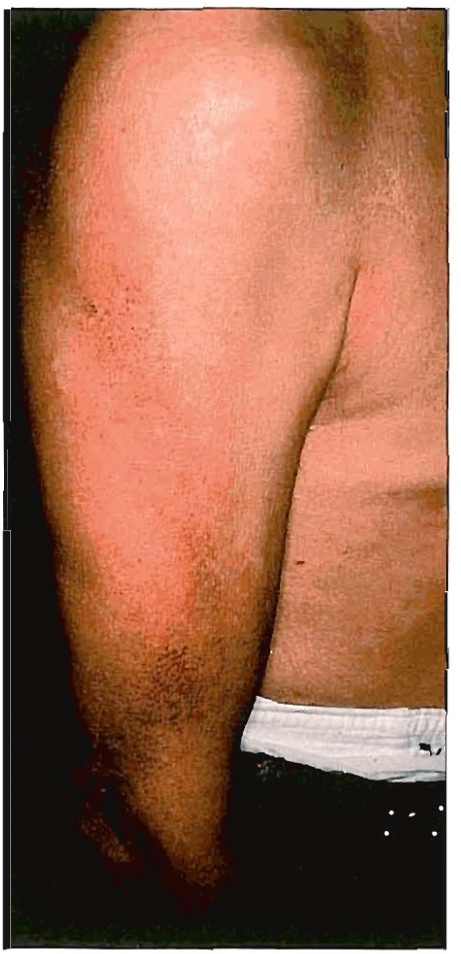

Fig. 29-2 Linear epidermal nevus, histologically this lesion showed epidermolytic hyperkeratosis.

be beneficial and the response may be enhanced by occlusion. CO_2 and Er:YAG laser treatment may also be effective.

Alam M, Arndt KA: A method for pulsed carbon dioxide laser treatment of epidermal nevi. J Am Acad Dermatol 2002; 46:554.

Hamanaka S, et al: Multiple malignant eccrine poroma and a linear epidermal nevus. J Dermatol 1996;23:469.

Ichikawa T, et al: Squamous cell carcinoma arising in a verrucous epidermal nevus. Dermatology (Switzerland) 1996; 193:135.

Kim JJ, et al: Topical tretinoin and 5-fluorouracil in the treatment of linear verrucous epidermal nevus. J Am Acad Dermatol 2000;43:129.

Park JH, et al: Er:YAG laser treatment of verrucous epidermal nevi. Dermatol Surg 2004;30:378.

Stosiek N, et al: Chromosomal mosaicism in two patients with epidermal verrucous nevus. J Am Acad Dermatol 1994;30:622.

Nevus Comedonicus

Nevus comedonicus is characterized by closely arranged, grouped, often linear, slightly elevated papules that have at their center keratinous plugs resembling comedones (Fig. 29-3). Cysts, abscesses, fistulas, and scars develop in about half the cases, which have been described as "inflammatory" nevus comedonicus. As with other epidermal nevi, lesions may be localized to a small area or have an extensive nevoid type of distribution. They are most commonly unilateral; however, bilateral cases are also seen. Lesions occur mostly on the trunk and follow the lines of Blascko. The lesions may develop any time from birth to age 15, but are usually present by the age of 10. Associated abnormalities of bone, the central nervous system (CNS), skin, and eyes, which may accompany epidermal nevi, may also be seen in extensive nevus comedonicus.

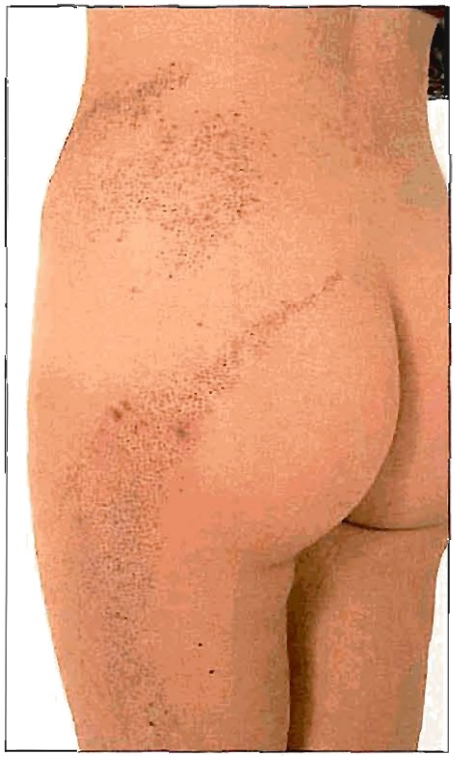

Fig. 29-3 Nevus comedonicus.

The pilosebaceous follicles are dilated and filled with keratinous plugs. On the palms, pseudocomedones are present. Histologic examination reveals large dilated follicles filled with orthokeratotic horny material and lined by atrophic squamous epithelium. The interfollicular epidermis is papillomatous, as is seen in typical epidermal nevi. Hair follicle differentiation, well-formed follicular structures, and normal sebaceous glands are not common in well-formed lesions. Occasionally, epidermolytic hyperkeratosis may be present, supporting the contention that nevus comedonicus is a form of "epidermal" nevus.

Treatment of lesions not complicated by inflammatory cysts and nodules is primarily cosmetic. Pore-removing cosmetic strips and comedone expression may improve the cosmetic appearance. Topical tretinoin may be beneficial. Patients with inflammatory lesions are much more difficult to manage. If the area affected is limited, surgical excision may be considered. Oral isotretinoin, chronically at the minimum effective dose (0.5 mg/kg/day or less if possible) may partially suppress the formation of cysts and inflammatory nodules; however, as in hidradenitis suppurativa, many cases of nevus comedonicus fail to respond. The comedonal lesions are not improved by the oral isotretinoin.

Ioue Y, et al: Two cases of nevus comedonicus: successful treatment of keratin plugs with a pore strip. J Am Acad Dermatol 2000;43:927.

Kargi E, et al: Nevus comedonicus. Plast Reconstr Surg 2003; 112:1183.

Kirtak N, et al: Extensive inflammatory nevus comedonicus involving half of the body. Int J Dermatol 2004;43:434.

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Schecter AK, et al: Linear nevus comedonicus with epidermolytic hyperkeratosis. J Cutan Pathol 2004;31:502.

Wakahara M, et al: Bilateral nevus comedonicus: efficacy of topical tacalcitol ointment. Acta Dermatol Venereol 2003; 83:51.

Woods KA, et al: Extensive naevus comedonicus in a child with Alagille syndrome. Clin Exp Dermatol 1994;19:163.

Epidermal Nevus Syndrome

In 1968, Solomon et al described the epidermal nevus syndrome (ENS), consisting of extensive epidermal nevi with abnormalities of the CNS, skeleton, skin, cardiovascular system, genitourinary system, and eyes. About 8% of patients with epidermal nevi have systemic involvement, and 10% to 18% have systemic developmental disorders (as compared to 1.7% of children without epidermal nevi). The more extensive the epidermal nevus, the more likely there is to be systemic disease. Bladder cancer at an early age (<21 years) has been reported in patients with epidermal nevi and pigmentary abnormalities.

Cutaneous lesions other than epidermal nevi in ENS that may occur are café-au-lait spots, speckled lentiginous nevi, multiple melanocytic nevi, and vascular malformations (phakomatosis pigmentovascularis). The combination of an organoid sebaceous nevus and a speckled lentiginous nevus is termed *phakomatosis pigmentokeratotica*. In virtually all cases, the cutaneous lesions and abnormalities are congenital. Since the original description of systemic involvement with keratotic epidermal nevi, similar cases have been

reported in association with sebaceous nevi and nevus comedonicus. This has led Happle to suggest a broader concept for the "epidermal nevus" syndrome. At least six types exist:

1. *Schimmelpenning syndrome* (sebaceous nevus associated with cerebral anomalies, coloboma, and lipodermoid of the conjuctiva) (Fig. 29-4)
2. *Nevus comedonicus syndrome* (associated with cataracts, scoliosis, and neurologic abnormalities)
3. *Pigmented hairy epidermal nevus syndrome* (Becker nevus, ipsilateral hypoplasia of the breast, and skeletal defects such as scoliosis)
4. *Proteus syndrome* (the epidermal nevus is of the verrucous/keratinocytic type)
5. *CHILD syndrome*
6. *Phakomatosis pigmentokeratotica* (hypophosphatemic rickets)

Many cases, especially those reported from pediatric dermatology referral centers, do not fit one of these categories. Final classification will await the finding of the genetic basis for each of these syndromes.

de Jalón AG, et al: Epidermal naevus syndrome (Solomon's syndrome) associated with bladder cancer in a 20-year-old female. Scand J Urol Nephrol 2004;38:85.

Davies D, Rogers M: Review of neurological manifestations in 196 patients with sebaceous naevi. Australas J Dermatol 2002;45:20.

Happle R: Epidermal nevus syndrome. Semin Dermatol 1995;14:111.

Rogers M, et al: Epidermal nevi and the epidermal nevus syndromes: a review of 233 cases. Pediatr Dermatol 1992;9:233.

Seo YJ, et al: A case of nevus comedonicus syndrome associated with neurologic and skeletal abnormalities. Int J Dermatol 2001;40:648.

Vidaurri-de la Cruz H, et al: Epidermal nevus syndromes: clinical findings in 35 patients. Pediatr Dermatol 2004;21:432.

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Zakrzewski JL, et al: Epidermal naevus and segmental hypermelanosis associated with an intraspinal mass: overlap between different mosaic neuroectodermal syndromes. Eur J Pediatr 2001;160:603.

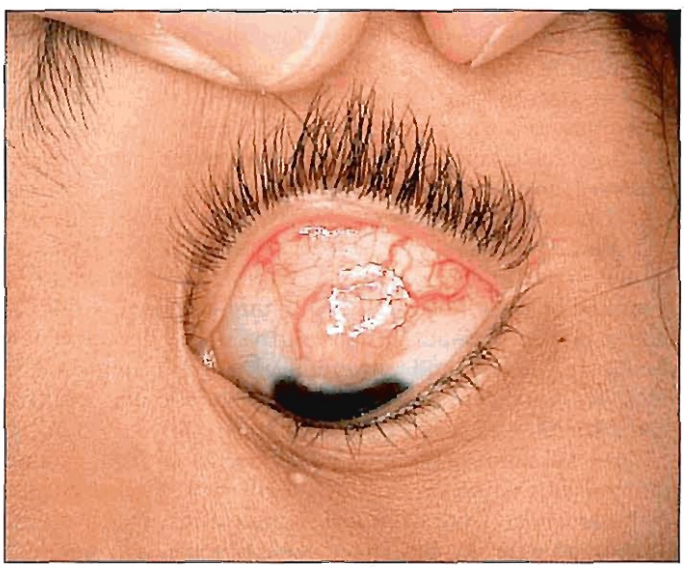

Fig. 29-4 Nevus sebaceous syndrome with lipodermoid of the conjunctiva.

Inflammatory Linear Verrucous Epidermal Nevus

The term ILVEN may encompass as many as four separate conditions. The most common form is the classic ILVEN or "dermatitic" epidermal nevus. At least three-quarters of these cases appear before age 5 years, most before age 6 months. Later onset in adulthood has been reported. ILVEN is characteristically pruritic and pursues a chronic course. Lesions follow the lines of Blascko. The individual lesions comprising the affected region are erythematous papules and plaques with fine scale (Fig. 29-5). The lesions are morphologically nondescript and, if the distribution is not recognized, could be easily overlooked as an area of dermatitis. Multiple widely separated areas may be affected, usually on only one side of the body; it may be bilateral, analogous to other epidermal nevi. Familial cases have been reported. Rarely, systemic involvement with musculoskeletal and neurologic sequelae (developmental delay, epilepsy) have been reported.

Histologically, classic ILVEN demonstrates abruptly alternating areas of hyperganulosis with orthokeratosis, and parakeratosis with agranulosis. The epidermis is acanthotic and the stratum corneum is hyperkeratotic throughout the lesion. An inflammatory infiltrate of lymphocytes is present in the upper dermis. At times the histology may simply be that of a subacute dermatitis. While the histologic diagnosis of psoriasis can be considered, the correct diagnosis can be established if the dermatopathologist is made aware of ILVEN as a consideration. If there is a question, the presence of involucrin expression in the parakeratotic areas can distinguish ILVEN from psoriasis.

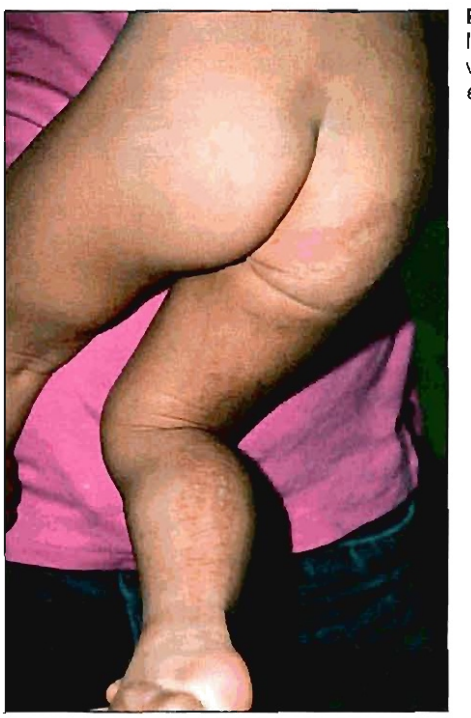

Fig. 29-5 Inflammatory linear verrucous epidermal nevus.

Three other types of inflammatory nevi have been included in this group. Some cases of "linear" lichen planus have been considered as "epidermal nevi," as they commonly follow lines of Blascko. CHILD syndrome, also considered a type of "inflammatory" epidermal nevus, is usually clinically distinct, demonstrating its characteristic hemidysplasia. The most confusing entity has been the so-called "nevoid" or "linear" psoriasis. These cases are of two types. The first type is a child with a family history of psoriasis who has a nevoid lesion at or near birth. The child later develops psoriasis which "koebnerizes" into the ILVEN lesion, suggesting it is a "locus minoris resistensiae" for psoriasis. Treatment of the psoriasis clears the psoriasis overlying the ILVEN, but not the ILVEN. Arthritis developed in one such case. The second type is one in which psoriasis initially presents in one band or area. Histologically, it resembles psoriasis. Most of these cases later develop typical psoriasis later in life, suggesting a mosaicism which allowed expression of the psoriasis earlier in the initially affected area.

ILVEN is differentiated from other epidermal nevi by the presence of erythema and pruritus clinically and by histologic features. Lichen striatus can be distinguished by its histology and natural history. Topical steroids and topical retinoids appear to have limited benefit in ILVEN. Topical Vitamin D (calcipotriol and calcitriol) and topical anthralin have been beneficial, however. Surgical modalities include excision, cryotherapy, and pulsed dye laser. In cases of "nevoid" psoriasis, eximer laser could be considered if topical treatments fail.

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Alsaleh QA, et al: Familial inflammatory linear verrucous epidermal nevus (ILVEN). Int J Dermatol 1994;33:52.

Böhm M, et al: Successful treatment of inflammatory linear verrucous epidermal naevus with topical natural vitamin D_3 (calcitriol). Br J Dermatol 2003;148:823.

Ginarte M, et al: Unilateral psoriasis: a case individualized by means of involucrin. Cutis 2000;65:167.

Goldman K, et al: Adult onset of inflammatory linear verrucous epidermal nevus in a mother and her daughter. Dermatology (Switzerland) 1994;189:170.

Lee SH, Rogers M: Inflammatory linear verrucous epidermal naevi: A review of 23 cases. Australas J Dermatol 2001; 42:252.

Menni S, et al: Inflammatory linear verrucous epidermal nevus (ILVEN) and psoriasis in a child? Int J Dermatol 2000;39:30.

Oram Y, et al: Bilateral inflammatory linear verrucous epidermal nevus associated with psoriasis. Cutis 1996;57:275.

Oskay T, Kutluay L: Inflammatory linear verrucous epidermal naevus associated with ipsilateral undescended testicle. Clin Exp Dermatol 2003;28:554.

Sidwell RU, et al: Pulsed dye laser treatment for inflammatory linear verrucous epidermal naevus. Br J Dermatol 2001; 144:1262.

Ulkur E, at el: Carbon dioxide laser therapy for an inflammatory linear verrucous epidermal nevus: a case report. Aesthetic Plast Surg 2004;28:428.

HYPERKERATOSIS OF THE NIPPLE AND AREOLA

Hyperkeratosis of the nipple and areola (HNA) is an uncommon benign, asymptomatic, acquired condition of unknown pathogenesis. Women represent 80% of cases and it presents in their second or third decade. In men the time of presentation is variable. Most cases are bilateral, although unilateral cases can occur. In about half the cases, both the areola and nipple are involved. Isolated involvement of the areola is more common than isolated involvement of the nipple. Breastfeeding is usually not affected. Clinically, there is verrucous thickening and brownish discoloration of the nipple and/or areola. Histologically, there is orthokeratotic hyperkeratosis with occasional keratinous cysts in the filiform acanthotic epidermis. The course is chronic. Treatment with calcipotriol has benefited some patients. It must be distinguished from epidermal nevi, ichthyosis, acanthosis nigricans, Darier's disease, and lichen simplex chronicus. Isolated papules or small plaques in this location probably represent seborrheic keratoses affecting the nipple or areola.

Baykal C, el al: Nevoid hyperkeratosis of the nipple and areola: A distinct entity. J Am Acad Dermatol 2002;46:414.

Bayramgürler D, et al: Nevoid hyperderatosis of the nipple and areola: Treatment of two patients with topical calcipotriol. J Am Acad Dermatol 2002;46:131.

Krishnan RZ, et al: Nevoid hyperkeratosis of the nipple and/or areola: a report of two cases and a review of the literature. Int J Dermatol 2002;41:775.

McHanna A, et al: Hyperkeratosis of the nipple and areola: report of 3 cases. Arch Dermatol 2001;137:1327.

Xifra M, et al: Nevoid keratosis of the nipple. J Am Acad Dermatol 1999;41:325.

CLEAR CELL ACANTHOMA (PALE CELL ACANTHOMA)

Clear cell acanthoma is also known as *Degos acanthoma* and *acanthome cellules claires of Degos and Civatte*. The typical lesion is a circumscribed, reddish, moist nodule with some crusting and peripheral scales; it is usually about 1 to 2 cm in diameter. A collarette is commonly observed and there may be pigmented variants. The favorite site is on the shin, calf, or occasionally the thigh, although other sites have been reported, such as the abdomen and scrotum. The lesion is asymptomatic, slow-growing, and can occur in either sex, usually after the age of 40. Solitary lesions are most common, but multiple ones have been described. Rarely, an eruptive form of the disease occurs, producing up to 400 lesions. Squamous cell carcinoma (SCC) arising from clear cell acanthoma has also been reported. Lesions occurring in plaques of psoriasis on the buttocks have been described.

The acanthotic epidermis consists of pale, edematous cells and is sharply demarcated. The basal cell layer is normal. Neutrophils are scattered within the acanthoma and in groups below and within the stratum corneum, a finding similar to the micropustules of psoriasis. The dermal blood vessels are dilated and tortuous, as seen in psoriasis. The clear keratinocytes abound in glycogen, staining positive with periodic acid-Schiff (PAS).

Clear cell acanthoma must be differentiated from eccrine poroma, which appears most frequently on the hair-free part of the foot, and from clear cell hidradenoma, which occurs most frequently on the head, especially on the face and eyelids. Treatment is surgical, either with cryotherapy or excision.

Betti R, et al: Successful cryotherapy treatment and overview of multiple clear cell acanthomas. Dermatol Surg 1995;21:342.
Burg G, et al: Eruptive hamartomatous clear-cell acanthomas. Dermatology (Switzerland) 1994;189:437.
Finch TM, Tan CY: Clear cell acanthoma developing on a psoriatic plaque: further evidence of an inflammatory aetiology? Br J Dermatol 2000;142:842.
Innocenzi D, et al: Disseminated eruptive clear cell acanthoma: a case report with review of the literature. Clin Exp Dermatol 1994;19:249.
Kavanagh GM, et al: Multiple clear cell acanthomas treated by cryotherapy. Australas J Dermatol 1995;36:33.
Langer K, et al: Pigmented clear cell acanthoma. Am J Dermatol 1994;16:134.
Murphy R, et al: Giant clear cell acanthoma. Br J Dermatol 2000;143:1114.
Parsons ME, et al: Squamous cell carcinoma in situ arising within clear cell acanthoma. Dermatol Surg 1997;23:487.

WAXY KERATOSES OF CHILDHOOD (KERINOKERATOSIS PAPULOSA)

Waxy keratosis of childhood is a genodermatosis that is either sporadic or familial. It may be generalized or segmental. Clinically, the lesions are keratotic, flesh-colored papules which affect the trunk and extremities. They appear before the age of 3 years. Histologically, there is papillomatosis with focal "church-spire" tenting of the epidermis and marked hyperkeratosis. The natural history of this rare disorder is unknown. Clinically and histologically the lesions must be distinguished from warts.

Happle R, et al: Kerinokeratosis papulosa with a type 2 segmental manifestation. J Am Acad Dermatol 2004;50:S84.
Mehrabi D, et al: Waxy keratoses of childhood in a segmental distribution. Pediatr Dermatol 2001;18:415.

MULTIPLE MINUTE DIGITATE HYPERKERATOSIS

Multiple minute digitate hyperkeratosis (MMDH) is a rare disorder. About half of cases are familial, inherited in an autosomal-dominant fashion, and the other half are sporadic. This condition has also been called *digitate keratoses*, *disseminated spiked hyperkeratosis*, *minute aggregate keratosis*, and *familial disseminated piliform hyperkeratosis*. Clinically, hundreds of asymptomatic tiny digitate keratotic papules appear on the trunk and proximal extremities. Histologically, each lesion represents a spiked, digitate or tented area of acanthotic epidermis with overlying orthohyperkeratosis. Similar lesions can be seen after inflammation and radiation therapy. The relationship of the familial/sporadic cases and the postinflammtory condition is unclear.

Takagawa S, et al: Multiple minute digitate hyperkeratoses. Br J Dermatol 2000;142:1044.

SEBORRHEIC KERATOSIS

Seborrheic keratoses are incredibly common and usually multiple. They present as oval, slightly raised, tan/light brown to black, sharply demarcated papules or plaques,

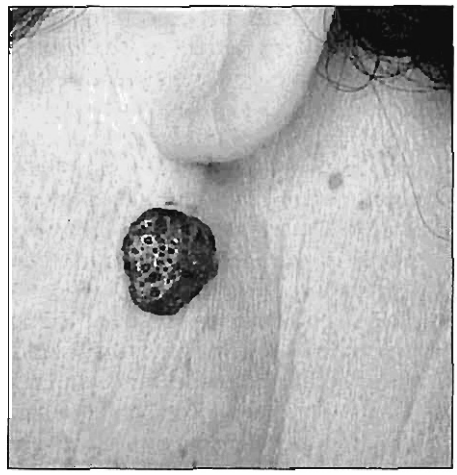

Fig. 29-6 Seborrheic keratosis.

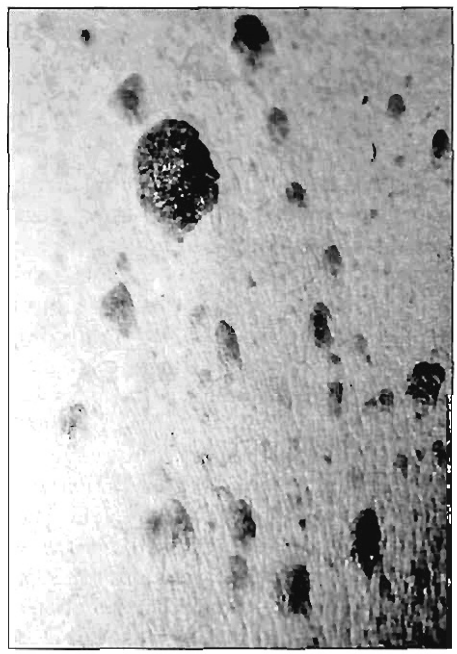

Fig. 29-7 Seborrheic keratosis.

rarely more than 3 cm in diameter. They appear "stuck-on" the skin, as if they could be removed with the flick of a fingernail (Fig. 29-6). They are located mostly on the chest and back, but also commonly involve the scalp, face, neck, and extremities (Fig. 29-7). An inframammary accumulation is common. Occasionally, genital lesions are seen. The palms and soles are spared; "seborrheic keratoses" in these areas are usually eccrine poromas. The surface of the warty lesions often becomes crumbly, like a crust that is loosely attached. When this is removed, a raw, moist base is revealed. Seborrheic keratoses may be associated with itching. Some patients have hundreds of these lesions on the trunk. While it had been thought that the age of onset is generally in the fourth to fifth decade, in Australia the prevalence of seborrheic keratoses was 20% in males and 25% in females aged 15 to 25 years. Typical lesions of the trunk are much more common in white persons; however, the "dermatosis papulosa nigra" variant of the central face is common in African Americans and Asians.

The pathogenesis of seborrheic keratoses is unknown. Clinically they usually originate de novo or appear initially

as a lentigo. A sudden eruption of many seborrheic keratoses may follow an exfoliative erythroderma, erythrodermic psoriasis, or an erythrodermic drug eruption. These lesions may be transient.

Histologically, most seborrheic keratoses demonstrate acanthosis, varying degrees of papillomatosis, hyperkeratosis, and at times keratin accumulations within the acanthotic epidermis (pseudo-horn cysts). The epidermal cells lack cytologic atypia, except at times in the irritated variant where typical normal mitoses may occur. Six histologic types—hyperkeratotic, acanthotic, adenoid or reticulated, clonal, irritated, and melanoacanthoma—are distinguished. There is a poor correlation between the clinical appearance and the observed histology, unlike for inverted follicular keratosis, dermatosis papulosa nigra, and stucco keratosis, where the histologic features are characteristic and match the clinical lesion. Melanoacanthoma differs from regular seborrheic keratosis by the presence of numerous dendritic melanocytes within the acanthotic epidermis. Oral melanoacanthoma, which has also been called *melanoacanthosis*, is clinically a reactive pigmented lesion seen primarily in young black patients (see Chapter 34). Many cases of inverted follicular keratosis represent irritated seborrheic keratoses.

The differential diagnosis usually poses no problems in most cases, but clinically atypical lesions can be a challenge. The most difficult, especially for the nondermatologist, is to differentiate the solitary black seborrheic keratosis from melanoma. The regularly shaped verrucous lesion is often different from the smooth-surfaced and slightly infiltrating pattern of melanoma. Dermoscopy can at times be of great value; however, at times seborrheic keratoses may demonstrate dermatoscopic features typical of melanocytic lesions, and the presence of horn cysts does not exclude a melanocytic lesions. Actinic keratoses are usually erythematous, more sharply rough, and slightly scaly. The edges are not sharply demarcated, and they occur most often on sun-exposed surfaces, especially the face, bald scalp, and backs of the hands. Nevi may be closely simulated. Clonal seborrheic keratoses demonstrate intraepidermal nests suggestive of intraepidermal epithelioma of Jadassohn. Rarely, Bowen's disease, SCC, basal cell carcinoma (BCC), or melanoma arise within typical-appearing seborrheic keratosis. It is prudent to biopsy any lesion that appears atypical, since even the most seasoned dermatologist has been humbled by the occasional diagnosis of melanoma in low-suspect lesions.

Seborrheic keratoses are easily removed with liquid nitrogen, curettage, or the combination of the two to avoid the need for local anesthesia to perform the curettage. The spray freezes the lesion to make it brittle enough for easy removal with the curette. Scarring is not produced by this method. Light freezing with liquid nitrogen alone is also effective, as is simple curettage with local anesthesia. Light fulguration, shave removal, and CO_2 laser vaporization are other acceptable methods.

Sign of Leser-Trélat

The sudden appearance of numerous seborrheic keratoses in an adult may be the cutaneous finding of internal malignancy. Sixty percent of the neoplasms have been adenocarcinomas, primarily of the stomach. Other common malignancies are lymphoma, breast cancer, and SCC of the lung, but many other types have been reported. To be considered a case of Leser-Trélat, the keratoses should begin at approximately the same time as the development of the cancer and run a parallel course in regard to growth and remission. The lesions are often pruritic and acanthosis nigricans, and tripe palms may accompany the appearance of the seborrheic keratoses of Leser-Trélat.

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DERMATOSIS PAPULOSA NIGRA

Dermatosis papulosa nigra occurs in about 35% of black persons and is also relatively common in Asians. It usually begins in adolescence, appearing first as minute, round, skin-colored or hyperpigmented macules or papules that develop singly or in sparse numbers on the malar regions or on the cheeks below the eyes. It has been described as early as the age of 3. The lesions increase in number and size over time, so that in the course of years the patient may have hundreds of lesions. They are distributed over the periorbital regions initially, but may occur on the rest of the face, neck, and upper chest. Lesions do not spontaneously resolve. These lesions closely simulate seborrheic keratoses. They are asymptomatic and do not develop scaling, crusting, or ulceration.

Microscopically, the chief alterations are in the epidermis. Irregular acanthosis, papillomatosis, and deposits of un-

commonly large amounts of pigment throughout the rete, and particularly in the basal layer, are characteristic. Many believe it to be a form of seborrheic keratosis.

Treatment is made difficult by the tendency for the development of dyspigmentation. Light curettage with or without anesthesia; light, superficial liquid nitrogen application; and light electrodesiccation are effective, but may result in hyper- or hypo-pigmentation. Aggressive treatment should be avoided to minimize dyspigmentation and scarring.

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STUCCO KERATOSIS

Stucco keratoses or keratoelastoidosis verrucosa of the extremities have been described as "stuck-on" lesions occurring on the lower legs, especially in the vicinity of the Achilles tendon. They are also seen on the instep, dorsa of the feet, forearms, and dorsal hands. The palms, soles, trunk, and head are never affected. Varying in diameter from 1 to 5 mm, they are loosely attached, so that they can easily be scratched off. They vary in number from a few to more than 50. Stucco keratoses are common in the US and Australia. They occur mostly in men over 40 years old. Histologically, the picture is that of a hyperkeratotic type of seborrheic keratosis, with no hypergranulosis and no wart particles seen by electron microscopy. The treatment, if any is required, consists of emollients, which soften the skin and cause the scaly lesions to fall off. Ammonium lactate lotion, 12%, may be effective in improving the appearance of the lesions. Imiquimod improved one widespread case, which may have represented widespread human papillomaviruses infection. Stucco keratoses must be distinguished from Flegel's disease.

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HYPERKERATOSIS LENTICULARIS PERSTANS (FLEGEL'S DISEASE)

Rough, yellow–brown keratotic, flat-topped papules, 2 to 5 mm in diameter, and primarily on the calves are characteristic. The palms, soles, and oral mucosa may rarely be involved. Familial cases have been reported.

The histologic findings are distinctive, with hyperkeratosis and parakeratosis overlying a thinned epidermis, and irregular acanthosis at the periphery. A bandlike inflammatory infiltrate occurs in the papillary dermis. Topical emollients, topical 5-FU, and PUVA have been reported as useful. Oral retinoids may cause improvement, but are hard to justify in this chronic asymptomatic condition. The lesions do not recur after shallow shave excision.

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Miranda-Romero A, et al: Unilateral hyperkeratosis lenticularis perstans (Flegel's disease). J Am Acad Dermatol 1998;39:655.

WARTY DYSKERATOMA

Warty dyskeratomas are most commonly solitary and found on the head and neck (70%), trunk (20%), or extremities. Rare oral lesions occur. The lesion is a brownish-red papule or nodule with a soft, yellowish, central keratotic plug. Histologically, a cup-like depression filled with a keratotic plug is most common. The epithelium lining the invagination shows the features of Darier's disease with intraepidermal clefts, acantholytic cells, and pseudovilli. Keratin pearls, corps ronds, and grains may be seen. Cystic lesions with prominent keratinous cysts can occur. Cutaneous lesions appear to originate from a hair follicle. Warty dyskeratoma must be distinguished histologically from keratoacanthoma and acantholytic SCC. Treatment is surgical.

Kaddu, et al: Warty dyskeratoma—"follicular dyskeratoma": Analysis of clinicopathologic features of a distinctive follicular adnexal neoplasm. J Am Acad Dermatol 2002;47:423.

BENIGN LICHENOID KERATOSES (LICHEN PLANUS-LIKE KERATOSIS)

Benign lichenoid keratoses are usually solitary dusky-red to violaceous papular lesions up to 1 cm in diameter, but are at times larger (Fig. 29-8). They occur most often on the distal forearms, hands, or chests of middle-aged white women. The lesions are commonly biopsied since the clinical features are identical to a superficial BCC. A slight violaceous hue or the presence of an adjacent solar lentigo can raise the suspicion of lichen planus-like keratosis. Multiple lesions may simulate a photodermatitis, such as lupus erythematosus. Evolution from preexisting solar lentigines is often noted histologically or by history.

Histologically, the lesion may be indistinguishable form idiopathic lichen planus. While idiopathic lichen planus

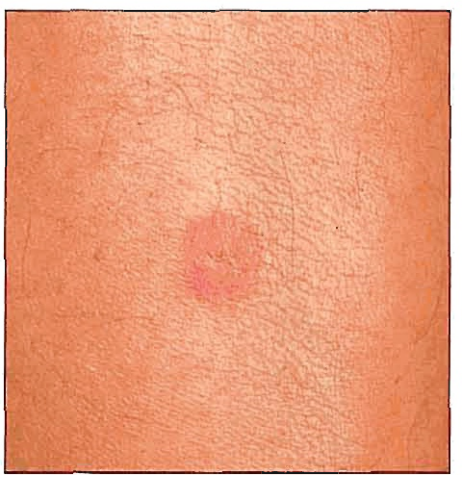

Fig. 29-8 Lichen planus-like keratosis.

rarely demonstrates parakeratosis, plasma cells or eosinophils, these may be present in lichen planus-like keratosis. The remnants of a solar lentigo may be seen at the periphery. These features, plus the clinical information that it represents a solitary lesion, suggest the correct diagnosis. Clinical correlation is essential, as similar histologic findings may be seen in lichenoid drug eruptions, acral lupus erythematosus, and lichenoid regression of melanoma. Direct immunofluorescence is positive, with clumped deposits of IgM in a lichen planus-like pattern at the dermoepidermal junction. This differs from the continuous granular immunoglobulin deposition of acral lupus erythematosus. Cryotherapy with liquid nitrogen is effective.

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ARSENICAL KERATOSES

Arsenical keratoses are keratotic, pointed, 2- to 4-mm wartlike lesions on the palms, soles, and sometimes ears of persons who have a history of drinking contaminated well water or taking medications containing arsenic trioxide, usually for asthma (Fowler's solution, Bell's Asthma Mixture), atopic dermatitis, or psoriasis, often years previously (Fig. 29-9). These lesions resemble palmar pits, but may have a central hyperkeratosis. When the keratosis is picked off with the fingernails, a small dell-like depression is seen.

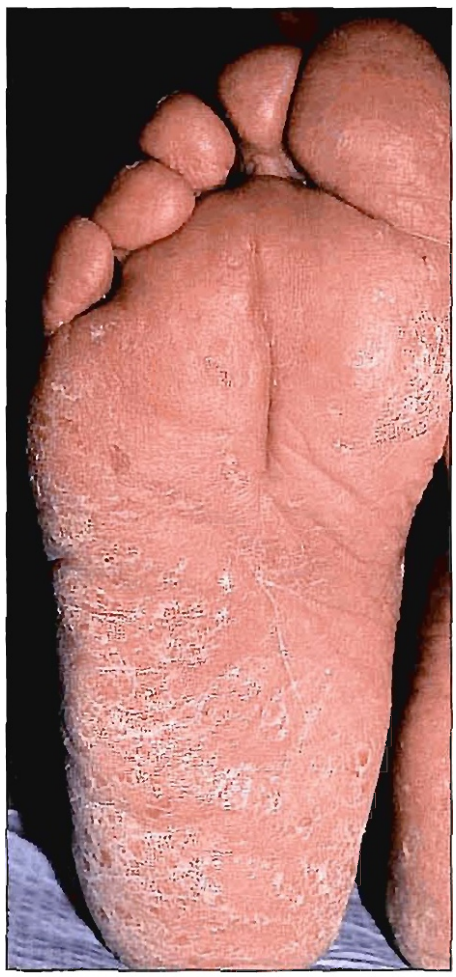

Fig. 29-9 Arsenical keratosis in a patient who had been exposed to arsenic in drinking water.

Bowen's disease and invasive arsenical SCC may be present, with the latent period being 10 and 20 years, respectively. The profound increase in Bowen's disease and SCC appears to be characteristic of patients with arsenic exposure from well water. In patients exposed to arsenic via elixirs, BCCs are more characteristically seen. The latency period for development of BCC is also 20 years. Lesions are most common on the scalp and trunk. Internal carcinoma also occurs with increased frequency, after an average latent period of 30 years, with pulmonary and genitourinary carcinoma being most common. Arsenic has also been implicated in causing Merkel cell carcinoma.

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NONMELANOMA SKIN CANCERS AND THEIR PRECURSORS

Nonmelanoma skin cancers (NMSCs) are the most common form of cancer diagnosed in the US, with 1.3 million cases diagnosed annually. One in two men and one in three women in the US will develop NMSC in their lifetime, usually after the age of 55. While these result in only about 2000 to 2500 deaths annually, due to their sheer numbers NMSCs represent about 5% of all Medicare cancer expenditures. Those at risk for skin cancer are fair-skinned individuals who tan poorly and who have had significant chronic or intermittent sun exposure. Red hair phenotype with loss-of-function mutations in the melanocortin-1 receptor may be a risk factor as well. Additional risk factors include a prior history of skin cancer, prior radiation therapy, PUVA treatment, arsenic exposure, and systemic immunosuppression (Fig. 29-10). Once an individual has developed a NMSC, his/her risk for a second is increased 10-fold. Over the 3-year period following the initial NMSC diagnosis, more than 40% of BCC and SCC patients develop a BCC, and 18% of SCC patients develop another SCC. By 5 years as many as 50% of women and 70% of men will develop a second NMSC. The rate of developing NMSCs is not different 3 years or 10 years after the initial NMSC diagnosis. Patients with a history of NMSC should be examined for NMSCs on a regular basis.

Ultraviolet radiation (UVR) is the major cause of nongenital NMSCs and actinic keratoses. The effect of UVR appears to be mediated through mutation of the p53 gene, which is found mutated in a substantial percentage of NMSCs

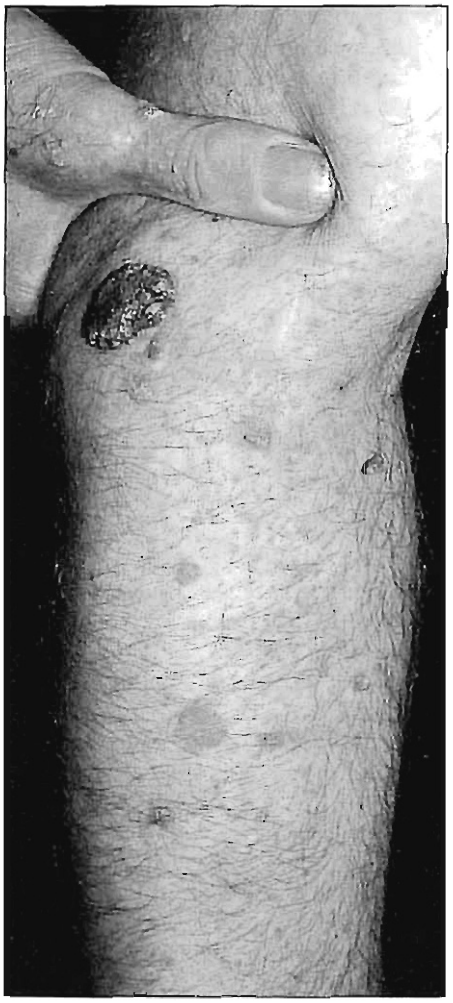

Fig. 29-10 Actinic keratosis/Bowen's disease in a transplant recipient.

and actinic keratoses. Most skin cancers are highly immunogenic, but the immune response is suppressed by continued actinic exposure. Both chronic sun exposure and intermittent intense exposure are risk factors for the development of NMSCs. It is believed that avoiding sun exposure reduces the risk for NMSC. The use of sunscreens in the prevention of NMSCs has been controversial, as they may inadvertently lead to prolonged intentional sun exposure, negating their possible beneficial effect. Nonetheless, dermatologists and their societies recommend a program of sunscreen use together with sun avoidance to patients at risk for skin cancer. This includes avoiding midday sun, seeking shade, wearing protective clothing, and regularly applying a sunblock of sun protection factor (SPF) 15 to 30 with both UVB and UVA coverage. This program, which was pioneered in Australia, has led to improvements in some skin cancer rates in that country. Lack of standards for label claims of UVA blockade remains a problem, but superior UVA-blocking sunscreen ingredients, such as avobenzone zinc oxide and titanium dioxide, are gaining consumer recognition.

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ACTINIC KERATOSIS (SOLAR KERATOSIS)

Actinic keratoses represent in situ dysplasias resulting from sun exposure. They are found chiefly on the chronically sun-exposed surfaces of the face, ears, balding scalp, dorsal hands, and forearms. They are usually multiple, discrete, flat or elevated, verrucous or keratotic, red, pigmented, or skin colored. Usually the surface is covered by an adherent scale, but sometimes it is smooth and shiny. On palpation the surface is rough, like sandpaper, and at times lesions are more easily felt than seen. The patient may complain of tenderness when the lesion is rubbed or shaved over with a razor. The lesions are usually relatively small, measuring 3 mm to 1 cm in diameter, most being less than 6 mm. Rarely, lesions may reach 2 cm in size, but a lesion larger than 6 mm should only be considered an actinic keratosis if confirmed by biopsy or if it completely resolves with therapy. The hypertrophic type, which may lead to cutaneous horn formation, is most frequently present on the dorsal forearms and hands.

Actinic keratoses are the most common epithelial precancerous lesions. While lesions typically appear in persons over 50 years of age, actinic keratoses may occur in the 20s or 30s in patients who live in areas of high solar irradiation and are fair-skinned. Patients with actinic keratoses have a propensity for the development of nonmelanoma cutaneous malignancies. Actinic keratoses can be prevented by the regular application of sunscreen and by a diet low in fats. Beta-carotene is of no benefit in preventing actinic keratoses.

Six types of actinic keratoses can be recognized histologically: hypertrophic, atrophic, bowenoid, acantholytic, pigmented, and lichenoid. The epidermis may be acanthotic or atrophic. Keratinocyte maturation may be disordered with overlying parakeratosis sometimes present. The basal cells are most frequently dysplastic, although in more advanced lesions dysplasia may be seen throughout the epidermis, simulating Bowen's disease (bowenoid actinic keratosis).

The clinical diagnosis of actinic keratosis is usually straightforward. Early lesions of chronic cutaneous lupus erythematosus and pemphigus foliaceus are sometimes confused for actinic keratoses. Seborrheic keratoses, even when they lack pigmentation, are usually more "stuck on" in appearance and more sharply marginated than actinic keratoses. Magnification may aid in this distinction. It is difficult to distinguish hypertrophic actinic keratoses from early SCC and a low threshold for biopsy is recommended. Similarly, actinic keratoses, which present as red patches, can not easily be distinguished from Bowen's disease or superficial BCC. If there is a palpable dermal component, or if on stretching the lesion there is a pearly quality, a biopsy should be considered. Any lesion larger than 6 mm, and any lesion which has failed to resolve with appropriate therapy for actinic keratosis should also be carefully evaluated for biopsy.

Since some percentage of actinic keratoses will progress to NMSC, their treatment is indicated. There are many effective therapeutic modalities. Cryotherapy with liquid nitrogen is most effective and practical when there are a limited number of lesions. A bulky cotton applicator dipped into liquid nitrogen or a handheld nitrogen spray device can be used. If the cotton-tip applicator method is used, the liquid nitrogen into which the applicator is dipped should be used for only one patient, as there is theoretical risk of cross-contamination from one patient to another. Infectious agents are not killed by freezing. For this reason, many dematologists now use the spray devices. We recommend using a small opening tip with continuous bursts of nitrogen spray in a circular motion, depending on the size of the lesion, attempting an even frosting. Only the lesion should be frosted and the duration of cryotherapy must be carefully controlled. A long freeze that results in significant epidermal–dermal injury produces white scars, which are easily seen on the fair skin of those at risk for actinic keratoses. When correctly performed, healing usually occurs within a week on the face, but may require up to 4 weeks on the arms and legs. Caution should be exercised when treating below the knee, since wound healing in these regions is particularly poor and a chronic ulcer can result. Also, use caution in persons at risk for having a cryoprotein (hepatitis C virus-infected patients, and patients with connective tissue disease or lymphoid neoplasia). They may have an excessive reaction to cryotherapy. It is better on the first visit to "under-treat" until the tolerance of a patient's skin to cryotherapy is known. Application of 0.5% 5-FU for 1 week prior to cryotherapy improves the response to cryotherapy.

For extensive, broad, or numerous lesions, topical chemotherapy is recommended. Any lesion which potentially might represent a NMSC should be biopsied prior to beginning topical chemotherapy for AK's. Foul self-treatment of AK's by patients should be discouraged. In both settings the diagnosis of NMSC may be delayed by ineffective topical chemotherapy. The two agents most commonly used are 5-FU cream, 0.5% to 5%, or imiquimod 5% cream. Topical tretinoin and adapalene do not have the efficacy of these two agents, but can be used for prolonged periods and represent an option for patients with a few early lesions. Three percent diclofenac in 2.5% hyaluronan gel when used for 60 days can also be effective for actinic keratoses.

The frequency and duration of treatment are determined by the individual's reaction and the anatomic site of application. 5-FU is applied once a day in most cases. For the face, 0.5% 5-FU tends to give a predictable response, which is a bit less severe than that produced by the 1% to 5% concentrations. Some patients prefer the stronger concentration for a briefer period, while others favor a slower onset of the reaction and a more prolonged course. For the 5% cream, treatment duration rarely needs to exceed 2 to 3 weeks. For the 0.5% cream, the treatment course is usually 3 to 6 weeks. Usually the central face will respond more briskly than the temples and forehead, which may require a longer duration of treatment. If the reaction is brisk, the treatment can be stopped and restarted at a lower concentration. Depending on the individual's sensitivity, an erythematous burning reaction will occur within several days. Treatment is stopped when a peak response occurs characterized by a change in color from bright to dusky-red, by reepithelialization, and by crust formation. Healing usually occurs within another 2 weeks after treatment has been stopped, depending on the treatment site. Certain areas of the face are prone to intense irritant dermatitis when exposed to 5-FU and tolerance can be improved if the patient avoids application to the glabella, melolabial folds, and chin. For the scalp, the 0.5% concentration may be adequate, but often prolonged or multiple treatment courses are required if this low concentration is used. The 5% cream produces a more predictable, albeit brisk, reaction. A thick cutaneous horn can prevent penetration of 5-FU and hypertrophic actinic keratoses on the scalp, dorsal hand, and forearm may respond poorly unless the area is pretreated with an agent to remove excessive keratin overlying the lesions. Pretreatment with tretinoin for 2 to 3 weeks can improve efficacy and shorten the duration of subsequent 5-FU treatment. It has been observed that 5-FU "seeks out" lesions that may not be clinically apparent. Clinically inapparent BCCs may be detected during or on completion of the treatment. Rarely, patients who have had multiple courses of 5-FU topical chemotherapy will develop a true allergic contact dermatitis to the 5-FU. This is manifested by the redness, edema or vesculation extending beyond the area of application and by the patient developing pruritus rather than tenderness on the treated areas. Patch testing can be confirmatory.

Imiquimod is an interferon inducer and apparently eradicates actinic keratoses by producing a local immunologic reaction against the lesion. The ideal protocol for application of imiquimod may not yet be determined. About 80% of patients respond to imiquimod and 20% may not respond at all, perhaps due to the fact that they lack some genetic component required to induce an inflammatory cascade when imiquimod is applied. If applied three times a week, patients develop an inflammatory reaction similar to that seen with daily application of 5-FU. It is somewhat unpredictable how severe the reaction will be, with a small subset of patients (especially fair-skinned women) developing a severe burning and crusting reaction after only one or a few applications. In others, no reaction at all occurs. With twice a week application, the treatment course is prolonged, up to 16 weeks. Severe erythema occurs in 17.7% and scabbing/crusting in 8.4% of patients so treated. The median percent reduction in actinic keratoses is 83.3% with this treatment protocol. Overall, while the reaction is less predictable from imiquimod, it is also typically less severe than with high concentrations of 5-FU. The adverse event

rates are similar to those with low concentration (0.5%) 5-FU. Another regimen is to apply imiquimod for long periods at a reduced frequency (once or twice a week). Applications can be in alternating 1-month cycles or continuous for many months. This may allow some patients who require treatment but cannot tolerate any significant changes in appearance to be managed. In the end, the choice between topical 5-FU and imiquimod will be based on patient preference, prior physician and patient experience with the modalities, and the cost of the medication. Imiquimod is significantly more expensive per gram than any form of 5-FU. A paired comparative trial would be of great value in determining the optimal and most cost-effective strategy for the treatment of extensive actinic keratoses. Surgical management of actinic keratoses with chemical peels, laser resurfacing, and photodynamic therapy is discussed in Chapters 37 and 38.

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CUTANEOUS HORN (CORNU CUTANEUM)

Cutaneous horns are encountered most frequently on the face and scalp. Lesions may also occur on the hands, penis, and eyelids. They are skin-colored, horny excrescences, 2 to 60 mm long, sometimes divided into several antler-like projections.

These lesions are most often benign, with the hyperkeratosis being superimposed on an underlying seborrheic keratosis, verruca vulgaris, angiokeratoma, molluscum contagiosum or trichilemmoma about 60% of the time. However, 20% to 30% may overlie premalignant keratoses and 20% may overlie SCCs or BCCs. The risk for a cutaneous horn overlying a malignancy is much higher in elderly fair-complexioned persons. Hyperkeratotic actinic plaques less than 1 cm in diameter on the dorsum of the hand, wrist, or forearms in white patients have been shown to have a malignancy rate of 50%. One-third of penile horns are associated with underlying malignancies. Excisional biopsy with histologic examination of the base is necessary to determine the best therapy, which would be dictated by the diagnosis of the underlying lesion and by the apparent adequacy of removal.

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KERATOACANTHOMA

Clinical Features

There are four types of keratoacanthomas: solitary, multiple, eruptive, and keratoacanthoma centrifugum marginatum. The exact biologic behavior of keratoacanthoma remains controversial. In the past it had been considered a reactive condition or pseudomalignancy which could be treated expectantly. Now the favored view is that keratoacanthomas are malignant tumors, which in many cases will regress. The regression may be partially mediated by immunity, but takes the form of terminal differentiation. The course of these tumors is unpredictable. Even those that ultimately involute can cause considerable destruction before they regress. Any lesions with the histologic features of keratoacanthoma and which appear in an immunosuppressed host should be managed as an SCC, with complete eradication.

Sunlight appears to play an important role in the etiology, especially in the solitary types. In addition, light-skinned persons are more apt to develop keratoacanthoma than dark-skinned persons. Instances of keratoacanthomas following trauma and surgical excisions suggest an isomorphic phenomenon may occur. Lesions histologically identical to keratoacanthomas can be seen rarely in patients with hypertrophic lichen planus and discoid lupus erythematosus. The biologic behavior of these lesions is unknown, but they have added to the controversy of keratoacanthoma as a reactive versus a malignant process. In Muir-Torre syndrome, sebaceous tumors and keratoacanthomas occur in association with multiple internal malignancies. A second, less common cancer syndrome is the keratoacanthoma visceral carcinoma syndrome (KAVCS). Only a handful of cases have been reported. Patients have multiple or large keratoacanthomas which appear at the same time as an internal malignancy, always of the genitourinary tract. The relation-

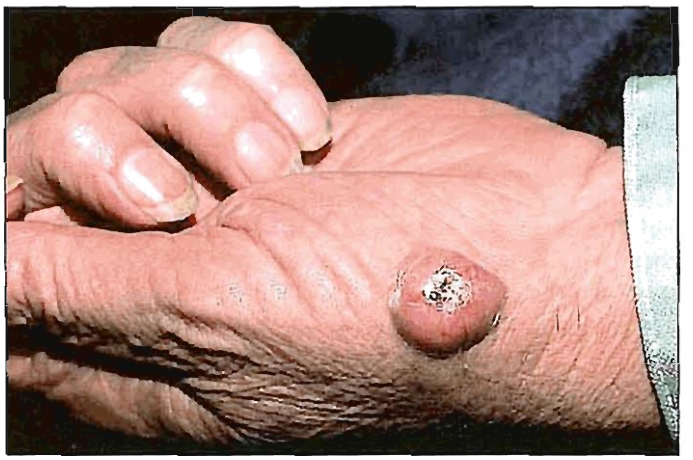

Fig. 29-11 Keratoacanthoma.

ship of Muir-Torre to KAVCS awaits identification of the genetic basis of both syndromes.

Solitary Keratoacanthoma

This type of keratoacanthoma is a rapidly growing papule that enlarges from a 1-mm macule or papule to as large as 25 mm in 3 to 8 weeks. When fully developed it is a hemispheric, dome-shaped, skin-colored nodule in which there is a smooth crater filled with a central keratin plug (Fig. 29-11). The smooth shiny lesion is sharply demarcated from its surroundings. Telangiectases may run through the lesion. Subungual keratoacanthomas are tender subungual tumors which usually cause significant nail dystrophy. Subungual lesions often do not regress spontaneously and induce early underlying bony destruction, characterized on radiograph as a crescent-shaped lytic defect without accompanying sclerosis or periosteal reaction.

The solitary keratoacanthoma occurs mostly on sun-exposed skin, with the central portion of the face, backs of the hands, and arms being the most commonly involved sites. Less frequently, other sites are involved, such as the buttocks, thighs, penis, ears, and scalp. Elderly fair-skinned individuals most commonly develop keratoacanthomas. Lesions of the dorsal hands are more common in men and keratoacanthomas of the lower legs are more common in women. The most interesting feature of this disease is the rapid growth for some 2 to 6 weeks, followed by a stationary period for another 2 to 6 weeks, and finally a spontaneous involution over another 2 to 6 weeks to leave a slightly depressed scar. The stationary period and involuting phase are variable; some lesions may take 6 months to a year to completely resolve. It has been estimated that some 5% of treated lesions recur. Invasion along nerve trunks has been documented and may result in recurrence after a seemingly adequate excision.

Histopathology

The histologic findings of keratoacanthoma and a low-grade SCC are so similar that it is frequently difficult to make a definite diagnosis on the histologic findings alone. When a properly sectioned specimen is examined under low magnification, the center of the lesion shows a crater filled with eosinophilic keratin. Over the sides of the crater, which seems to have been formed by invagination of the epidermis, a "lip" or "marginal buttress" of epithelium extends over the keratin-filled crater. At the base and sides of the crater, the epithelium is acanthotic and composed of keratinocytes which are highly keratinized and have an eosinophilic, glassy cytoplasm. Surrounding the keratinocyte proliferation, a dense inflammatory infiltrate is frequently seen. Neutrophilic microabscesses are common within the tumor and trapping of elastic fibers is commonly identified at the periphery of the tumor. These features favor a diagnosis of keroacanthoma. The most definitive histologic feature is evidence of terminal differentiation, where the scalloped outer border of the tumor has lost its infiltrative character and is reduced to a thin rim of keratinizing cells lining a large keratin-filled crater. The presence of acantholysis within the tumor is incompatible with a diagnosis of keroacanthoma. It is also important to distinguish keratoacanthoma from marked pseudoepitheliomatous hyperplasia as seen in prurigo nodularis.

Treatment

Although keratoacanthomas spontaneously involute, it is impossible to predict how long this will take. The patient may be faced with destructive growth of a tumor for as long as a year. More importantly, clinically SCC cannot always be excluded. Therefore, excisional biopsy of the typical keratoacanthoma of less than 2 cm in diameter should be considered in most cases. If the history is characteristic or multiple lesions have appeared simultaneously, less aggressive interventions may be considered. Nonsurgical therapy may also be considered in certain sites to preserve function or improve cosmetic outcome.

Intralesional injections of 5-FU solution, 50 mg/mL (undiluted from the ampule) at weekly intervals; bleomycin 0.5 mg/mL; or methotrexate 25 mg/mL can be effective. For a typical lesion, four injections along the base at each pole are recommended. Low-dose systemic methotrexate can be considered if multiple lesions are present and there is no contraindication. For clinically typical lesions these modalities may be tried before resorting to surgical removal, especially if the latter presents any problem. Excision is recommended if there is not at least 50% involution of the lesion after 3 weeks. Radiation therapy may also be used on giant keratoacanthomas when surgical excision or electrosurgical methods are not feasible.

Multiple Keratoacanthomas (Ferguson Smith Type)

This type of keratoacanthoma is frequently referred to as the *Ferguson Smith type of multiple self-healing keratoacanthomas*. These lesions are identical clinically and histologically to the solitary type. There is frequently a family history of similar lesions. This condition has been traced to two large Scottish kindreds. Affected families from other countries have also been reported. Beginning on average at about the age of 25, but as early as the second decade, patients develop crops of keratoacanthomas that begin as small red macules and rapidly become papules which evolve to typical keratoacanthomas. Lesions may number from a few to hundreds but generally only 3 to 10 lesions are noted at any one time. Sun-exposed sites are favored, especially the ears and nose, and in most cases scalp lesions occur. In addition, these patients typically develop keratoacanthomas at sites of

trauma. Lesions grow over 2 to 4 weeks reaching a size of 2 to 3 cm, then remain stable for 1 to 2 months before slowly involuting. They leave a prominent crateriform scar. If the early lesions are aggressively treated with cryotherapy, shave removal, or curettage, the scar may be less marked than that induced by spontaneous involution. Treatment with etretinate can be effective in stopping the appearance of new lesions and causing involution of existing ones.

Generalized Eruptive Keratoacanthomas (Grzybowski Variant)

This type of keratoacanthoma is very rare and sporadic, with most patients having no affected family members. The usual age of onset is between 40 and 60. The patients are usually in good health and are not immunosuppressed. The cause of this condition is unknown. Human papilloma viruses have not been detected in most cases in which it was sought. The clinical features are characteristic and unique. Grzybowski type of multiple keratoacanthomas is characterized by a generalized eruption of numerous dome-shaped, skin-colored papules from 2 to 7 mm in diameter. Multiple larger typical keratoacanthomas may also appear. Thousands of lesions may develop. The eruption is usually generalized, but spares the palms and soles. The oral mucous membranes can be involved. Severe pruritus may be a feature. Clinically, pityriasis rubra pilaris or widespread lichen planopilaris are often considered. Bilateral ectropion, narrowing of the oral aperture, and severe facial disfigurement can result. Linear arrangement of some lesions, especially over the shoulders and arms, has also been noted. Despite the multiplicity of lesions, no case of "metastasis" from a skin lesion or increased risk of internal malignancy has been reported in the Grzybowski variant of keratoacanthoma. Dr Grzybowski's original patient died 16 years after diagnosis of a myocardial infarction. Treatment with oral retinoids may improve the larger keratoacanthomas but they are at best partially beneficial for the widespread lesions.

There are reports of multiple keratoacanthomas appearing after surgical procedures in the setting of immunosuppression and after treatment with infliximab. These cases of "eruptive" keratoacanthomas are considered multiple "solitary" keratoacanthomas, rather than the Grzybowski variant of keratoacanthoma.

Keratoacanthoma Centrifugum Marginatum

This uncommon variant of keratoacanthoma is most commonly solitary, but multiple lesions can occur. Keratoacanthoma centrifugum marginatum is characterized by progressive peripheral expansion and concomitant central healing leaving atrophy. Spontaneous involution, as may be seen in other variants of keratoacanthoma, does not occur. Lesions range from 5 to 30 cm in diameter (Fig. 29-12). The dorsum of the hands and pretibial regions are favored sites. Treatment with oral etretinate and oral methotrexate with prednisone have been effective in isolated cases.

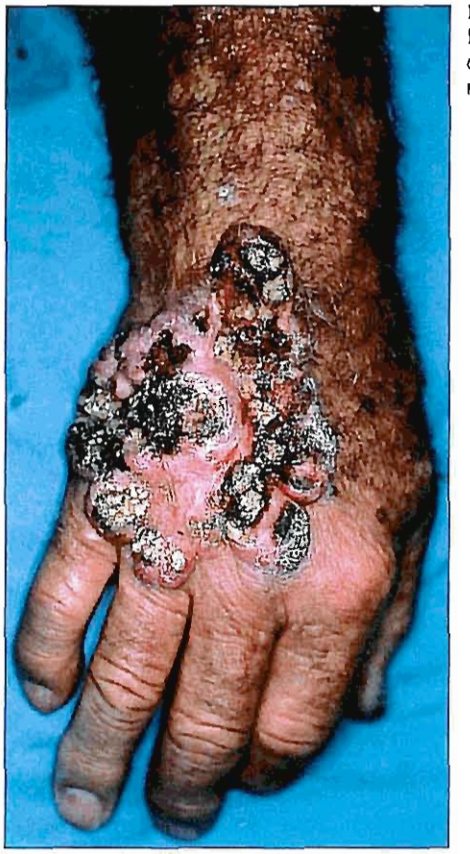

Fig. 29-12
Keratoacanthoma centrifugum marginatum.

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BASAL CELL CARCINOMA

BCC is the most common cancer in the US, Australia, New Zealand, and many other countries with a largely white, fair-skinned population with the opportunity to expose their skin to sunlight. Intermittent intense sun exposure, as identified by prior sunburns; radiation therapy; a positive family history of BCC; immunosuppression; a fair complexion, especially red hair; and easy sunburning (skin types I or II); and blistering sunburns in childhood are risk factors for the development of BCC. Of interest, actinic elastosis and wrinkling are not risk factors for the development of BCC. In fact, BCCs are relatively rare on the dorsal hand, where sun exposure is high, and actinic keratoses and SCCs abound. SCC is three times more common than BCC on the dorsum of the hand. These findings suggest that the mechanism by which UVR induces BCC is not related solely to the total amount of UVR received.

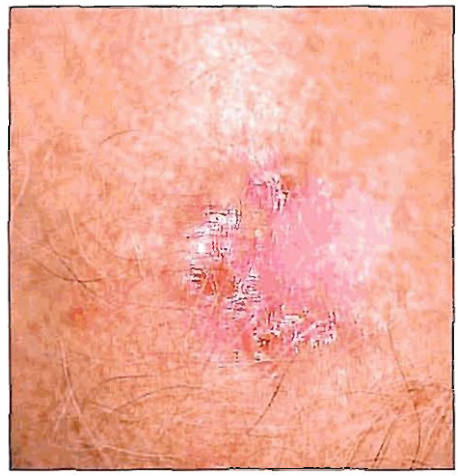

Fig. 29-13 Basal cell carcinoma.

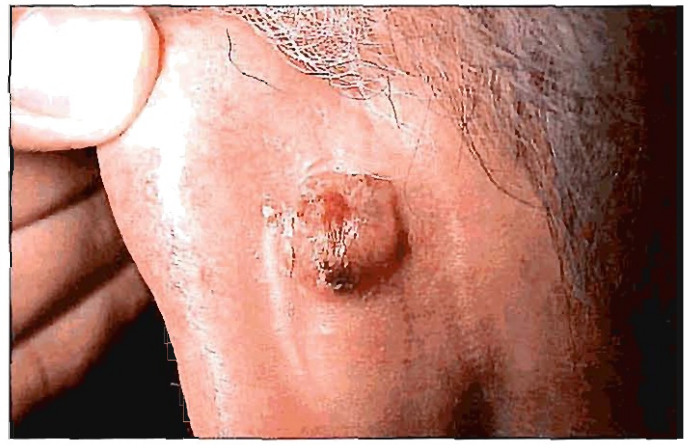

Fig. 29-14 Basal cell carcinoma, nodular type.

Many clinical morphologies of BCC exist. Clinical diagnosis is dependent on the clinician being aware of the many forms BCC may take. Since these clinical types may also have different biologic behavior, histologic classification of the type of BCC may also influence the form of therapy chosen.

Nodular Basal Cell Carcinoma (Classic Basal Cell Carcinoma)

The classic or nodular BCC comprises 50% to 80% of all BCCs. Nodular BCC is composed of one or a few small, waxy, semitranslucent nodules forming around a central depression that may or may not be ulcerated, crusted, and bleeding (Fig. 29-13). The edge of larger lesions has a characteristic rolled border. Telangiectases course through the lesion. Bleeding on slight injury is a common sign.

As growth progresses, crusting appears over a central erosion or ulcer, and when the crust is knocked or picked off, bleeding occurs and the ulcer becomes apparent. This ulcer is characterized by chronicity and gradual enlargement over time. The lesions are asymptomatic and bleeding is the only difficulty encountered. The lesions are most frequently found on the face (85–90% are found on the head and neck) and especially on the nose (25–30%). The forehead, ears (Fig. 29-14), periocular areas, and cheeks are also favored sites. Any part of the body may be involved, however.

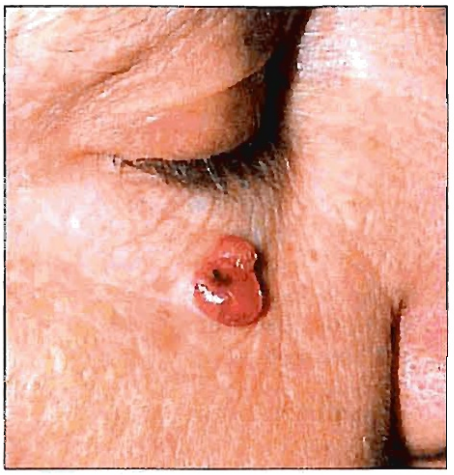

Fig. 29-15 Basal cell carcinoma, cystic.

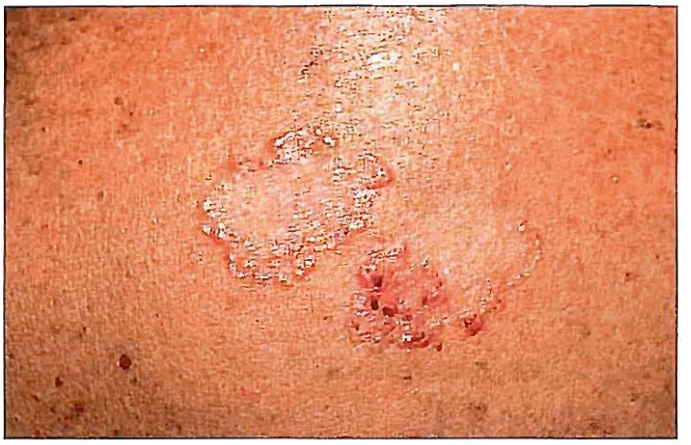

Fig. 29-16 Basal cell carcinoma.

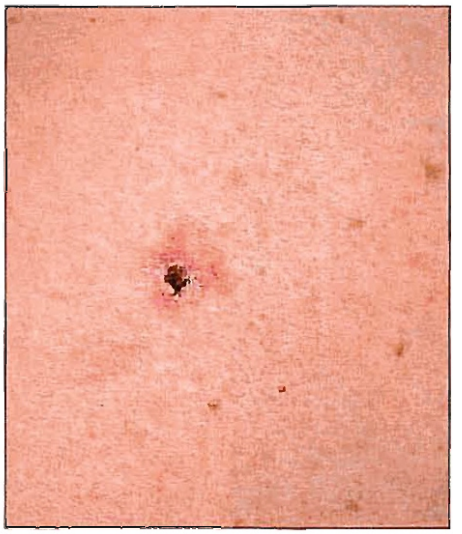

Fig. 29-17 Basal cell carcinoma, superficial.

Cystic Basal Cell Carcinoma

These dome-shaped, blue-gray cystic nodules are clinically similar to eccrine and apocrine hidrocystomas (Fig. 29-15).

Morphoeic, Morpheaform, or Cicatricial Basal Cell Carcinoma

This type of BCC presents as a white sclerotic plaque. Ninety-five percent of these BCCs occur on the head and neck. Ulceration, a pearly rolled border, and crusting are usually absent. Telangiectasia is variably present. For this reason, the lesion is often missed or misdiagnosed for some time. The differential diagnosis includes desmoplastic trichoepithelioma, a scar, microcystic adnexal carcinoma, and desmoplastic melanoma. The unique histologic feature is the strands of basal cells interspersed amid densely packed, hypocellular connective tissue. Morpheic BCCs constitute 2% to 6% of all BCCs.

Infiltrative Basal Cell Carcinoma

Infiltrative BCC is an aggressive subtype characterized by deep infiltration of spiky islands of basaloid epithelium in a fibroblast rich stroma. Clinically, it lacks the scarlike appearance of morphoeic BCC. Histologically, the stroma is hypercellular, the islands are jagged in outline and squamous differentiation is common.

Micronodular Basal Cell Carcinoma

These tumors are not clinically distinctive, but the micronodular growth pattern makes them less amenable to curettage.

Superficial Basal Cell Carcinoma

Superficial BCC is also termed *superficial multicentric BCC*. This is a very common form of BCC, comprising at least 15% of BCCs. This form favors the trunk (45%) or distal extremities (14%). Only 40% occur on the head and neck. The multicentricity is merely a histologic illusion created by the passing of the plane of section through the branches of a single, multiply branching lesion.

This type of BCC most frequently presents as a dry, psoriasiform, scaly lesion. They are usually superficial flat growths, that in many cases exhibit little tendency to invade or ulcerate. They enlarge very slowly and may be misdiagnosed as patches of eczema or psoriasis. These lesions may grow to be 10 to 15 cm in diameter. Close examination of the edges of the lesion will show a thread-like raised border (Figs 29-16 and 29-17). These erythematous plaques with telangiectasia may show atrophy or scarring occasionally. Some lesions may develop an infiltrative component in their deeper aspect and grow into the deeper dermis. When this occurs they may induce dermal fibrosis and multifocal ulceration, forming a "field of fire" type of large BCC. Sometimes the lesion will heal at one place with a white atrophic scar and then spread actively to the neighboring skin. It is not uncommon for a patient to have several of these lesions simultaneously or with time. This form of BCC is the most common pattern seen in patients with human immunodeficiency virus (HIV) infection and BCC.

Pigmented Basal Cell Carcinoma

This variety has all the features of nodular BCC, but in addition, brown or black pigmentation is present (Fig. 29-18). When dark-complexioned persons such as Latin Americans, Hispanics, or Asians develop BCC, this is the type they tend to develop. Pigmented BCCs comprise 6% of all BCCs. In the management of these lesions it should be known that if ionizing radiation therapy is chosen as the therapeutic modality, the pigmentation remains at the site of the lesion.

Rodent Ulcer

Also known as *Jacobi ulcer*, rodent ulcer is a neglected BCC which has formed an ulceration (Fig. 29-19). The pearly

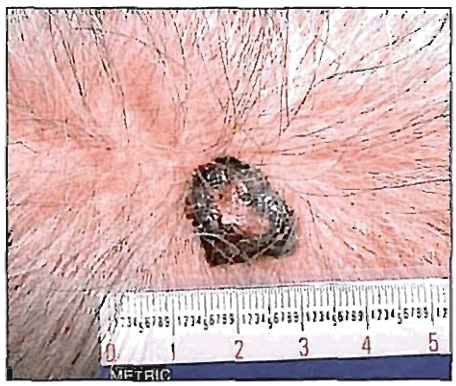

Fig. 29-18 Basal cell carcinoma, pigmented.

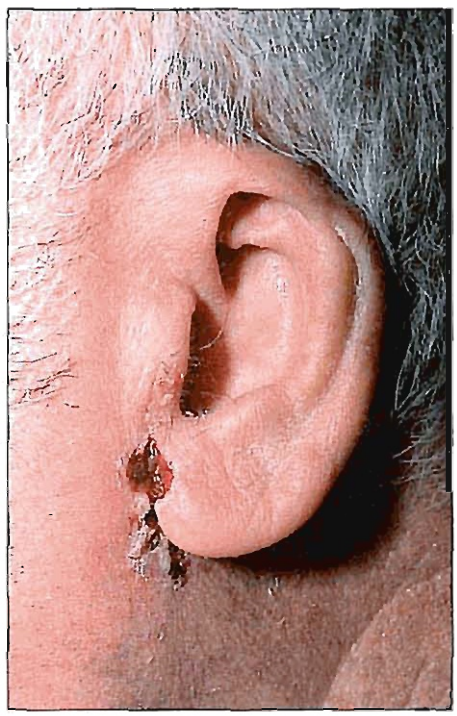

Fig. 29-19 Basal cell carcinoma, rodent ulcer.

border of the lesion may not be recognized. If it occurs on the lower extremity it may be misdiagnosed as a vascular ulceration.

Fibroepithelioma of Pinkus

First described by Pinkus as premalignant fibroepithelial tumor, the tumor is usually an elevated, skin-colored, sessile lesion on the lower trunk, the lumbosacral area, groin, or thigh and may be as large as 7 cm. The lesion is superficial and resembles a fibroma or papilloma.

Histologically, there are interlacing basocellular sheets that extend downward from the surface to form an epithelial meshwork enclosing a hyperplastic mesodermal stroma. Like infundibulocystic BCC, fibroepithelioma is composed of pink epithelial strands with blue basaloid buds. Fibroepitheliomas has a more prominent fibromucinous stroma and lacks the horn cysts characteristic of infundibulocystic BCC. Fibroepithelioma often demonstrates sweat ducts within the pink epithelial strands. A slight inflammatory infiltrate may also be present. Simple removal by excision or electrosurgery is the treatment of choice.

Polypoid Basal Cell Carcinoma

These tumors present as exophytic nodules of the head and neck.

Pore-Like Basal Cell Carcinoma

Patients with thick sebaceous skin of the central face may develop a BCC that resembles an enlarged pore or stellate pit. The lesions virtually always occur on the nose, melolabial fold, or lower forehead. Affected patients are generally men and the majority are smokers. Many years pass from the appearance of the lesion until a diagnostic biopsy is taken because the lesion is considered inconsequential.

Aberrant Basal Cell Carcinoma

Even in the absence of any apparent carcinogenic factor, such as arsenic, radiation, or chronic ulceration, BCC may occur in odd sites, such as the scrotum, vulva, perineum, nipple, and axilla.

Solitary Basal Cell Carcinoma in Young Persons

These curious lesions are typically located in the region of embryonal clefts in the face and are often deeply invasive. Complete surgical excision is much safer than curettage for their removal. Cases in children and teenagers, unassociated with the basal cell nevus syndrome or nevus sebaceus, are well-documented.

Natural History

BCCs run a chronic course as the lesion slowly enlarges and tends to become more ulcerative. As a rule, there is a tendency for the lesions to bleed without pain or other symptoms. Some of the lesions tend to heal spontaneously and to form scar tissue as they extend. Peripheral spreading may produce configurate, somewhat serpiginous, patches. The ulceration may burrow deep into the subcutaneous tissues or even into cartilage and bone, causing extensive destruction and mutilation. At least half of the deaths that occur from BCC result from direct extension into a vital structure rather than metastases.

Metastasis

Metastasis is extremely rare, occurring in 0.0028% to 0.55% of BCCs. This low rate is believed to be due to the fact that the tumor cells require supporting stroma to survive. The following criteria are now widely accepted for the diagnosis of metastatic BCC:

1. The primary tumor must arise in the skin
2. Metastases must be demonstrated at a site distant from the primary tumor and must not be related to simple extension
3. Histologic similarity between the primary tumor and the metastases must exist
4. The metastases must not be mixed with SCC

Metastatic BCC is twice as common in men as in women. Immunosuppression does not appear to increase the risk of metastasis of BCC. Most BCCs which metastasize arise on the head and neck, and tend to be large tumors that have recurred despite multiple surgical procedures or radiation therapy. The histologic finding of perineural or intravascular BCC increases the risk for metastasis. The regional lymph nodes are the most frequent site of metastasis, followed by

the lung, bone, skin, liver, and pleura. Spread is equally distributed between hematogenous and lymphatic. An average of 9 years elapses between the diagnosis of the primary tumor and metastatic disease, but the interval for metastasis ranges from under 1 year to 45 years. Although the primary tumor may be present for many years before it metastasizes, once metastases occur the course is rapidly downhill. Fewer than 20% of patients survive 1 year and less than 10% will live past 5 years after metastasis.

Association with Internal Malignancies

Frisch et al reported a series of 37,674 patients with BCCs followed over 14 years. Comparison of cancer rates for the general population was remarkable with 3663 new cancers compared with 3245 in the control population. Malignant melanoma and lip cancers were the most frequently found; however, internal malignancies were also noted to be excessive, involving the salivary glands, larynx, lung, breast, kidney, and lymphatics (non-Hodgkin lymphoma). The rate of non-Hodgkin lymphoma was particularly high. Patients receiving the diagnosis of BCC before the age of 60 were found to have a higher rate of breast cancer, testicular cancer, and non-Hodgkin lymphoma.

Immunosuppression

Immunosuppression for organ transplantation increases the risk for the development of BCC by about 10-fold. Some increased risk for BCC is considered also to occur in HIV infection and in persons on immunosuppressive medications for other reasons. Patients with chronic lymphocytic leukemia are also at increased risk for BCC. In the immunosuppressed population, a history of blistering sunburns in childhood is a strong risk factor for the development of BCC following immunosuppression.

Etiology and Pathogenesis

It appears that BCCs arise from immature pluripotential cells associated with the hair follicle. Mutations that activate the hedgehog signaling pathway, which controls cell growth, are found in most BCCs. The affected genes are sonic hedgehog, Patched 1, and Smothened genes. Inactivation of the Patched 1 gene is most common.

Histopathology

There is a general belief that there is a correlation between histologic subtype of BCC and biologic behavior. BCCs are considered low or high risk, depending on their probability of causing problems in the future: subclinical extension, incomplete removal, aggressive local invasive behavior, and local recurrence. Therefore, the dermatopathology report of a BCC should include a subtype descriptor when possible. Unfortunately, many shave biopsy specimens do not allow for accurate typing and the presence of an indolent growth pattern superficially does not exclude the possibility of a more aggressive deeper growth pattern. The common histologic patterns are nodular, superficial, infiltrative, morphoeic, micronodular, and mixed. The nodular type is a low-risk type. High-risk types include the infiltrative, morphoeic, and micronodular types, due to aggressive local invasive behavior and a tendency to recurrence. Superficial BCC is prone to increased recurrence due to inadequate removal. When evaluating the histologic margin of superficial BCC, tumor stroma involving the margin should be considered a positive margin.

The early lesion shows small, dark staining, polyhedral cells resembling those of the basal cell layer of the epidermis, with large nuclei and small nucleoli. These occur within the epidermis as thickenings or immediately beneath the epidermis as downgrowths connected with it. After the growth has progressed, regular compact columns of these cells fill the tissue spaces of the dermis and a connection with the epidermis may be difficult to demonstrate. At the periphery of the masses of cells, the columnar cells may be characteristically arranged like fence posts (palisading). This may be absent when the tumor cells are in cord arrangement or in small nests. Cysts may form. The interlacing strands of tumor cells may present a lattice-like pattern. The dermal stroma is an integral and important part of the BCC. The stroma is loose and fibromyxoid with a sparse lymphoid infiltrate commonly present. The stroma can be highlighted by metachromatic toluidine blue staining, which can be useful during Mohs surgery.

Differential Diagnosis

Distinguishing between small BCCs and small SCCs is largely an intellectual exercise. Both are caused chiefly by sunlight; neither is likely to metastasize; and both will have to be removed, usually by simple surgical excision or curettage. A biopsy is always indicated, but may be performed at the time of the definitive procedure when the likelihood of the diagnosis of NMSC is high and the patient is fully informed and gives consent.

A waxy, nodular, rolled edge is fairly characteristic of BCC (Fig. 29-20). The SCC is a dome-shaped, elevated, hard, and infiltrated lesion. The early BCC may easily be confused with sebaceous hyperplasia, which has a depressed center with yellowish small nodules surrounding the lesion. These lesions never bleed and do not become crusted.

Bowen's disease, Paget's disease, amelanotic melanoma, and actinic and seborrheic keratoses may also simulate BCC. Ulcerated BCC on the shins is frequently misdiagnosed as a stasis ulcer and a biopsy may be the only way to differentiate the two. Pigmented basal cell epithelioma is frequently misdiagnosed as melanoma or as a pigmented nevus. The superficial BCC is easily mistaken for psoriasis or eczema. The careful search for the rolled edge of the peripheral nodules is important in differentiating BCC from all other lesions.

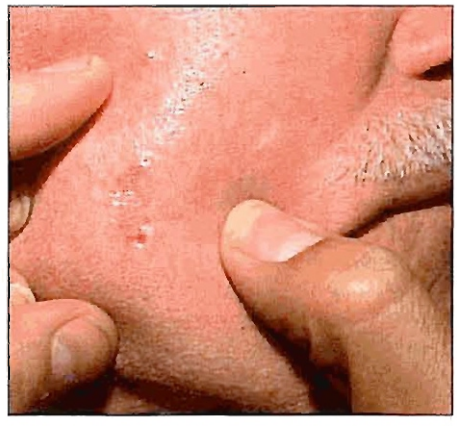

Fig. 29-20 Basal cell carcinoma, accentuation of the pearly border when the skin is stretched.

Treatment

Each lesion of BCC must be thoroughly evaluated individually. Age and sex of the patient as well as the size, site, and type of lesion are important factors to be considered when choosing the proper method of treatment. No single treatment method is ideal for all lesions or all patients. The choice of treatment will also be influenced by the experience and ability of the treating physician in the various treatment modalities. A biopsy should be performed in all cases of suspected BCC, to determine the histologic subtype and to confirm the diagnosis.

The aim of treatment is for a permanent cure with the best cosmetic results. This is important because the most common location of BCC is the face. Recurrences result from inadequate treatment and are usually seen during the first 4 to 12 months after treatment. A minimum 5-year follow-up is indicated, however, to continue a search for new lesions, since the development of a second BCC is common.

Treatment of BCC is usually surgical (see Chapter 37), but some forms of BCC are amenable to medical treatment.

Topical Therapy

Topical treatment appears to be most effective in the treatment of superficial BCC. For nodular BCCs the cure rates are only 65% which is unacceptable given the other options available. On the other hand, superficial BCCs may be cured 80% of the time with topical treatment. Topical 5-FU is not extraordinarily effective and recurrence rates are high. Imiquimod applied three times a week with occlusion or five times a week without occlusion is the favored form of topical, patient-applied treatment for superficial BCC. Duration of treatment is for 6 weeks, but may be extended if the lesion does not appear to have been eradicated. Cosmetic results are excellent, especially for lesions of the anterior chest and upper back where significant scarring usually results from surgical procedures. Photodynamic therapy has also emerged as a treatment option for BCC.

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NEVOID BASAL CELL CARCINOMA SYNDROME (GORLIN SYNDROME)

Clinical Features

The nevoid BCC syndrome or basal cell nevus syndrome (BCNS) is an autosomal-dominantly inherited disorder characterized by the development of multiple BCCs (Fig. 29-21); odontogenic cysts of the jaws; pitted depressions on the hands and feet; osseous anomalies of the ribs, spine, and skull; and multiple other disorders. Keratin cysts are frequently seen and calcium deposits in skin, especially in the scalp, may be present. A characteristic facies is present with frontal bossing, a hypoplastic maxilla, a broad nasal root, and true ocular hypertelorism being features.

Of 105 patients reported in one series, 80% were white. The first tumor developed by the mean age of 23 years for white patients. Palmar pits were seen in 87%. Jaw cysts were found in 74%, with 80% manifested by the age of 20. The total number of cysts ranged from 1 to 28. Medulloblastomas developed in four patients and three had cleft lip or palate.

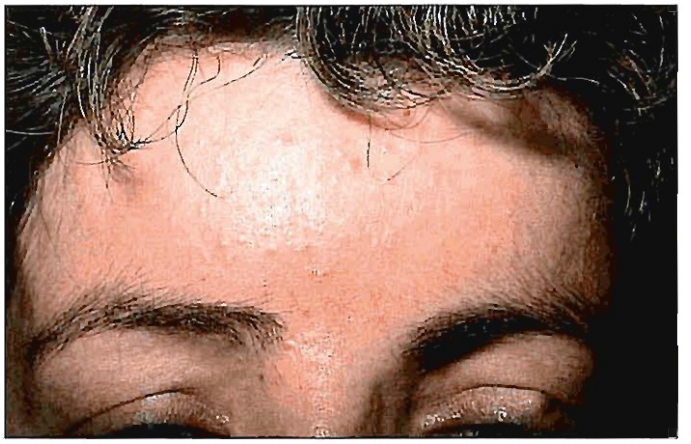

Fig. 29-21 Multiple basal cell carcinomas in BCNS.

Physical findings in this series included "coarse face" (54%), macrocephaly (50%), hypertelorism (42%), frontal bossing (27%), pectus deformity (13%), and Sprengel deformity (11%). Previously described features not found in this series include short fourth metacarpal, scoliosis, cervical ribs, and spina bifida occulta.

Skin Tumors

The BCCs occur at an early age or any time thereafter as multiple lesions, usually numerous. The usual age of appearance is between 17 and 35 years. Although any area of the body may be affected, there is a marked tendency toward involvement of the central facial area, especially the eyelids, periorbital area, nose, upper lip, and cheeks. Any variety of BCC may be present. In children there may be pigmented papules resembling skin tags.

Jaw Cysts

Jaw cysts occur in 70% of patients. Both the mandible and the maxilla may show cystic defects by x-ray, with mandibular involvement occurring twice as often. The patient may complain of jaw pain and tenderness, fever, difficulty in closing the mouth, and swelling of the jaw. The cysts are uni- or multi-locular and may occur anytime during life, with the first decade being the most common time of appearance. They may have a keratinized lining and some are ameloblastomas.

Pits of Palms and Soles

An unusual pitting of palms and soles is a distinguishing feature of the disease. They usually become apparent in the second decade of life. Up to 87% of patients with nevoid BCC syndrome will have pits. Histologically, they show basaloid proliferation, but the lesions do not progress or behave like a BCC.

Skeletal Defects

Numerous skeletal defects are easily detected by roentgenograms. Such defects may be spina bifida; bifid, fused missing or splayed ribs; scoliosis; and kyphosis. An interesting finding is shortened fourth metacarpal and metatarsal bones. The shortened fourth metacarpal results clinically in a dimple over the fourth metacarpophalangeal joint (Albright's sign). Radiographic evidence of multiple lesions is highly suggestive of this syndrome and since most are present congenitally, roentgenograms may be useful in diagnosing this syndrome in patients too young to manifest other abnormalities. Seventy to 75% of patients manifest skeletal abnormalities. Flame-shaped lucencies of the phalanges, metacarpal, and carpal bones of the hands were found in 30% of 105 patients. Other radiographic findings in this series include bifid ribs (26%), hemivertebra (15%), and fusion of the vertebral bodies (10%).

Disorders of the Central Nervous System

Important radiographic signs include calcification of the falx cerebri (65%), of the tentorium cerebelli (20%), and of the bridged sella (68%). On computed tomography (CT) the calcification of the falx is distinctly lamellar. Varying mental problems may be encountered in patients.

Other Defects

Ophthalmologic abnormalities and mesenteric, ovarian, and mammary cysts, as well as uterine fibromas, lipomas, epithelial cysts, milia, and renal calculi are known to occur at times in these patients. Calcified multinodular ovarian fibromas are characteristic.

Etiology

This is a genetic disorder with an autosomal-dominant inheritance. Penetrance may be as high as 95%. Mutations in the Patched 1 (PTCH1) tumor suppressor gene and less commonly in the sonic hedgehog (SHH) or Smoothened (SMOH) genes are responsible for this syndrome.

Histopathology

The histology of BCCs arising in syndrome patients is identical to those arising in non-syndrome patients, with the solid and superficial types being most common.

Differential Diagnosis

Several other unique types of presentation of BCCs should not be confused with BCNS. One is the linear unilateral BCC syndrome, in which a linear arrangement of close-set papules, sometimes interspersed with comedones, is present at birth. Biopsy reveals basal cell epitheliomas; however, they do not increase in size with the age of the patient. The second type, referred to as Bazex syndrome, is an X-linked dominantly inherited disease comprising follicular atrophoderma of the extremities, localized or generalized hypohidrosis, hypotrichosis, and multiple BCCs of the face, which often arise at an early age. The third is the syndrome of multiple hereditary infundibulocytic BCCs, which is also an autosomal-dominant syndrome. It is distinguished from BCNS by the absence of palmar pits and jaw cysts in most cases. Clinically, patients appear to have multiple trichoepitheliomas. Numerous skin-colored pearly papules affect the center face, accentuated in the nasolabial folds. The generalized basaloid follicular hamartoma syndrome differs from BCNS by having basaloid follicular hamartomas instead of BCCs. It is reported from a large kindred in the southeastern US (see below). Tiny palmar pits are present. Histologically, infundibulocystic BCC and basaloid follicular hamartoma may be indistinguishable, so the two familial syndromes may be difficult to separate. Rombo syndrome, reported in one large Swedish family, has multiple BCCs and vermiculate atrophoderma and hypotrichosis. A patient with multiple BCCs and myotonic dystrophy has been reported,

suggesting yet another genodermatosis associated with multiple BCCs.

Treatment

Genetic counseling is essential. Strict sun avoidance and maximum sun protection, as recommended for xeroderma pigmentosa patients, is recommended. Treatment involves very regular monitoring and biopsying of suspicious lesions. Topical therapy with tazarotene and imiquimod may find some use in preventing and treating the superficial tumors. Surgical treatments are used for most lesions. One case with intractable lesions responded to systemic chemotherapy with paclitaxel. Oral retinoid therapy may reduce the frequency of new BCCs.

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SQUAMOUS CELL CARCINOMA

SCC is the second most common form of skin cancer. Most cases of SCC of the skin are induced by UVR. Chronic, long-term sun exposure is the major risk factor and areas which have had such exposure (the face, scalp, neck, and dorsal hands) are favored locations. SCC is relatively more common as the annual amount of UVR increases, so SCC is more common in Texas than in Minnesota, for example. Immunosuppression greatly enhances the risk for the development of SCC. Etanercept treatment has been associated with the appearance of cutaneous SCC in patients with rheumatoid arthritis also being treated with methotrexate. Human papilloma viruses (HPV-16, -18, -31, and -35 primarily) play a role in SCCs that develop on the genitalia and perungually. A chronic ulcer, hidradenitis suppurativa, prior X-radiation exposure, PUVA treatment, recessive dystrophic epidermolysis bullosa, lesions of discoid lupus, and erosive lichen planus are all risk factors for the development of SCC. Metastasis, with a mortality rate of 18%, is very uncommon for SCCs arising in sites of chronic sun damage, whereas it is relatively high (20–30%) in SCCs occurring in the various scarring processes. Patients with epidermodysplasia verruciformis (EDV) also develop SCCs on sun-exposed sites, associated with unique HPV types. These unique EDV HPV types (HPV-5, -8, and others) may also play a role in SCCs which develop in immunosuppressed persons. SCC of the oral mucosa is discussed in Chapter 34. Because the vast majority of cutaneous SCCs are induced by UVR, sun protection with avoidance of the midday sun, protective clothing, and the regular application of a sunblock of SPF 15 to 30 is recommended. Some researchers have suggested that smoking is also a risk factor for cutaneous SCC, but this is controversial.

Clinical Features

Frequently, SCC begins at the site of actinic keratosis on sun-exposed areas such as the face and backs of the hands. BCCs far outnumber SCCs on the facial skin, but SCCs on the hand occur three times more commonly than BCCs. The lesion may be superficial, discrete, and hard, and arises from an indurated, rounded, elevated base (Figs 29-22 and 29-23). It is dull-red and contains telangiectases. In the course of a few months the lesion becomes larger, deeply nodular, and

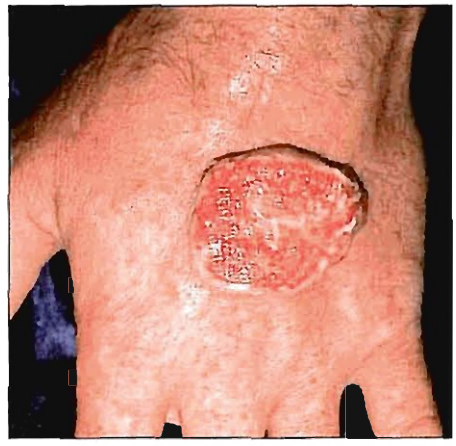

Fig. 29-22 Squamous cell carcinoma, ulcerating tumor in an area of chronic sun exposure.

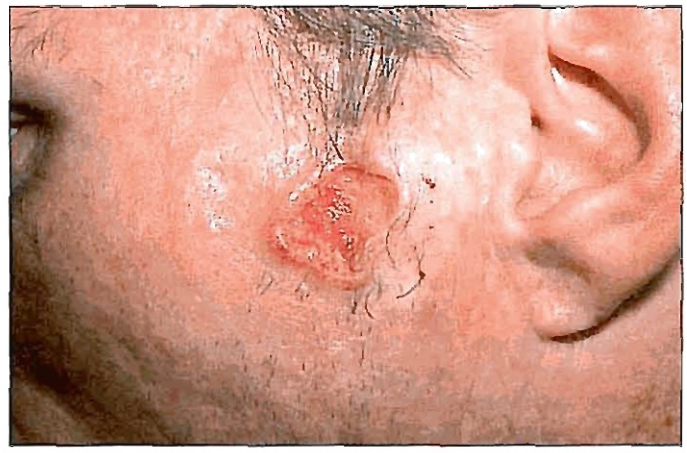

Fig. 29-23 Squamous cell carcinoma, preauricular ulceration in a patient with AIDS.

ulcerated. The ulcer is at first superficial and is hidden by a crust. When this is removed, a well-defined, papillary base is seen and on palpation a discrete hard disk is felt. In the early phases this tumor is localized, elevated, and freely movable on the underlying structures; later it gradually becomes diffuse, more or less depressed, and fixed. The growth eventually invades the underlying tissues. The tumor above the level of the skin may be dome-shaped, with a core-like center that later ulcerates. The surface in advanced lesions may be cauliflower-like, composed of densely packed, filamentous projections, between which are clefts filled with a viscid, purulent, malodorous exudate.

In black patients SCCs are 20% more common than BCCs. The most common sites are the face and lower extremities, with involvement of non-sun-exposed areas more common. Elderly women (mean age, 77) are primarily affected in cases involving the lower legs. Prior direct heat exposure from open fireplaces may be the predisposing factor. In contrast, in white patients the frequent predisposing conditions are scarring processes, such as burns, leg ulcers, and hidradenitis suppurativa.

On the lower lip, SCC often develops on actinic cheilitis. From repeated sunburn the vermilion surface becomes dry, scaly, fissured, and actinic cheilitis develops. Cancer usually arises on fissure or keratosis. At the beginning only a local thickening is noticeable. This then becomes a firm nodule. It may grow outward as a sizable tumor or inward with destructive ulceration. A history of smoking is also frequent and a significant predisposing factor. Lower lip lesions far outnumber upper lip lesions, men far outnumber women (12:1), and the median age is the late 60s. SCCs occurring on the lower lip metastasize approximately 10% to 15% of the time. SCC of the lip may also occur in areas of discoid lupus (DLE) in black patients. Neoplastic transformation into SCC may develop in 0.3% to 3% of patients with DLE of the lip.

Periungual SCC frequently presents with signs of swelling, erythema, and localized pain. It commonly arises in the nailfolds of the hands and initially resembles a periungual wart. Fifty percent of those x-rayed show changes in the terminal phalanx. There is a low rate of metastases (3%), but local excision with Mohs microsurgery is recommended as it reduces the risk of recurrence. Periungual SCC is strongly associated with genital HPV types, primarily 16, 18, 31, and 35.

Given the numerous presentations of SCC on the skin, there should be a low threshold for biopsy of any suspicious lesions, especially in the background of chronic sun exposure.

Histopathology

SCC is characterized by irregular nests of epidermal cells invading the dermis to varying degrees. The degree of cell differentiation has been used to grade SCC. Although interpretations vary, it is believed that the greater the differentiation, the less the invasive tendency, and therefore the better the prognosis. In grade I SCC, most of the cells are well-differentiated, whereas in grade IV most are undifferentiated or anaplastic. The anaplastic type of tumors may be difficult to differentiate from other tumors such as melanoma, lymphoma, and mesenchymal tumors. This is true also when the tumor is of the spindle cell type. Immunoperoxidase staining for keratins is very useful in this setting. Desmoplastic SCCs by light microscopy have prominent trabecular growth patterns, narrow columns of atypical epithelial cells, and marked desmoplastic stromal reaction. Acantholytic SCC is a recognized histologic subtype, but its behavior parallels that of cutaneous SCC. The finding of perineural and vascular invasion are bad prognostic features for recurrence and metastasis in any form of cutaneous SCC.

Differential Diagnosis

The differentiation of SCC from keratoacanthoma is of academic interest in most cases as simple surgical excision is performed on most of these lesions. However, if nonsurgical modalities are contemplated, a biopsy confirming the diagnosis of keratoacanthoma is recommended. In the setting of immunosuppression, keratoacanthoma-like lesions should be managed as SCCs. The rapid growth and presence of a rolled border with a keratotic central plug suggest the diagnosis of keratoacanthoma, as does explosive growth. An early SCC may be confused with a hypertrophic actinic keratosis and indeed the two may be indistinguishable clinically. Biopsy to include the base of the lesion is necessary to make the diagnosis.

Pseudoepitheliomatous hyperplasia must be distinguished histologically from true SCC. Marked pseudoepitheliomatous hyperplasia may be seen in granular cell tumor, bromoderma, blastomycosis, granuloma inguinale, and chronic pyodermas. It is frequently mistaken for SCC in chronic stasis ulcers, ulcerations occurring in thermal burns, lupus vulgaris, leishmaniasis, and even in sporotrichosis. Pseudoepitheliomatous hyperplasia (PEH) arises from adnexal structures as well as the surface epidermis. Hyperkeratosis and hypergranulosis of adjacent hair follicles is often present. Strands of epidermal cells may extend into the reticular dermis and commonly trap elastic fibers, a finding also seen in keratoacanthoma, but rarely in conventional SCCs. A potential diagnostic pitfall is the presence of benign PEH adjacent to and overlying invasive SCC. This is particularly common in lesions that have been picked or scratched.

Metastases

The rate of SCC metastasis from all skin sites ranges from 0.5% to 5.2%. Careful attention should be paid to regional lymph nodes draining the site of the SCC. These should be examined at the time of the initial evaluation when the suspicious lesion is identified and at the regular visits which follow the treatment of the SCC. Risk factors for local recurrence and metastasis include: 1) treatment with a modality that does not check the margins of the specimen (such as curettage and desiccation, cryotherapy or radiation); 2) recurrence after prior treatment; 3) location (temples, scalp, ear, lip); 4) size; 5) depth; 6) histologic differentiation; 7) histologic evidence of perineural invasion; 8) histologic evidence of desmoplastic features; 9) precipitating factors other than UV light; and 10) host immunosuppression. In reference to metastatic disease, the highest rates occur from scars (37.9%), the lip (13.7%), and the external ear (8.8%). Risk of metastasis rises for lesions larger than 2 cm in diameter, skin lesions deeper than 4 mm, and lip lesions deeper than 8 mm. Patients with perineural spread have a local recurrence rate of 47.2% and a metastatic rate of 34.8%. Desmoplastic SCCs are six times more likely to metastasize than other histologic patterns, excluding neurotropic forms.

Patients with SCC are at increased risk of developing other malignancies, such as cancers of the respiratory organs,

buccal cavity, pharynx, small intestines (in men), non-Hodgkin lymphoma, and leukemia.

Treatment

The primary treatment of SCC of the skin is surgical (see Chapter 37). Oral retinoids may be useful as a preventive strategy in patients with immunosuppression who develop frequent cancers.

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VERRUCOUS CARCINOMA (CARCINOMA CUNICULATUM)

Verrucous carcinoma is a distinct, well-differentiated variety of SCC. It affects mostly elderly men. The primary characteristic of these lesions is their close resemblance, clinically and histologically, to a wart. The lesions present as a bulbous mass with a soft consistency and often multiple sinuses opening to the surface, resembling "rabbit burrows." Lesions of this type are most common on the sole, but also occur in the genital area (giant condyloma of Buschke and Lowenstein), on the sacrum, and in the oral mucosa. In some cases, as in the Buschke-Lowenstein tumor, verrucous carcinomas are induced by HPV. These HPV may be of the "low-risk" types, such as HPV-6 or -11, or the high-risk types, such as HPV-16. In other cases no HPV can be found and pressure or other factors (but not UV light) are felt to play a role. The natural history is of a slow-growing and invading mass that over years may invade the bony structure beneath the tumor.

Histologically, the lesion shows a characteristic picture of bulbous rete ridges that are topped by an undulating keratinized mass. The squamous epithelium is well-differentiated and cytologic atypia is minimal. The cytoplasm is often apple pink and may have a glassy appearance. The tumor border is smooth and bulldozing, rather than spiky and infiltrative.

Excision is the best treatment and Mohs microsurgery may be a helpful technique. Radiotherapy may induce anaplastic transformation and is best avoided if other treatment options exist. Lymph node metastasis is rare and the prognosis is favorable when complete excision is accomplished. In SCC of the penis derived from verrucous forms, the prognosis is much better than other causes of penile SCC.

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BOWEN'S DISEASE (SQUAMOUS CELL CARCINOMA IN SITU)

Bowen's disease is an intraepidermal SCC that probably arises from adnexal epithelium and invades the adjacent epidermis. It may ultimately become invasive. When it does, it tends to behave like an anaplastic adnexal carcinoma.

Clinical Features

Bowen's disease may be found on any part of the body as an erythematous, slightly scaly and crusted, noninfiltrated patch from a few millimeters to many centimeters in diameter (Figs 29-24 to 29-26). The lesion is sharply defined. The scale may be pronounced enough for the lesions to be mistaken for psoriasis or the plaque may have a stuck-on appearance and may be mistaken for a broad sessile seborrheic keratosis.

As the lesion slowly enlarges, spontaneous cicatrization may develop in portions of the lesion. When the intraepithelial growth becomes invasive, the lesion may appear ulcerated and fungating. The squamous carcinoma that evolves from Bowen's disease tends to be more aggressive than SCC arising in actinic keratosis. When SCC in situ occurs as a velvety plaque on the glans penis it is referred to as *erythroplasia of Queyrat.*

Etiology

Bowen's disease affects mostly older white men in whom the lesions occur primarily on sun-exposed surfaces. Most patients with Bowen's disease have chronic sun damage. Chronic arsenism produces Bowen's disease in non–sun-exposed sites and a history of exposure to arsenic should be sought when Bowen's disease is found on the palms, soles, and covered nongenital sites. High-risk HPV types (HPV-16, -18, -31, and -35) have been implicated in lesions involving the periungual and genital regions.

Histopathology

The atypical keratinocytes may invade the adjacent epidermis in a buckshot or clonal nested pattern. With time, they may replace the entire epidermis, often with deep full-thickness involvement of adnexal structures. The epidermis shows hyperkeratosis, parakeratosis, and broad acanthosis or anastamosis of adjacent rete ridges. Epidermal maturation is absent, so the epidermis appears disorganized, and individually keratinizing cells and atypical cells are seen at all levels of the epidermis. There is, however, a sharp delineation between dermis and epidermis, and the basement membrane is intact. The upper dermis usually shows a chronic inflammatory infiltrate. Although the cells tend to be anaplastic with a high nuclear-to-cytoplasmic ratio, variants with smaller nuclei and abundant cytoplasm exist and transitional areas between the patterns may be seen.

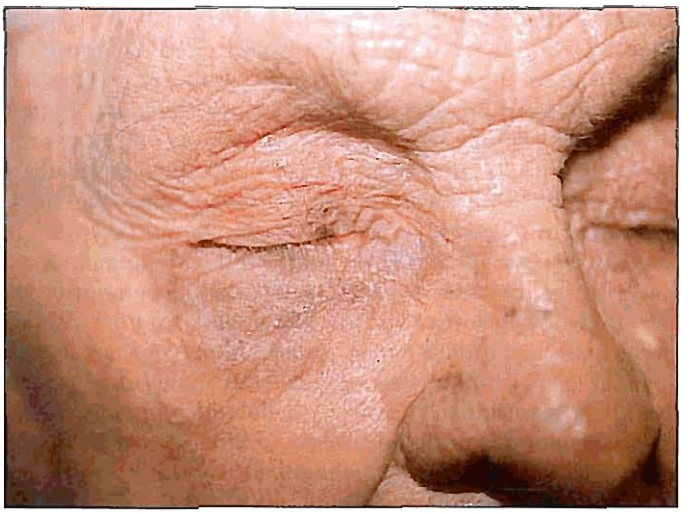

Fig. 29-24 Bowen's disease.

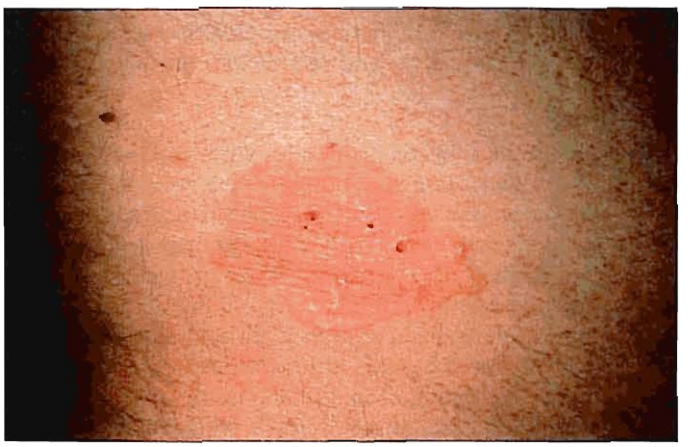

Fig. 29-25 Bowen's disease.

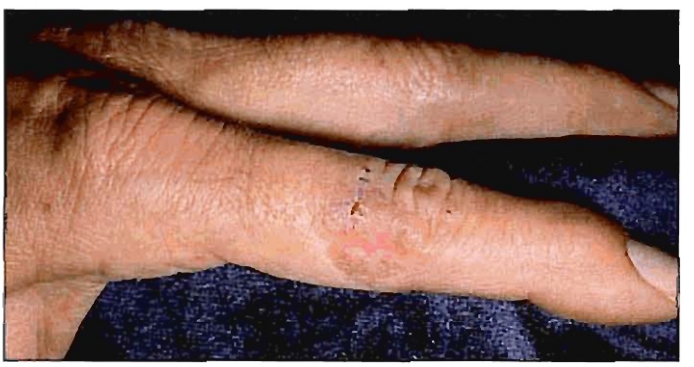

Fig. 29-26 Bowen's disease.

Differential Diagnosis

Bowen's disease is frequently misdiagnosed as psoriasis, superficial multicentric BCC, tinea corporis, nummular eczema, seborrheic keratosis, and actinic keratosis. Paget's disease, especially the extramammary type, not only clinically but also histologically may mimic Bowen's disease. There is no dyskeratosis in Paget's disease and the intervening nonvacuolated epidermal cells are not atypical in Paget's disease. Stains for mucin and carcinoembryonic antigen are positive in Paget's disease and negative in pagetoid Bowen's disease. Bowen's disease may be heavily pigmented, especially when occurring in the anogenital region. Lesions of bowenoid papulosis show a histologic spectrum from genital warts with buckshot atypia to full-thickness atypia indistinguishable from Bowen's disease. If the lesions are multicentric and behave like genital warts, the term bowenoid papulosis may be applied. Treatment is guided completely by the clinical pattern. Since genital SCC is induced by high-risk HPV, bowenoid papulosis represents the initial clinical lesion in the progression from HPV infection to carcinoma. There is no clear boundary where bowenoid papulosis stops and SCC in situ begins.

Treatment

Topical treatment of SCC in situ with cryotherapy and topical 5-FU has been disappointing due to a high rate of recurrence. Iontophoresis will enhance the response to 5-FU, but is not commonly performed by dermatologists. Imiquimod 5% cream applied once a day for up to 16 weeks seems to be effective enough to recommend it as a therapeutic option. Response rates have been as high as 90% in limited series. It may allow treatment of large lesions which might be difficult to approach surgically. The combination treatment with imiquimod 5% cream three times a week and 5% 5-FU twice a day (except at the times of the imiquimod application) has also been reported as effective.

Simple excision of small lesions is a reasonable treatment option. Large, ill-defined lesions, or lesions in which preservation of normal tissue is critical, are indications for Mohs microsurgery. Other surgical techniques to treat SCC in situ are described in Chapter 37. Curettage and desiccation may also be performed, but recurrence may occur if the extension down the follicles is not eradicated. Lesions of the lower legs are particularly problematic, as they are often multiple, and in the elderly are often found in conjunction with significant venous insufficiency. Any form of therapy may result in chronic leg ulceration in this setting. Consideration should be given to using a compression bandage after surgery identical to one applied to a chronic leg ulcer. This may prevent ulceration.

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ERYTHROPLASIA OF QUEYRAT

Erythroplasia of Queyrat is SCC in situ of the glans penis or prepuce. SCC in situ on the penile shaft also occurs and is probably similar. Both conditions are caused by high-risk HPV types (16, 18, 31, 35). Clinically, erythroplasia of Queyrat is characterized by single or multiple fixed, well-circumscribed, erythematous, moist, velvety or smooth, red-surfaced plaques on the glans penis (Fig. 29-27). Uncircumcised men, usually over age 40 are most commonly affected, and when Bowen's disease affects the penile shaft it is usually distally under the foreskin. The differential diagnosis includes Zoon balanitis, candidiasis, penile psoriasis, irritant balanitis, and Paget's disease. A biopsy is usually indicated to confirm the diagnosis. Since red lesions on the glans of elderly uncircumsized men are common, the following factors suggest a biopsy is indicated: 1) the lesion is fixed (does not move or resolve); 2) the patient lacks other stigmata of psoriasis or another skin disease that could affect the glans penis; 3) the patient's sexual partner has cervical dysplasia; and 4) the

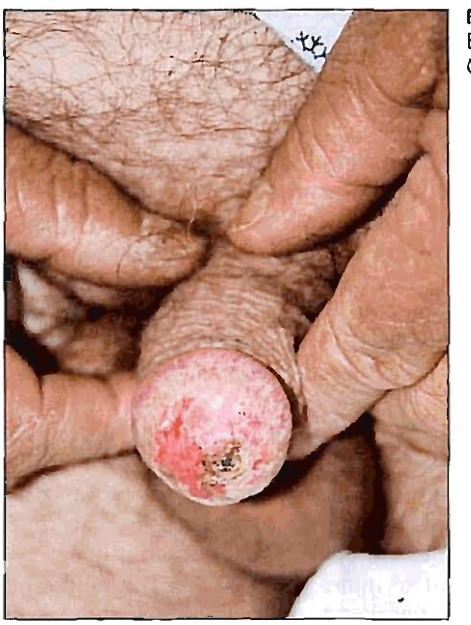

Fig. 29-27
Erythroplasia of Queyrat.

lesion does not resolve with effective topical therapy for irritant balanitis, candidiasis, and psoriasis. Once the diagnosis of SCC in situ of the penis is made, the patient's sex partner(s) should be referred for evaluation. Sexual partners of men with SCC of the penis are more likely to develop preinvasive and invasive cancer of the cervix or anus.

Progression to invasive SCC is more common in erythroplasia of Queyrat than in Bowen's disease of the nongenital skin, and the resulting SCCs are more aggressive and tend to metastasize earlier than those that develop in Bowen's disease of the nongenital skin. There is no evidence of an increase in internal malignancy in patients with erythroplasia.

Topical therapy can be effective in the treatment of erythroplasia of Queyrat and has the advantage that it can identify and treat areas not visible clinically. Topical 5% 5-FU cream applied once a day under occlusion (with the foreskin or a condom) can be effective. It will induce a brisk reaction and superficial erosion, which can be uncomfortable. Treatment is continued for 3 to 12 weeks, depending on the response. Imiquimod cream 5% applied between once a day and three times a week will similarly induce a significant reaction, but after 3 to 12 weeks may clear the lesion. Careful follow-up is required, especially for the first few years. Surgical modalities such as excision, laser treatments, and photodynamic therapy are reserved for cases failing topical treatments. Radiation therapy can also be effective.

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BALANITIS PLASMACELLULARIS (ZOON)

Balanitis plasmacellularis is also known as *balanoposthitis chronica circumscripta plasmacellularis*. It is a benign inflammatory lesion characteristically with a plasma cell infiltrate. The plasma cell infiltrate, while characteristic, may not be present in all lesions of this type, and in fact, some researchers feel there is a spectrum of histology in idiopathic, benign, nonscarring balanitis, from lesions containing few plasma cells to lesions containing many plasma cells. Clinically, Zoon balanitis is characterized by a red patch, which is usually sharply demarcated and usually on the inner surface of the prepuce and the glans penis (Fig. 29-28). The lesion is erythematous, moist, and shiny. It occurs as a single lesion, but it may consist of several confluent macules. It is asymptomatic and does not produce inguinal adenopathy. Uncircumcised men from ages 24 to 85 are most often affected.

Vulvitis chronica plasmacellularis is the counterpart of balanitis in women. The vulva shows a striking lacquer-like luster. Erosions, punctate hemorrhage, synechiae, and a slate-to-ochre pigmentation may supervene.

Plasmacytosis circumorificialis is the same disease on the oral mucosa, lips, cheeks, and tongue, clinically suggestive of SCC.

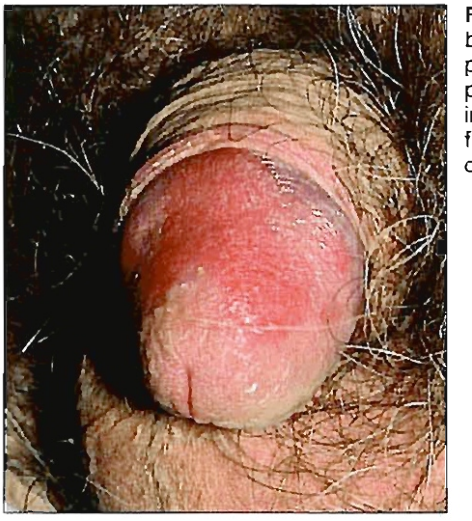

Fig. 29-28 Zoon balanitis, fixed red papule on the glans penis indistinguishable from erythroplasia of Queyrat.

Histologically, the epidermis is atrophic with flattened diamond-shaped keratinocytes and mild spongiosis. In the papillary dermis a band of infiltrate consisting almost exclusively of plasma cells is present. Dilated vessels are also seen. This picture is strikingly different from that of the main clinical differential diagnosis, erythroplasia of Queyrat, in which the epidermis is principally involved, with atypia of keratinocytes throughout the entire epithelium. HPV has not been detected. Topical steroids, alone or in combination with anticandidal treatment, are helpful. Circumcision may be curative. Laser ablation can also be effective.

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PSEUDOEPITHELIOMATOUS KERATOTIC AND MICACEOUS BALANITIS

Pseudoepitheliomatous keratotic and micaceous balanitis was described by Lortat-Jacob and Civatte in 1966. The lesions occurring on the glans penis are verrucous excrescences with scaling. Ulcerations, cracking, and fissuring on the surface of the glans frequently are present. The keratotic scale is usually micaceous and resembles psoriasis. Most patients are over the age of 50 and frequently have been circumcised for phimosis in adult life.

Histologically, there is marked hyperkeratosis and parakeratosis, as well as pseudoepitheliomatous hyperplasia. Acanthotic masses give rise to a crater-like configuration. HPV has not been detected. This is probably best considered

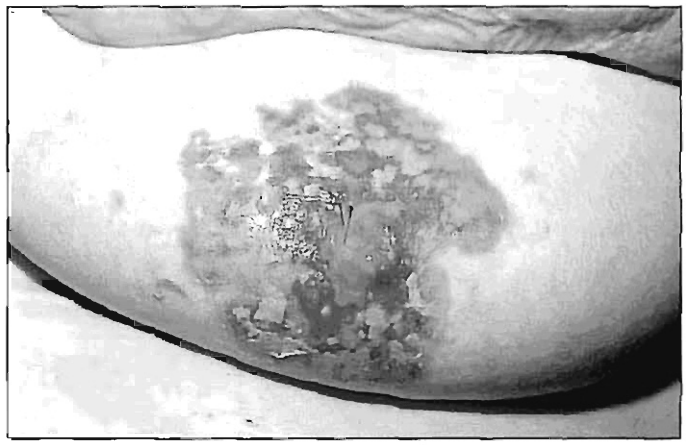

Fig. 29-29 Paget's disease of the breast.

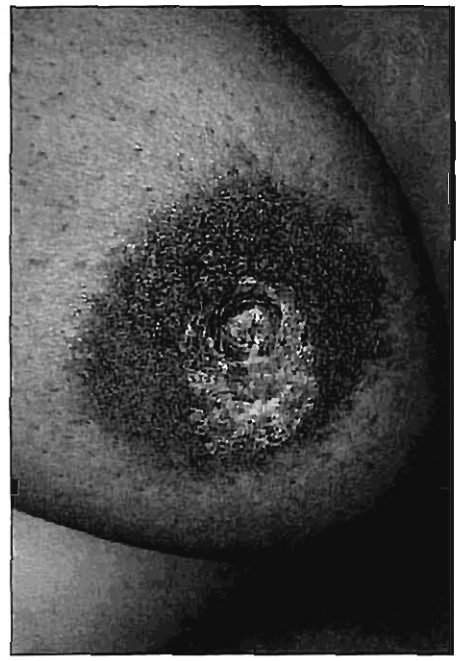

Fig. 29-30 Paget's disease of the breast.

as a form of verrucous carcinoma. The treatment is usually surgical and might include Mohs microsurgery. Topical 5-FU has been effective, but the hyperkeratotic scale may make penetration suboptimal. If topical chemotherapy is utilized, post-treatment biopsies are recommended.

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PAGET'S DISEASE OF THE BREAST

Clinical Features

Paget's disease of the nipple is characterized by a unilateral, sharply marginated, erythematous, and at times a crusted patch or plaque affecting the nipple and occasionally the areola (Figs 29-29 and 29-30). In the course of months or years it may become infiltrated and ulcerated. The nipple may or may not be retracted. A subjacent mass and ipsilateral axillary adenopathy may be palpable. There is virtually always an invasive or in-situ ductal adenocarcinoma of the affected breast.

Histopathology

Paget's disease is characterized by the presence of Paget cells: large, round, pale-staining cells with large nuclei. Intercellular bridges are absent. The cells appear singly or in small nests between the squamous cells. Usually, acanthosis is present, the granular layer is preserved, and there is no parakeratosis, but atypical cells may be "spat out" into the stratum corneum. Frequently a layer of basal cells separates the Paget cells from the basement membrane and is seen crushed beneath the nests of Paget cells. This histologic feature helps to distinguish Paget's disease from pagetoid melanoma and Bowen's disease. In the dermis an inflammatory reaction is often present.

The Paget cell is PAS positive, diastase resistant, CEA positive, almost always HER-2/neu positive, EMA positive, and stains with CAM 5.2 and CK 7. This staining profile and negativity for S-100 and cytokeratins 5/6 allow clear distinction from pagetoid melanoma and pagetoid Bowen's disease. The Toker cell, a normal clear cell of the breast, stains similarly and is proposed as the precursor cell of Paget's disease. Clear cell papulosis is an intraepidermal proliferation of benign Toker cells. Lack of atypia distinguishes it from Paget's disease.

Diagnosis

The presence of unilateral eczema of the nipple recalcitrant to simple treatment is suspicious for Paget's disease and the lesion should be biopsied. The presence of bilateral lesions suggests a benign process, usually atopic dermatitis. Papillary adenoma of the nipple clinically resembles Paget's disease, but on biopsy shows a papillary and adenomatous growth in the dermis with connection to the surface. There is a lining of apocrine-type secretory epithelium. Hyperkeratosis of the nipple and areola may occasionally be unilateral, but histologically reveals only hyperkeratosis, acanthosis, and papillomatosis. Clear cell papulosis of the skin presents with scattered, white, flat-topped lesions distributed on the lower abdomen and along the milk line in otherwise healthy children (adult cases are very rare). Histologic examination reveals benign pagetoid clear cells in the basal layer. The clear cells are AE1 positive and CAM5.2 positive, suggesting they derive from glandular secretory cells.

Treatment

Patients with Paget's disease of the breast should be referred to a center with expertise in the management of breast cancer.

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EXTRAMAMMARY PAGET'S DISEASE

Extramammary Paget's disease (EMPD) presents most commonly as a unifocal process, but multifocal lesions may occur. Lesions typically affect apocrine sites, including the groin (vulva, scrotum, perianal, penis, inguinal folds) (Fig. 29-31) and axilla, but rare cases can affect other anatomic locations. EMPD typically affects persons older than 50. The lesions of extramammary Paget's disease are clinically similar to those of Paget's disease, but often go undiagnosed longer as they are initially misdiagnosed as pruritus ani, a fungal infection, or intertrigo. A nonhealing banal eczematous patch persisting in the anogenital or axillary region should raise concern for EMPD. Intense pruritus is common. Bleeding is a late sign. Lesions may simulate lichen simplex chronicus or leukoplakia.

Extramammary Paget's disease can be divided into four forms: 1) primary EMPD (arising intraepidermally); 2) EMPD associated with an underlying apocrine carcinoma; 3) EMPD associated with an underlying gastrointestinal malignancy; and 4) EMPD associated with an underlying carcinoma of the genitourinary tract. The majority of patients with EMPD do not have underlying carcinoma and the process apparently begins as an intraepidermal neoplasm, which can then invade (invasive EMPD). The clinical appearance of all types of EMPD is identical.

Histologically, the findings are similar to those found in mammary Paget's disease: hyperkeratosis, parakeratosis, acanthosis, and the pale, vacuolated Paget cells in suprabasilar levels of the epithelium. Histologic staining cannot distinguish Paget's disease of the breast and EMPD due to intraepidermal or underlying apocrine carcinoma. Cytokeratin staining is unable to clearly distinguish forms of EMPD, except that CK 20 stains cases of EMPD with underlying transitional carcinoma (but not cases of primary EMPD), and PSA (prostate specific antigen) may stain cases of EMPD due to underlying prostate cancer. The mucin core proteins may be used to distinguish other forms of EMPD. Mammary Paget's disease stains positively for MUC1 (mammary type apomucin), but negative for MUC2 (intestinal type mucin) and MUC5AC (gastric surface mucin). Vulvar EMPD with underlying apocrine carcinoma stains in a pattern similar to mammary Paget's disease (some of these cases may represent "extramammary breast cancer"). Lesions of perianal EMPD and underlying gastrointestinal adenocarcinomas stain with MUC2, but only variably with MUC1 or MUC5AC. EMPD with no underlying carcinoma (primary EMPD) are MUC1+, MUC2–, and MUC5AC+.

EMPD can remain within the epithelium or "invade" the dermis. "Invasive" EMPD has a high rate of metastases and a very poor prognosis. Sentinal node examination of patients with "invasive" EMPD should be considered as it predicts the risk for metastases.

Surgical removal is the treatment of choice, which may require Mohs microsurgery. Despite what appears to be adequate margins, recurrence rates are high because of the multifocal nature of extramammary Paget's disease. The recurrence rate following micrographic surgery exceeds 25%. One case of scrotal EMPD responded to imiquimod 5% cream applied daily. Radiation therapy, photodynamic therapy, and laser treatments have also been used.

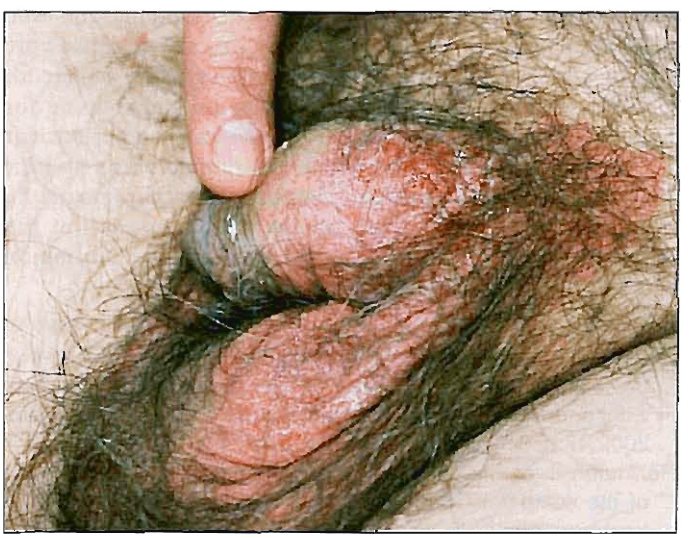

Fig. 29-31 Extramammary Paget's disease.

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Merkel Cell Carcinoma (Trabecular Carcinoma)

Merkel cell carcinoma (MCC) was first described by Toker in 1972. The cell of origin is felt to be the Merkel cell, a slow-acting mechanoreceptor in the basal layer of the epidermis. MCC is a rare tumor with an incidence of about 2 in a million per year in the white population. Ninety-five percent of cases occur in persons over the age of 50 years (mean age 69 years). Men outnumber women by more than 2:1. MCC are felt to be induced by sun exposure since 90% of cases occur on sun-exposed sites, 50% on the head and neck, and 40% on the extremities. PUVA therapy and arsenic exposure may also be potential causes. Immunosuppression by organ transplantation, chronic lymphatic leukemia, and HIV infection all substantially increase the risk for developing MCC.

Clinically, it presents as a rapidly growing, red-to-violaceous nodule with a shiny surface and overlying telangiectasia. Most lesions are diagnosed when they are less than 2 cm in size, but the diagnosis is rarely suspected at the time of biopsy. MCC is an aggressive tumor with a propensity for dermal and nodal spread. At presentation about one-third of cases have regional node involvement and hematogenous spread will eventuate in 50% of cases. Spontaneous remissions occur, and between 10% and 20% of cases present with no primary tumor evident.

Patients should be staged for therapy and prognosis. Physical examination and CT scanning of the relevant nodal region, chest, and liver should be performed. Stage I, or localized disease, represents 70% to 80% of patients at presentation. Five-year survival is 64%. Stage II patients have locoregional disease and are 10% to 30% of patients at diagnosis. Five-year survival is 47%. Stage III disease is distant metastases, and accounts for 1% to 4% of patients at presentation. Median survival is 9 months. Lymph node involvement at presentation is the major predictor of survival. Lesions on the legs are particularly difficult to control because wide excisions and complete courses of radiation therapy are hard to perform on the lower extremity in elderly patients. Undertreatment of lower leg lesions is common, resulting in a poor outcome.

The treatment of MCC should be directed by persons with expertise in managing this rare tumor. Therapy may need to be individualized, depending on various risk factors present. The goal of treatment for patients with stage I and II disease is cure and local control. This involves the combined use of surgery and radiation therapy in most cases. For stage I patients, local removal (by standard surgery with 2–3-cm margins on the trunk or Mohs micrographic surgery on the head and neck) is recommended. Comparative trials are not available to demonstrate the benefit of radiation therapy following excision. However, since radiation therapy alone has induced sustained remissions, MCC is radiosensitive. Radiation therapy added to surgery may provide additional benefit. Both the local area with 3- to 5-cm margins and the draining lymph nodes should be treated. Untreated lymph nodes experience recurrence from 46% to 76% of the time. Even after Mohs surgery, radiation therapy seems to provide additional benefit. Prophylactic lymph node dissection enhances local control, but does not improve survival. Stage II patients are treated with the same principals as stage I patients. The affected nodal masses are either removed surgically then the area radiated, or treated with radiation alone. It is unclear if surgery improves outcome. Adjunctive chemotherapy may provide some benefit in patients with high-risk disease, using synchronous chemoradiotherapy and adjuvant chemotherapy. Treatment of patients with stage III disease is palliative.

Histologically, MCC is a dermal tumor that may extend into the subcutaneous tissue. The cells are about 15 μm in diameter and have very scanty cytoplasm and hyperchromatic nuclei with a distinctive smudged chromatin pattern. Mitoses and apoptotic cells are numerous. The cells are arranged in sheets and cords. MCC must be distinguished from small cell lung cancer, lymphoma, neuroblastoma, small cell endocrine carcinoma, Ewing sarcoma, melanoma, and even BCC. While electron microscopy may detect the dense core granules, this is rarely used diagnostically. Instead, immunoperoxidase markers with characteristic staining for both keratins such as CK 20, CK 7, CAM 5.2 (in a perinuclear "dot" pattern) and neuroendocrine markers (neuron-specific enolase, neurofilament protein, neuropeptides, chromogranin, synaptosyn) are the primary method used to confirm the diagnosis of MCC. MCC is S-100 and leukocyte common antigen (LCA) negative.

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SEBACEOUS NEVI AND TUMORS

Nevus Sebaceus (Organoid Nevus)

Nevus sebaceus of Jadassohn occurs in approximately 3 in 1000 neonates. It presents as a sharply circumscribed, yellow–orange, hamartoma varying from a few millimeters to several centimeters in size. These lesions are usually solitary, congenital, and linear in configuration. The scalp is the most common location (50%), but other areas of the head and neck (45%) are also common. The trunk is involved in 5% or less of cases. The lesions persist throughout life and are usually alopecic. In childhood they are slightly papillated or velvety, but in adulthood, with hyperplasia of the sebaceous elements, the lesions become more elevated and cerebriform (Figs 29-32 and 29-33). Numerous neoplasms, most of them adnexal, have been described arising in nevus sebaceus. The most common tumors are trichoblastoma and syringocystadenoma papilliferum, each occurring in about 5% of nevus sebaceus. Both of these tumors present as new, often pigmented, papules or nodules arising in the nevus sebaceus. BCC is uncommon, occurring in less than 1% of lesions. Many cases previously diagnosed as BCC are actually trichoblastomas. Many of the tumors are difficult to classify precisely as a well-described entity. Development of benign tumors occurs in less than 5% of nevus sebaceus before the age of 16 and malignant tumors are rare in childhood or adolescence. The risk for tumor development increases with age. Rarely, aggressive malignant adnexal neoplasms may arise. Familial cases have been described and a paradominant pattern of transmission has been suggested.

Nevus sebaceus may be associated with multiple internal abnormalities, making it one of the cutaneous abnormalities to be included within the epidermal nevus syndrome (see above). In cases of nevus sebaceus syndrome, the nevus sebaceus is usually on the scalp, linear, and of larger size (several centimeters).

Histologically, in prepubertal lesions, the epithelium is acanthotic and papillomatous. Pilosebaceous structures are immature and resemble the fetal pilar germ. After puberty, the epidermis is more hyperplastic and at times papillomatous. It may resemble a seborrheic keratosis, acanthosis nigricans, or have features of an epidermal nevus. Sebaceous glands are usually abundant, placed high in the dermis, and connect directly to the epidermal surface, but may be partially lipidized near puberty. Follicular structures, if present are usually vellus or partially formed. Apocrine glands are present in about half of the lesions. The dermis is thickened with increased vascularity and fibrous connective tissue. Mature lesions have been described as broad, bald, bumpy (papillomatous), and bubbly (sebaceous).

Although the risk of development of malignancy exists, it is small, and virtually always occurs after adolescence. For

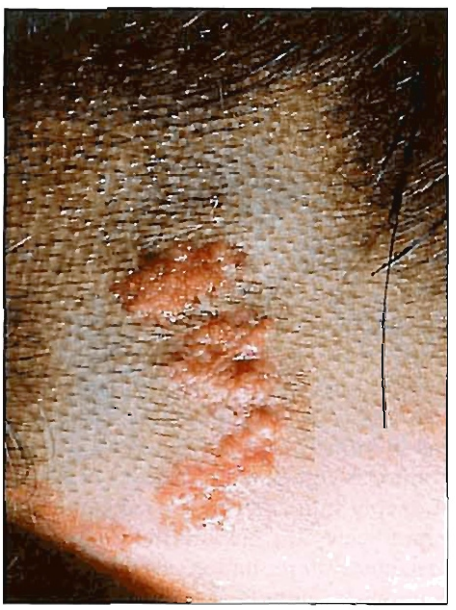

Fig. 29-32 Nevus sebaceus.

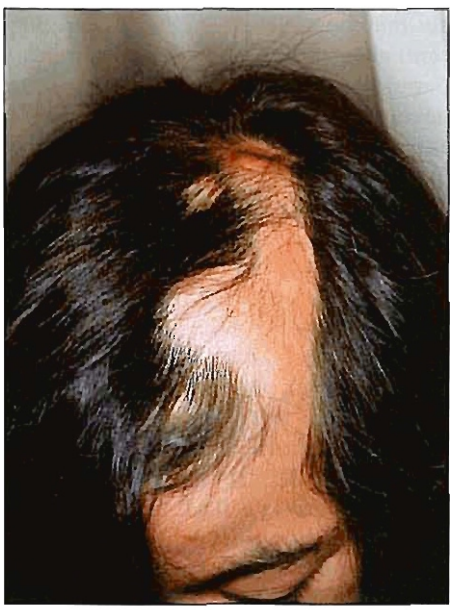

Fig. 29-33 Nevus sebaceus in a prepubescent child.

this reason, surgical removal can be delayed until adulthood, when the patient can make an informed decision regarding removal. If the lesion leads to disfigurement, stigmatization, or symptomatology, it may be removed at any age.

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Sebaceous Hyperplasia

This condition is especially common in persons with significant chronic sun exposure. The age of onset is usually past 40. The areas of predilection are the forehead, infraorbital regions, and temples. The lesions are small, cream-colored or yellowish umbilicated papules 2 to 6 mm in diameter. Unusual sites may be affected, such as the areolas, nipples, penis, neck, and chest, where they occur as solitary lesions, clustered papules or beaded lines. Prominent sebaceous hyperplasia occurs in 10% to 15% of patients taking cyclosporin and may involve ectopic sites such as the oral mucosa. It often appears many years after the cyclosporin is begun. Histologically, the sebaceous glands are hypertrophied, with normal-appearing acini. The glands are multilobulated, each dividing into other lobules to produce a cluster resembling a bunch of grapes. Clinically, they may mimic an early BCC.

Premature sebaceous hyperplasia, also known as *familial presenile sebaceous hyperplasia*, presents with extensive sebaceous hyperplasia with onset at puberty and worsening with age. Familial patterns have been reported, inherited in an autosomal-dominant fashion. It involves the face, neck, and upper thorax but spares the periorificial regions.

Treatment is solely for cosmetic purposes and employs electrosurgery, laser treatment, photodynamic therapy, or even shallow shave biopsy. Isotretinoin will reduce lesions, but they immediately recur when it is stopped, so it is probably not indicated for this condition.

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Sebaceous Adenoma

This slow-growing tumor usually presents as a pink, flesh-colored, or yellow papule or nodule. It occurs primarily on the head and neck in the elderly. Histologically, the tumor is composed of multiple sharply marginated sebaceous lobules. Each lobule has a basal layer of darker germinative cells, but the maturation is not as well-developed as in a normal sebaceous gland. Multiple openings directly to the overlying epidermis may be found. Sebaceous adenoma may be a cutaneous marker of the Muir-Torre syndrome and immunohistochemical staining for MLH-1 and MSH-2 may be used to demonstrate microsatellite instability.

Sebaceoma (Sebaceous EpFithelioma)

Clinically, sebaceomas have the same morphologic characteristics as BCCs. They appear as yellow or orange papules, nodules, or plaques, usually on the scalp, face, and neck. They may be associated with Muir-Torre syndrome. Histologically, the tumor consists of oval nests of irregularly shaped basaloid cells with differentiation toward sebaceous cells. Also, there may be cystic spaces containing vacuolated amorphous material.

Sebaceous Carcinoma

This rare carcinoma most frequently arises on the eyelids from the meibomian or Zeis glands. It usually appears in the tarsal region of the upper eyelids (75%) and represents 1% or more of eyelid malignancies. It frequently is misdiagnosed as a chalazion, delaying appropriate treatment. The scalp, other areas of the face, and the trunk are the next most common areas involved. Rarely, it has been reported to involve the feet, external genitalia, and the oral mucosa. Fatal metastatic disease occurs in up to 30% of eyelid cases and the 5-year survival for this tumor is 80%. Sebaceous carcinomas arising in nonocular locations can also metastasize, usually to regional lymph nodes. Sebaceous carcinoma may be seen in Muir-Torre syndrome (Fig. 29-34).

Histologically, the tumor is composed of lobules or sheets of cells which extend deeply into the dermis, subcutaneous fat, or muscle. The tumor cells are pleomorphic and show various degrees of sebaceous differentiation, manifested by a vacuolated rather than clear cytoplasm. Undifferentiated

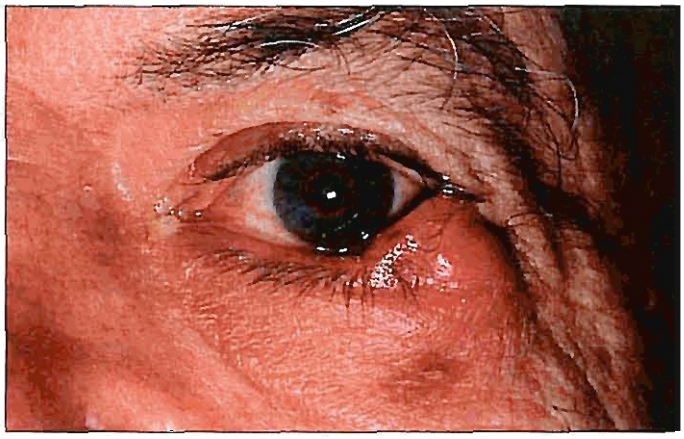

Fig. 29-34 Sebaceous carcinoma in a patient with Muir-Torre syndrome.

cells with mitotic figures can be found. The cells vary greatly in size and shape. A characteristic feature in ocular tumors is pagetoid or bowenoid spread of the tumor onto the overlying conjunctiva or skin. Sebaceous differentiation may be minimal in this in situ component, leading to the misdiagnosis of SCC in situ. Treatment is surgical with Mohs' microsurgery having had good results in some cases. Given their extent, oculoplastic reconstruction is usually required. In extraocular cases, complete excision, as for an adnexal carcinoma, and careful follow-up is recommended.

Muir-Torre Syndrome

Sebaceous tumors of the skin were first reported by Muir in 1967 and Torre in 1968 to be associated with the development of internal malignancy, a combination that has been called the Muir-Torre syndrome. The internal tumors often occur a decade or two before the cutaneous lesions, but may occur before or simultaneously with the internal malignancies. The age of presentation of the internal tumors is variable, even within the same kindred. Exacerbation of the syndrome occurs with immunosuppression.

The most common malignancy is colonic adenocarcinoma, but neoplasms of the genitourinary tract may also occur. The visceral tumors are malignant or premalignant, but may not behave as aggressively as predicted. Muir-Torre syndrome is allelic to hereditary nonpolyposis colorectal cancer syndrome. The cutaneous lesions may be sebaceous adenomas, sebaceomas, sebaceous carcinomas, or keratoacanthomas. Cystic sebaceous neoplasms are seen only in patients with Muir-Torre syndrome. Since sebaceous neoplasms are very uncommon, even the presence of one of these lesions should trigger an evaluation for Muir-Torre syndrome. In one study, 60% of patients with a sebaceous neoplasm were found to have Muir-Torre syndrome.

The genetic basis of Muir-Torre syndrome is an inactivating germline mutation of the DNA mismatch repair genes, very commonly MSH-2 and at times MLH-1, resulting in microsatellite instability. Loss of expression of MSH-2 or MLH-1 can be demonstrated in associated neoplasms by means of immunohistochemical staining. Since the genetic defects and the presence of microsatellite instability can be detected in routinely processed pathology specimens, the diagnosis can be confirmed from both skin biopsies and any visceral tumors removed from the patient. Once the diagnosis is confirmed, the patient and his/her genetically-related family members should be appropriately screened for the presence of the mutation and for underlying malignancies. Genetic counseling should be provided.

Surgical excision of cutaneous lesions is recommended. Grossly involved lymph nodes should also be excised. Patients have responded well to 40 mg/day of isotretinoin and may continue to experience good results with doses as low as 10 mg/day. Patients with this syndrome should have regular examinations for gastrointestinal and genitourinary cancer, including annual colonoscopy beginning at age 25 and first morning urine for cytology. Asymptomatic relatives should also be counseled and evaluated.

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SWEAT GLAND TUMORS

Syringoma

Syringoma are very common neoplasms demonstrating sweat duct differentiation. They present as small papules 1 to 3 mm in diameter. The may be yellow, brown, or pink. They are virtually always multiple and most frequently occur on the eyelids and upper cheeks (Fig. 29-35). They are disproportionately common in these sites in Japanese women. Other sites of involvement include the axillae, abdomen, forehead, penis, and vulva. Genital syringomas may cause genital pruritus and be mistaken for genital warts. Rarely they may be unilateral or linear. Symmetrical distal extremity involve-

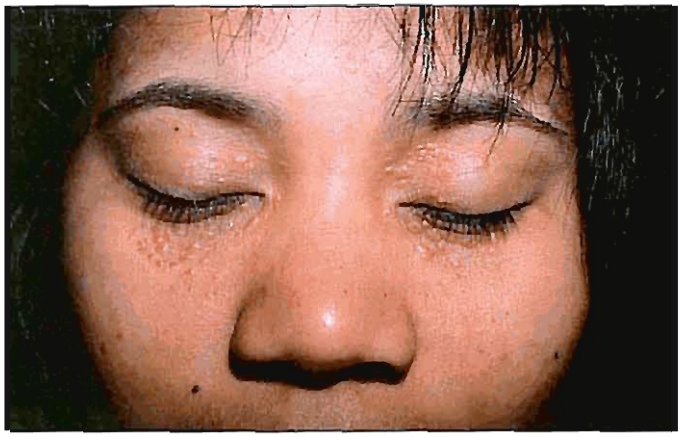

Fig. 29-35 Syringomas.

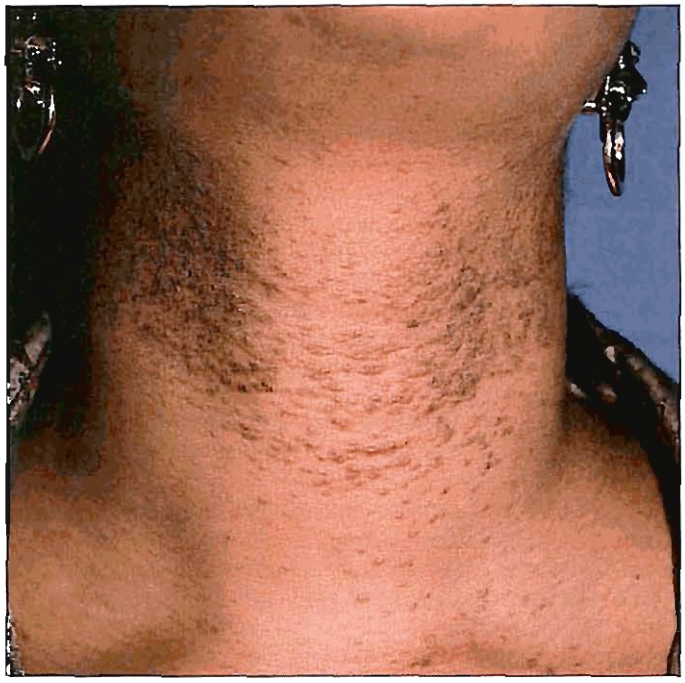

Fig. 29-36 Syringomas.

ment has also been reported. Eruptive syringomas are histologically identical to syringomas of the eyelid, but appear suddenly as numerous lesions on the neck, chest, axillae, upper arms, and periumbilically, usually in young persons (Fig. 29-36). Many individual case reports document unusual clinical variants of syringomas. These include types limited to the scalp, associated with alopecia; a unilateral linear or nevoid distribution; those limited to the vulva or penis; those limited to the distal extremities; and the lichen planus- and milia-like types.

Familial cases of syringomas occur. In general, except in eruptive cases, syringomas develop slowly and persist indefinitely without symptoms. Syringomas occur in 18% of adults with Down syndrome, particularly females. This is approximately 30 times the frequency seen in patients with other mental disabilities.

Histologically, syringomas are characterized by dilated cystic spaces lined by two layers of cuboidal cells and epithelial strands of similar cells. Some of the cysts have small comma-like tails to produce a distinctive picture, resembling tadpoles or the pattern of a paisley tie. There is a dense fibrous stroma. At times the cells of the syringoma have abundant clear cytoplasm which represents accumulated glycogen. This has been called "clear cell syringoma" and is often associated with diabetes mellitus. Syringomas stain positive for EKH-6 and CEA, a pattern similar to normal eccrine ducts, but are negative for EKH-5 and SKH1, which label the ductal portions of the eccrine glands. The microscopic differential diagnosis of "paisley tie" epithelial islands embedded in a sclerotic stroma includes microcystic adnexal carcinoma (sclerosing sweat duct carcinoma), desmoplastic trichoepithelioma, and morphoeiform BCC.

Treatment is difficult, but many lesions respond to very light electrodessication or shave removal. For larger lesions, surgical removal may be considered.

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Hidrocystomas

Hidrocystomas are 1 to 3 mm translucent papules that occasionally have a bluish tint (Fig. 29-37). They usually are

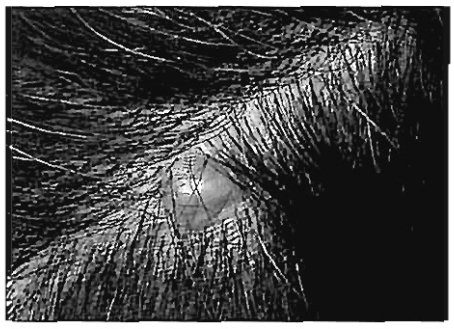

Fig. 29-37 Hidrocystoma.

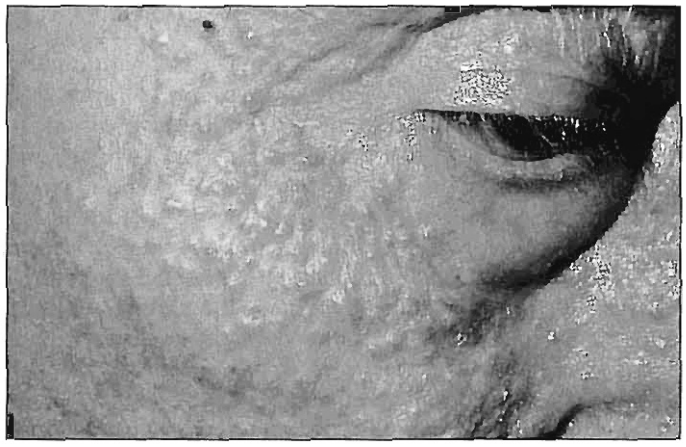

Fig. 29-38 Hidrocystomas.

solitary, occur on the face or scalp, and are more common in women. In some patients, multiple lesions may be present (Fig. 29-38) and they may be pigmented. They may become more prominent during hot weather. Multiple hidrocystomas of the eyelids may be found in Schopf-Schulz-Passarge syndrome, an adult-onset form of focal dermal hypoplasia. Microscopically, a single cystic cavity lined by two layers of small cuboidal epithelial cells is present. Apocrine differentiation in the form of decapitation secretion is common. Lesions with papillary proliferations of the lining are classified as cystadenomas. Treatment, if desired, is by excision for solitary lesions. Laser treatment may be effective. Topical atropine ointment 1% or scopolamine cream 0.01% (1.2 mL of 0.25% scopolamine eyedrops in 30 g of Eucerin) once daily, have been used with variable success in patients with multiple lesions. Pupil size may increase with these agents. Botulinum toxin may also be effective.

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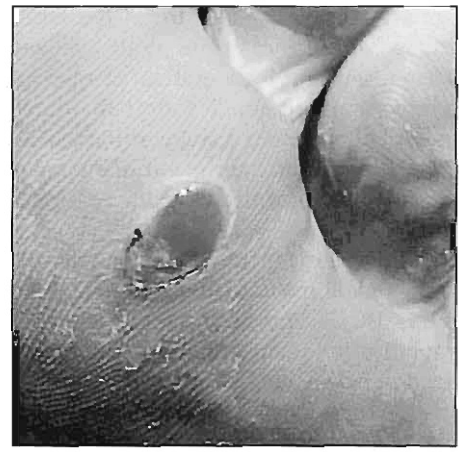

Fig. 29-39 Poroma.

Acrospiromas (Poroma, Hidroacanthoma Simplex, Dermal Duct Tumor, Nodular Hidradenoma, Clear Cell hidradenoma)

Acrospiromas are benign tumors with acrosyringial differentiation. A poroma presents as a slow-growing, 2- to 12-mm, slightly protruding, sessile, soft, reddish tumor that occurs most often on the sole (Fig. 29-39) or side of the foot. Palmar lesions may also occur and more rarely lesions appear wherever sweat glands are found. The lesion will bleed on slight trauma. A distinctive finding is the cup-shaped shallow depression from which the tumor grows and protrudes. Poromas tend to occur singly, but multiple lesions may also occur. A rare variant is called eccrine poromatosis, in which more than 100 lesions may involve the palms and soles and may be associated with hidrotic ectodermal dysplasia. These may represent acrosyringeal nevi. Dermal duct tumors present deep nodules that may involve any part of the body. Nodular and clear cell hidradenomas are larger nodules that often involve the head or neck, but may occur anywhere. Hybrid combinations of different patterns of acrospiroma are very common.

Histologically, poromas demonstrate solid masses of uniform, cuboidal epithelial cells with ample cytoplasm and focal duct differentiation. The cells are smaller than those in the contiguous epidermis and tend to arrange themselves in cords and broad columns extending downward from the normal epidermis. Areas of clear cell and cystic degeneration may be present, and an underlying dermal duct tumor or hidradenoma may be present. The surrounding stroma is highly vascular with telangiectatic vessels. Hidroacanthoma simplex represents an intraepidermal eccrine poroma. They resemble clonal seborrheic keratoses except for the presence of focal duct differentiation. Dermal duct tumors are composed of the same small acrosyringeal cells as other acrospiromas. The cells form small dermal islands with ductal differentiation. When the cells form a large nodule, the tumor is referred to as a nodular hidradenoma. When clear cells and cystic degeneration are prominent, the tumor is referred to as

a clear cell hidradenoma. A distinctive feature of the latter two tumors is the presence of areas of eosinophilic hyalized stroma. These areas represent a degenerative change of vascular walls, and always contain small endothelial-lined lumens. The appearance of these areas has been likened to that of osteoid stroma. Much of this unique stroma appears to represent massive reduplication of the vascular basement membrane.

The clinical differential diagnosis includes porocarcinoma, granuloma pyogenicum, melanoma (amelanotic and melanotic), Kaposi sarcoma, BCC, and seborrheic keratosis. The lesions are benign, but often recur following inadequate excision. Malignant degeneration may occur, and atypia is sometimes minimal within tumors that have metastasized. For these reasons, simple complete excision is recommended when feasible.

Malignant Acrospiroma (Malignant Poroma, Porocarcinoma)

This represents the most common form of sweat duct carcinoma. Most malignant acrospiromas appear clinically similar to poromas, but may also manifest as a blue or black nodule, plaque, or ulcerated tumor. Porocarcinoma affects men and women equally at an average age of 70 years. The most frequent sites of involvement are the legs (30%), feet (20%), face (12%), thighs (8%), and arms (7%). Of interest is the rare involvement of the palms and soles, despite these having the greatest concentration of sweat glands. The average age from onset to treatment is 8 years. These tumors are of intermediate aggressiveness, with metastases usually occurring to regional lymph nodes and less commonly hematogentously.

Histologically, the tumor may be seen adjoining benign acrospiroma. Atypia may be marked or minimal, with pleomorphic or monomorphous nuclei and abundant or scant eosinophilic cytoplasm. Most commonly, the cells are smaller and more basophilic than those in benign acrospiromas with a high mitotic rate. Just as in benign acrospiromas, clear cell and cystic degeneration may be present. The degree of ductal differentiation is variable. The tumors can be deeply infiltrative.

Mohs surgery can be a valuable technique, particularly on the face. As with other cutaneous neoplasms, margins should be free of tumor islands and tumor stroma to be considered negative.

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Spiradenoma

Spiradenoma clinically presents as a solitary, 1-cm, deep-seated nodule occurring most frequently on the ventral surface of the body, especially over the upper half. Normal-appearing skin covers the nodule, which may be skin-colored, blue, or pink. Occasionally, multiple lesions may be present and may occur in a linear or segmental pattern. Lesions may be painful, but not universally. Spiradenoma has a generally benign clinical course and occurs most frequently between the ages of 15 and 35, although it has also been reported in infancy and childhood. Familial cases have been described. Rarely, malignant transformation occurs and the subsequent tumor may also have features of a cylindroma (spiradenocylindrocarcinoma).

Microscopically, it demonstrates either a single nodule or multiple basophilic nodules within the dermis. Tumor cells have little to no visible cytoplasm. They are often arranged in characteristic small rosettes. Three cell types are present: cells with large, pale gray nuclei; those with smaller, darker gray nuclei; and jet-black lymphocytes peppered throughout the nodule. Duct-like structures are often present, as are large pink hyaline globules that resemble the bright red hyaline basement membrane material that outlines the islands of cylindromas. In fact, spiradenomas and cylindromas commonly occur together in the same patient and hybrid collision tumors are quite common.

When painful, eccrine spiradenoma may be mistaken for leiomyoma, glomus tumor, neuroma, and angiolipoma. Treatment is simple excision.

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Carlsten JR: Spiradenocylindrocarcinoma: a malignant hybrid tumor. J Cutan Pathol 2005;32:166.

Fernandez-Acenero MJ, et al: Malignant spiradenoma: report of two cases and literature review. J Am Acad Dermatol 2001; 44:395.

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Kao GF, et al: Eccrine spiradenoma occurring in infancy mimicking mesenchymal tumor. J Cutan Pathol 1990;17:214.

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Yoshida A, et al: Two cases of multiple eccrine spiradenoma with linear or localized formation. J Dermatol 2004;31:564.

Cylindroma

Cutaneous cylindroma, also known as dermal eccrine cylindroma, occurs predominantly on the scalp and face as a solitary lesion. The tumor is firm, but rubber-like, pinkish to blue, and ranging from a few millimeters to several centimeters. The solitary cylindroma is considered to be nonhereditary and may at times be found in areas other than the head and neck. Women are affected more than men.

The dominantly inherited form, Brooke-Spiegler syndrome, appears soon after puberty as numerous rounded masses of various sizes on the scalp. The lesions resemble bunches of grapes or small tomatoes. Sometimes they cover the entire scalp like a turban and are frequently associated with trichoepitheliomas and milia. In the familial form the cylindromas may be widespread. This syndrome is due to a mutation in the CYLD1 gene on chromosome 16q12–13.

Histologically, these are cylindrical masses of epithelial cells surrounded and segmented by thick bands of a hyaline material. Cylindroma may be mistaken for pilar cyst, but the distinctive appearance and consistency makes diagnosis easy, especially in the multiple type. Treatment is surgical.

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Leonard N, et al: Loss of heterozygosity at cylindromatosis gene locus, CYLD, in sporadic skin adnexal tumours. J Clin Pathol 2001;54:689.

Ly H, et al: Case of the Brooke-Spiegler syndrome. Australas J Dermatol 2004;45:220.

Nonaka D, et al: Cylindroma of the breast of skin adnexal type: a study of 4 cases. Am J Surg Pathol 2004;28:1070.

Stoll C, et al: Familial cylindromatosis. Genet Couns 2004; 15:175.

Tarstedt M, Molin L: Nd:YAG laser for effective treatment of multiple cylindroma of the scalp. J Cosmet Laser Ther 2004;6:41.

Mixed Tumor (Chondroid Syringoma)

Cutaneous mixed tumor is an uncommon skin tumor, representing about 1 in 1000 skin lesions electively removed. It favors men between the ages of 25 and 65. Mixed tumor presents clinically as a firm intradermal or subcutaneous nodule, virtually always located on the head and neck. These tumors are usually asymptomatic and measure 5 to 30 mm in diameter.

Histologically, nests of cuboidal or polygonal epithelial cells in the dermis give rise to tubuloalveolar and ductal structures and occasionally, keratinous cysts. These structures are embedded in a matrix varying from a faint, bluish chondroid substance to an acidophilic hyaline material. Myoepithelial and lipomatous elements may also be found in the tumor, in addition to the chondroid stroma. Ossification may occur. The treatment is surgical. Mixed tumors may also occur in other organs, especially salivary glands. Tumors with only focal glandular elements, or with no epithelial elements, have been called "cutaneous myoepitheliomas." They are tumors of the myoepithelial cells. Myopeithelial cells surround the sweat glands and by their contraction help deliver the product of the glands to the surface.

Malignant Mixed Tumor (Malignant Chrondroid Syringoma)

This rare tumor favors the trunk and extremities (whereas benign mixed tumor of the skin favors the head and neck). At presentation the masses range from 1 to 10 cm, with a median size of 4 cm, and often grow rapidly. The chance of metastasis is more than 50%, with a predilection for visceral spread. Metastases are usually as an adenocarcinoma and the chondroid stroma found in primary lesions is often not found. Histologic features that distinguish it from chondroid syringoma include cytologic atypia, pleomorphism, increased mitotic activity, and focal necrosis. Treatment is surgical.

Awasthi R, et al: Benign mixed tumour of the skin with extensive ossification and marrow formation: a case report. J Clin Pathol 2004;57:1329.

Barreto CA, et al: Intraosseous chondroid syringoma of the hallux. J Am Acad Dermatol 1994;30:374.

Hong JJ, et al: Role of radiation therapy in the management of malignant chondroid syringoma. Dermatol Surg 1995;21:781.

Mandeville JTH, et al: Cutaneous benign mixed tumor (chondroid syringoma) of the eyelid: clinical presentation and management. Ophthal Plast Reconstr Surg 2004;20:110.

Mentzel T, et al: Cutaneous myoepithelial neoplasms: clinicopathologic and immunohistochemical study of 20 cases suggesting a continuous spectrum ranging from benign mixed tumor of the skin to cutaneous myoepithelioma and myoepithelial carcinoma. J Cutan Pathol 2003;30:294.

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Ohata C, Hanada M: Lipomatous apocrine mixed tumor of the skin. Am J Dermatopathol 2003;25:138.

Radhi JM: Chondroid syringoma with small tubular lumina. J Cutan Med Surg 2004;8:23.

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Steinmetz JC, et al: Malignant chondroid syringoma with widespread metastasis. J Am Acad Dermatol 1990;22:845.

Yavuzer R, et al: Chondroid syringoma: a diagnosis more frequent than expected. Dermatol Surg 2003;29:179.

Ceruminoma

Ceruminous glands, modified apocrine glands of the external ear, may give rise to both benign and malignant tumors. Their distinction may be very difficult, hence both the malignant and benign tumors have been termed ceruminomas. The tumors present as a firm papule or nodule in the external auditory canal. Ulceration and crusting may occur and continued growth may obstruct the meatus.

Histologically, glands and cysts are present, lined by a tuboglandular proliferation with two layers—an inner layer of ceruminous cells (containing cerumen and with decapitation secretion) and a basal spindled or cuboidal myoepithelial layer. Treatment is excision, which is curative if margins are clear.

Iqbal A, Newman P: Ceruminous gland neoplasia. Br J Plast Surg 1998;51:317.

Mills RG, et al: "Ceruminoma": a defunct diagnosis. J Laryngol Otol 1995;109:180.

Schenk P, et al: Ultrastructural morphology of a middle ear ceruminoma. ORL J Otorhinolaryngol Relat Spec 2002;64:358.

Thompson LD, et al: Ceruminous adenomas: a clinicopathologic study of 41 cases with a review of the literature. Am J Surg Pathol 2004;28:308.

Hidradenoma Papilliferum

Hidradenoma papilliferum is a benign apocrine adenoma that is located almost exclusively in the vulvar and perianal

areas. The tumor is covered by normal skin. On palpation it is a firm papule less than 1 cm in diameter.

Microscopically, it is encapsulated and lies in the dermis, and has no connection with the epidermis. There is a cyst-like cavity lined with villi. The walls of the cavity and the villi are lined, occasionally with a single layer, but usually a double layer of cells—luminal secretory cells and myoepithelial cells. Electron microscopy shows hidradenoma and myoepithelial cells, confirming the apocrine origin of hidradenoma papilliferum. This is a benign lesion and the diagnosis and treatment are accomplished by excisional biopsy.

Handa Y, et al: Large ulcerated perianal hidradenoma papilliferum in a young female. Dermatol Surg 2003;29:790.
Lee HJ, et al: Nevus comedonicus with hidradenoma papilliferum and syringocystadenoma papilliferum in the female genital area. Int J Dermatol 2002;41:933.
Nishie W, et al: Hidradenoma papilliferum with mixed histopathologic features syringocystadenoma papilliferum and anogenital mammary-like glands. *J Cutan Pathol* 2004;31:561.
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Syringadenoma Papilliferum (Syringocystadenoma Papilliferum)

This lesion develops in a nevus sebaceus of Jadassohn on the scalp (Fig. 29-40) or face in about one-third of cases. About half are present at birth and approximately 25% arise on the trunk and genital and inguinal regions during adolescence. The lesions are rose-red papules of firm consistency; they vary from 1 to 3 mm and may occur in groups. Vesicle-like inclusions are seen, pinpoint to pinhead in size, filled with clear fluid. Some of the papules may be umbilicated and simulate molluscum contagiosum. Extensive verrucous or papillary plaques may also be present.

Histologically, the tumor shows ductlike structures that extend from the surface epithelium. Numerous papillary projections may extend into the lumina, which may be cystic. The papillary projections are lined by glandular epithelium, often consisting of two rows of cells. The tumor cells stain positively for carcinoembryonic antigen. The dermal stroma contains numerous plasma cells. Rarely, malignant transformation may occur. Verrucous carcinoma may develop in syringocystadenoma papilliferum. Excision is recommended and radiation therapy is ineffective.

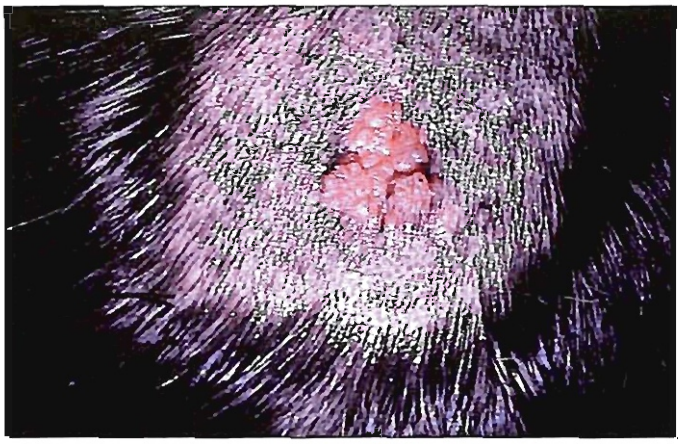

Fig. 29-40 Syringocystadenoma papilliferum.

Ahn BK, et al: A case of tubular apocrine adenoma with syringocystadenoma papilliferum arising in nevus sebaceous. J Dermatol 2004;31:508.
Arai Y, et al: A case of syringocystadenocarcinoma papilliferum in situ occurring partially in syringocystadenoma papilliferum. J Dermatol 2003;30:146.
Askar S, et al: Syringocystadenoma papilliferum mimicking basal cell carcinoma on the lower eyelid: a case report. Acta Chir Plast 2002;44:117.
Chi CC, et al: Syringocystadenocarcinoma papilliferum: successfully treated with Mohs micrographic surgery. Dermatol Surg 2004;30:468.
Dawn G, Gupta G: Linear warty papules on the neck of a young woman: syringocystadenoma papilliferum (SP) in a sebaceous nevus (SN). Arch Dermatol 2002;138:1091.
Goshima J, et al: Syringocystadenoma papilliferum arising on the scrotum. Eur J Dermatol 2003;13:271.
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Monticciolo NL, et al: Verrucous carcinoma arising within syringocystadenoma papilliferum. Ann Clin Lab Sci 2002;32:434.
Saricaoglu H, et al: A case of syringocystadenoma papilliferum: *an unusual localization on postoperative scar.* J Eur Acad Dermatol Venereol 2002;16:534.
Townsend TC, et al: Syringocystadenoma papilliferum: an unusual cutaneous lesion in a pediatric patient. J Pediatr 2004;145:131.

Papillary Eccrine Adenoma (Tubular Apocrine Adenoma)

This uncommon benign sweat gland neoplasm presents clinically as dermal nodules located primarily on the extremities of black patients, especially on the dorsal hand or foot. Histologic findings consist of a well-circumscribed, dermal, unencapsulated growth composed of dilated ductlike structures lined by two or more layers of cells. Intraluminal papillations may project into the cystic spaces. Because of its tendency to recur locally, complete surgical excision with clear margins is recommended.

Jackson EM, Cook J: Mohs micrographic surgery of a papillary eccrine adenoma. Dermatol Surg 2002;28:1168.

Syringofibroadenoma (Acrosyringeal Nevus of Weedon and Lewis)

First described by Mascaro in 1963, four variants of eccrine syringofibroadenoma (ESFA) are now recognized: 1) the solitary variant; 2) multiple in Schopf syndrome; 3) multiple without other skin manifestations; and 4) nonfamilial unilateral linear type. The solitary type presents frequently as a hyperkeratotic nodule or plaque involving the extremities. The linear type may be linear, blashkoid, or zosteriform in appearance and some cases may represent an acrosyringeal nevus. Multiple lesions have been termed *eccrine syringofibroadenomatosis* and occur in both variants of hidrotic ectodermal dysplasia, Schopf syndrome, and Clouston syndrome. The multiple eccrine syringofibroadenomas may appear in a mosaic pattern. In Clouston syndrome, HPV-10

has been detected in the tumors. Multiple lesions have also been reported without any other associated cutaneous findings. Many cases represent a reactive epithelial proliferation, whereas others represent a true neoplasm of acrosyringeal cells. Histologically, the strands resemble those of the fibroepithelial tumor of Pinkus, but with broader anastomosing cords without the basaloid buds. "Reactive eccrine syringofibroadenoma" most commonly occurs on the lower leg and may show adjacent changes of an associated dermatosis. Carcinomatous transformation of ESFA has been reported.

Bjarke T, et al: Carcinoma and eccrine syringofibroadenoma: a report of five cases. J Cutan Pathol 2003;30:382.

Katane M, et al: Carcinomatous transformation of eccrine syringofibroadenoma. J Cutan Pathol 2003;30:211.

Kawaguchi M, et al: Eccrine syringofibroadenoma with diffuse plantar hyperkeratosis. Br J Dermatol 2003;149:885.

Starink TM: Eccrine syringofibroadenoma: multiple lesions representing a new cutaneous marker of the Schopf syndrome, and solitary nonhereditary tumors. J Am Acad Dermatol 1997;36:569.

Trauner MA, et al: Eccrine syringofibroadenoma treated with a dual pulse width flashlamp pumped pulsed dye laser. Dermatol Surg 1999;25:418.

Utani A, et al: Reactive eccrine syringofibroadenoma: an association with chronic foot ulcer in a patient with diabetes mellitus. J Am Acad Dermatol 1999;41:650.

Microcystic Adnexal Carcinoma (Sclerosing Sweat Duct Carcinoma)

The tumor generally presents as a very slow-growing plaque or nodule. It occurs most commonly on the upper lip (Fig. 29-41) or face. Microcystic adnexal carcinomas have occurred at sites of prior therapeutic radiation. It is very locally aggressive, with local recurrences in 50% of cases. Metastasis probably does not occur. Histologically, the superficial part of the tumor is composed of ducts, keratinous cysts, and small cords of cells, superficially resembling a syringoma. The deeper component consists of nests and strands in a dense stroma. Perineural invasion is common and may be extensive. This explains the frequent recurrence after initial excision. Mohs microsurgery is the treatment of choice. Radiation treatment of the tumor is ineffective and may lead to recurrence with more aggressive behavior.

Callahan EF, et al: Microcystic adnexal carcinoma (MAC) of the scalp with extensive pilar differentiation. Dermatol Surg 2002; 28:536.

Hodgson TA, et al: Microcystic adnexal carcinoma: an unusual cause of swelling and paraesthesia of the lower lip. Oral Oncol 2003;39:195.

Leibovitch I, et al: Microcystic adnexal carcinoma: Treatment with Mohs micrographic surgery. J Am Dermatol 2005;52:295.

Ohtsuka H, Nagamatsu S: Microcystic adnexal carcinoma: review of 51 Japanese patients. Dermatology 2002;204:190.

Ong T, et al: Microcystic adnexal carcinoma of the eyebrow. Ophthal Plast Reconstr Surg 2004;20:122.

Ozbek C, et al: Microcystic adnexal carcinoma of the external ear canal. Otolaryngol Head Neck Surg 2004;130:148.

Salerno S, Terrill P: Will MAC be back? ANZ J Surg 2003; 73:830.

Stein JM, et al: The effect of radiation therapy on microcystic adnexal carcinoma: a case report. Head Neck 2003;25:251.

"Eccrine" Carcinoma (Syringoid Carcinoma)

Eccrine carcinoma is rare and presents as a plaque or nodule on the scalp (Fig. 29-42), trunk, or extremities. Local recurrence is common, but metastases are rare. It is composed of ducts and tubules with atypical basaloid cells. A more cellular tumor with numerous tubules and ducts has been termed *polymorphous sweat gland carcinoma*. Overlap features with microcystic adnexal carcinoma occur, but in general eccrine carcinoma has a less desmoplastic stroma.

Mucinous Carcinoma

This tumor is commonly a round, elevated, reddish, and sometimes ulcerated mass, usually located on the head and neck (75%). Forty percent occur on the eyelid. It grows slowly and is usually asymptomatic. Local recurrence is seen in 36%, but the rate of metastasis and widespread dissemination is low (15%). Rare tumors on the eyelid (derived from the glands of Moll) may express estrogen and progesterone receptors, analogous to mucinous carcinoma of the breast. Mucinous gut carcinomas may also metastasize to skin and must be excluded before diagnosing a primary cutaneous mucinous carcinoma.

Histologically, tumors are characterized by the presence of large areas of mucin in which small islands of basophilic epithelial cells are embedded (blue islands floating in a sea of mucous). Basaloid cells in a cribiform pattern, with duct-

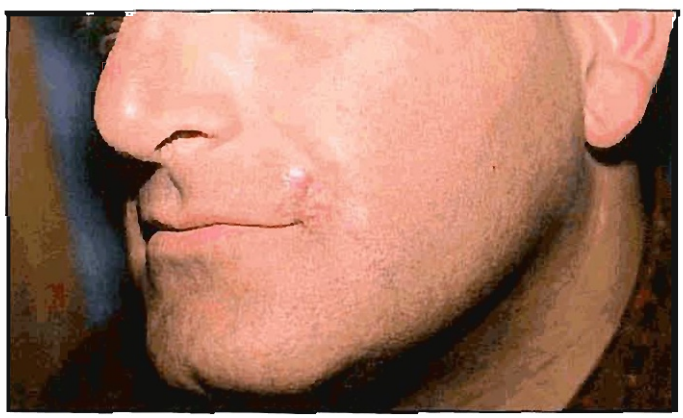

Fig. 29-41 Microcystic adnexal carcinoma.

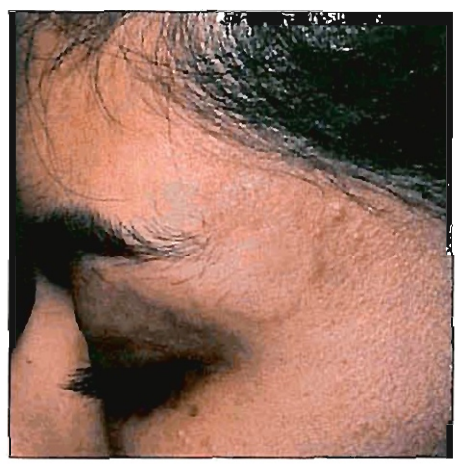

Fig. 29-42 Eccrine carcinoma.

like structures, is typical). The recommended treatment is local surgical excision.

Marra DE, et al: Mohs micrographic surgery of primary cutaneous mucinous carcinoma using immunohistochemistry for margin control. Dermatol Surg 2004;30:799.
Mitsui H, et al: Mucinous carcinoma of the skin could have either an eccrine or an apocrine origin. Br J Dermatol 2004; 151:1285.
Terada T, et al: Primary cutaneous mucinous carcinoma initially diagnosed as metastatic adenocarcinoma. Tohoku J Exp Med 2004;203:345.
Wako M, et al: Mucinous carcinoma of the skin with apocrine-type differentiation: immunohistochemical studies. Am J Dermatopathol 2003;25:66.

Aggressive Digital Papillary Adenocarcinoma (Digital Papillary Adenocarcinoma)

This aggressive malignancy involves the digit between the nailbed and the distal interphalangeal joint spaces in most cases, or just proximal to this region. It presents as a solitary cystic nodule. Ulceration and bleeding can occur and rarely the malignancy may be fixed to underlying tissues. Most patients are men in their 50s. Metastases occur in about 15% of cases, particularly pulmonary. The tumor is poorly circumscribed and composed of tubuloalveolar and ductal structures with areas of papillary projections. The tumor is positive for S-100, and the cystic contents are positive for CEA and EMA. Complete excision is the treatment of choice. Cases previously called aggressive digital papillary "adenoma" are best regarded as adenocarcinoma.

Duke WH, et al: Aggressive digital papillary adenocarcinoma (aggressive digital papillary adenoma and adenocarcinoma revisited). Am J Surg Pathol 2000;24:775.
Mori O, et al: Aggressive digital papillary adenocarcinoma arising on the right great toe. Eur J Dermatol 2002;12:491.

Primary Cutaneous Adenoid Cystic Carcinoma

This rare cutaneous tumor presents usually on the chest, scalp, or vulva of middle- to older-aged persons. It is similar histologically to adenoid cystic carcinoma of the salivary gland, with a proliferation of small duct-like islands and larger islands with a "Swiss cheese" or cribriform pattern. It may recur locally or rarely metastasizes. Surgical excision, perhaps with Mohs micrographic surgery, is the treatment of choice.

Doganay L, et al: Primary cutaneous adenoid cystic carcinoma with lung and lymph node metastases. J Eur Acad Dermatol Venereol 2004;18:383.
Krunic AL, et al: Recurrent adenoid cystic carcinoma of the scalp treated with Mohs micrographic surgery. Dermatol Surg 2003;29:647.
Marback EF, et al: Eyelid skin adenoid cystic carcinoma: a clinicopathological study of one case simulating sebaceous gland carcinoma. Br J Ophthalmol 2003;87:118.

Apocrine Gland Carcinoma

Apocrine gland carcinoma, unrelated to Paget's disease, is rare. The axilla or anogenital region are the most common sites, but occasionally other areas with apocrine glands may be involved. Lesions present as a mass. Widespread metastases occur in at least 40% of cases.

Bratthauer GL, et al: Androgen and estrogen receptor mRNA status in apocrine carcinomas. Diagn Mol Pathol 2002;11:113.
Chintamani, et al: Metastatic sweat gland adenocarcinoma: A clinico-pathological dilemma. World J Surg Oncol 2003;1:13.
Kiyohara T, et al: Apocrine carcinoma of the vulva in a band-like arrangement with inflammatory and telangiectatic metastasis via local lymphatic channels. Int J Dermatol 2003;42:71.
Kuno, Y, et al: Adenocarcinoma with signet ring cells of the axilla: two case reports and review of the literature. J Dermatol 1999;26:390.
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Paridaens D, Mooy CM: Apocrine sweat gland carcinoma. Eye 2001;15:253.

HAIR FOLLICLE NEVI AND TUMORS

Pilomatricoma (Calcifying Epithelioma of Malherbe)

Also known as *Malherbe calcifying epithelioma* and *pilomatrixoma*, this benign tumor is derived from hair matrix cells. It usually occurs as a single lesion which is most commonly found on the face, neck, or proximal upper extremity. Lesions may also be located on the scalp, trunk, and lower extremities. Pilomatricoma is an asymptomatic, deeply seated, 0.5- to 7.0-cm, firm nodule, covered by normal or pink skin, which on stretching may show the "tent sign," with multiple facets and angles (Fig. 29-43). Overlying epidermal atrophy is common, leading to an appearance that may resemble anetoderma or striae. In a review of 209 patients, the youngest was 18 months and the oldest 86 years. There is a bimodal age distribution, in the first and sixth decades. Girls are more commonly affected than boys.

Multiple pilomatricomas are uncommon. They are usually seen in association with myotonic dystrophy—Steinert syndrome. They may also occur in Ruinstein-Taybi syndrome and Turner syndrome. Patients with Gardner syndrome have

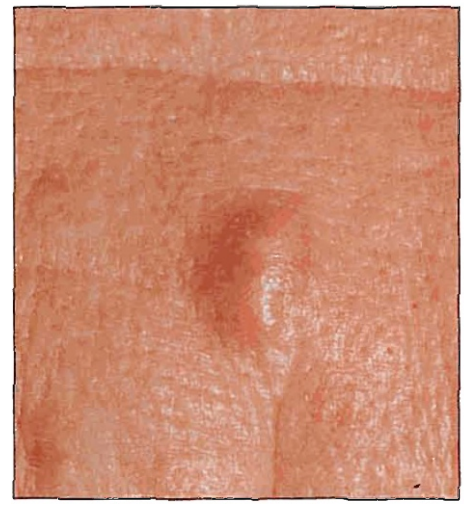

Fig. 29-43
Pilomatrixoma.

epidermoid cysts with focal areas of pilomatricoma-like changes. Rarely, multiple pilomatricomas will be inherited in an autosomal-dominant pattern with no other association.

The histopathology shows an encapsulated mass. Basophilic cells with little cytoplasm resemble those of the hair matrix. They evolve into eosinophilic "shadow" cells. Calcification occurs commonly. Ossification, melanin deposits, and foreign-body reaction with giant cells may all be present. Activating mutations in β-catenin are present in the majority of pilomatricomas. It is expressed in the basophilic but not the shadow cells. "Melanocytic matricoma" is a rare lesion presenting as a small papule which histologically is composed of metrical cells, some shadow cells, and numerous dendritic melanocytes containing melanin.

Clinical differential diagnosis is usually impossible in the adult, but in children, since epidermoid cysts are rare, this diagnosis should be considered for any firm cystic mass of the face and upper body. When palpated, pilomatricomas are firmer and more faceted than epidermoid and pilar cysts. Fine needle aspiration has led to misdiagnosis, with the basophilic cells being interpreted as carcinoma. Treatment is surgical excision.

Malignant Pilomatricoma (Pilomatrix Carcinoma, Pilomatrical Carcinoma)

Malignant pilomatricomas are rare tumors. Described as being locally aggressive, but with limited metastatic potential, many cases described as "malignant" may actually have been "proliferating" pilomatricomas. Metastases to regional lymph nodes are most frequent. Mohs micrographic surgery may be considered to obtain clear margins.

Barberio E, et al: Guess what! Multiple pilomatricomas and Steinert disease. Eur J Dermatol 2002;12:293.

Bassarova A, et al: Pilomatrix carcinoma with lymph node metastases. J Cutan Pathol 2004;31:330.

Bayle P, et al: Multiple perforating and non perforating pilomatricomas in a patient with Churg-Strauss syndrome and Rubinstein-Taybi syndrome. J Eur Acad Dermatol Venereol 2004;18:607.

Berberian BJ, et al: Multiple pilomatricomas in association with myotonic dystrophy and a family history of melanoma. J Am Acad Dermatol 1997;37:268.

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Fernandez R, et al: Giant pilomatricoma (epithelioma of Melherbe): Report of a case and review of literature. J Oral Maxillofac Surg 2003;61:634.

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Hassanein AM, Glanz SM: Beta-catenin expression in benign and malignant pilomatrix neoplasms. Br J Dermatol 2004;150:511.

Hubbard VG, Whittaker SJ: Multiple familial pilomatricomas: an unusual case. J Cutan Pathol 2004;31:281.

Inui S, et al: Pilomatricoma with a bullous appearance. J Dermatol 1997;24:57.

Julian CG, et al: A clinical review of 209 pilomatricomas. J Am Acad Dermatol 1998;39:191.

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Lemos LB, Brauchle RW: Pilomatrixoma: a diagnostic pitfall in fine-needle aspiration biopsies. A review from a small county hospital. Ann Diagn Pathol 2004;8:130.

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Preuss SF, et al: Inverted malignant pilomatricoma of the neck. Eur Arch Otorhinolaryngol 2004,262:269.

Sable D, Snow SN: Pilomatrix carcinoma of the back treated by Mohs micrographic surgery. Dermatol Surg 2004;30:1174.

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Trichofolliculoma

Trichofolliculoma is a benign, highly-structured tumor of the pilosebaceous unit, characterized by a small, dome-shaped nodule some 5 mm in diameter on the face or scalp. From the center of the flesh-colored nodule a small wisp of fine, vellus hairs protrudes through a central pore (Fig. 29-44). It may occur at any age but mostly affects adults.

Histologically, the tumor consists of one or more large follicles with smaller radiating secondary follicular structures (sometimes referred to as the mother follicle with her babies). The secondary follicles range from an immature rudimentary matrix to well-formed follicles with papillae, matrix, trichohyaline, and fine hairs ("fingers of fully formed follicles forming fiber"). The tumor may have little stroma or may be embedded in a fibrous orb. Sebaceous glands may be prominent, a variant termed "sebaceous trichofolliculoma." The follicular structures in trichofolliculomas transition through phases of the hair cycle. In telogen, they may resemble fibrofolliculomas. The presence of hair shafts helps distinguish the two. Folliculosebaceous cystic hamartoma may represent a sebaceous trichofolliculoma in telogen. Treatment is surgical removal.

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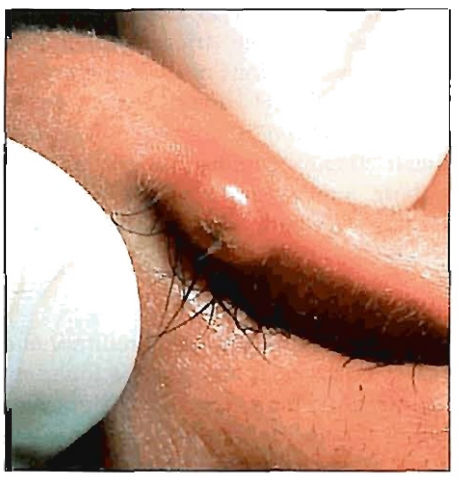

Fig. 29-44
Trichofolliculoma.

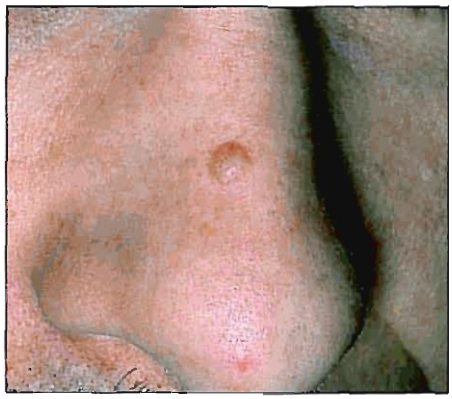

Fig. 29-45
Trichoepithelioma.

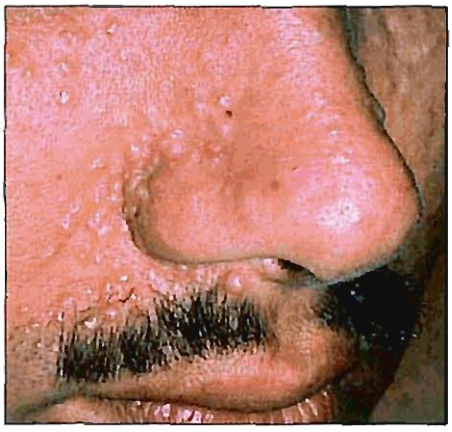

Fig. 29-46
Trichoepitheliomas.

Multiple Familial Trichoepithelioma (Epithelioma Adenoides Cysticum, Brooke-Spiegler Syndrome)

This autosomal-dominant condition usually presents in childhood or around puberty. Multiple cystic and solid nodules appear on the face, favoring the upper lip, nasolabial folds, and eyelids. The individual lesions are small, round, smooth, shiny, slightly translucent, firm, circumscribed papules or nodules (Fig. 29-45). The individual lesions average 2 to 4 mm in diameter. The center may be slightly depressed. Most frequently the lesions are grouped but discrete. On the face they are often symmetrical (Fig. 29-46). Other sites may be the scalp, neck, and trunk. Multiple linear and dermatomal trichoepitheliomas may rarely be seen. Cylindromas and multiple spriadenomas may occur in association with multiple trichoepitheliomas. Multiple trichoepitheliomas was originally associated with mutations on the long arm of chromosome 9, near or in the PTCH gene. Recently, mutations of the CYLD gene on 16q12–q13 have been described in families with multiple trichoepitheliomas and cylindromas. Some individuals in these families have primarily trichoepitheliomas and resemble patients with Brooke-Spiegler syndrome.

Solitary Trichoepithelioma

The single occurring trichoepithelioma is nonhereditary and occurs mostly on the face; however, it may also be found on the scalp, neck, trunk, and proximal extremities. It presents as a firm dermal papule or nodule and must be distinguished from BCC.

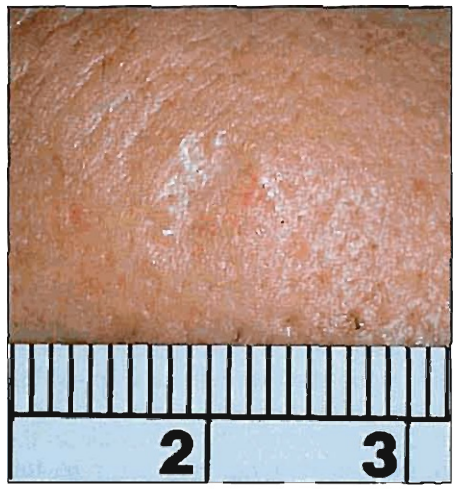

Fig. 29-47
Trichoepithelioma, desmoplastic type.

Giant Solitary Trichoepithelioma

The lesions may be several centimeters in diameter, occurring most commonly on the thigh or perianal regions. They are found in older adults.

Desmoplastic Trichoepithelioma

This lesion, which is difficult to differentiate from morpheiform BCC histologically, occurs as solitary or multiple lesions on the face. Desmoplastic trichoepithelioms are firm, slightly indented (central dell sign), and have a raised, annular border (Fig. 29-47). Young women are most commonly affected and familial solitary and multiple desmoplastic trichoepitheliomas have been described.

Histology

Trichoepithelioma are dermal tumors with multiple nests of basaloid cells, some of which show abortive follicular differentiation. Keratinous cysts, calcification, and amyloid may all be seen. The stroma in most trichoepitheliomas resembles the fibrous sheath of a normal hair follicle. It contains many fine collagen fibers and fibroblasts that surround the tumor islands in a concentric array. Clusters of plump nuclei resembling the cells of the follicular papilla (papillary mesechymal bodies) are common. In the desmoplastic variety, the tumor is composed of small cords of epithelium embedded in a dense eosinophilic stroma with fewer fibroblasts. The islands often present a "paisley tie" appearance, and the microscopic differential diagnosis includes morpheaform BCC, syringoma, and microcystic adnexal carcinoma. The clinical features may distinguish these entities. Focal calcification, horn cysts, and a central dell favor trichoepithelioma. In desmoplastic trichopeithelioma, clefts form between collagen fibers in the stroma, while in BCC, clefts form between the tumor islands and stroma. Trichoepitheliomas are best classified as benign tumors of the hair germ. As such, they may be considered variants of trichoblastoma. Histologically, trichoepithelioma must be differentiated from keratotic BCC, for which it is frequently confused.

Treatment

Solitary lesions can be treated by surgical excision. Multiple lesions can be smoothed down by resurfacing the skin with laser, dermabrasion, or electrosurgery. This procedure must be repeated at regular intervals, as the lesions recur gradually.

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Trichoblastoma

These benign neoplasms of follicular germinative cells usually present as asymptomatic nodules greater than 1 cm in size in the deep dermis or subcutaneous tissue. The scalp is the most common location. They occur in male and female adults. The lesions may be pigmented. Trichoblastomas arise in organoid nevi and represent the majority of basaloid neoplasms described as "basal cell carcinomas" in nevus sebaceus. Histologically, trichoblastoma is a dermal or subcutaneous tumor composed of basaloid cells with areas of follicular differentiation of the tumor. The islands may connect with the overlying epidermis, especially in the setting of an organoid nevus. The stroma is identical to that seen in trichoepithelioma and typically contains papillary mesechymal bodies. Merkel cells may be prominent within the tumor and amyloid can be found. Cutaneous lymphadenoma is a variant of trichoblastoma with extensive infiltration of the tumor islands by lymphocytes and histiocytes. The stroma resembles that of other trichoblastomas. A single or double row of basaloid tumor cells is seen at the periphery of each island, while the center is composed of histiocytes and lymphocytes. Surgical excision is curative.

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Trichilemmoma and Cowden Syndrome (Cowden's Disease, Multiple Hamartoma Syndrome)

Trichilemmoma is a benign neoplasm that differentiates toward cells of the outer root sheath. It may occur as a small solitary papule on the face, particularly the nose and cheeks. Most lesions are clinically misdiagnosed as BCC or benign keratosis.

Trichilemmomas may also occur as multiple facial lesions. When they do, it is a specific cutaneous marker for Cowden syndrome, an autosomal-dominantly inherited condition. Diagnostic criteria for Cowden syndrome have been established and certain of the mucocutaneous manifestations are considered "pathognomic." The trichilemmomas are generally limited to the head and neck; however, unusual sites may be involved. Eighty-seven percent of patients with Cowden syndrome have these facial papules (Fig. 29-48). Most consider all the facial papules variants of trichilemmoma, but some contend that some of the facial lesions are trichilemmomas and others are HPV-induced and contain epidermodysplasia-verruciformis HPV types. Since not all facial papules have characteristic histology, the presence of "papillomatous" lesions is a diagnostic criteria. The other pathognomic mucocutaneous benign features include oral mucosal papillomas and acral keratotic papules. Some patients may lack cutaneous findings. Malignancies develop in up to 40% of patients with Cowden syndrome. They are major criteria for the diagnosis and include breast, endometrial, and thyroid carcinoma. Macrocephaly and Lhermitte-Duclos disease are other major criteria. Although not criteria for the diagnosis, gastrointestinal malignancies also occur. Minor criteria included thyroid lesions (adenomas or goiter), mental retardation, fibrocystic disease of the breast, lipomas, fibromas (multiple sclerotic fibromas), and genitourinary tumors. The adult form of Lhermitte-Duclos disease, or

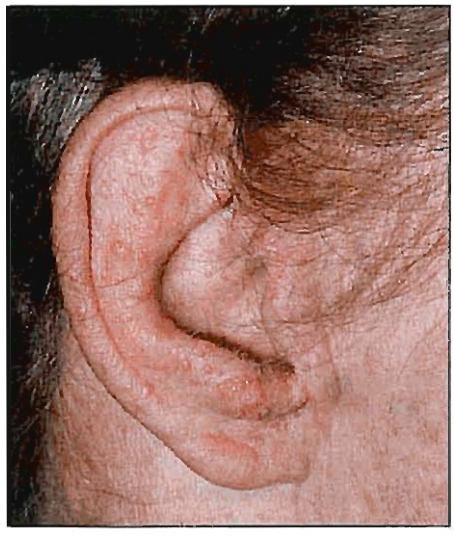

Fig. 29-48 Cowden syndrome.

dysplastic gangliocytoma of the cerebellum, may represent the neurologic manifestation of Cowden's disease. A number of mucocutaneous malignancies have been found in patients with Cowden's disease, including melanoma, BCC, SCC, Merkel cell carcinoma, and trichilemmal carcinoma. Mutations in a tumor suppressor gene (called PTEN) are responsible for Cowden syndrome. Another disorder caused in 60% of cases by mutations in PTEN is Bannayan-Riley-Ruvalcaba syndrome (autosomal-dominantly inherited, macrocephaly, genital lentigines, motor and speech delay, mental retardation, hamartomatous polyps, myopathies, lipomas, and hemangiomas). Some patients with a Proteus-like syndrome also have mutations in PTEN. These diseases have been called the "PTEN hamartoma tumor syndrome."

Microscopically, trichilemmomas show variable hyperkeratosis and parakeratosis. Tumor lobules extend downward from the epidermis and demonstrate glycogen-rich clear cells, peripheral palisading, and a thick hyalinized basement membrane.

Some have advocated bilateral simple mastectomies in affected females to prevent the development of subsequent malignancies. Women with the syndrome who have lost many loved ones to breast cancer have not regarded this recommendation as excessive. With better screening techniques, this recommendation may be modified. Isotretinoin has been used to treat the cutaneous lesions, but even those that regress tend to recur when it is discontinued. Facial papillomas can be removed with surgical procedures, but new lesions continue to appear throughout life. Some patients get satisfactory cosmetic results from dermabrasion or CO_2 laser.

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Trichilemmal Carcinoma

Trichilemmal carcinomas are reported to arise on sun-exposed areas, most commonly the face and ears. They present as a slow-growing papule, indurated plaque, or nodule with a tendency to ulcerate. They may arise in the association of immunosuppression. It may be difficult to distinguish trichilemmal carcinoma from invasive Bowen's disease (which often shows adnexal differentiation) or a clear cell SCC. Surgical removal is recommended; Mohs micrographic surgery has been used successfully.

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Trichodiscoma, Fibrofolliculoma, Perifollicular Fibromas, Mantleomas and Birt-Hogg-Dubé Syndrome

These benign tumors form a spectrum of neoplasms combining a follicular element and the specialized periadventitial dermis of the upper portion of the hair follicle. They may represent variations of the same tumor cut in different planes of section. All these lesions clinically appear as 2- to 4-mm, asymptomatic, skin-colored, dermal papules, affecting the face and upper trunk. They may be single, but are frequently multiple. When multiple, they are often numerous and are a marker for Birt-Hogge-Dubé syndrome (BHD). The histomorphology of these hair follicle tumors is identical in patients with BHD and in cases unassociated with BHD. Fibrofolliculoma demonstrates cords and strands of two to four cell epithelium eminating from a follicular structure. The epithelial elements may anastomose and sebaceous elements may be present. This follicular structure is surrounded by a collagenous or fibromucinous orb. Trichodiscomas represent a sectioning artifact that demonstrates only the tumor stroma.

BHD syndrome is caused by a mutation in the gene folliculin (FLCN) which is located on chromosome 17p. Many of the mutations occur in a hypermutable region of the gene. This gene is conserved in many species and expressed in many tissues, especially those with secretory function. Homozygous loss of function of the folliculin gene is embryonically lethal, suggesting it has important functions. In addition to the cutaneous lesions noted above, patients are at risk for the development of renal tumors and spontaneous pneumothorax. The renal tumor risk is seven times the general population and especially affects men (at twice the risk) and those over 40. Almost 12% of BHD patients over the age of 40 develop renal tumors. Renal tumors may be multiple and bilateral. BHD patients develop renal oncocytomas and chromophobe renal carcinomas, otherwise rare renal cancers. Persons with BHD have greater than 50 times the risk of developing a spontaneous pneumothorax compared

to unaffected persons. Pneumothorax is inversely related to age and young persons with BHD have a high risk of pneumothorax—17% of BHD patients under 40 will have a spontaneous pneumothorax. Spontaneous pneumothorax results from multiple pulmonary cysts, which affect 83% of BHD patients. Familial spontaneous pneumothorax is also an autosomal-dominant disorder and in at least one kindred was associated with a deletion in the folliculin gene. Colonic polyps and neoplasms, which were initially reported to be associated with BHD syndrome, have been shown *not* to be increased in BHD syndrome. However, microsatellite stable colonic polyps and carcinomas frequently have loss of heterozygosity for the region of chromosome 17p where the BHD gene is located. The BHD gene may thus be involved in colorectal tumor progression in sporadic colorectal carcinomas. BHD mutations have also been reported in spontaneous renal tumors. Inherited renal cancer in the German shepherd dog and rat is due to mutation in the BHD gene. Although they are often small and not cosmetically problematic, larger lesions in patients with BHD may be treated with laser therapy or shave excisions.

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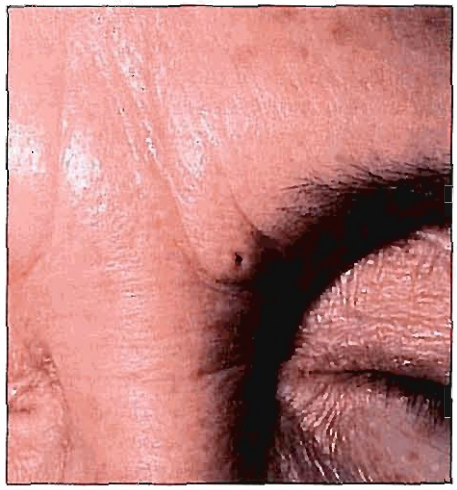

Fig. 29-49 Dilated pore of Winer.

Other Hair Follicle Tumors

Dilated Pore (Winer) This lesion typically presents as a solitary, prominent, open comedo on the face or upper trunk of an elderly individual (Fig. 29-49). Histologically, it is composed of a markedly dilated follicular pore lined by outer root sheath epithelium. Multiple short bulbous, acanthotic projections extend from the central infundibulum-like pore.

Pilar Sheath Acanthoma Most often found on the face, particularly above the upper lip in adults, patients present with a solitary 5- to 10-mm skin-colored nodule with a central keratinous plug. Histologically, pilar sheath acanthoma differs from a dilated pore by having larger tumor lobules radiating from the central infundibulum-like pore.

Trichoadenoma Presenting as a solitary growth ranging from 3 to 15 mm in diameter, clinically it may be mistaken for a seborrheic keratosis, having a vegetative or verrucous appearance. Although most frequently found on the face, it may occur at other sites, especially the buttock, which is the second most common location. Trichoadenomas also differentiate towards the follicular infundibulum. Histologically, they are quite distinctive, being composed of a collection of ring-like eosinophilic structures that often occur in pairs (resembling spectacles). No hair shafts are present.

Basaloid Follicular Hamartoma Basaloid follicular hamartoma (BFH) is a distinctive benign adnexal tumor that has four described variants: solitary papule, localized plaque of alopecia, linear or Blashkoid unilateral plaque, and generalized papules. This latter form has also been termed "generalized hair follicle hamartoma." Most often affecting the skin of the face and scalp, BFHs are solitary or multiple skin-colored 2- to 3-mm papules or infiltrating plaques associated with progressive hair loss in the affected areas. Congenital and adult appearance has been described. In some generalized cases there is an association with alopecia, myasthenia gravis, and/or circulating autoantibodies (antinuclear and anti-acetylcholine receptor antibodies). Cystic fibrosis and generalized follicular hamartomas have been reported in three

siblings, suggesting a possible genetic linkage. A familial, autosomal-dominant form with numerous milia; comedo-like lesions; hyperpigmented papules of the face, scalp, ears, neck and trunk; hypotrichosis; hypohidrosis; and pinpoint palmar pits has been described. It presents in early childhood.

Histologically, basaloid follicular hamartomas may be indistinguishable from infundibulocystic basal cell carcinoma. They are characterized by thin, branching eosinophilic strands and thick cords with associated basaloid buds and keratin cysts. Unlike most other pilar tumors, the stroma is loose, fibrillar, or mucinous. In nevoid and generalized forms, apparently normal skin may also demonstrate small islands of basaloid cells. Trichoblastomas may occur within nevoid lesions. PTCH gene signaling is upregulated in the cells contacting the dermis in BFH. Generalized basaloid follicular hamartoma syndrome must be distinguished from Bazex-Dupre-Christol syndrome, Brown-Crounse syndrome, Rombo syndrome, basal cell nevus syndrome, and Brooke-Spiegler syndrome. Its differentiation from multiple hereditary infundibulocystic basal cell carcinoma syndrome may be difficult.

Folliculosebaceous Cystic Hamartoma Folliculosebaceous cystic hamartoma is a benign hamartoma of epithelial and mesenchymal elements. It presents as a solitary 0.5- to 1.5-cm papule or nodule virtually always on the head, with two-thirds occurring on or adjacent to the nose. Rare giant lesions up to 15 cm in diameter have been reported. Age of onset ranges from infancy to the sixth decade. Histologically, the lesion is composed of three elements: an intradermal cystic structure lined by squamous epithelium identical to that of the infundibulum; numerous sebaceous lobules radiating from the cystic structure; and a surrounding stroma with fibrous, adipose, vascular, and neural tissues. Stromal spindle cells are positive for CD34. The tumor may represent a sebaceous trichofolliculoma biopsied during telogen phase.

Tumors of the Follicular Infundibulum These flat, keratotic papules of the head and neck are usually solitary but may be multiple. They appear in adulthood. The term eruptive infundibulomas and infundibulomatosis has been used to describe the cases with multiple lesions. In the rare generalized cases there is a strong clinical resemblance to Darier's disease, with accentuation on the neck, central chest, groin, and axillae. Histologically, the solitary and multiple cases are identical. There is a platelike proliferation of epidermal cells growing parallel to the epidermis and connecting to it at multiple sites. Clear glycogenated cells like that of a trichilemmoma, sebaceous differentiation, cystic and ductal structures, and papillary mesenchymal bodies may be seen.

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EPITHELIAL CYSTS AND SINUSES

Epidermal Cyst (Epidermal Inclusion Cyst, Infundibular Cyst)

Epidermal inclusion cyst is one of the most common benign skin tumors. It presents as a compressible, but not fluctuant, cystic mass from a half to several centimeters in diameter (Fig. 29-50). The surface of the overlying skin is usually smooth and shiny from the upward pressure. These nodules are freely movable over underlying tissue and are attached to the normal skin above them by a comedo-like central infundibular structure or punctum. The pasty contents of the cysts are formed mostly of macerated keratin which has a cheesy consistency and pungent odor. Epidermal inclusion cysts occur most commonly on the face, neck, and trunk, but may be found almost anywhere. They frequently result from plugging of the follicular orifice, often in association with acne vulgaris. They may also occur by epidermal implantation. Deep penetrating injuries, such as with a sewing machine

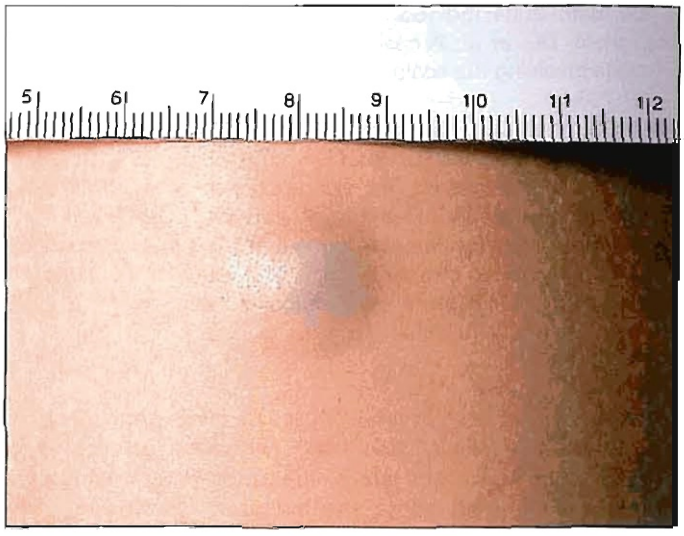

Fig. 29-50 Epidermal inclusion cyst.

needle or stapler, may result in epidermoid cysts growing within bone. In pigmented races, the lining of the epidermoid cyst and its contents may be pigmented. Epidermoid cysts rarely appear before puberty and earlier onset should suggest an alternative diagnosis (e.g. pilomatrixoma, dermoid cyst, or Gardner syndrome). Lesions of the scalp are usually trichilemmal cysts. Rare cysts of the soles are due to infection by HPV-60.

Epidermoid cysts may rupture and induce a vigorous foreign body inflammatory response, after which they are firmly adherent to surrounding structures and are more difficult to remove. Rupture is associated with the sudden onset of redness, pain, swelling, and local heat, simulating an abscess. Incision and drainage will confirm the diagnosis of inflamed cyst, when the smelly, cheesy material is evacuated. This will also lead to rapid resolution of symptoms. These episodes are often misdiagnosed as "infection" of the cyst, but cultures are usually negative and antibiotic treatment is not required. Intralesional triamcinolone may hasten resolution of the symptoms.

The epidermoid cyst is a keratinizing cyst the wall of which is stratified squamous epithelium containing keratohyalin granules. It is differentiated from the pilar cyst by the different pattern of keratinization. Idiopathic scrotal calcinosis is the end stage of calcification of epidermoid cysts of the scrotum. Pilomatrical differentiation within an epidermoid cyst should raise a suspicion of Gardner syndrome.

Surgical excision is curative, but the complete cyst and any associated "daughter" cysts must be removed. Enucleation of the cyst through a small incision or a hole made with a 4- or even a 2-mm biopsy punch may be attempted. A curette may be used to scrape out and snag all the fragments of the cyst wall. Inflamed cysts may also be treated in this way, but the inflammation makes complete removal of the cyst more difficult. If any fragment of the cyst wall is left behind, the cyst may recur.

Proliferating Epidermoid Cyst

These tumors derived from epidermoid cysts occur more commonly in men (64%) and the most frequent sites are the pelvic/anogenital areas (36%), scalp (21%), upper extremities (18%), and trunk (15%). Carcinomatous changes on histology, with anaplasia, high mitotic rate, and deep invasion occur in up to 20% of cases. They are locally aggressive, but distant metastasis is rare. Malignant onycholemmal cyst may describe a rare slow-growing tumor arising from a subungual keratinous cyst.

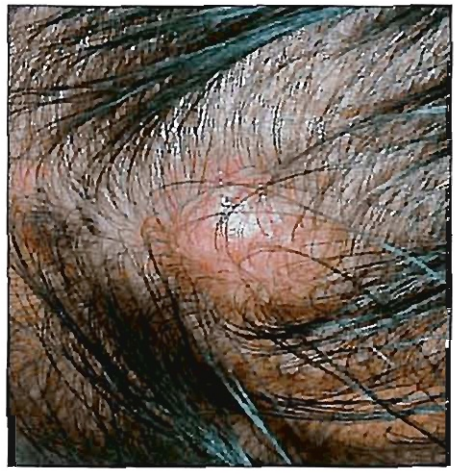

Fig. 29-51 Pilar cyst.

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Pilar Cyst (Trichilemmal Cyst, Isthmust-Catagen cyst)

The trichilemmal cyst, also known as a *wen*, is similar clinically to the epidermoid cyst except that about 90% of pilar cysts occur on the scalp (Fig. 29-51) and inheritance by the autosomal-dominant mode is common. It may be found rarely on the face, trunk, and extremities. An overlying punctum is not present and lesions tend to be more mobile and firmer than epidermoid cysts. Hereditary trichilemmal cysts link to the short arm of chromosome 3, but not to β-catenin or MLH1.

The trichilemmal cyst is lined by stratified squamous epithelium which is derived from the outer root sheath. The lining cells demonstrate trichilemmal keratinization, increasing in size as they approach the cyst cavity and abruptly keratinizing without forming a granular cell layer. The cyst contents are homogenous and commonly calcify. Hybrid cysts with features of both an epidermoid cyst and pilar cyst can be seen.

Treatment is the same as that for the epidermoid cyst. They are much more easily enucleated, so more limited incision is required to remove the lesion.

Proliferating Trichilemmal Cyst/Malignant Trichilemmal Cyst

There is a spectrum of lesions from typical pilar cysts with focal areas of epithelial proliferation to solid proliferating growths with atypia that are best considered SCCs. They are large (up to 25 cm), exophytic neoplasms confined almost exclusively to the scalp and back of the neck. They are approximately five times more common in women and the mean age of patients is 65 years. They gradually enlarge and may undergo ulceration (Fig. 29-52). The vast majority of lesions are cured by local excision. Some lesions may recur and less commonly be locally aggressive. In rare cases, local invasion or metastases occurs, resulting in death.

Proliferating trichilemmal cysts are composed of proliferations of squamous cells with trichilemmal differentiation forming scroll-like structures or small cysts. Lesions are usually well-circumscribed. Focal cellular atypia, mitoses, and necrosis may be present and do not necessarily predict aggressive behavior. Cases with aggressive growth and metastases usually have cytologic atypia as well as an invasive growth pattern. The presence of a clearly benign component and a second anaplastic component growing outward suggests the development of a carcinoma. Proliferating pilar cysts and their malignant counterparts express hair cytokeratins (cytokeratin 7) and malignant trichilemmal tumors express CD34, suggesting fetal hair root phenotype and trichilemmal differentiation.

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Weiss J, et al: Malignant proliferating trichilemmal cyst. J Am Acad Dermatol 1995;32:870.

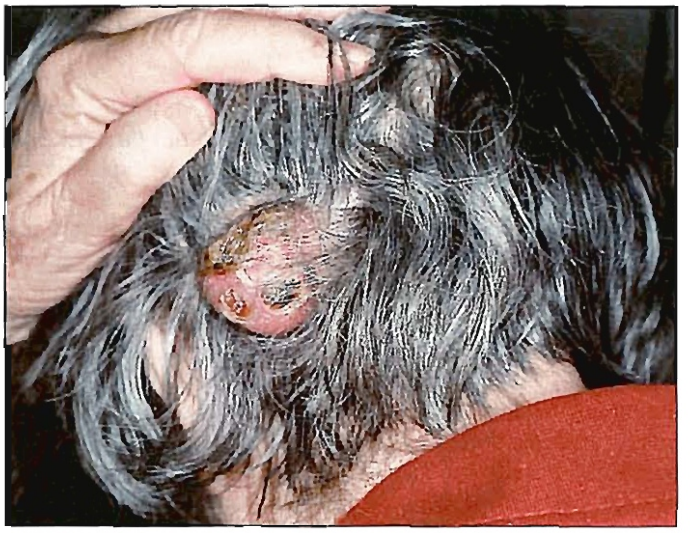

Fig. 29-52 Pilar cyst, proliferating type.

Dermoid Cyst

Cutaneous dermoid cysts, also called congenital inclusion *dermoid cysts*, result from local anomalies in embryonic development and occur along embryonic closure zones. On the face they occur above the lateral end of the eyebrow (external angular dermoid) (Fig. 29-53), at the nasal root, along the midline of the forehead, over the mastoid process on the floor of the mouth, and anywhere along the midline of the scalp from the frontal to the occipital region. They may also be found on the chest, back, abdomen, and perianally. Nasal and external angular dermoids may be seen in multiple members of a family, suggesting a genetic component. Lesions usually present within the first year of life, although only 70% of lesions have been identified by age 5 years. The typical lesion is a few millimeters to several centimeters in diameter and located in the subcutaneous fat. A tethering to the underlying tissues and an underlying bony defect may be noted. They are nonpulsatile, firm, and cystic, and do not transilluminate. A punctum or opening to the skin surface may sometimes be present, but they are commonly not attached to the overlying skin. Inflammation of the cyst due to rupture or infection may first bring the patient to the physician. Since the dermoid may connect to underlying structures, including the pleura and CNS, infection may spread to the CNS or lungs, causing potentially serious infections. Patients with spina bifida frequently develop dermoid cysts of the repaired portion of their spinal column. Dermoids overlying the lower spine may be associated with tethered cord and late development of ambulating difficulties.

Histologically, the cyst wall is lined with keratinizing

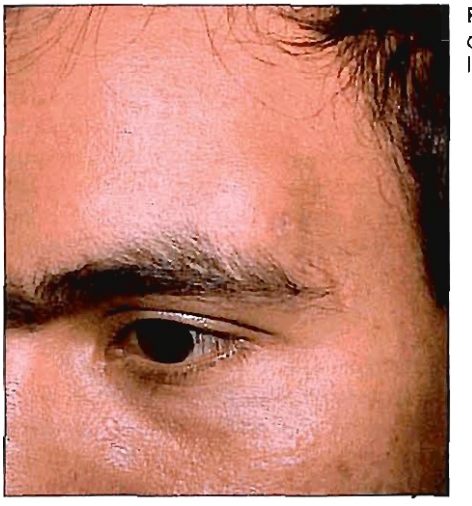

Fig. 29-53 Dermoid, cystic nodule of the lateral eyebrow.

stratified squamous epithelium containing skin appendages, including lanugo hair. Portions of the cyst lining may demonstrate a wavy eosinophilic (shark tooth) pattern like that of a steatocystoma.

In a child, attempts at surgical removal or biopsy of a cyst over cleavage planes (including along the midline of the back) should not be attempted without proper assessment to rule out a intraspinal or intracranial communication. A CT scan or magnetic resonance imaging (MRI) is required to rule this out. Any underlying bony changes detected by CT scan should be followed up with an MRI scan, since the cranial penetration by the cyst may at times be difficult to identify by CT scan. If an intracranial connection is detected, the patient should be referred to a neurosurgeon.

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Nocini PF, et al: Dermoid cyst of the nose: a case report and review of the literature. J Oral Maxillofac Surg 1996;54:357.

Pilonidal Sinus

Pilonidal cyst or sinus occurs in the midline sacral region at the upper end of the cleft of the buttocks. A pit may be all that is visible before puberty. Pilonidal cysts/sinuses usually become symptomatic during adolescence. The lesion becomes inflamed due to rupture or, less commonly, infection. Pilonidal sinus/cyst often occurs with nodulocystic acne, dissecting cellulitis, and hidradenitis suppurativa (the acne tetrad). Histologically, the cyst/sinus is lined by stratified squamous epithelium of the type seen in normal epidermis or follicular infundibulum. Some pilonidal cysts/sinuses are composed of epithelium which keratinizes without formation of a granular cell layer, analogous to outer root sheath. Referral to a general surgeon is recommended, as recurrences following simple cystectomy and marsupialization. SCCs have been reported to arise from chronic inflammatory pilonidal disease.

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Steatocystoma Simplex

Solitary steatocystoma (simple sebaceous duct cyst, steatocystoma simplex) occurs with equal frequency in adult women and men and can occur on the face, trunk or extremities. The oral mucosa may also be involved. It is not familial, and solitary lesions are much less common than multiple ones. The cysts are usually 0.5 to 1.5 cm in size, although rarely solitary steatocystomas over 8 cm have been reported. The cyst contains an oily, yellow fluid and may contain vellus hairs. Histologically, the cyst is lined by stratified squamous epithelium. Small, mature, sebaceous lobules are present along the cyst wall and empty into the cyst. The luminal surface of the cyst is eosinophilic, wavy (shark tooth pattern), and ribbon-like, analogous to the sebaceous duct. "Hydrid" cysts may have portions of their lining of the steatocystoma type, with the other portions resembling pilar cyst, epidermoid cyst, or even pilomatrixoma. Simple excision is curative.

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Steatocystoma Multiplex

Steatocystoma multiplex consists of multiple, uniform, yellowish, cystic papules 2 to 6 mm in diameter, located principally on the upper anterior portion of the trunk (Fig. 29-54), upper arms, axillae, and thighs. The lesions lack a punctum. Lesions usually appear in adolescence or early adulthood, when sebaceous activity is at its peak. In severe cases, the lesions may be generalized, with sparing only of the palms and soles. At times the lesions may be limited to the face or scalp, a distinct form termed the facial papular variant. Congenital and adolescent onset linear lesions have rarely been reported. Steatocystoma may be larger (up to 2 cm) and prone to rupture and suppuration (steatocytoma multiplex suppurativum). If these lesions are widespread, the condition can be very disfiguring. Steatocytomas contain a syrup-like, yellowish, odorless, oily material. In the suppurative type, as in hidradenitis suppurativa, colonization with bacteria can occur, leading to foul odor and social isolation.

Histologically, the lining of the cyst is stratified squamous epithelium with the cyst lining containing mature sebaceous

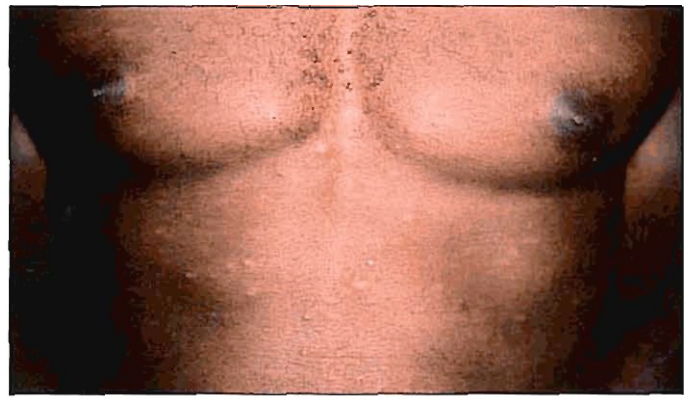

Fig. 29-54 Steatocystoma multiplex.

glands. The epithelial lining is identical to the sebaceous duct. In some instances, hair follicles occur in the cyst wall and vellus hairs may be present in the cavity. A relationship with eruptive vellus hair cysts has been suggested because of a similar clinical appearance, time of onset, and overlapping histologic features. It has been proposed that these clinical entities are a spectrum of the same disease process and should be classified as multiple pilosebaceous cysts.

Steatocystoma multiplex is often familial, demonstrating an autosomal-dominant mode of inheritance. Sporadic cases are not uncommon, however. Keratin 17 missense mutations occur in familial (but not sporadic) steatocytoma multiplex, usually in a hypermutable site of exon 1 of the gene (the helix initiation motif). Keratin 17 is specialization keratin expressed in the nailbed, hair follicles, and sebaceous glands. This same genetic mutation also causes pachyonychia congenita type 2 (PC-2). This form of pachyonychia congenita has milder keratoderma, but also natal teeth, pili torti, angular chelosis, and hoarseness. These patients have multiple cysts, some of which are steatocystomas and some eruptive vellus hair cysts. Milia, flexural abscesses identical to hidradenitis, and scrotal and vulvar cysts can also be seen in these kindreds. Hybrid cysts may occur. It is unclear why patients with hereditary steatocytoma multiplex and keratin 17 mutations identical to those seen in PC-2 have no other stigmata of PC-2.

The definitive treatment of individual lesions is excision. However, the sheer number of the cysts usually precludes this type of treatment. In such instances, incision and complete expression of the cyst contents or aspiration using an 18-gauge needle may be effective in temporarily reducing the lesions. Laser incision of the cysts may also be effective. They may remain clinically improved for many months; however, eventual recurrence is the rule. For inflammatory and noninflammatory lesions, cryotherapy has been reported as beneficial. Isotretinoin orally at a dose of 0.75 to 1 mg/kg has been reported to benefit the suppurative variant of steatocystoma. Long-term follow-up has not been reported.

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Eruptive Vellus Hair Cysts

Eruptive vellus hair cysts (EVHCs) appear as multiple (up to hundreds) of 1- to 4-mm skin-colored or hyperpigmented dome-shaped papules of the mid-chest and proximal upper extremities. They may be congenital but usually have their onset between ages 17 and 24. Disseminated lesions have been reported. Hidrotic and anhidrotic ectodermal dysplasia have been associated with EVHC. As noted above, there is debate as to whether steatocystoma multiplex and EVHC are distinct entities. Clinically, EVHCs tend to be smaller than steatocystomas and may have an area of central hyperkeratosis or umbilication, a feature lacking in steatocystoma. Histologically, the cystic epithelium is of the stratified squamous type; the cyst contents are composed of laminated keratin and multiple vellus hairs, and follicle-like invaginations may be present in the cyst wall. Treatment is surgical, with laser or needle evacuation.

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Milia

Milia are white keratinous cysts, 1 to 4 mm in diameter, appearing chiefly on the face, especially on the eyelids. They are white and easily seen as cystic through the overlying attenuated skin. Multiple lesions are common, especially in middle-aged women. They occur in up to 50% of newborns.

Primary milia develop without a predisposing condition and are most commonly found in adults or during the newborn period. Secondary milia can develop as a consequence of blistering skin diseases, such as epidermolysis bullosa, pemphigus, bullous pemphigoid, porphyria cutanea tarda, herpes zoster, and contact dermatitis. They also tend to occur after trauma, such as dermabrasion. Long-term topical corticosteroid therapy and the use of occlusive moisturizers may result in the appearance of milia.

Multiple milia have been reported in a number of genodermatoses, such as congenital ectodermal defect; reticular pigmented genodermatosis with milia (Naegeli-Franceschetti-

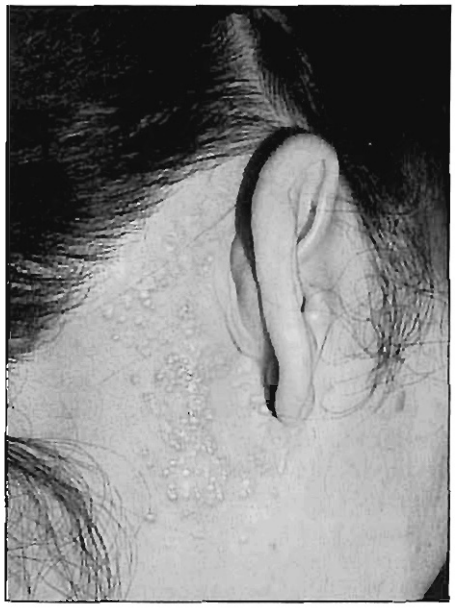

Fig. 29-55 Milia en plaque.

Jadassohn syndrome); congenital absence of dermal ridges, syndactyly, and facial milia; Rombo syndrome; and Bazex syndrome.

Idiopathic multiple eruptive milia describes the appearance of multiple widespread milia over weeks to months. Rare familial cases have been reported. The etiology of this condition is unknown. Milia en plaque presents with grouped milia forming a plaque. It can affect the face (especially the periauricular area) (Fig. 29-55), trunk, or extremities. Milia en plaque has been reported in association with pseudoxanthoma elasticum, renal failure and chronic cutaneous lupus erythematosus. The cause of Milia en plaque is unknown.

Primary milia are small epidermoid cysts, derived from the infundibulum of the vellus hair. Like epidermoid cysts, they are fixed and persistent. Secondary milia may be derived from eccrine ducts or hair follicles as they attempt to re-epithelialize eroded epidermis. They are often transient and spontaneously disappear. Milia must be distinguished from milia-like idiopathic calcinosis cutis, military osteomas, syringomas with milia-like structures, trichoepitheliomas, comedonal acne, flat warts, and xanthelasma. Lesions of cutaneous T-cell lymphoma with prominent follicular mucinosis may have many milia. Milia can occur on the nasal crease in preadolescent children with allergic rhinitis who frequently rub their noses. These milia may rupture and simulate acne vulgaris. This has been termed "*pseudoacne of the nasal crease*."

Treatment is incision and expression of the contents with a beveled cutting tipped hypodermic needle, 11 blade, or comedo extractor. No anesthesia is needed for most patients. Topical tretinoin (Retin-A) has been reported as effective in treating milia en plaque and more generalized forms of milia involving the face. Minocycline has been used to treat milia en plaque.

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Bryden AM, et al: Milia complicating photocontact allergy to absorbent sunscreen chemicals. Clin Exp Dermatol 2003; 28:666.

Cairns ML, Knable AL: Multiple eruptive milia in a 15-year-old boy. Pediatr Dermatol 1999;16:108.

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Verrucous Cysts (Cystic Papillomas)

Verrucous cysts resemble epidermoid cysts, except that the lining demonstrates papillomatosis and coarse hypergranulosis. Koilocytes may be present. On the sole, red granules resembling those in myrmecia are commonly seen. They have been shown to contain HPV and probably form as a result of HPV infection of a follicular unit or sweat duct (see Chapter 19).

Pseudocyst of the Auricle (Auricular Endochondral Pseudocyst)

Pseudocyst of the auricle clinically presents as a fluctuant, tense, noninflammatory swelling on the upper half of the ear. Most affected persons are between the ages of 20 and 45 and up to 90% are male. While it may be associated with trauma, especially rubbing due to pruritus, patients frequently deny trauma. Microtrauma or an embryologic defect in the cartilage may play a role. The fluid collection is between the two layers of the bilaminate cartilage of the pinna. There is no cyst lining, with the affected cartilage showing focal degeneration and granulation tissue. Needle aspiration yields serous or bloody fluid. Simple aspiration is ineffective. Aspiration or drainage followed by the application of a bolster or pressure dressing for several weeks is usually effective. Since application of pressure for several weeks is required, a sutured-on bolster with buttons or gauze is easier for the patient than an externally applied dressing. Intracystic injections of corticosteroids, fibrin glue, or minocycline have been used in recurrent cases. Surgical intervention involves removal of the thinner anterior portion of the cyst.

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Cutaneous Columnar Cysts

Five types of cysts that occur in the skin are lined by columnar epithelium. *Bronchogenic cysts* are small, solitary cysts or sinuses, most typically located in the region of the suprasternal notch or over the manubrium sterni. They also can occur on the chin, neck, shoulder region, and abdominal wall. Boys are four times more commonly affected than girls. Lesions are typically subcutaneous and rarely connect to deeper structures. Histologically, the cyst is composed of a wall lined by respiratory epithelium and may contain seromucinous glands and underlying fibromuscular connective tissue or cartilage.

Branchial cleft cysts present as cysts, sinuses, or skin tags along the anterior border of the sternocleidomastoid muscle or near the angle of the mandible (Fig. 29-56). Branchial cysts are lined primarily with stratified squamous epithelium. Lymphoid follicles are often present and smooth muscle is absent, distinguishing them from bronchogenic cysts, although some evidence suggests that these cysts are related.

Thyroglossal duct cysts virtually always occur on the anterior portion of the neck, near the hyoid bone. They present as a sinus, cyst, or recurrent abscess of the neck. They are the most common cause of congenital neck anomalies in childhood. Presentation in adult life can occur. Malignancies (papillary adenocarcinoma, follicular adenocarcinoma, mixed papillary/follicular adenocarcinoma, adenocarcinoma, and SCCs) arising from cysts have been reported in 1% of cases. Clinically, thyroglossal duct cysts are deep to subcutaneous tissue and usually are not managed by dermatologists.

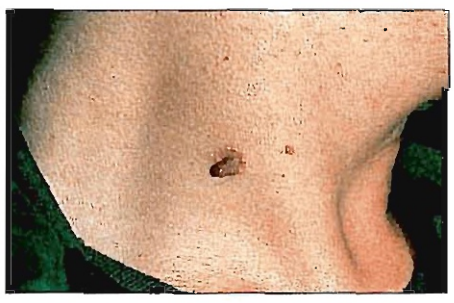

Fig. 29-56 Brachial cleft cyst.

Cutaneous ciliated cysts are usually solitary and located on the legs of females. Men account for only 10% of cases. They have also been described in the perineum and vulva (vulvar ciliated cysts). The epithelium lining the cysts is cuboidal to columnar with pseudostratified areas. Cilia are seen and the lining cells stain strongly for dynein. This histology is similar to the normal fallopian tube, suggesting the cysts are of müllerian origin. Ciliated metaplasia of eccrine duct has been proposed for those lesions occurring on the upper half of the body and in men. Like the median raphe cyst, the cavity is often filled with debris.

Median raphe cysts of the penis are developmental defects lying in the ventral midline of the perineum from the anus to the urethra, but most commonly on the distal shaft near the glans. They most commonly present as less than 1-cm dermal lesions in young men and may appear suddenly after sexual intercourse-associated trauma. These cysts are lined by pseudostratified columnar epithelium with focal areas of mucin secreting epithelium present. Ciliated cells may be present and, like ciliated cysts in females, the cavity is typically filled with debris. Melanocytes may occasionally be present in the cyst wall giving the cysts a pigmented appearance. Median raphe cysts do not stain with human milk fat globulin 1, distinguishing them from apocrine cystadenomas. All these forms of cysts are treated with surgical excision.

CONGENITAL PREAURICULAR FISTULA

This anomaly occurs as a pit in the preauricular region, often in several members and generations of a family. On each side, just anterior to the external ear, there is a small dimple, pore, or fistulous opening that may extend even into the middle ear. Most are benign and do not require surgery. Complications of surgery are frequent, and complete excision of both the pit and sinus tract should be the goal if surgery is attempted.

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CHAPTER

30 Melanocytic Nevi and Neoplasms

Melanocytes originate in the embryonal neural crest and migrate to the epidermis, dermis, leptomeninges, retina, mucous membrane epithelium, and inner ear, cochlea, and vestibular system. Nevus cells are a form of melanocyte with a tendency to aggregate into clusters of cells. They lack dendritic processes, but are otherwise similar to other melanocytes.

EPIDERMAL MELANOCYTIC LESIONS

The melanocytes occurring at the dermoepidermal junction are dendritic cells that supply melanin to the skin. These cells contain pigment granules (melanosomes). They stain with the dopa reaction and silver stains because they contain melanin. Immunohistochemical stains, such as S100, HMB-45 and Mart-1, do not depend on the presence of melanin. These stains have largely replaced silver stains for the identification of melanocytes in biopsy specimens. Melanocytes of the epidermis transfer melanosomes through their thin dendritic processes, where they are actively taken up by keratinocytes. Melanocyte numbers vary by anatomic site and are increased in sun-damaged skin, but vary little among racial groups. The type, number, size, dispersion, and degree of melaninizatin of the melanosomes determine the pigmentation of the skin and hair.

Treatment of epidermal pigmented lesions can be directed at pigmented keratinocytes, melanocytes or melanosomes. Q-switched lasers target the melanosome. Lasers with a longer pulse duration lasting milliseconds result in melanocyte destruction. Laser treatment produces consistent lightening of ephelides, but the response is variable for café-au-lait macules, Becker nevus, and nevus spilus.

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Ephelis

The common freckle occurs in light-skinned individuals in response to sun exposure. Histologically, they demonstrate pigmented basilar keratinocytes, and a mild increase in the number of melanocytes.

Nevus Spilus

Nevus spilus (speckled lentiginous nevus) presents as a light brown or tan macule, speckled with smaller, darker macules or papules (Fig. 30-1). It frequently occurs on the trunk and lower extremities, and is noted in approximately 2% of the population.

The nevus spilus may be small, measuring less than 1 cm in diameter, or may be quite large and follow a segmental distribution, referred to as a *zosteriform lentigo*. Multiple sites may be involved in the same individual, and may be widely separated by normal skin.

Nevus spilus in combination with a nevus flammeus is called *phakomatosis pigmentovascularis* (see Chapter 28). Phakomatosis pigmentokeratotica includes a speckled lentiginous nevus, organoid nevus, hemiatrophy, and neurologic findings such as muscular weakness. Generalized nevus spilus has been associated with nevus anemicus and primary lymphedema.

Histologically, the flat, tan background may show only basilar hyperpigmentation, such as is present in a café-au-lait spot, or lentiginous proliferation of the epidermis with bulbous rete ridges. The darker speckles usually contain nevus cells and may occasionally demonstrate blue nevi or Spitz nevi.

Because nevus cells are often present in the dark speckles, melanoma may rarely arise in them. A changing lesion should be biopsied. Removal by Q-switched (QS) ruby laser or QS alexandrite laser rarely has been reported as effective, but may require many sessions for acceptable results.

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Moreno-Arias GA, et al: Treatment of widespread segmental nevus spilus by Q-switched alexandrite laser (755 nm, 100 nsec). Dermatol Surg 2001;27:841.

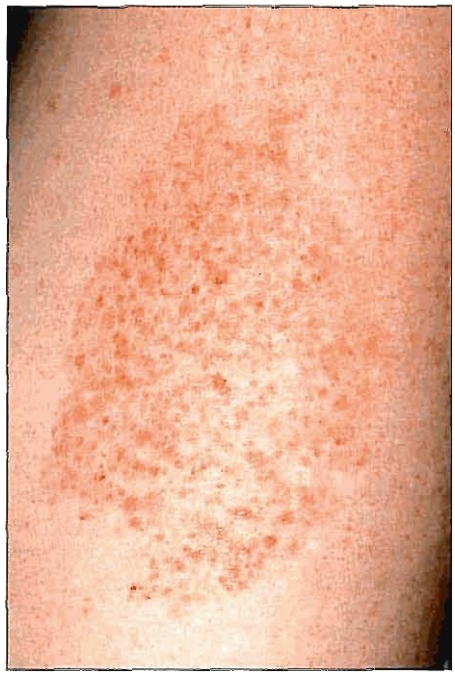

Fig. 30-1 Nevus spilus.

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Yoneyama K, et al: Malignant melanoma and acquired dermal melanocytosis on congenital nevus spilus. J Dermatol 2005; 32:454.

Lentigo

Lentigo Simplex These lesions occur as sharply defined, round to oval, brown or black macules. The lesions usually arise in childhood but may appear at any age. There is no predilection for areas of sun exposure.

Histologically, lentigo simplex shows hyperpigmentation of basilar keratinocytes and an increase in the number of melanocytes in the basal layer. Melanophages are commonly present in the upper dermis.

Solar Lentigo (Lentigo Senilis) Solar lentigines are commonly known as *liver spots.* They are persistent, benign, discrete, hyperpigmented round-to-oval macules occurring on sun-damaged skin. The backs of the hands, cheeks, and forehead are favorite sites in the typical older patient. Red-haired, light-skinned individuals, especially those with high solar exposure, may develop many of these on the shoulders and central upper chest, even at an early age. Solar lentigines may be accompanied by depigmented macules, actinic purpura, and other chronic actinic degenerative changes in the skin. They may evolve into benign lichenoid keratoses and reticulated seborrheic keratoses.

Histologically, the rete ridges appear club-shaped or show narrow, budlike extensions. There is a marked increase in pigmentation in the basal cell layer, especially at the tips of the bulbous rete. The number of melanocytes is slightly increased, and the upper dermis often contains melanophages.

Application of liquid nitrogen with a cotton-tip applicator or cryospray unit is often effective. Argon, Q-switched Nd:YAG, frequency doubled Nd:YAG, Q-switched alexandrite, Q-switched ruby, and Er:YAG lasers have been reported as effective.

Sun protection will reduce the number of new lesions. Bleaching creams containing 4% or 5% hydroquinone, used over a period of several months, will induces temporary lightening. Hydroquinone-cyclodextrin (2%), 4-hydroxyanisole (4-HA), chemical peels, local dermabrasion, topical tretinoin, and adapalene are other treatment options. The combination of 2% 4-HA and 0.01% tretinoin is superior to either active component alone.

Early lesions of lentigo maligna (melanoma in situ) may be light-to-medium brown and mimic solar lentigines. When in doubt, a biopsy is appropriate. Lentigo maligna, benign solar lentigo, and pigmented actinic keratosis all occur on sun-damaged skin, and collision lesions are common. If a lesion is not homogeneous clinically, representative biopsies should be taken from each area.

PUVA Lentigines Individuals receiving oral methoxsalen photochemotherapy (PUVA) may develop persistent pigmented macules in which there may be melanocytic atypia. These lesions may occur on sites that are normally protected from sunlight. High-dose single exposures to radiation may result in similar radiation lentigines in exposed skin.

Ink Spot Lentigo (Sunburn Lentigo) These lesions commonly occur on the shoulders as small markedly irregular, reticulated, dark gray–black macules resembling spots of ink on the skin. Histologically, there is a mild increase in the number of melanocytes and increased melanin in both the basilar keratinocytes and the stratum corneum.

Labial, Penile, and Vulvar Melanosis (Melanotic Macules, Mucosal Lentigines) Melanotic macules are usually light brown on the oral labial mucosa, but may be strikingly irregular and darkly pigmented in the genitalia. In females, the labia minora are most often affected, while in males, the glans and prepuce are most frequently involved. Histologically, these lesions demonstrate broad "box car" rete ridges with prominent basilar hyperpigmentation, and a normal to slightly increased number of melanocytes. The melanocytes are usually morphologically normal.

Multiple Lentigines Syndrome The lesions appear shortly after birth and develop a distinctive speckled appearance that has given rise to the designation *LEOPARD syndrome*. LEOPARD is Gorlin's mnemonic acronym for lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, retardation of growth, and deafness. Inheritance is autosomal dominant. Multiple lentigines occur mainly on the trunk, but other areas may also be involved, such as the palms and soles, buccal mucosa, genitalia, and scalp. PTPN11 gene mutations are seen in both LEOPARD syndrome and Noonan syndrome.

Moynahan Syndrome Moynahan syndrome consists of multiple lentigines, congenital mitral stenosis, dwarfism, genital hypoplasia, and mental deficiency.

Generalized Lentiginosis An occasional patient will have generalized lentiginosis without associated abnormalities.

Centrofacial Lentiginosis Centrofacial lentiginosis is characterized by lentigines on the nose and adjacent cheeks, variously associated with status dysraphicus, multiple skeletal anomalies, and central nervous system (CNS) disorders. Mucous membranes are spared. Onset is in the first years of life. Lentigines of the central face are also typical of Carney complex.

Carney Complex Carney complex is also known as *NAME syndrome* and *LAMB syndrome.* This designation comprises cardiocutaneous myxomas, lentigines, blue nevi, and endocrine abnormalities. It is discussed in more detail with myxomas in Chapter 28.

Inherited Patterned Lentiginosis in Black Persons O'Neill and James reported 10 light-complexioned black patients with autosomal-dominant lentigines beginning in infancy or early childhood, but no internal abnormalities (Fig. 30-2). The lentigines were distributed over the central face and lips, with variable involvement of the dorsal hands and feet, elbows, and buttocks. The mucous membranes were spared.

Partial Unilateral Lentiginosis Partial unilateral lentiginosis is a rare disorder of cutaneous pigmentation characterized by the presence of multiple simple lentigines, wholly or partially involving half of the body. Conjunctival involve-

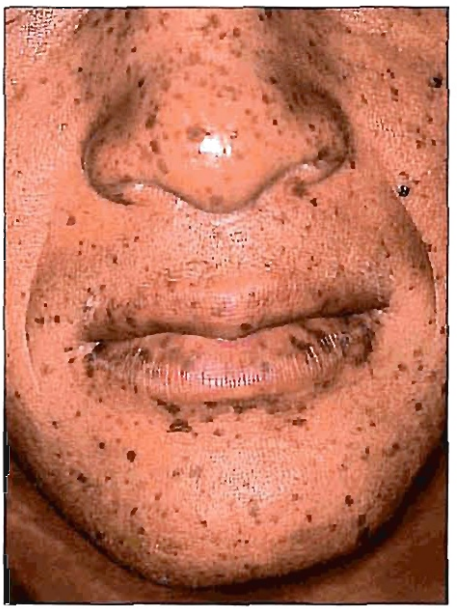

Fig. 30-2 Inherited patterned lentiginosis of Black persons.

ment has been reported. Agminated lentiginosis appears to be a similar if not identical entity.

Peutz-Jeghers Syndrome Peutz-Jeghers syndrome is an autosomal-dominant syndrome consisting of pigmented macules on the lips, oral mucosa, and perioral and acral areas. Gastrointestinal polyps, especially prominent in the jejunum, are frequently associated. It is discussed further under disorders of pigmentation in Chapter 36.

Blum RR, et al: Genital lentigines in a 6-year-old boy with a family history of Cowden's disease: clinical and genetic evidence of the linkage between Bannayan-Riley-Ruvacalba syndrome and Cowden's disease. J Cutan Med Surg 2001; 5:228.

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Becker nevus

Becker nevus presents as a hyperpigmented, hypertrichotic patch on the upper trunk (Fig. 30-3) or proximal upper extremity. The lesion usually begins before puberty, and almost all patients are males. The lesion may be associated with a smooth muscle hamartoma on histology. Lesions have also been associated with connective tissue nevus and phakomatosis pigmentovascularis.

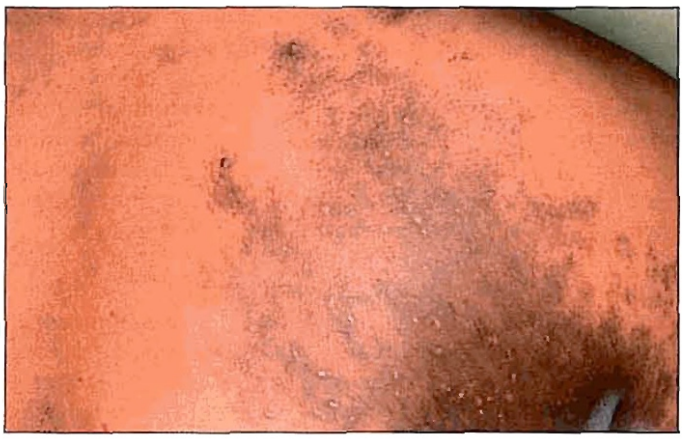

Fig. 30-3 Becker nevus.

Hsu S, et al: Becker's melanosis in a woman. J Am Acad Dermatol 2001;45(6 Suppl):S195.

MELANOACANTHOMA

Cutaneous melanoacanthoma is an uncommon lesion first described by Bloch. Clinically, it resembles a pigmented seborrheic keratosis or pigmented basal cell carcinoma, and tends to occur in older white males. Histologically, it is a benign epidermal neoplasm composed of keratinocytes and dendritic melanocytes. It is best considered a form of seborrheic keratosis.

Oral melanoacanthoma is also a proliferation of two cell types, melanocytes and epithelial cells, but appears to be a reactive lesion. It occurs as a macular or slightly raised pigmented area on the buccal mucosa, predominantly in adult black women. Rapid onset and spontaneous resolution is typical.

Fornatora ML, et al: Oral melanoacanthoma: a report of 10 cases, review of the literature, and immunohistochemical analysis for HMB-45 reactivity. Am J Dermatopathol 2003;25:12.

BENIGN MELANOCYTIC NEVI

Common moles, also known as a *nevocytic nevi* or *banal nevi* tend to increase in number during the first three decades of life. They are less common in doubly covered areas, such as the buttocks. They typically begin as sharply defined macular lesions, become papular, then gradually become soft and loose their pigment.

Sun exposure increases the number of moles in the exposed skin. Habitual sun exposure is more significant than intermittant exposure. Australians have more moles than Europeans. White persons have more than black persons, and individuals with a light complexion have more nevi than those with a dark complexion. Women have more total nevi and more nevi on the legs. Men have more on the trunk. Black persons have more nevi on the palms, soles, conjunctivae, and nailbeds.

Eruptive nevi may occur in association with bullous diseases, severe sunburn, immunosuppression, or sulfur mustard gas exposure. The cheetah phenotype refers to patients with more than 100 uniform dark-brown to black pigmented

macules 4 mm or smaller. The evaluation of these patients can be challenging, as similar-appearing lesions range from junctional nevi to melanoma histologically.

Melanocytic lesions with a junctional component are more commonly removed during the summer months, while excision of intradermal nevi is relatively constant during the year. This suggests that some change in these lesions draws more attention during the summer months.

Clinical and Histologic Features

Features of benign nevi include a diameter of 6 mm or less, perfectly uniform pigmentation, flaccid epidermis, smooth, uniform border, and an unchanging size and color. Benign nevi tend to be round to oval, and undergo a predictable course of maturation.

Junctional nevi are smooth brown macules, varying in diameter from 1 to 6 mm. They usually appear between 3 and 18 years of age. During adolescence and adulthood, some become compound or intradermal. Small, well-nested junctional melanocytic proliferations are almost invariably benign. Benign junctional nevi associated with bulbous hyperplasia of the rete ridges are referred to as junctional lentiginous nevi. Lentigo maligna can appear well nested with an appearance similar to that of junctional lentiginous nevi. Any broad junctional melanocytic lesion on sun-damaged skin should be viewed with suspicion.

Compound nevi demonstrate both junctional and intradermal melanocytes. Benign compound nevi are well nested at the junction, with dispersion of individual melanocytes at the base of the lesion. They demonstrate bilateral symmetry, but are not symmetrical from top to bottom. Instead, with descent into the dermis, the melanocytes become smaller and spindled in appearance. Nests at the junction tend to be round to oval and are roughly equidistant from one another. Dermal nests are generally smaller than the junctional nests, and become progressively smaller deeper in the dermis. Individual cells rather than nests are present at the base. Pigment is most prominent at the junction, and becomes progressively less prominent deeper in the dermis. Intradermal nevi look similar to compound nevi without the junctional nests.

In most benign nevi, there are no melanocytes above the dermoepidermal junction. Individual melanocytes in a "buckshot" scatter throughout the epidermis are typical of superficial spreading melanoma. Sunburned benign nevi may demonstrate buckshot intraepidermal scatter of melanocytes. Buckshot scatter may also be seen in the central portion of acral nevi and Spitz nevi.

On the palms and soles, the rete pattern follows the dermatoglyphs (Fig. 30-4). Nests in these locations tend to run along the rete ridges. If a benign palmar nevus is bisected across the dermatoglyphs, the nests will appear round to oval. If the same lesion is sectioned parallel to the dermatoglyphs, the nests will appear elongated and may mimic those of melanoma as an artifact of sectioning. Careful communication with the pathologist is essential when submitting an acral melanocytic lesion to the laboratory.

Malignant Degeneration

Almost half of melanomas occur in preexisting nevi, and an increased number of nevi represents a risk factor for melanoma. The signs of malignant transformation in pigmented nevi are recent enlargement, an irregular or scalloped border, asymmetry, changes or variegation in color (especially red, white, or blue), surface changes (scaling, erosion, oozing, crusting, ulceration, or bleeding), development of a palpable thickening, signs of inflammation, or the appearance of satellite pigmentation. Symptoms may include development of pain, itch or tenderness. The "ugly duckling" sign refers to the fact that nevi in an individual generally tend to share a similar appearance, so one that does not share the same characteristics should be considered for biopsy. Moles with small dark dots that do not lie entirely within the lesion, but produce a small extension beyond the border, may represent melanoma arising in association with a preexisting nevus. The clinician should alert the pathologist about these dots and the pathologist should section through the appropriate area. Perifollicular hypopigmentation is a common finding in benign nevi. When it occurs at the edge of the nevus it may give the lesion a notched appearance. Dermatoscopic exam may be of value in this setting.

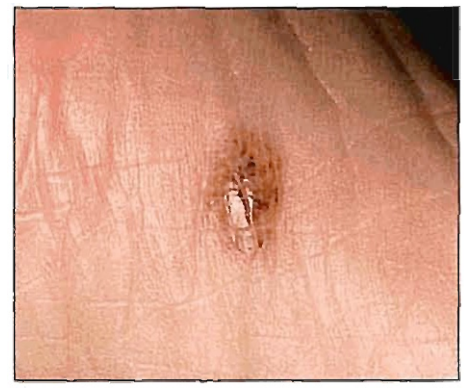

Fig. 30-4 Acral nevus.

Nevi commonly darken with pregnancy or with oral contraceptive use. Nevi from normal persons have no estrogen or progesterone receptors, but there may be positive estrogen receptor binding in nevi from pregnant women, as is also found in malignant melanoma. The development of what appears to be a new pigmented nevus in a patient over 35 years of age should alert the physician to possible melanoma, as patients without the dysplastic nevus syndrome usually do not develop new nevi at this age.

Treatment

Acquired nevi should be removed if they show signs of malignant transformation. Nevi of the neckline, beltline, or other areas that are irritated may be removed to relieve the patient of the irritation. Nevi may also be removed if they are in a location where it is impractical to observe them. If a solitary darkly pigmented lesion is present on the oral or genital mucous membrane, a biopsy should be performed, because nevi are uncommon in these locations. Nail matrix nevi and lentigines produce a pigmented nail band. The proximal matrix gives rise to the dorsal nail plate, and the distal matrix gives rise to the ventral nail plate. When the nail is observed end-on, the level of the pigment may be evident, and indicates the location of the pigmented lesion in the matrix. A widening band indicates a matrix lesion increasing in diameter. Biopsy of a solitary expanding acquired longitudinal pigmented band in an adult is typically necessary to ascertain the cause. Hutchinson's sign (pigmentation of the nailfold) is an indicator of melanoma. Nail matrix melanoma in children is exceptional.

Conjunctival nevi occur, and most can be serially followed if the lesion has been present since childhood or has shown no evidence of growth. Changing pigmented lesions and those acquired after childhood are best evaluated by an ophthalmologist or other physician skilled in the evaluation of ocular pigmented lesions. Most conjunctival nevi occur on the bulbar conjunctiva and commonly abut the nasal or temporal corneoscleral limbus. Suspicion of melanoma should arise if a pigmented lesion occurs in the palpebral or forniceal conjunctiva, if they are not hinged at the limbus and are immovable, if they extend into the cornea, if there is canalicular obstruction that leads to tearing, or if adjacent dilated vessels are noted.

Combined melanocytic nevi are common. They consist of a banal nevus together with a blue nevus, Spitz nevus or deep penetrating nevus. Two or more distinct populations of melanocytes are evident.

Melanocytic nevi may occur in lymph nodes and are present in about 10% of sentinel node biopsies. Nodal nevi typically occur in the capsule, in contrast to melanoma metastases which are typically subcapsular. Nodal nevi are commonly associated with cutaneous nevi in the draining basin, especially nevi with congenital features.

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Pseudomelanoma (Recurrent Nevus)

Melanotic lesions clinically resembling a superficial spreading melanoma may occur at the site of a recent shave removal of a melanocytic nevus. Melanocytic nevi occurring in areas of lichen sclerosus or bullous disease often have similar features. Histologically, the junctional component often demonstrates a predominance of non-nested melanocytes, confluence of nests, and nests that vary in size and shape. The presence of a superficial dermal scar with remnants of the original nevus beneath this zone of fibrosis is an important clue to the correct diagnosis. Although atypical in appearance, the junctional proliferation remains entirely confined to the area overlying the scar.

Recurrent Spitz nevus is a particular problem because many of the histologic features of benign Spitz nevi overlap with those of melanoma. In benign recurrent Spitz nevi, the dermal component typically retains cytologic maturation, dispersion at the base of the lesion, and an immunostaining pattern typical for benign nevi. Recurrent blue nevi also present special difficulties. High cellularity, cellular pleomorphism, mitotic figures, and a lymphoid host response may be present. In the absence of marked cytologic atypia, frequent mitotic figures or necrosis en mass, the lesions are likely to be benign. Because of the special problems posed by recurrent Spitz and blue nevi, the initial biopsy of these lesions should be a complete excisional biopsy whenever possible.

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Harvell JD, et al: Persistent and recurrent blue nevi. Am J Dermatopathol 1999;21:506.

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Hoang MP, et al: Recurrent melanocytic nevus: a histologic and immunohistochemical evaluation. J Cutan Pathol 2001;28:400.

Balloon Cell Nevus

Clinically, balloon cell nevi are indistinguishable from ordinary nevi. Histologically, they are composed of large, pale, polyhedral balloon cells. Generally, foci of ordinary nevus cells are also evident. Rarely, the lesions are composed entirely of balloon cells. Balloon cell change has been reported in cellular blue nevus as well. Balloon cell melanoma does exist, but the nuclei are large and pleomorphic, and the architecture of the lesion is that of melanoma.

Perez MT, et al: Balloon cell change in cellular blue nevus. Am J Dermatopathol 1999;21:181.

Halo Nevus

Halo nevus is also known as *Sutton nevus*, *perinevoid vitiligo*, and *leukoderma acquisitum centrifugum*. The lesions are characterized by a pigmented nevus with a surrounding depigmented zone (Fig. 30-5). Halo nevi tend to be multiple and occur most frequently on the trunk, mostly in teenagers. The central nevus gradually loses its pigmentation, turns pink, then disappears leaving a round-to-oval area of depigmentation. Over time, the area repigments. Darkening of the central nevus rather than lightening has also been reported in association with the halo phenomenon.

The infiltrate contains many cytotoxic T-cells, and may represent immunologically-induced rejection. The peripheral

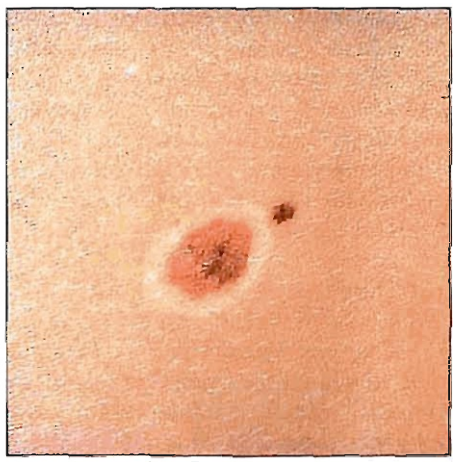

Fig. 30-5 Halo nevus.

blood has been shown to contain activated adhesive lymphocytes that disappear when the lesion is excised. Patients also demonstrate antibodies to melanocytes and cell-mediated immunity to melanoma cells. There may be associated vitiligo.

Regressing melanoma may also have associated leukoderma, but the pattern is usually haphazard and confined to the pigmented lesion. Other lesions that may also have a surrounding zone of leukoderma include blue nevi and neurofibromas.

Histologically, halo nevi demonstrate a band of lymphocytes that extends throughout the lesion, intimately mingling with the melanocytes. In contrast, the lymphoid infiltrate associated with melanoma tends to aggregate at the periphery of the lesion. In early halo nevi, amelanotic melanocytes may be found in the leukodermic halo. Later, melanocytes are absent until repigmentation occurs.

A full mucocutaneous examination at the time of diagnosis is indicated to exclude a concurrent melanoma, but this is rarely found. The decision to remove the nevus at the center of the halo is based on its morphologic features, just as with any other nevus.

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Congenital Melanocytic Nevus

Giant Pigmented Nevus (Giant Hairy Nevus, Bathing Trunk Nevus) Giant pigmented nevi appear as large, darkly pigmented hairy patches in which smaller, darker patches may be interspersed or present as small satellite lesions. The skin may be thickened and verrucous. The trunk is a favored site, especially the upper or lower parts of the back. Giant hairy nevi are present at birth and grow proportionally with the body. Widespread congenital dermal nevus with large nodules may affect the entire body, including the palms, soles, and oral mucous membrane. Some congenital melanocytic nevi have associated placental infiltration by benign melanocytes.

The incidence of melanomas developing in giant congenital pigmented nevi is between 2% and 15%. Approximately 60% of these melanomas appear within the first decade of life, and the majority arise in the dermis or subjacent tissue, rather than at the dermoepidermal junction. About 40% of the malignant melanomas seen in children occur in large congenital nevi. The risk is greatest for axial lesions. Large axial lesions may be associated with neurocutaneous melanocytosis. The risk is greatest for large axial lesions with many satellite lesions, and almost half of patients with symptomatic neurocutaneous melanosis develop leptomeningeal melanoma. Neurocutaneous melanosis can be detected by magnetic resonance imaging (MRI).

Histologically, giant congenital nevi extend into the deep dermis, and may involve the subcutis, fascia, muscle, and other underlying structures. Nevus cells are found in a patchy perivascular distribution and often extend in a patchy single-file fashion between collagen bundles. Nests are commonly seen in association with adnexal structures or nerves. Extensive desmoplasia has been described. Estrogen and progesterone binding has been noted in congenital nevi. These receptors are generally absent from common acquired nevi.

Benign proliferative nodules within giant congenital nevi may be confused histologically with malignant change. Features useful in distinguishing the two include lack of high-grade atypia, lack of necrosis, rarity of mitoses, evidence of transition between the cells of the nodule and those of the adjacent nevus, and lack of compressive expansile growth. Comparative genomic hybridization has demonstrated chromosomal aberrations in atypical nodular proliferations in congenital nevi, but many of these are numerical aberrations of whole chromosomes, suggesting a mitotic spindle defect. These differ from the chromosomal aberrations seen in melanoma.

Treatment decisions must be individualized. Half of all melanomas in giant congenital nevi occur in deep structures. Extensive surgery to remove the upper portions of the lesion reduces, but does not eliminate, the risk of melanoma. In patients with leptomeningeal melanosis, the risk of melanoma remains high. Satellite lesions and extremity lesions have a lower incidence of neoplastic conversion than large axial lesions, and the risk-to-benefit ratio of extensive surgery on these lesions differs accordingly. Some lesions are not amenable to excision as they involve functionally critical areas.

Serial excision is the method of choice whenever possible. Tissue expansion and flap closure are especially useful in the head and neck region. Alternative approaches to treatment, such as dermabrasion, curettage, CO_2 laser ablation or treatment with Q-switched Nd:YAG, ruby, and alexandrite lasers can lead to improvement in appearance. They may also eliminate some nevus cells, with theoretic lowering of the melanoma risk. It is important to note that most melanomas in giant congenital nevi occur in the dermal component, rather than at the dermoepidermal junction. Any treatment that alters the surface may alter detection of deep melanoma. Malignant transformation has been reported 20 years after dermabrasion. Regardless of the method of choice, lifelong periodic cutaneous examinations and general medical evaluations are indicated.

Small and Medium-Sized Congenital Nevocytic Nevus Small congenital nevocytic nevi are generally defined as less than 2 cm in greatest diameter, and medium-sized lesions measure more than 2-cm but less than 20 cm.

They are found in about 1% of newborns. About half eventually become hairy.

Histologically, they share many features with giant congenital nevi, but usually do not extend into the subcutaneous tissue. Many of the histologic features associated with congenital nevi also occur in acquired nevi.

The risk of melanoma in small-to-medium sized congenital nevi is extremely low. It may be no greater than the risk of melanoma arising in ordinary acquired nevi. Most of the melanomas that do occur do so after puberty. Excision is recommended for changing lesions, and may be considered for those of cosmetic concern, and those in areas that are difficult to observe.

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Zutt M, et al: Multicentric malignant melanoma in a giant melanocytic congenital nevus 20 years after dermabrasion in adulthood. Dermatol Surg 2003;29:99.

Epithelioid and Spindle-Cell Nevus (Benign Juvenile Melanoma, Spitz Nevus)

Spitz nevi commonly appear as pink (Fig. 30-6), smooth-surfaced, raised, round, firm papules. Most frequently, Spitz nevi occur during the first two decades of life, although they occur in adulthood in about a third of cases. Infrequently, multiple lesions present as agminate (clustered) (Fig. 30-7) or disseminated lesions in children and adults. Although they usually contain no visible pigment, some lesions are pigmented. Occasionally, Spitz nevi can be blue–black in color (Fig. 30-8).

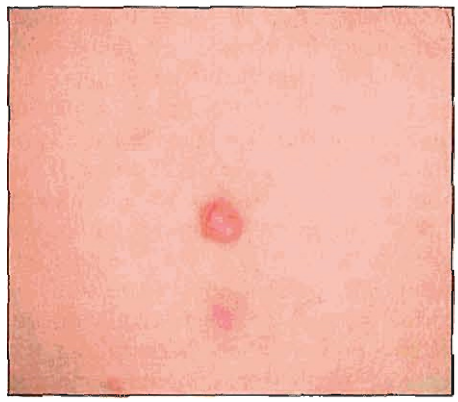

Fig. 30-6 Spitz nevus.

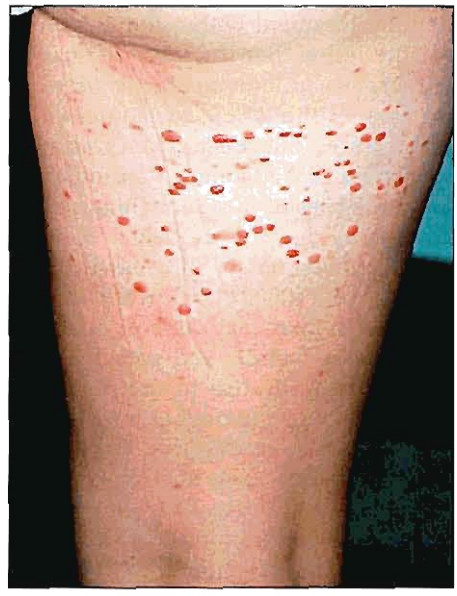

Fig. 30-7 Agminated Spitz nevi. (Courtesy of Brooke Army Medical Center Teaching File)

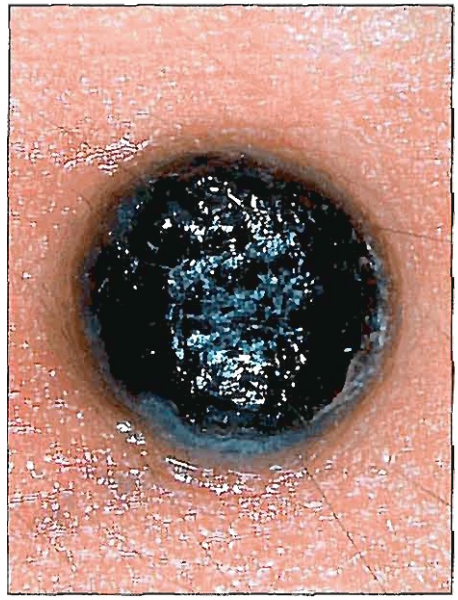

Fig. 30-8 Spitz nevus. (Courtesy of Brooke Army Medical Center Teaching File)

Like other nevi, Spitz nevi may be junctional, compound or intradermal. Compound nevi are most common, and are characterized by compact hyperkeratosis, hypergranulosis,

and pseudoepitheliomatous hyperplasia. The cells are large, with round to spindled nuclei. Epithelioid cells have large vesicular nuclei with prominent nucleoli and ample pink cytoplasm. Adjacent to the nucleus, the cytoplasm typically has a more amphophilic hue, giving it a characteristic two-tone appearance, similar to the cytoplasm of the cells in reticulohistiocytic granuloma. The nests tend to be oval, and oriented in a vertical direction, as are the nuclei within the nests, so that they appear to be "raining down" the adjacent rete ridges. Clefts are typically present adjacent to some of the nests, and superficial vascular ectasia is characteristic. Dull pink globules (Kamino bodies) are seen within the epidermis. These represent trapped basement membrane zone material, and stain like collagen with a trichrome stain as well as with immunostains for type IV collagen. Buckshot scatter of melanocytes may be noted within the epidermis overlying the center of the lesion, but the lesion is sharply circumscribed, and cells disperse as individual units between collagen bundles at the base of the lesion. Melanomas may have many of the above features, but generally lack Kamino bodies, and often demonstrate broad lateral extension, deep mitoses, and large nests at the base of the lesion. In questionable cases, adjunctive studies may be of value. S100A6 shows strong and diffuse expression in Spitz nevi. Other melanocytic nevi often express S100A6 weakly and only in the dermal component. Melanomas may express S100A6, but the expression tends to be weaker and patchy in the dermal component and is often negative in the junctional component. HMB-45 often stains Spitz nevi in a top-heavy fashion, while melanomas stain uniformly top to bottom. MIB-1 (Ki-67), a proliferation marker, may also be helpful as an adjunct to the histopathologic diagnosis of Spitz nevi. Few nuclei mark in the deep portion of a Spitz nevus compared to melanoma. Comparative genomic hybridization demonstrates chromosomal aberrations in the majority of melanomas, but most Spitz nevi show no aberrations. A minority of Spitz nevi show an isolated gain of chromosome 11p, but this aberration is not observed in melanoma. Specific gains or losses can be demonstrated with fluorescent in situ hybridization probes.

Junctional Spitz nevi commonly show some degree of buckshot scatter of melanocytes, and share many histologic features with melanoma. Lesions that lack sharp lateral circumscription are more likely to represent melanoma. Intradermal Spitz nevi lack overlying hyperkeratosis, hypergranulosis, and pseudoepitheliomatous hyperplasia, but the cells disperse as individual units at the deep margin. Dermal spitzoid lesions that remain nested at the deep margin are likely to represent melanoma. Desmoplastic Spitz nevi may be compound or intradermal and are characterized by a dense hypocellular collagenous stroma.

Pigmented spindle cell nevus is regarded by many as a variant of Spitz nevus. The lesions tend to be pigmented macules on the legs of young women. The cells are smaller and uniformly spindled, but other histologic features are similar to those of Spitz nevi.

Because of the histologic overlap with melanoma, Spitz nevi should be completely excised whenever possible. Critical differentiating histologic features include sharp lateral circumscription and dispersion at the base of the lesion. An incomplete excision will fail to demonstrate either the later or deep aspect of the tumor, and these diagnostic features will not be evident. Therefore, whenever possible, complete excisional biopsy is the most appropriate method for sampling. When a lesion is incompletely excised, most authorities recommend re-excision of the site to ensure complete removal. However, there are times when the dogma that all Spitz nevi should be completely excised must be tempered in the best interest of the patient. An otherwise typical Spitz nevus that extends to the deep margin on a young child's nose may be difficult to excise without disfigurement. The risks of anesthesia must also be weighed against the likelihood that the lesion is anything but a benign Spitz nevus.

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Dysplastic Nevus

In 1978, Clark et al described families with unusual nevi and multiple inherited melanomas, a condition they referred to as the *B-K mole syndrome* (after Family B and Family K). About the same time, Lynch et al recognized similar findings in other families, and they designated this the *familial atypical multiple mole-melanoma syndrome*. The most widely accepted term for the marker lesions is *dysplastic nevus*, with the patient's condition called the *dysplastic nevus syndrome* (DNS). The lesions may also be referred to as atypical nevi (Fig. 30-9). Patients with dysplastic nevi who have at least two blood relatives with dysplastic nevi and melanoma have the worst prognosis for development of melanoma. In these individuals, there may be a 100% lifetime risk of melanoma. An associated increased risk of developing pancreatic carcinoma is present in some families. Some studies have indicated ocular melanomas may occur in these patients.

The genetic basis for familial melanoma is being elucidated. A quarter to a third of patients have germline mutations on chromosome 9p in the CDKN2A tumor-suppressor gene (also known as p16, MTS1, and p16INK4A). It encodes for

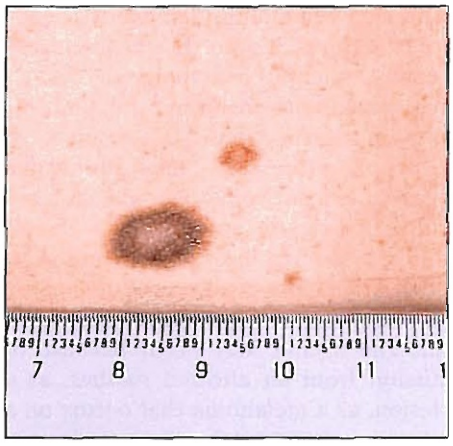

Fig. 30-9 Fried egg appearance of a dysplastic nevus.

an inhibitor of a cyclin-dependent kinase 4 (CDK4), which functions to suppress proliferation. In patients with mutations that impair the function of the p16 suppressor protein, referred to as the *p16M alleles*, there is a concomitant predisposition to pancreatic cancer. In other families where this is not present and who have 16W alleles, the predisposition to melanoma does not correlate with an elevated risk of pancreatic cancer.

Mutations in the CDK4 gene have also been found to be responsible for a lesser number of cases of familial melanomas. The products of this gene interact with the same cell growth cycle process as p16.

Dysplastic nevi also occur commonly in patients without a personal or family history of melanoma, with 5% to 20% of patients having at least one clinically dysplastic nevus, depending on the criteria used. During the growth phase, many nevi demonstrate junctional extension beyond the dermal component. This "shouldering" phenomenon is one of the criteria for dysplastic nevi. Many growing nevi will have features of dysplastic nevi. The same is true for many congenital nevi, genital nevi, and breast nevi.

When a biopsy specimen is read as a dysplastic nevus, clinical correlation is needed to determine if the patient has the dysplastic nevus syndrome. Examination of the patient, personal and family history of moles and melanoma, and inspection of other family members may be important in establishing the diagnosis. The presence of many moles and atypical moles are risk factors for melanoma. Other risk factors include skin type, freckle density, eye color, and history of blistering sunburns.

Dysplastic nevi differ from common acquired nevi in several respects. Clinically, dysplastic nevi are characterized by a variegated tan, brown, and pink coloration, with the pink hues seen mainly in the macular portion of the nevus. A macular component is always present and may comprise the entire lesion, but frequently surrounds a papular center. The nevi are larger than common nevi, usually 5 to 12 mm in diameter (common nevi usually measure 6 mm or less). The shape of dysplastic nevi is often irregular, with indistinct borders. Atypical nevi are most commonly seen on the back, and exposure to sun promotes the development of these lesions in individuals with DNS. In patients with the familial variety, it is not uncommon to see 75 to more than 100 pigmented lesions on the trunk. Although dysplastic nevi may not be evident until puberty in affected children, these nevi continue to develop over a lifetime, whereas common nevocytic nevi usually develop only in childhood or the early adult years. Atypical moles are associated with an increased risk of melanoma, which may be as much as 150-fold greater than that of the general population. Familial atypical moles with inherited melanoma confer a 500-fold greater risk. The lesions appear to be precursors for melanoma as well as serving as a marker for an increased risk of de novo melanoma. Most of the melanomas that occur in these patients will arise in normal appearing skin.

Criteria for histologic diagnosis of dysplastic nevi vary. The National Institutes for Health (NIH) consensus conference published the following as characteristic histologic features: basilar melanocytic hyperplasia with bulbous elongation of the rete ridges; spindle-shaped or epithelioid melanocytes arranged horizontally and aggregating in nests that fuse with adjacent rete ridges; lamellar and concentric superficial dermal fibrosis; and cytologic atypia (usually present but not essential for diagnosis). In compound dysplastic nevi, the junctional component generally extends at least three rete ridges beyond the dermal component. Grading of atypia is variable from one observer to another. Much of the atypia is focal, and localized to the periphery of the lesion. Atypia that extends throughout the lesion is more significant, and lesions with high-grade atypia may be difficult to distinguish from melanoma arising in conjunction with a dysplastic nevus.

When a patient with clinically dysplastic nevi is seen, initial examination should include a total body inspection, including the scalp. A family history should be obtained with special attention paid to items such as moles, skin cancer, and melanoma. In general, excision of individual atypical nevi should be limited to those suspicious for melanoma. In some patients, many lesions may be suspicious for melanoma, and very irregular lesions may be difficult to follow clinically. It is not unreasonable to excise the worst looking lesions in such cases, but this does not eliminate the need for surveillance for changing moles and de novo melanoma. There should be prudent sun avoidance and sunscreen use. Patients should be educated in self-examination and encouraged to examine themselves monthly. Physician examination every year is also prudent. Baseline dermatologic photography may aid surveillance examinations. This is particularly helpful for detecting new lesions. Digital epiluminescence microscopic surveillance of atypical nevi may also be of value. Indications for removal of a lesion include an increase in diameter, focal enlargement, radial streaming, peripheral black dots, and clumping within the pigment network.

In patients with dysplastic nevi and a positive family or personal history of melanoma, physician examination every 3 to 6 months is recommended, with excision of those nevi that change in clinical appearance and of new lesions suspicious for melanoma. The use of photographs or digital images is particularly helpful in patients with the familial syndrome.

Narrow excisional biopsies of dysplastic nevi often fail to remove the subclinical junctional component of the lesion. The pathologist is left to comment on a specimen with melanocytic atypia at a positive margin. When the lesions recur, they often appear atypical both clinically and histologically. Recurrent lesions may easily be misinterpreted as melanoma by someone unfamiliar with the preceding lesion. In general, the most appropriate biopsy technique for a dysplastic nevus is a broad saucerization that extends 2 mm

beyond the clinically evident border of the lesion. After wound contraction, the 2 mm margin results in little difference in the appearance of the final scar, and the risk of a recurrent lesion is far lower. Especially on the upper shoulders and limb girdle area, saucerized biopsies often result in scars with a better appearance than those produced by suture closure. When faced with a positive lateral margin, it is best to re-excise lesions with moderate atypia. The re-excision may take the form of a wider saucerization. When a lesion with low-grade atypia extends to a lateral margin, it is reasonable to observe the lesion for signs of recurrence. Because recurrent lesions can be confused with melanoma, it is best to advise the patient to return to a physician who is familiar with the original lesion. It is also best to send the specimen from the recurrence to a pathologist who is familiar with the original specimen. Clearly indicate on the laboratory request form that the lesion is a recurrence of a dysplastic nevus with low-grade atypia. As high-grade dysplastic nevi may be difficult to distinguish from evolving melanoma in situ, they should be treated as such.

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MELANOMA (MALIGNANT MELANOMA)

Except in the setting of giant congenital nevi, melanomas typically originate from melanocytes at the dermoepidermal junction. Almost half will develop in preexisting nevi, but the rest will develop on previously normal appearing skin. Usually there is a prolonged, noninvasive, radially oriented growth phase in which the lesion enlarges asymmetrically. Eventually, a tumor nodule develops, reflecting a vertical growth phase. Although the presence of a vertical growth phase may represent an independent risk factor for metastasis, the single greatest risk factor is the depth of invasion.

The ABCD criteria for melanoma are imperfect, but are simple for lay individuals to understand and have proved helpful for the detection of melanoma. The letters stand for asymmetry, border irregularity, color variegation, and a large diameter (>6 mm). Epiluminescence microscopy is a noninvasive technique for examining pigmented lesions that makes subsurface structures visible. In the hands of experienced users, it can be a helpful technique.

The incidence of melanomas has increased dramatically, probably because of patterns of sun exposure. It occurs most often in light-skinned people, often at the most productive time of their lives. Melanoma is not commonly encountered in the darker races, and acral lesions account for a greater share of melanomas in dark-skinned individuals. The lowest incidence is found among Asians. The incidence of melanoma is low until after puberty. Children rarely manifest congenital or acquired melanoma. The former may occur because of transplacental transmission from an affected mother, as a primary intrauterine lesion, as a melanoma that occurs on a congenital nevus in utero, or as prenatal metastatic lesions from neurocutaneous melanosis. All of these have a poor prognosis. In children, melanomas occur at least half of the time from preexisting normal skin, where the clues to diagnosis are the same as in adults, but there is often delayed recognition because of its overall low incidence in this population. Melanomas may also develop in preexisting nevi, most importantly deep within giant congenital nevi.

During pregnancy, pigmented nevi often become uniformly darker, and may enlarge symmetrically. Estrogen and progesterone receptors develop on the melanocytes and these changes are likely hormonally induced. If, however, changes occur that would normally incite worry about melanoma, such as irregular pigmentation or asymmetrical growth, a biopsy should be performed. Women who develop melanoma during pregnancy have a shorter disease-free interval following excision; however, there is no adverse survival effect.

Etiologic Factors

A light complexion, light eyes, blond or red hair, the occurrence of blistering sunburns in childhood, heavy freckling, and a tendency to tan poorly and sunburn easily indicate increased risk for melanoma. Large numbers of common nevi, the presence of large nevi, and the presence of clinically dysplastic lesions all increase the risk of melanoma. Axial giant congenital nevi or mutations in the p16-CDK4 gene are potent risk factors. The risk of developing multiple primary melanomas is elevated if there is a family history of melanoma, if there are clinically or histologically atypical nevi, if there are greater than 50 benign nevi, and if the patient is a nonuser of sunscreen. Sunscreens should be applied daily to sun-exposed areas, but must be used in conjunction with sun avoidance.

Other implicated factors include PUVA, tanning lamps, xeroderma pigmentosum, burn scars, and immunodeficiency. An association between administration of levodopa therapy for Parkinson's disease and the onset of melanoma remains unproved.

Melanoma Types

Clinicopathologic types of melanoma include lentigo maligna, superficial spreading melanoma, acral-lentiginous melanoma, nodular melanoma, desmoplastic melanoma, *mucosal melanoma*, *ocular melanoma*, primary CNS melanoma, and primary soft tissue malignant melanoma. Clinically, melanomas may be pedunculated, polypoid, *amelanotic*, or hyperkeratotic.

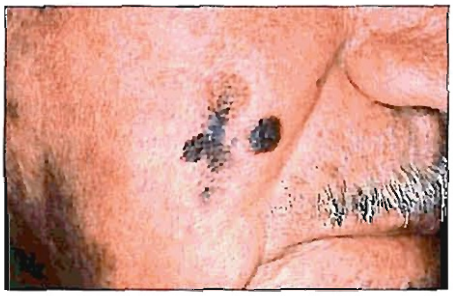

Fig. 30-10 Lentigo maligna melanoma.

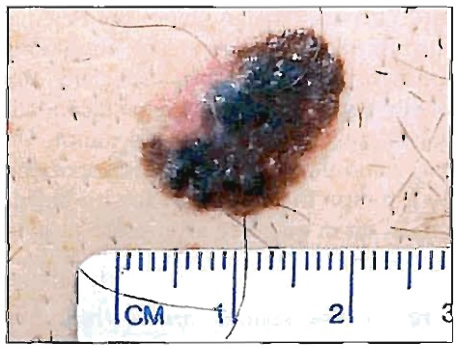

Fig. 30-11 Superficial spreading malignant melanoma.

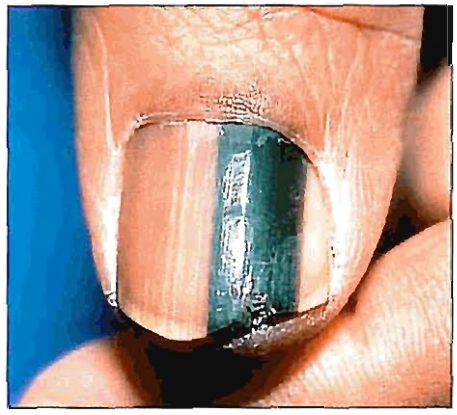

Fig. 30-12 Malignant melanoma.

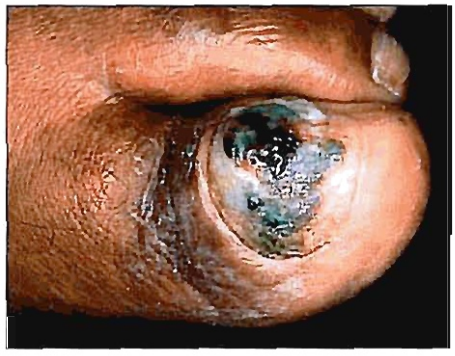

Fig. 30-13 Malignant melanoma.

Lentigo Maligna (Lentiginous Melanoma on Sun-Damaged Skin) Lentigo maligna begins as a tan macule that extends peripherally, with gradual uneven darkening over the course of years. It is more common in older patients with heavily sun-damaged skin, and is more common in sunny climates. The spread and darkening are usually so slow that the patient pays little attention to this insidious lesion. After a radial growth period of 5 to 20 years, a vertical growth phase of invasive melanoma can develop (Fig. 30-10). The lesion is then referred to as *lentigo maligna melanoma*. A palpable nodule within the original macular lesion is the best evidence that this has occurred, though there may be darkening or bleeding as well. Lentiginous types of melanoma also give rise to desmoplastic melanoma, which may appear as a papule, firm plaque or inconspicuous area of induration.

The lentiginous melanomas (lentigo maligna and acral lentiginous melanoma) proliferate principally at the dermoepidermal junction, with little buckshot scatter into the overlying epidermis. Because the junctional involvement is often only one cell thick, they often extend laterally far beyond the clinically apparent margin. The lateral subclinical extension frequently exceeds the "standard" 5-mm margin for in situ melanoma, and asymmetrical growth is common.

Superficially Spreading Melanoma Superficially spreading melanoma affects adults of all ages, with the median age in the fifth decade. Unlike lentigo maligna, it has no preference for sun-damaged skin. The upper back in both sexes and the legs in women are the most common sites. There is a tendency to multicoloration, not just with different shades of tan, but variegated black, red, brown, blue, and white (Fig. 30-11). They may arise de novo or in association with a preexisting nevus. Areas of color change within a nevus, especially dark areas that extend beyond the border of the remainder of the lesion, are suspicious for melanoma arising in a nevus. As a vertical growth phase develops, a papule or nodule usually appears. Skin markings disappear as the lesion expands. Regression may appear as variation in pigmentation or a scalloped margin. The radial growth phase is characterized by buckshot scatter of melanocytes throughout the epidermis. Because of this, the borders tend to be more sharply defined than those of lentiginous types of melanoma.

Acral-Lentiginous Melanoma Acral-lentiginous melanoma is the most common type of melanoma in dark-skinned and Asian populations. This is because the frequency of the other types is low in these patients, not because the incidence of acral-lentiginous melanoma is any higher than in white persons. The median age of patients is 50 years, with equal sex distribution. The most common site of melanoma in black persons is the foot, with 60% of patients having subungual or plantar lesions. All lentiginous melanomas demonstrate a junctional growth pattern and tend to have indistinct margins. Over time, a vertical growth phase develops. Periungual hyperpigmentation, Hutchinson's sign, a black discoloration of the proximal nailfold at the end of a pigmented streak (melanonychia striata), is an ominous sign suggesting melanoma in the matrix of the nail (Fig. 30-12).

The early changes of acral-lentiginous melanoma may be light brown and uniformly pigmented. The thumb and hallux are more frequently involved than the other digits. In time, the lesion becomes darker, nodular, and may ulcerate. Metastases to the epitrochlear and axillary nodes are common, because there is often a delay in diagnosis. Subungual melanoma (Fig. 30-13) may be misdiagnosed as onychomycosis, verruca vulgaris, chronic paronychia, subungual hyperkeratosis, pyogenic granuloma, Kaposi sarcoma, glomus tumor, or subungual hematoma.

Mucosal Melanoma Primary melanoma of the mucous membranes is rare, but typically demonstrates a lentiginous (junctional) growth pattern. In the mouth, especially the palate, the lesion is usually pigmented and may be ulcerated. It may occur in the nasal mucosa as a polypoid tumor. On the lip it is apt to be an indolent ulcer. Melanoma of the vulva is manifested by a tumor, often ulcerated, with bleeding and pruritus. It is most often detected after metastasis to the groin has occurred.

Nodular Melanoma These lesions arise without a clinically apparent radial growth phase, but usually large atypical melanocytes can be found in the epidermis beyond the region of vertical growth. Primary dermal melanomas in congenital nevi are also nodular, and lack a radial growth phase. Nodular melanoma constitutes about 15% of all melanomas. It occurs twice as often in men as in women, primarily on sun-exposed areas of the head, neck, and trunk. The tumors may be smooth and dome-shaped, fungating, friable, or ulcerated. Bleeding is usually a late sign.

Polypoid Melanoma This is a variant of nodular melanoma, presenting as a pedunculated tumor. At its base the polypoid melanoma does not appear to descend for any appreciable distance into the dermis. Nevertheless, the 5-year survival rate is only 42%, compared with 57% for other nodular melanomas. The prognosis relates to the thickness (a measure of the volume of the tumor), and the presence of a vertical growth phase.

Desmoplastic Melanoma This deeply infiltrating type of melanoma usually has a spindle-cell pattern histologically in which collagen fibers extend between the tumor cells. It most often occurs on the head or neck of older men, many times within a subtle lentigo maligna. The lesions may also occur on the digits, in association with a subtle acral lentiginous melanoma. One-third of cases present with only a palpable dermal irregularity and are amelanotic. The biopsy demonstrates a spindle cell proliferation with a dense fibrous stroma. Atypia is variable. The lesions are commonly neurotropic, and demonstrate extensive growth along the perineurium beyond the bulk of the tumor. Nodular lymphoid aggregates are frequently present and are an important clue to the diagnosis. S100 protein is the most reliable immunostain. HMB-45 and Mart-1 are commonly negative.

Amelanotic Melanoma Nonpigmented melanoma differs from other melanomas only in its lack of pigment. The lesion is pink (Fig. 30-14), erythematous, or flesh colored, and commonly mimics basal cell carcinoma or granuloma pyogenicum. Amelanotic melanoma is the typical variant seen in albinos.

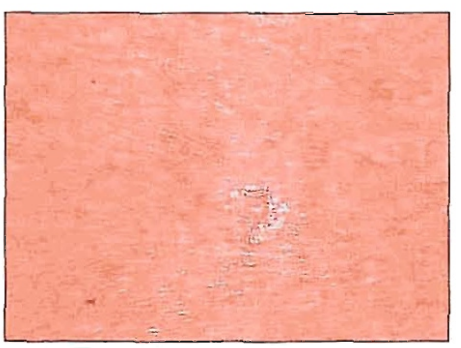

Fig. 30-14 Amelanotic malignant melanoma.

Soft-Tissue Melanoma Primary soft-tissue melanoma (clear-cell sarcoma, melanoma of the soft parts) contains melanosomes and stains positively for S-100 and HMB-45. It occurs most frequently on the lower extremities of young people. The average age at onset is 27. The history is of an enlarging often painful mass on an extremity, with the foot or ankle involved 43% of the time. The tumors arise in and are bound to the aponeuroses, tendons, or fascia, and only uncommonly invade the overlying skin. Histologically, there are compact nests and fascicles of polygonal or fusiform cells with a clear cytoplasm present between dense fibrous tissue septa that connect with tendonous or aponeurotic tissue. Multinucleated cells are frequent. Metastases are often present at first diagnosis and the prognosis is poor. Local recurrence or distant metastases after the initial excision are frequent and result in death in more than 50% of reported cases. Treatment is with wide excision and lymph node dissection. Radiotherapy and chemotherapy are used as an adjunct in some cases. The lesion appears to arise from neural crest cells. Frequently translocations of chromosomes 12 and 22 are present.

Differential Diagnosis

Melanoma may clinically simulate a wide variety of lesions, including pigmented basal cell carcinoma, darkly pigmented seborrheic keratosis, pyogenic granuloma, and Kaposi sarcoma. Melanomas may appear pearly, contain horn cysts, and exhibit a collarette, and none of these is sufficient to forego a biopsy. Other melanoma-simulating lesions include subungual traumatic hematoma, cherry angioma, pigmented Bowen's disease, and pigmented Paget's disease.

Biopsy

Complete excision with a 1- to 3-mm margin of skin is the preferred method of biopsy for a lesion suspected to be melanoma. Although the National Comprehensive Cancer Network (NCCN) recommends avoiding wider margins to permit accurate lymphatic mapping for sentinel node biopsy, some evidence suggests that accurate mapping is usually still possible even after wide excision.

In lesions too large for simple excision, an incisional or punch biopsy, deep enough to permit measurement of thickness, has no effect on prognosis. When melanoma is suspected in a giant pigmented nevus, an incisional biopsy should be performed. Biopsy of lentigo maligna is problematic, as the lesions tend to be quite large and arise in cosmetically sensitive areas. Skip areas are common in these lesions and may lead to misdiagnosis. Areas of the tumor may undergo lichenoid regression and resemble benign lichenoid keratosis. Collision with other pigmented lesions, such as benign solar lentigo, pigmented large-cell acanthoma, and pigmented actinic keratosis, is common. Because of the potential for sampling error, small biopsies frequently result in misdiagnosis. The best biopsy technique in the setting of suspected lentigo maligna is generally a broad superficial shave biopsy. This results in minimal scarring and provides the pathologist with a broad area of dermoepidermal junction for examination. If the lesion is heterogeneous, multiple areas may need to be sampled. If

lentigo maligna melanoma or desmoplastic melanoma is suspected, an incisional biopsy should be performed. Punch biopsies are more prone to sampling error.

Histopathology

Biopsies should be read by a dermatopathologist or other pathologist experienced in pigmented lesions. The report should include thickness and an assessment of the deep and peripheral margins. The presence of ulceration should be noted. Several studies demonstrate that concordance for assessment of Clark's level is poor, but as Clark's level may add prognostic information, it is still noted in many cases. The presence of satellitosis is a powerful adverse prognostic indicator, and its presence should be noted in the report. Other factors that may be important to note include regression, mitotic rate, tumor infiltrating lymphocytes, vertical growth phase, angiolymphatic invasion, neurotropism and histologic subtype.

Whereas benign nevi are well nested at the junction, melanomas usually demonstrate junctional areas where nonnested melanocytes predominate. Benign nevi demonstrate dispersion of individual melanocytes at the base of the lesion, while melanomas remain nested at the base. Melanomas may be asymmetrical, but metastatic and nodular melanoma may present as perfectly symmetrical spheres. Benign nevi demonstrate bilateral symmetry and show maturation (smaller more neuroid cells) with descent into the dermis. Most melanomas lack bilateral symmetry and show little maturation with descent into the dermis. In nevi, nests at the junction tend to be round to oval and are roughly equidistant from one another. In melanoma, junctional nests are often elongated or have irregular shapes. They are randomly distributed, and often involve the apex of the dermal papillae as well as the tips and sites of the rete ridges. Confluent runs of melanocytes are frequently seen at the dermoepidermal junction, and often continue down the adnexal structures. In nevi, dermal nests are generally smaller than the junctional nests, and become progressively smaller deeper in the dermis. In melanoma, dermal nests generally fail to become smaller in the deeper dermis. In nevi, pigment is most prominent at the junction, and becomes progressively less prominent deeper in the dermis. Melanomas often retain pigment deep in the lesion. In superficial spreading melanoma, individual melanocytes are present in a "buckshot" scatter throughout the epidermis. Lentiginous types of melanoma tend to proliferate at the dermal epidermal junction with little associated buckshot scatter. Invasive melanoma is commonly associated with a lymphoid infiltrate that forms a band at the periphery of the lesion. Plasma cells may be numerous. A vertical growth phase is identified by the presence of a dermal nest larger than the largest junctional nest, or invasion of the reticular dermis or solar elastotic band. Melanoma depth is measured from the granular layer or base of the ulcer. If invasion has taken place from follicular extension of the tumor, the lesion is measured from the inner root sheath. Rare variants of melanoma include balloon cell melanoma and dendritic "equine type" melanoma.

Some types of benign nevi mimic individual features of melanoma. Sunburned nevi, acral nevi, and Spitz nevi may demonstrate buckshot intraepidermal scatter of melanocytes. Blue nevi typically are pigmented to the base of the lesion, and extend into the dermis as a bulbous projection with little maturation and no dispersion of cells at the base. The silhouette, sclerotic stroma, and bland cytology are key to the diagnosis.

Comparative genomic hybridization has shown that chromosomal aberrations are common in melanoma. They occur earlier in the progression of acral melanoma than in melanomas on the trunk. In general, melanomas tend to have abnormalities involving chromosomes 9, 10, 7, and 6. Acral melanomas are more likely to have aberrations involving chromosomes 5p, 11q, 12q, and 15, and many amplifications are found at the cyclin D1 locus. Lentigo maligna melanomas are more likely to show losses of chromosomes 17p and 13q. Chromosomal aberrations are rare in benign banal nevi. A minority of Spitz nevi may show an isolated gain involving the entire short arm of chromosome 11.

Metastasis

Early metastases typically occur via the lymphatics, and regional lymphadenopathy may be the first sign. Satellite metastases appear as pigmented nodules around the site of the excision (Fig. 30-15). Later, metastases occur via the blood stream, and may become widespread. The chief site for metastatic melanoma is the skin, but all other organs are at risk. CNS metastasis is the most common cause of death. Although most metastatic spread occurs in the first 5 years after diagnosis, late-onset metastases occur, especially in premenopausal women. Melanemia, melanuria, and cachexia are likely to occur in terminal disease. In extreme cases, the entire integument may become deeply pigmented (generalized melanosis), with melanin in melanophages, endothelial cells, and tissue histiocytes. Occasionally, patients present with metastatic melanoma from an unknown source. Full-body skin examination may reveal a depigmented or irregularly pigmented atrophic patch consistent with a regressed primary lesion. Such patients are estimated to have a 40% chance of 5-year survival.

Staging

The American Joint Committee on Cancer developed a staging system for cutaneous melanoma. The system's categories depend on definitions for primary tumors, lymph

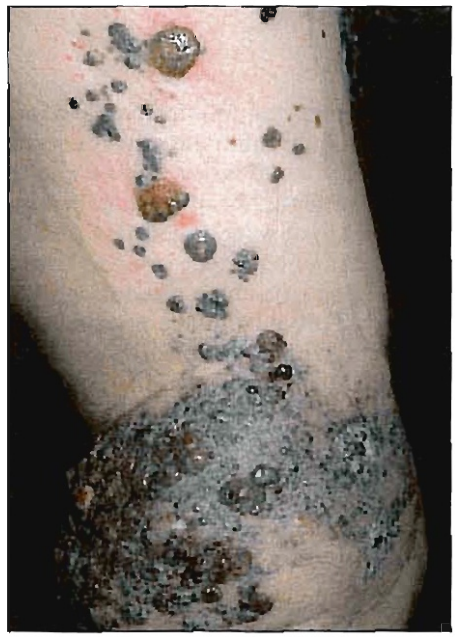

Fig. 30-15 Metastatic malignant melanoma. (Courtesy of Brooke Army Medical Center Teaching File)

Box 30-1 Summary of American Joint Committee on Cancer melanoma staging

T0: No evidence of primary tumor
Tis: Melanoma in situ
T1: Up to 1.0 mm in thickness
T1a: Level II or III
T1b: Level IV or V or with ulceration
T2: 1.01–2.0 mm in thickness
T2a: No ulceration
T2b: Ulceration
T3: 2.01–4.0 mm in thickness
T3a: No ulceration
T3b: Ulceration
T4: >4.0 mm in thickness
T4a: No ulceration
T4b: Ulceration
N0: No regional lymph node metastasis
N1: Metastasis in one lymph node
N1a: Clinically occult
N1b: Clinically apparent
N2: Two to three regional nodes or in-transit metastasis
N2a: Clinically occult
N2b: Clinically apparent
N2c: Satellite or in-transit metastases
N3: Four or more nodes, matted nodes or in-transit metastasis with positive nodes
M0: No distant metastases
M1: Distant metastases
M1a: Skin or nodes
M1b: Lung
M1c: All other viscera or any distant metastases with elevated LDH

node involvement, and distant metastases (Box 30-1; www.cancerstaging.net). The *NCCN concensus statement* regarding staging and management of melanoma can be found at www.nccn.org/physician_gls/f_guidelines.html.

Prognosis

The prognosis for a patient with stage I melanoma is primarily related to tumor thickness. Cure rates by stage are:
Stage I (T1 or T2a, N0, M0) >80%
Stage II (T2b–4, N0, M0) 60–80%
Stage III (N1–3, M0) 10–60%
Stage IV (M1) <10%

Many variables have been reported to influence survival, including the presence of tumor infiltrating lymphocytes (brisk response is best), mitotic rate (0 is best and >6/mm^2 is worst), *ulceration (adverse effect)*, *location (hair-bearing* limbs yield a better prognosis than when lesions are present on the trunk, head, neck, palm, or sole), sex (women have a better prognosis than men), age (younger patients have a better prognosis), the presence of leukoderma at distal sites (improves the prognosis), and regression (associated with a poorer prognosis). Multivariant analysis shows that some are not independently predictive and others are of variable significance in different series. Pregnancy does not have an adverse effect on survival in patients with clinically localized melanoma. Tumor thickness, ulceration, and lymph node involvement have the greatest predictive value and are used to determine therapy.

The presence or absence of melanoma in regional lymph nodes is the single most important prognostic factor for melanoma. Sentinel lymph node dissection using lymphoscintigraphy with ^{99m}Tc-labeled colloids is widely used for the staging of clinically node-negative melanomas. The success rate in localizing the sentinel lymph node approaches 98% at centers experienced in the technique. When combined with the vital blue dye technique the success rate can approach 99%. About 20% of patients with melanoma between 1.5 and 4 mm in depth will have metastasis in their sentinel node(s). For desmoplastic and neurotropic melanoma (mean Breslow depth, 4.0 mm; median, 2.8 mm), published data suggest that up to 12% have at least one positive sentinel lymph node. Tumor thickness and ulceration are the major independent predictors of sentinel lymph node metastases. Age and axial tumor location are also significant. Patients with larger metastases to the sentinel node (metastatic deposits >2 mm in diameter) have significantly decreased survival.

Local recurrence related to a positive margin should not be equated to local recurrence representing dermal in-transit lymphatic metastasis. The latter is associated with a poor prognosis, while the former may be cured in many cases by re-excision.

Work-Up and Follow-Up

There is no definite proof that any routine laboratory work or imaging studies affect longevity. Some advocate only ordering studies as prompted by signs or symptoms. Other guidelines recommend limited studies varying by stage. For all stages, studies should be ordered if signs or symptoms occur. Lactic acid dehydrogenase (LDH) is not a sensitive screening tool, but has prognostic value. The yield of computed tomography (CT), MRI, and positron emission tomography (PET) scanning is low. There is broad consensus that no x-rays or blood work are routinely indicated for those with stage IA melanoma. For stage IB and II, a baseline chest x-ray and LDH level are optional in the NCCN guidelines. For stage IIIA disease, a chest x-ray and LDH are recommended by NCCN guidelines. For stage IIIB or IIIC disease, fine needle aspiration should be attempted to confirm nodal involvement. A chest x-ray and LDH are recommended by NCCN guidelines. A pelvic CT scan is recommended in those with inguinofemoral lymphadenopathy. For stage IV disease, the work-up should be similar to that for stage IIIB disease along with consideration of abdominal and pelvic CT scan, head MRI, or PET scanning. The highest yield for CT scans is in the area adjacent to nodal disease. As glucose metabolism is increased in malignant tumors, PET using the glucose analog fluorine-18-fluorodeoxyglucose (F18-FDG) can be used to detect metastases.

Periodic examinations are important to detect second primary tumors as well as metastatic disease. In general, laboratory tests and imaging studies should be performed when prompted by signs or symptoms. For those with stage IB–IV melanoma, periodic evaluations may include chest x-ray, LDH, and complete blood count at the discretion of the physician. Skin and lymph node examination should be performed at least yearly.

Treatment

Early excision remains the most important determinant of outcome. Most published guidelines are based on data that relate largely to superficial spreading melanoma, and may

not be applicable to all melanomas. A margin of 0.5 cm is recommended for excision of a melanoma in situ, a 1.0 cm margin for melanomas less than or equal to 1.0 mm thick, a 1- to 2-cm margin for those less than or equal to 2 mm, and a 2-cm margin for those thicker than 2.0 mm. In the case of lentigo maligna and acral lentiginous melanoma, subclinical extension of the in situ tumor commonly exceeds 0.5 cm, and asymmetrical growth is common. In such cases, a symmetrical "standard" margin may do a disservice to the patient. It may result in a positive lateral margin, and difficult closure because excessive uninvolved skin was sacrificed. Mohs micrographic surgery may be useful in this setting. Although H&E-stained frozen sections have been used, immunostains such as Mart-1 are easier to interpret. "Slow Mohs" staged excision with permanent sections is another option. In patients who are poor surgical candidates, nonsurgical treatments such as topical imiquimod and radiotherapy may be utilized. Nail apparatus melanoma may necessitate amputation of a digit or skin grafting. This is another setting where Mohs micrographic surgery may be considered as a tissue sparing technique.

Sentinel node biopsy (SNB) should be discussed with patients whose melanomas are 1 mm or greater in thickness. SNB should be considered for thinner lesions in patients who have ulceration, Clark level IV or V invasion, regression, a vertical growth phase, or a positive deep margin on initial biopsy. Dual-basin drainage from the trunk is not independently associated with an increased risk of nodal metastases, but each basin must be identified and sampled. Those with a positive SNB or nodal metastasis confirmed by fine needle aspiration should receive counseling regarding dissection of the remainder of the nodal basin. Experimental treatments should be approached with careful counseling and full informed consent, usually in the setting of a clinical trial. For in transit metastases, surgical excision, interferon, hyperthermic isolated limb perfusion with melphalan, CO_2 laser ablation, and intralesional BCG are used. Dinitrochlorobenzene in the setting of in-transit melanoma metastases has been reported to induce local remission but did not prevent metastatic lymph node and liver involvement. For stage IV disease, treatment options include resection, radiation, dacarbazine, temazolamide, interleukin-2, and combination chemotherapy. Before surgical intervention, a period of observation to rule out more widespread metastasis may be reasonable.

Adjuvant therapy should be discussed with patients with positive nodes or node-negative melanoma that is 4 mm thick, ulcerated or Clark's level IV or V. Interferon-α 2b is FDA-approved as adjuvant therapy and is used most commonly. Although meta-analysis suggests that interferon therapy may increase relapse-free survival, an advantage for overall survival is uncertain. The results of trials have been mixed. Reports of long-term survival after resection of distant melanoma metastases suggest that cytoreductive surgery may play a role in selected patients.

Clinical vaccine trials are ongoing, and some have shown promising results. However, despite numerous trials only a few patients have been shown to exhibit strong antigen-specific cellular responses.

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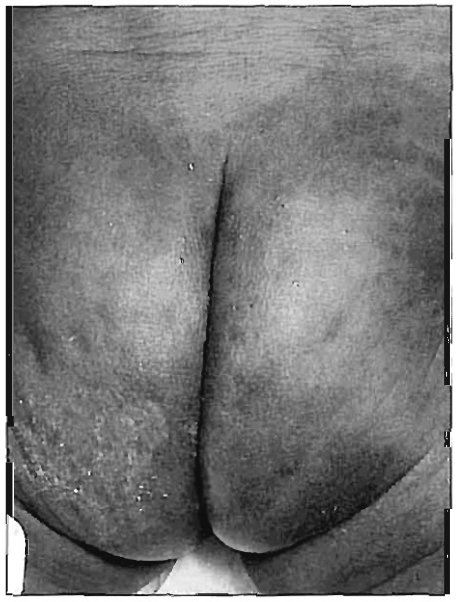

Fig. 30-16
Mongolian spot.

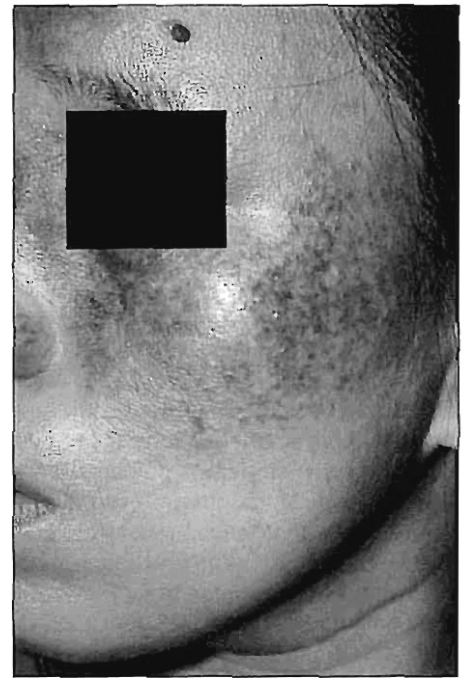

Fig. 30-17 Nevus of Ota.

DERMAL MELANOCYTIC LESIONS

Mongolian Spot

The Mongolian spot is a bluish-gray macule that varies in diameter from 2 to 8 cm. It occurs typically in the sacral region of the newborn (Fig. 30-16), in 80% to 90% of Asian, Southern European, American black, and Native American persons. The Mayan Indians uniquely take great pride in it as an indicator of pure Mayan inheritance. The Mongolian spot may be situated in other locations. Multiple spots may occur in a widespread distribution. These have been called *generalized dermal melanocytosis* or *dermal melanocytic hamartomas*. They may occur in phakomatosis pigmentovascularis types II, IV, and V. Extensive Mongolian spots have been associated with Hunter syndrome and with trisomy 20 mosaicism.

Histologically, the Mongolian spot shows elongated dendritic dermal melanocytes, widely scattered among normal collagen bundles. It usually disappears during childhood, although rarely, it may persist into adulthood.

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Nevus of Ota (Oculodermal Melanocytosis)

This nevus is also known as *nevus fuscoceruleus ophthalmomaxillaris*. It is usually present at birth in the two-thirds of patients who have ocular involvement. Other lesions may not appear until the teen years. The conjunctiva and skin about the eye supplied by the first and second branch of the trigeminal nerve, as well as the sclera, ocular muscles, retrobulbar fat, periosteum, and buccal mucosa, may be involved. On the skin, brown, slate gray, or blue-black macules grow slowly larger and deeper in color (Fig. 30-17). It persists throughout life. Eighty percent occur in females; 5% are bilateral. Glaucoma or ipsilateral sensorineural hypoacusia may also occasionally complicate nevus of Ota. Malignant melanoma rarely occurs in nevus of Ota. Malignant degeneration is more frequent in white patients. The most common site of malignancy is the choroid. Histologically, elongated dendritic dermal melanocytes are seen scattered in the upper portion of the dermis.

Q-switched lasers have been used successfully to treat nevus of Ota. Nd:YAG laser at 1064 nm is suitable for use in a wide range of skin types. Acquired dermal melanocytosis (acquired bilateral nevus of Ota-like macules, Hori nevus) is recalcitrant to laser therapy compared with nevus of Ota. Good results have been reported after treatment with Q-switched ruby laser. Initial topical bleaching with 0.1% tretinoin and a 5% hydroquinone ointment containing 7% lactic acid was used to reduce epidermal melanin prior to laser treatment. Q-switched ruby laser has also been used after epidermal ablation using a scanned CO_2 laser. Lesions of phacomatosis pigmentovascularis have been treated successfully with Q-switched ruby laser and Q-switched alexandrite laser, with flashlamp pumped pulsed dye laser for the vascular component.

Nevus of Ito

Also known as *nevus fuscoceruleus acromiodeltoideus*, the nevus of Ito has the same features as nevus of Ota except that it occurs in the distribution of the posterior supraclavicular and lateral cutaneous brachial nerves, to involve the shoulder, side of the neck, and supraclavicular areas.

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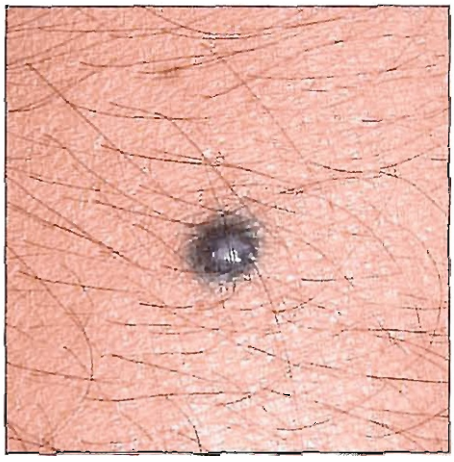

Fig. 30-18 Blue nevus.

Blue Nevus

Blue nevi appear as well-defined blue papules or nodules (Fig. 30-18). Histologically, they share the silhouette of a bulbous finger-like or wedge-shaped protrusion into the dermis. All variants show little maturation, and no dispersion of melanocytes in the deep portion of the lesion. All except epithelioid blue nevi and some cellular blue nevi are associated with a dense sclerotic stroma. They commonly occur as combined nevi (combinations of various types of blue nevi, blue nevus combined with banal nevus, or blue nevus combined with Spitz nevus).

Blue Nevus of Jadassohn-Tiche (Common Blue Nevus, Nevus Ceruleus) The typical lesion is a steel-blue papule or nodule that begins in early life. The slowly growing lesion is rarely more than 2 to 10 mm in diameter, and occurs most frequently on the dorsal hands, feet, and face. Histologically, the lesion is composed of dendritic dermal melanocytes and melanophages. The sclerotic stroma is particularly prominent in this variant.

Cellular Blue Nevus Usually a cellular blue nevus is a large, firm, blue or blue-black nodule. It is most frequently seen on the buttock and sacrococcygeal region, and occasionally is present at birth. Women have cellular blue nevus 2.5 times as frequently as men, and the average age of the patient seen with this lesion is 40 years. Uncommonly, these may invade underlying structures such as the skull in scalp lesions. Histologically, in addition to deeply pigmented melanophages, islands of cells are observed with large fusiform vesicular nuclei, prominent nucleoli, and abundant pale cytoplasm. The cellular islands contain little or no pigment.

Epithelioid Blue Nevus Epithelioid blue nevi are mostly seen in patients with the *Carney complex* (myxomas, spotty skin pigmentation, endocrine overactivity, and schwannomas). They occur on the extremities and trunk, and less frequently on the head and neck. They may also be noted in the absence of Carney complex, and may occur on the genital mucosa. The lesions are composed of large polygonal and epithelioid melanocytes often laden with melanin. These cells are admixed with heavily pigmented dendritic melanocytes, spindled melanocytes, and melanophages. Some melanocytes are situated among the dermal collagen bundles singly, in short rows, and small groups. The nuclei are vesicular with very pale chromatin and a single prominent nucleolus. They may demonstrate moderate pleomorphism and rare mitotic figures. In contrast with other blue nevi, they lack the usual sclerotic stroma.

Deep Penetrating Nevus This unique type of nevus is commonly seen in combination with other forms of blue nevus. The fascicles of cells have small hyperchromatic nuclei with a smudged chromatin pattern and inconspicuous nucleoli. Adjacent melanophages are noted.

Amelanotic Blue Nevus (Hypomelanotic Blue Nevus) In the amelanotic or hypomelanotic variant of cellular blue nevus, mild cytologic atypia and pleomorphism may be present. Mitotic activity (up to three mitoses/mm) may also be observed. It is important to recognize the entity so as not to confuse it with a malignant lesion.

Malignant Blue Nevus The term "malignant blue nevus" has been used to refer to melanomas arising in a blue nevus (usually a cellular blue nevus). It has also been used for de novo melanoma resembling a cellular blue nevus. When melanoma occurs in a blue nevus, an abrupt transition can be seen between the nevus and the melanoma. The melanoma demonstrates a sheet-like growth pattern, mitoses, necrosis, and nuclear atypia.

Treatment

Excision is the mainstay of treatment for blue nevi. Successful results have been reported with the Q-switched ruby laser. Treatment of the malignant variety is the same as for a malignant melanoma.

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CHAPTER

31 Macrophage/Monocyte Disorders

PALISADED GRANULOMATOUS DERMATOSES

Granuloma Annulare

Granuloma annulare (GA) is a relatively common idiopathic disorder of the dermis and subcutaneous tissue. It occurs in all races and at all ages, but much more frequently affects women (2:1). Granuloma annulare may exhibit the isomorphic response of Koebner, affect healed areas of herpes zoster, and may be restricted to sun-exposed areas. While most cases spontaneously resolve, leaving entirely normal skin, loss of elastic tissue may occur, leaving atrophic lesions resembling mid-dermal elastolysis or anetoderma. GA lesions will sometimes spontaneously resolve when biopsied.

Many clinical morphologies of GA exist. Usually, patients exhibit primarily one clinical type during the course of their illness, except in the subcutaneous form, in which typical papular or localized GA may also occur.

Localized Granuloma Annulare This form of GA tends to affect children and young to middle-aged adults. Usually only one or a few lesions are present at any one time. Localized GA usually appears on the lateral or dorsal surfaces of the fingers or hands, elbows, dorsal feet, and ankles (Figs 31-1 to 31-3). Rarely, the eyelid or even a Becker nevus may be affected. Lesions are erythematous, fawn colored, or violaceous, thinly bordered plaques or papules, which slowly spread peripherally, at the same time undergoing central involution, so that roughly annular lesions are formed. The overlying skin usually remains completely normal. Lesions may coalesce and sometimes form scalloped patterns or firm plaques. The lesions never ulcerate and on resolving virtually always leave no residua. The lesions develop slowly and often involute spontaneously. Although more than 50% of patients clear within 2 years, in 40% lesions will recur. Autoimmune thyroiditis may be present in women with localized GA.

Generalized Granuloma Annulare This form of GA affects mostly women in the fifth and sixth decades, adolescents and children. The association of generalized GA with diabetes mellitus has been questioned. The eruption presents as a diffuse but symmetrical, papular or annular eruption of more than 10 lesions, and often hundreds (Fig. 31-4). Lesions favor the nape of the neck, upper trunk, and proximal upper extremities, and rarely exceed 5 cm in diameter. The palms, soles, and eyelids may be affected. The face and genital area are usually spared. In some cases sun exposure

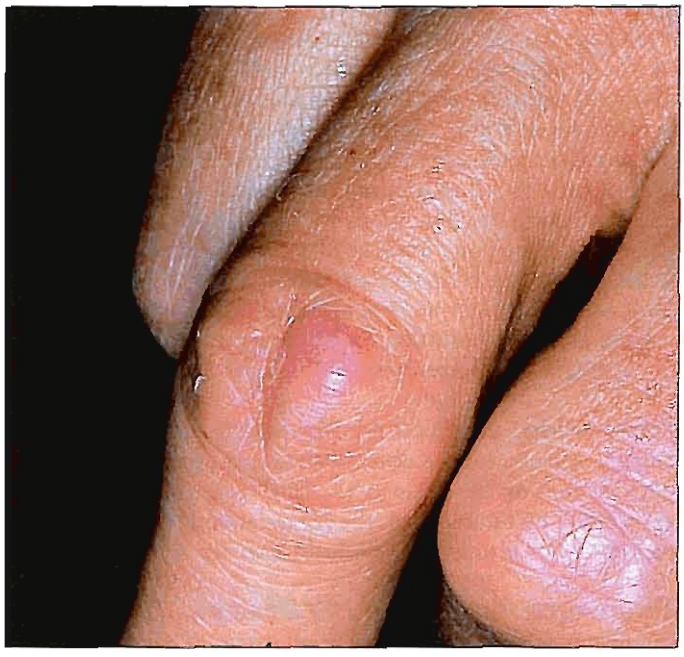

Fig. 31-1 Granuloma annulare, dermal papule on the knuckle.

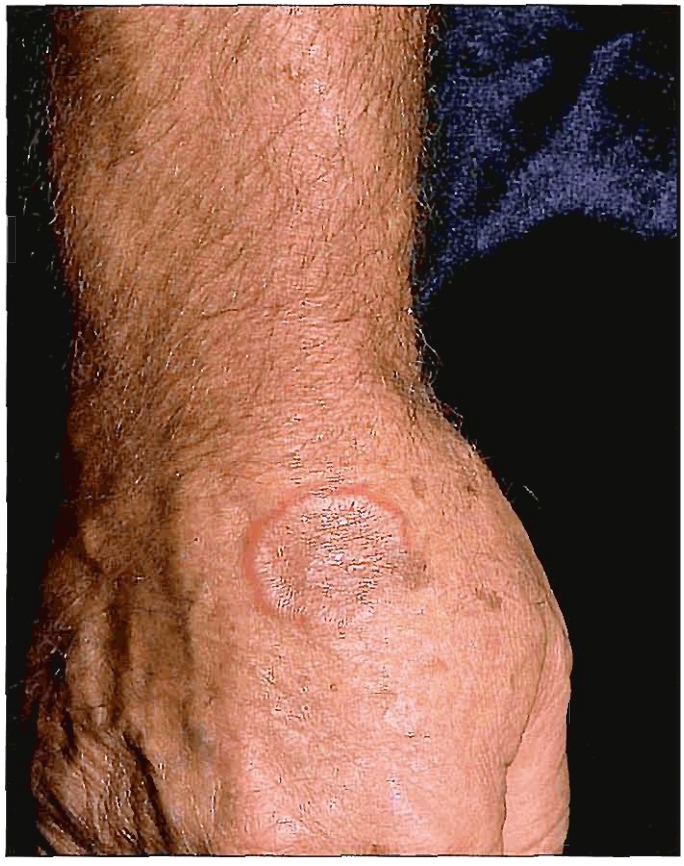

Fig. 31-2 Granuloma annulare, annular, localized type.

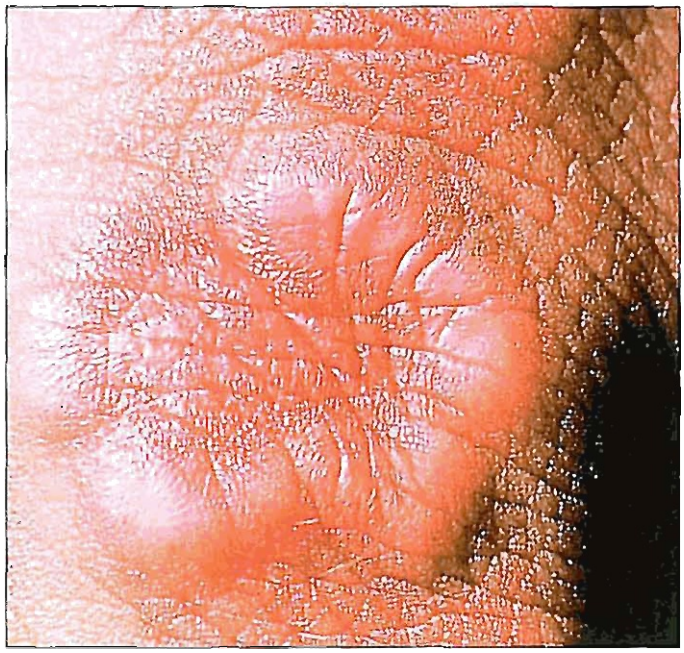

Fig. 31-3 Granuloma annulare, annular plaque composed of coalescing papules.

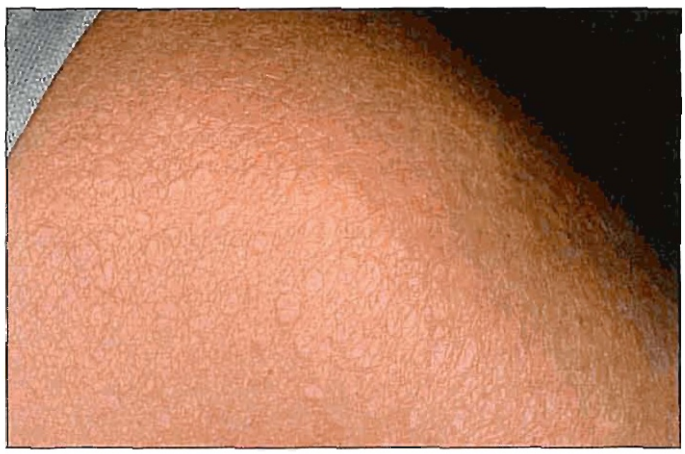

Fig. 31-4 Granuloma annulare, generalized small papules and annular plaques.

seems to be a trigger (see section on *actinic granuloma* below). Some patients are completely asymptomatic, whereas others complain of severe pruritus. Spontaneous clearing usually occurs but at variable times. The average duration is 3 to 4 years but may be as short as 4 months or longer than a decade.

Patch-Type or Macular Granuloma Annulare This form of GA is significantly more common in women, usually between 30 and 70 years of age. Flat or only slightly palpable erythematous or red–brown lesions occur (Fig. 31-5), especially on the upper medial thighs and in bathing-trunk distribution Lesions may closely simulate cutaneous T-cell lymphoma or morphea. Individual lesions average at least several centimeters in diameter but may be much larger. On careful palpation, small papules can be felt in some cases and on stretching the skin the papules or small annular lesions can be seen. Such papules are the most fruitful sites for biopsies. Both well-formed necrobiotic granulomas and the interstitial pattern of GA may be seen on biopsy.

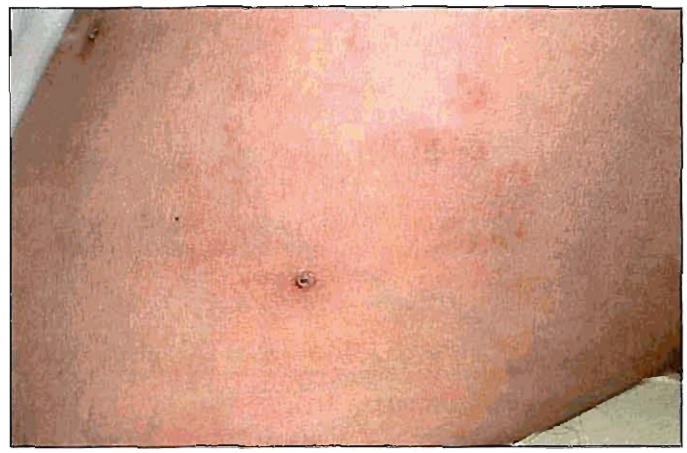

Fig. 31-5 Granuloma annulare, macular lesion of the medial thigh.

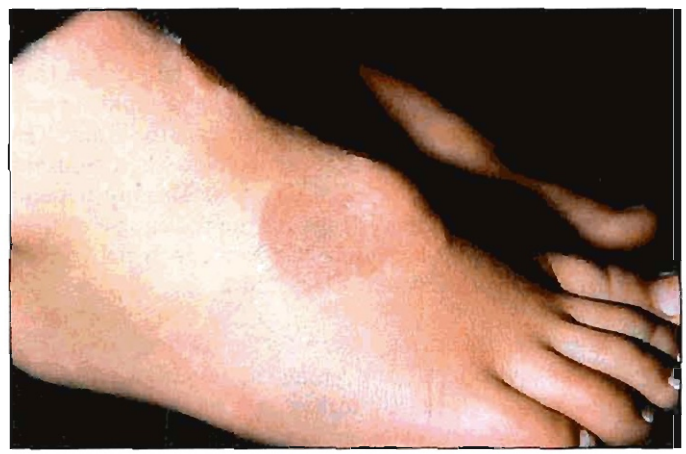

Fig. 31-6 Granuloma annulare, subcutaneous and dermal lesion.

Subcutaneous Granuloma Annulare (Deep Granuloma Annulare, Pseudorheumatoid Nodule) Subcutaneous GA is most common in children, with boys affected twice as commonly as girls. Childhood cases appear at any age from 1 year to adolescence. Lesions tend to occur on the lower legs, but may also occur on the distal upper extremity or scalp. Multiple lesions are usually present. There is often a history of trauma to the affected area preceding the appearance of a lesion. Typically lesions are skin-colored, deep dermal or subcutaneous nodules, and up to several centimeters in diameter (Fig. 31-6). Superficial papular lesions are present in about one-quarter of patients with subcutaneous GA. Lesions in general are asymptomatic and resolve over a few years. The major clinical problem occurs when the initial pathologic interpretation is rheumatoid nodule and an unnecessary extensive rheumatologic work-up is performed.

Perforating Granuloma Annulare Perforating GA usually appears on the dorsal hands and presents as papules with a central keratotic core. This core represents transepidermal elimination of the degenerated material in the center of GA lesions and clinically can resemble a pustule.

Granuloma Annulare in HIV Disease GA may occur in persons with HTV infection at all stages of disease. Lesions are typically papular and generalized GA is more common

(60%) than localized GA (40%). Photodistributed and perforating lesions may also occur. The histology is identical to GA in the normal host. The natural history of GA in HIV is unknown.

Granuloma Annulare and Malignant Neoplasms

The occurrence of GA and a cancer in the same patient is rare, but has been reported in at least 18 cases. Most of these patients are between 35 and 75, older than the typical GA patient. Half the cases occur in lymphoma/leukemia patients and half in solid tumor patients. The diagnosis of the neoplasm usually predates the diagnosis of GA, but may precede it. Lesions are described as "atypical" in that they may be painful.

Histology

Because there are many clinical patterns of GA, skin biopsies are often performed to confirm the diagnosis. In general, there are two histopathologic patterns that often coexist in the same patient. The classic pattern of GA is a palisading granuloma characterized by histocytes and epithelioid cells surrounding a central zone of altered collagen. In well-developed lesions, there is mucin deposition within the foci of altered collagen. Fibrin and nuclear dust may also be present in the degenerated foci. Lesions are most typically located in the upper and mid-reticular dermis, but may involve the deep dermis or subcutaneous tissue. At the periphery of lesions a leukocytoclastic vasculitis may rarely be found. IgM and C3 in the blood vessels of the skin lesions are found in about half of patients.

The second pattern of GA is the interstitial pattern. Lesions may be entirely interstitial or an interstitial pattern may be seen adjacent to well-formed palisaded lesions. A patchy dermal infiltrate of histiocytes and other mononuclear cells with occasional neutrophils is interspersed between collagen bundles. The patchy distribution within the dermis is best appreciated at scanning magnification. Interstitial mucin is often present in the affected areas, and is best demonstrated with a colloidal iron stain. Although these features are sufficient to confirm the diagnosis of GA, further sectioning may reveal typical palisaded granulomas.

Treatment

Patients regularly report that a biopsy of the lesion will cause its involution. Because the lesions are often asymptomatic and spontaneous involution occurs, no treatment is required in many mild cases. The intralesional injection of triamcinolone suspension is effective for individual lesions and is a reasonable initial treatment. Most cases relapse within 3 to 7 months. Superpotent topical steroids or topical tacrolimus 0.1% ointment may be effective in some patients, especially those with more macular lesions.

Generalized cases represent a major therapeutic challenge. Although systemic steroids may be very effective, the high doses required and the usual immediate relapse as the steroids are tapered make this approach untenable in most situations. In addition, because diabetes may be present, systemic steroids may complicate the management of the diabetes. Many systemic agents have been reported as effective, but few have been tested in large numbers of cases or in blinded or controlled fashion. The combination of tetracycline 500 mg twice a day with nicotinamide 500 mg three times a day or PUVA (either oral or bath delivery) are the most dependable options. Anecdotal reports have suggested response from dapsone, 100 mg once or twice a day; pentoxifylline 400 mg three times a day; systemic retinoids (acitretin or isotretinoin); potassium iodide (SSKI) up to 10 drops three times a day; cyclosporin up to 5 mg/kg/day; UVA-1 phototherapy; defibrotide 400 mg/day; tranilast 300 mg/day; and antimalarials. Infliximals may be considered in severe cases. With all treatments, relapse may occur with discontinuation.

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Annular Elastolytic Giant Cell Granuloma (Meischer's) and Actinic Granuloma (O'Brien)

Annular elastolytic giant cell granuloma (AEGCG) and actinic granuloma are unified by their histopathologic appearance. Non–diabetes-associated necrobiosis lipoidica of the face has been included in this category. It is currently unclear whether they simply represent variants of GA occurring on sun-damaged skin or are distinct diseases.

AEGCG typically presents in two patterns. One is a single, asymptomatic, atrophic-appearing, yellow, thin plaque on the forehead (Fig. 31-7). Fine wrinkling and loss of elasticity characterize the skin within the ring. Clinically, this pattern resembles facial necrobiosis lipoidica more than GA. The second variant is of multiple trunk lesions, and occurs more frequently in women and largely in sun-exposed areas. In these cases the lesions have an active erythematous border with central clearing. The condition is chronic and refractory to treatment.

Actinic granuloma as described by O'Brien presents as papules and plaques on sun-exposed skin (Fig. 31-8). Lesions are frequently numerous and may coalesce to cover much of the exposed skin. The diagnosis is suspected by a history of onset after significant sun exposure and the distribution on physical examination. A few lesions may occur on sun-protected sites or spill over from affected areas to more photoprotected sites. This condition affects older adults (usually over age 50) and can be intensely pruritic. It is not associated with diabetes mellitus, but there are numerous reports of it occurring in patients with temporal arteritis. It is speculated that the vasculitis is also due to actinic injury to the connective tissue surrounding the temporal artery.

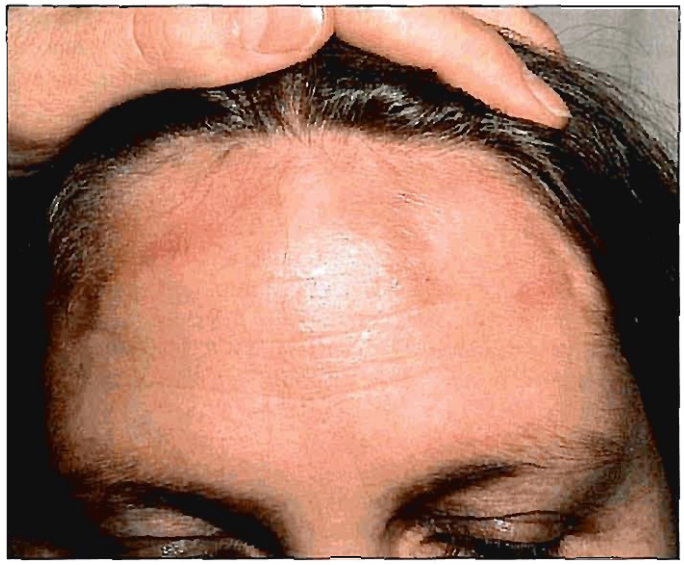

Fig. 31-7 Granuloma annulare, annular elastolytic giant cell granuloma (Meischer), atrophic annular plaque.

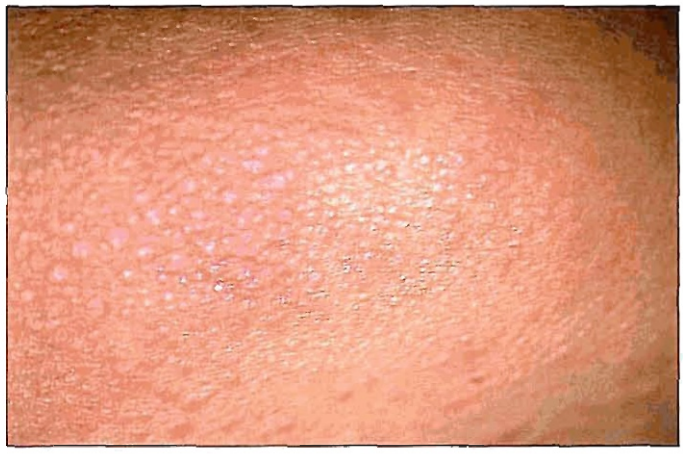

Fig. 31-8 Granuloma annulare, generalized papular lesions localized to sun-exposed sites.

Histologically, both conditions show a characteristic histology. The dermal infiltrate of macrophages is largely interstitial and well-formed palisaded granulomas are rare. Multinucleated giant cells, often quite large, are numerous. Mucin is scant or lacking. The macrophages characteristically contain fragments of actinically-damaged elastic tissue (elastophagocytosis). When this typical histology is seen in concert with the classic clinical features noted above, it may be reasonable to make these specific diagnoses. These conditions cannot, however, be diagnosed based on clinical or histologic grounds alone. Some cases with the clinical features of AEGCG or actinic granuloma will show a histology more characteristic of typical granuloma annulare, suggesting there is a spectrum of both clinical and histologic features in these patients.

Treatment of these conditions has been difficult. Cases with an active erythematous border tend to respond to systemic steroids, but relapse immediately when the steroids are

tapered or discontinued. Tranilast 300 mg/day and chloroquine 250 mg/day have been reported as effective.

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Granuloma Multiforme (Leiker)

Granuloma multiforme is seen most commonly in central Africa, where it is a common disorder, and rarely elsewhere. It affects adults aged over 40 and is more common in females. Lesions are most frequent on the upper trunk and arms, and in sun-exposed areas. It begins as small papules that evolve within a year into round or oval plaques up to 15 cm wide. The active edge of lesions may be elevated to as much as 4 mm in height and the center may be slightly depressed and hypopigmented. Pruritus can occur and coalescing lesions may form unusual polycyclic shapes. The course is chronic. It is most importantly separated from tuberculoid leprosy. Histologically, it resembles GA, but multinucleated giant cells are prominent. Giant cells typically contain phagocytosed connective tissue and elastic tissue is decreased in the areas affected by the granulomas. In these regards it shares features with AEGCG and may represent actinic granuloma/GA of sun-exposed skin.

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Interstitial Granulomatous Drug Reaction

Interstitial granulomatous drug reaction (IGDR) is an uncommon, yet under-recognized, pattern of adverse reactions to medication. While it may occur within a few days of starting the medication, most patients with IGDR have been on the offending medication for months to years. A wide variety of medications have been implicated, including calcium-channel blockers (most common cause reported), lipid-lowering agents, angiotensin-converting enzyme (ACE) inhibitors, diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), antihistamines, allopurinol, gold, sennoside (a common over-the-counter laxative), and even soy. Clinically the lesions are erythematous annular plaques with an indurated border and sometimes a tendency to central clearing. Lesions favor the creases (groin, axillae, popliteal fossae), but may also affect the trunk, proximal extremities, dorsal hands, palms, and soles. Lesions may be photodistributed. Pruritus is minimal or absent. Mucous membranes and the face are spared. Histologically, there is a diffuse deep dermal infiltrate which is pervascular but has a prominent interstitial component. The inflammatory infiltrate is centered in the lower two-thirds of the dermis; contains neutrophils, eosinophils, histiocytes, and multinucleated giant cells; degenerated collagen bundles may be surrounded by histiocytes, neutrophils, and eosinophils forming "Churg-Strauss" granulomas; and mucin is usually scant or absent. Necrobiotic granulomas are usually incomplete, but have at times been reported to resemble those seen in GA. Unique features are an interface component and "atypical" lymphocytes in the infiltrate. The histologic differential diagnosis includes interstitial granulomatous dermatitis associated with arthritis and interstitial GA. Lesions resolve over months once the offending ingestant is stopped.

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Necrobiotic Xanthogranuloma

Necrobiotic xanthogranuloma is a multisystem disease with prominent skin findings that affects older adults. The characteristic skin lesions are periorbital yellow (xanthomatous) plaques and nodules, which occur in 80% of cases. These lesions resemble xanthelasmas, except that they are deep, firm, indurated, and may extend into the orbit. The trunk and proximal extremities may have orange–red plaques with an active red border and an atrophic center with superficial telangiectasias (Fig. 31-9). These plaques may grow to 25 cm in diameter. The skin lesions often ulcerate, leading to atrophic scarring. Acral nodules may also occur. The eyes are prominently involved with orbital masses, conjunctivitis, keratitis, scleritis, uveitis, iritis, ectropion or proptosis. Blindness may result. Lymphadenopathy, hepatosplenomegaly,

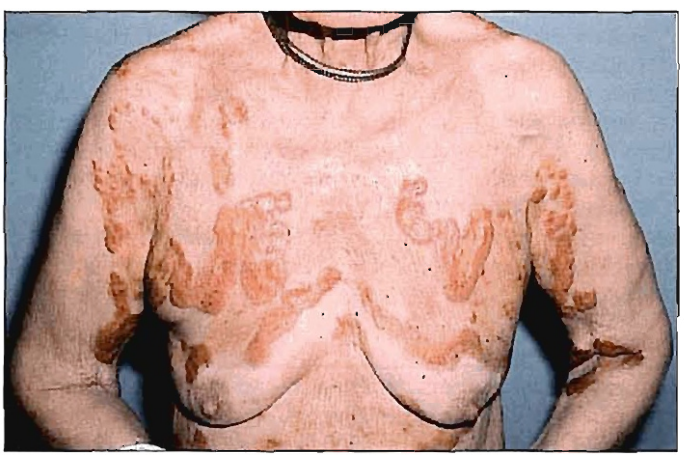

Fig. 31-9 Necrobiotic xanthogranuloma.

mucosal, myocardial, and pulmonary lesions may occur. There is a monoclonal IgG (usually κ) paraproteinemia in 80% of cases, and rarely an IgA paraproteinemia (one patient had both). Thrombocytopenia, neutrophilia and eosinophilia may be present. The bone marrow may show plasmacytosis and in some cases anemia, leukopenia, myeloma or myelodysplastic syndromes may evolve. The cause is unknown, and the course is chronic and often progressive.

Histologically, there are extensive zones of degenerated collagen surrounded by palisaded macrophages. These macrophages are of various forms—foamy, Touton cells, epithelioid, and giant cells sometimes with more than 50 nuclei. The process extends into the fat, obliterating fat lobules. Cholesterol clefts and extracelluar lipid deposits are prominent. Within this process is a perivascular and interstitial infiltrate of lymphocytes and plasma cells. Lymphoid follicles are present.

The treatment is usually directed at the paraprotein and consists of systemic corticosteroids, low-dose chlorambucil, plasmapheresis, or local radiation therapy (for eye lesions). Anecdotally, interferon (IFN)-α 2b, 3 to 6 MU three times a week, in combination with systemic corticosteroids and pulse cytoxan with dexamethasone both led to dramatic improvement. Topical nitrogen mustard and BCNU as used in mycosis fungoides or simple excision are options.

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SARCOIDOSIS

Sarcoidosis is a systemic granulomatous disease that involves the skin and many of the internal organs with an acute or persistent course interrupted by remissions and relapses. In addition to the skin, which is involved in approximately 25% of cases, other sites of involvement are the lungs, mediastinal and peripheral lymph nodes, eyes, phalangeal bones, myocardium, central nervous system (CNS), kidneys, spleen, liver, and parotid glands.

Sarcoidosis occurs worldwide. In Europe it is most prevalent in Scandinavia, especially in Sweden, with a prevalence of 64 in 100,000. In the UK, the rate is 20 in 100,000, and in France and Germany about 10 in 100,000, with lower rates in Spain and Japan of 1.4 in 100,000. In the US the southeastern states and certain areas in urban centers (New York City, Detroit, and Washington DC) show the highest prevalence. In the US there is a marked racial variation with a rate of 10 to 14 in 100,000 for white persons and 35 to 64 in 100,000 for African Americans. The disease begins most frequently between the ages of 20 and 40, and is slightly more common in women. The highest annual incidence is in African American women between the ages of 30 and 39 who have an annual incidence of 107 in 100,000. Children may also develop sarcoidosis. There are two distinct forms of pediatric sarcoidosis. Early-onset disease, usually before the age of 4, is unique and characterized by the triad of skin lesions, uveitis, and arthritis. It may be confused with juvenile rheumatoid arthritis. Older children, aged 8 to 14, present similarly to adults with lymphadenopathy and pulmonary disease.

Cutaneous involvement in sarcoidosis may be classified as *specific*, which reveals granulomas on biopsy, or *nonspecific*, which is mainly reactive, such as erythema nodosum. In about 20% of cases the skin lesions appear before the systemic disease, in 50% there is simultaneous appearance of the skin and systemic lesions, and in 30% the skin lesions appear up to 10 years after the systemic disease has occurred. This is often coincidental with the tapering of systemic steroids for pulmonary sarcoidosis. The cutaneous manifestations of sarcoidosis are quite varied and numerous morphologic lesion types have been described. The morphology of the lesions in sarcoidosis might include papules, nodules, plaques, subcutaneous nodules, scar sarcoidosis, erythroderma, and ulcerations. The lesions may be verrucous, ichthyosiform, hypomelanotic, psoriasiform, or alopecic. In sarcoidosis, lesions are usually multiple and firm and elastic when palpated. They extend to involve the entire thickness of the dermis. The overlying epidermis may be slightly thinned, discolored, telangiectatic, or scaly. The color is faint, showing dull tints of red, purple, brown, or yellow according to the stage of development. Usually the lesions are asymptomatic, but approximately 10% to 15% of patients itch. There is a racial difference in the frequency of cutaneous lesions in sarcoidosis. Among white patients erythema nodosum is as frequent as the specific cutaneous manifestations and both types of cutaneous involvement occur in about 10% of patients with sarcoidosis. In black patients, erythema nodosum is much less common; however, specific cutaneous manifestations occur in 50% or more of patients. The skin lesions in general do not correlate with the extent or nature of systemic involvement or with prognosis. The exceptions are erythema nodosum, which is associated with a good prognosis, and lupus pernio which is associated with bone cysts, sarcoidosis of the upper respiratory tract, and pulmonary fibrosis.

Papular Sarcoid

Papules are the most common morphology of cutaneous sarcoidosis and are usually less than 1 cm in diameter. Lesions

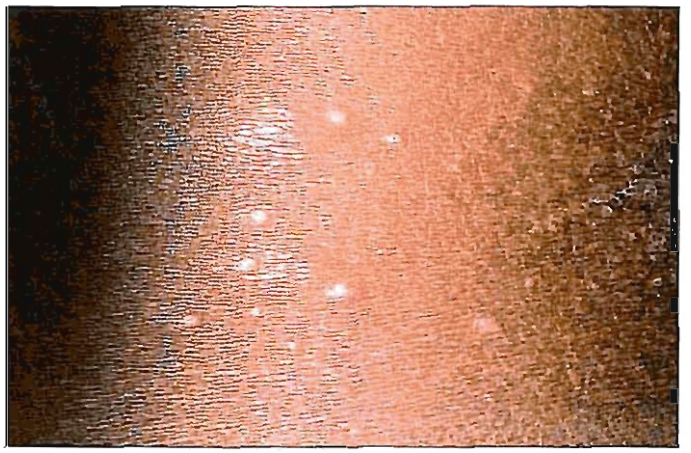

Fig. 31-10 Sarcoidosis, hypopigmented papules.

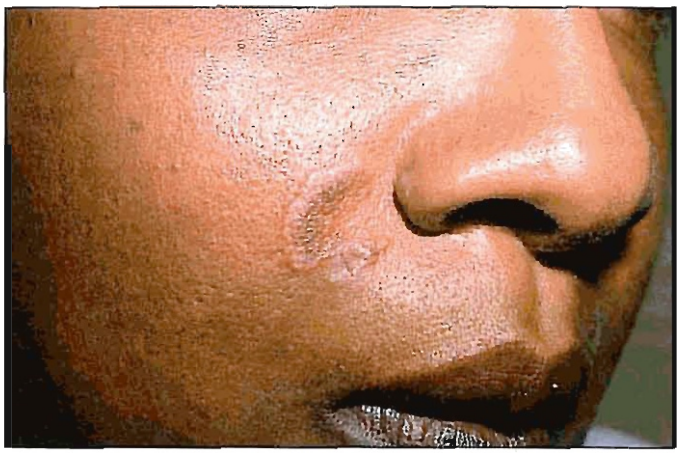

Fig. 31-12 Sarcoidosis, annular plaque.

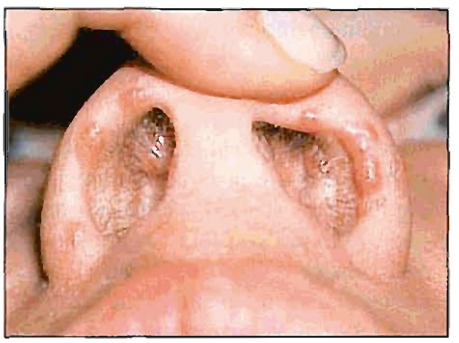

Fig. 31-11 Sarcoidosis, characteristic papules on the nares.

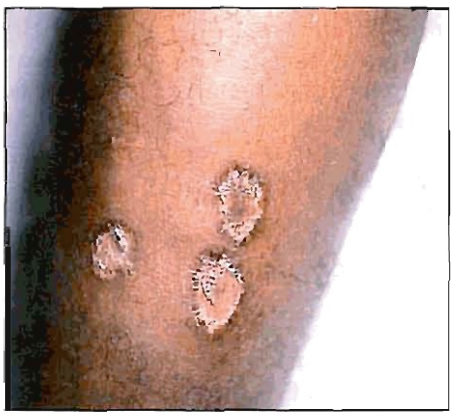

Fig. 31-13 Sarcoidosis, hypopigmented and annular plaques.

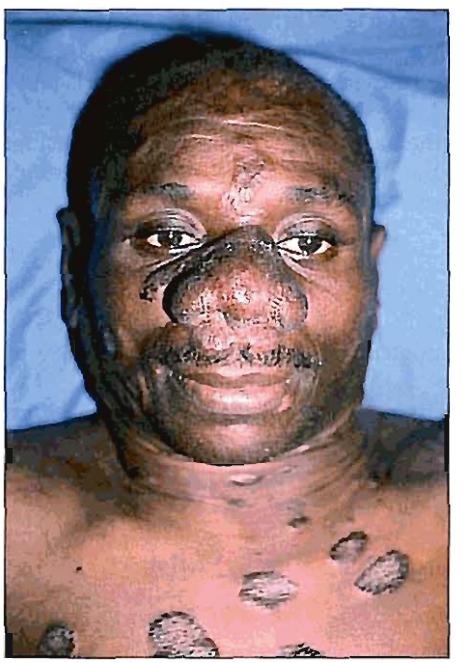

Fig. 31-14 Sarcoidosis, lupus pernio with rhinophymatous nasal changes.

may be localized or generalized, in which case small papules predominate (Figs 31-10 and Fig. 31-11). This is also known as *miliary sarcoid*. The papules are especially numerous over the face, eyelids, neck, and shoulders. Plaques may occur by the expansion or coalescence of papules. In time the lesions involute to faint macules. Hyperkeratosis may rarely be prominent, giving the lesions a verrucous appearance.

Annular Sarcoidosis

Papular lesions may coalesce or be arranged in annular patterns, usually with a red–brown hue (Fig. 31-12). On palpation the lesions are indurated. Central clearing with hypopigmentation, atrophy, and scarring may occur. Lesions favor the head and neck and are usually associated with chronic sarcoidosis.

Hypopigmented Sarcoidosis

Hypopigmentation may be the earliest sign of sarcoidosis and is usually diagnosed in darkly pigmented races (Fig. 31-13). Lesions vary from a few millimeters to more than a centimeter in diameter and favor the extremities. Although they appear macular by visual inspection, on palpation a dermal or subcutaneous component is often palpable in the center of the lesion.

Lupus Pernio

Lesions typically are brown to violaceous, smooth, and shiny plaques on the head and neck, especially the nose, cheeks, lips, forehead, and ears (Fig. 31-14). Lesions can be very disfiguring. Involvement of the nasal mucosa and underlying bone may occur and lead to nasal perforation and collapse of the nasal bridge. Upper aerodigestive tract involvement is also common. ENT evaluation is recommended. In three-quarters of cases of lupus pernio, chronic fibrotic respiratory tract involvement is found. In 43% of cases, lupus pernio is associated with granulomas in the bones (punched-out cysts), most commonly of the fingers. Chronic ocular lesions occur in 37% of cases. Lupus pernio is typically seen in women in

their fourth or fifth decade of life. The skin lesions rarely involute spontaneously. At times, lupus pernio may resemble rhinophyma. It is important to make the correct diagnosis, as ulceration of sarcoidal lesions may occur with laser treatment, even with pulsed dye laser.

Ulcerative Sarcoidosis

Ulcerative sarcoidosis is very rare, affecting about 5% of patients with sarcoidosis. It affects primarily black women in young adulthood. In half of cases it is the presenting finding of sarcoidosis. The ulcerations may occur de novo or in sarcoidal plaques. Lesions favor the lower extremities. The clinical appearance may not be specific, but skin biopsies are diagnostic. Lupus pernio may also be present. Many patients have multisystem sarcoidosis, although uncommonly no other evidence of sarcoidosis is found.

Subcutaneous Sarcoidosis

Subcutaneous sarcoidosis is also known as *Darier-Roussy sarcoid* and consists of a few to numerous 0.5- to 3-cm deep-seated nodules on the trunk and extremities; only rarely do they appear on the face. The overlying epidermis may be slightly violaceous. A biopsy is usually required to confirm the diagnosis. Five percent or fewer patients with sarcoidosis have subcutaneous nodules.

Sarcoidosis in Scars (Scar Sarcoid)

Infiltration and elevation of tattoos and old flat scars are two variants of scar sarcoid. Previously flat scars raise up and may become erythematous or violaceous. These lesions may be confused with keloids. Infiltration of tattoos may be the first manifestation of sarcoidosis and can be confused with a granulomatous hypersensitivity reaction to the tattoo pigment (Fig. 31-15). From 22% to 50% of biopsies from patients with cutaneous sarcoidosis will contain polarizable foreign material, suggesting that scar sarcoidosis is very common. Scar sarcoid may sometimes occur in patients with acute disease and erythema nodosum, especially if the lesions are small papules on the knees. It may also occur in patients with chronic sarcoidosis.

Plaques

These distinctive lesions are flat-surfaced, slightly elevated plaques that appear with greatest frequency on the cheeks, limbs, and trunk symmetrically. Superficial nodules may be superimposed and coalescence of plaques may lead to serpiginous lesions. Involvement of the scalp may lead to permanent alopecia.

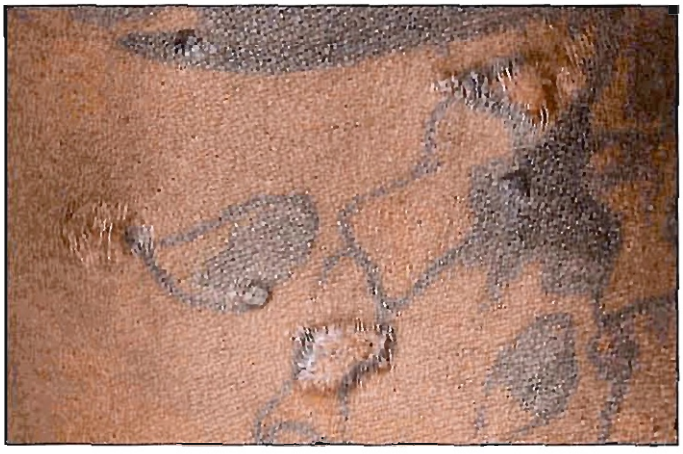

Fig. 31-15 Sarcoidosis, papules and plaques arising in a tattoo.

Erythrodermic Sarcoidosis

Erythrodermic sarcoidosis is an extremely rare form of sarcoidosis. A diffuse infiltrative erythroderma of the skin usually begins as erythematous, scaling patches that merge to involve large portions of the body.

Ichthyosiform Sarcoidosis

Ichthyosiform sarcoidosis resembles ichthyosis vulgaris or acquired ichthyosis, with fine scaling usually on the distal extremities (Fig. 31-16). It is virtually always seen in non-white persons, especially African Americans. Virtually all patients have or will develop systemic disease. In 75% of patients, the skin lesions precede or occur at the same time as the diagnosis of systemic sarcoidosis. Although the lesions have no palpable component, a biopsy will reveal dermal noncaseating granulomas.

Alopecia

Alopecia on the scalp due to sarcoidosis can have multiple morphologies. Plaques may extend into and involve the scalp leading to scarring hair loss (Fig. 31-17). More rarely, macular lesions from one to several centimeters in diameter appear on the scalp and closely resemble alopecia areata. This form may be permanent or reversible. Diffuse alopecia, scaly plaques resembling seborrheic dermatitis, and cicatricial lesions may also occur. A biopsy of all forms of alopecic

Fig. 31-16 Sarcoidosis, ichthyosiform type; biopsy showed noncaseating granuloma although there was no palpable dermal component to the lesions.

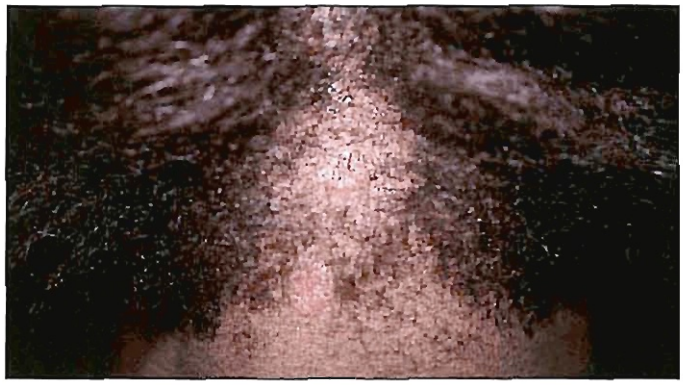

Fig. 31-17 Sarcoidosis, scarring alopecia of the scalp.

sarcoid will reveal dermal granulomas and sometimes loss of follicular structures. Scalp sarcoidosis is virtually always seen in African or African American women. In cases where sarcoidosis affects the scalp causing alopecia, the patient virtually always has other cutaneous lesions and the vast majority of cases will demonstrate systemic involvement.

Morpheaform Sarcoidosis

Very rarely, specific cutaneous lesions of sarcoidosis may be accompanied by substantial fibrosis and simulate morphea. Lesions are more typically generalized plaques, but may be localized and resemble linear morphea. Skin biopsy will demonstrate noncaseating granulomas. African American women are most commonly affected. Some patients respond to antimalarial therapy.

Mucosal Sarcoidosis

The lesions in the mouth are characterized by pinhead-size papules that may be grouped and fused together to form a flat plaque. The hard palate, tongue, buccal mucosa, or posterior pharynx may be involved. They may simulate Fordyce spots. In lupus pernio the nasal mucosa is frequently involved.

Erythema Nodosum in Sarcoidosis

Erythema nodosum is the most common nonspecific cutaneous finding in sarcoidosis. Sarcoidosis may first appear with fever, polyarthralgias, uveitis, bilateral hilar adenopathy, fatigue, and erythema nodosum. This combination, known as *Lofgren syndrome*, occurs frequently in Scandinavian white persons and is uncommon in American blacks. The typical red, warm, and tender subcutaneous nodules of the anterior shins are distinctive and are most frequently seen in young women. The face, upper back, and extensor surfaces of the upper extremities may less commonly be involved. There is a strikingly elevated erythrocyte sedimentation rate (ESR), frequently above 50. Erythema nodosum is associated with a good prognosis, with the sarcoidosis involuting within 2 years of onset in 80% of cases. Conversely, the absence of erythema nodosum is a risk factor for persistent disease activity.

Systemic Sarcoidosis

Sarcoidosis may involve virtually every internal organ and its presentations are protean. Many instances of sarcoidosis are asymptomatic and it is only when routine radiographs of the chest reveal some abnormality that sarcoidosis is suspected. Fever may be the only symptom of the disease or be accompanied by weight loss, fatigue, and malaise.

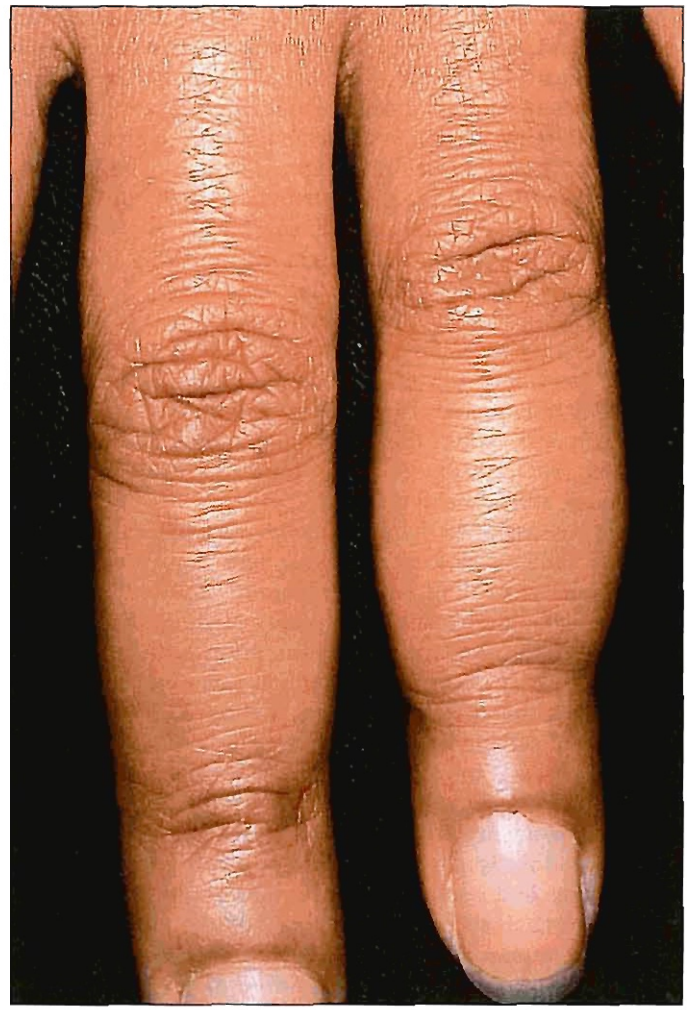

Fig. 31-18 Sarcoidosis, fusiform swelling of the digits.

Intrathoracic lesions, including parenchymal lung lesions and hilar adenopathy, are the most common manifestation of the disease, occurring in 90% of cases of sarcoidosis. Pulmonary changes are staged as follows: stage 0, normal; stage I, bilateral hilar and/or paratracheal adenopathy; stage II, adenopathy with pulmonary infiltrates; stage III, pulmonary infiltrates only; stage IV, pulmonary fibrosis. Transbronchial lung biopsy and needle aspiration have a high yield in confirming the diagnosis of sarcoidosis, even in patients with only stage I changes on chest x-ray.

Lymphadenopathy, especially of the mediastinal and hilar nodes, and generalized adenopathy, or adenopathy confined to the cervical or axillary areas, may be an initial sign of sarcoidosis or occur during the course of the disease.

Polyarthralgias may be seen with acute sarcoidosis or as a component of chronic disease. Chronic arthritis may occur (Fig. 31-18). Osseous involvement is often present in chronic disease. The most characteristic changes are found radiographically in the bones of the hands and feet, particularly in the phalanges. They consist of round, punched-out, lytic, cystic lesions. These are seen frequently in patients with lupus pernio. The bone lesions represent epithelioid granulomas.

Ocular involvement is present in 30% to 50% of patients, with granulomatous uveitis the most characteristic lesion.

The lacrimal gland may be involved uni- or bi-laterally by painless nodular swellings. Lesions of the iris are nodular and painless. There may also be lesions of the retina, choroid, sclera, and optic nerve. Ophthalmic disease is highly correlated with systemic involvement. All patients, even those who have no ocular symptoms, should be seen by an ophthalmologist. Sarcoidal involvement of the eye can progress to blindness. Conjunctival biopsy is positive in about 50% of patients with sarcoidosis, making it an easy site to sample and confirm the diagnosis.

Parotid gland and lacrimal gland enlargement with uveitis and fever may occur in sarcoidosis; this is known as *uveoparotid fever* or *Heerfordt syndrome* and usually lasts 2 to 6 months if not treated. Facial nerve palsy and CNS disease frequently are seen in this syndrome. Mikulicz syndrome is bilateral sarcoidosis of the parotid, submandibular, sublingual, and lacrimal glands.

Clinically apparent hepatic involvement occurs in about 20% of patients; however, a blind liver biopsy will reveal granulomas in 60% of cases. Hepatomegaly with elevation of serum alkaline phosphatase, biliary cirrhosis with hypercholesterolemia, and portal hypertension with esophageal varices are some of the manifestations. Liver biopsy showing hepatic granulomas is an excellent means of confirming the diagnosis of sarcoidosis.

Renal disease may be due to direct involvement with granulomas or secondary to hypercalcemia. Hypercalcemia is due to pulmonary alveolar macrophage secretion of vitamin D. Nephrolithiasis may result. Cardiac involvement occurs in 5% of cases, but in a higher percentage of autopsy cases.

Neurosarcoidosis occurs in 5% to 10% of patients. It can present in numerous ways from focal cranial nerve involvement (most commonly facial nerve palsy), to aseptic meningitis, seizures, psychiatric changes, stroke, and space-occupying lesions. Neurosarcoidosis tends to be chronic and relapsing with a higher mortality rate. Vision loss in sarcoidosis after heat exposure is called the Uhthoff phenomenon.

Most patients with sarcoidosis have an increased ESR. Leukopenia, lymphopenia, anemia, eosinophilia, and thrombocytopenia may be found. Elevated serum proteins occur because of polyclonal hyperglobulinemia. With liver or bone lesions, serum alkaline phosphatase may be elevated. If hypercalcemia is present, anorexia, vomiting, muscle weakness, and polyuria may occur. ACE levels may be elevated in all granulomatous diseases, including sarcoidosis. An elevated ACE level is suggestive, but not diagnostic for granulomatous inflammation. A normal ACE level cannot be used to rule out sarcoidosis and an elevated level does not necessarily indicate the presence of multisystem involvement. If elevated, ACE levels may be used to monitor the activity of the disease.

Etiology/Pathogenesis

The cause of sarcoidosis remains elusive. An attractive hypothesis has been that sarcoidosis occurs after exposure to an appropriate environmental or infectious agent in a genetically susceptible individual. Environmental and infectious etiologies have been sought, but identification of a reproducible infectious agent has remained elusive. *Propionobacteria* remain possible infectious triggers. One case of sarcoidosis appearing after Bacillus Calmette-Guèrin (BCG) immunization has been reported. The strong racial proclivity and increased risk for a person to develop sarcoidosis if other family members are affected suggest a genetic predisposition. Polymorphisms in various molecules involved in the inflammatory cascade that results in granuloma formation have been reported. These include genes in the major histocompatibility complex (MHC), some of which increase susceptibility and some of which are protective. Tumor necrosis factor (TNF)-α activating polymorphisms have been associated with Lofgren syndrome. TNF levels are elevated in sarcoidosis and alveolar macrophages spontaneously release more TNF. The rate of spontaneous TNF release correlates with disease progression and steroid resistance. IFN A genotype polymorphism resulting in increased IFN-α and interleukin-12 production is also associated with the development of sarcoidosis. It is unlikely that a single genetic mutation is sufficient to cause the disease, but rather multiple genetic factors would be required for an individual to develop sarcoidosis.

Histopathology

The histology of sarcoidosis in all affected tissues is identical. The characteristic finding is that of the "naked tubercle" composed of collections of large, pale-staining, epithelioid histiocytes. There may be small foci of necrosis in the center of the granulomas and multinucleate giant cells, sometimes with inclusions (asteroid bodies and Schaumann bodies), may be present. Although classically there are few lymphocytes around the granulomas, they may be numerous. The granulomas may be nodular, diffuse, or tubular along neurovascular structures.

The histologic differential diagnosis is broad and the diagnosis of sarcoidosis cannot be definitely made histologically. Allergic granulomas caused by zirconium or beryllium are histologically identical to sarcoidosis. Other foreign-body granulomas (especially as a result of silica), granulomatous rosacea, granulomatous secondary syphilis, tuberculoid leprosy, and leishmaniasis may closely simulate sarcoidosis.

The diagnosis of sarcoidosis is established by the demonstration of involvement consistent with sarcoidosis in two different organ systems. This is usually done histologically. If cutaneous sarcoidal granulomas are identified in a patient with no prior history of sarcoidosis, the first diagnostic test to be performed should be a chest radiograph. If this is abnormal, further pulmonary evaluation is indicated. Ophthalmologic evaluation and conjunctival biopsy may be useful. Blind biopsy of the minor salivary glands may demonstrate sarcoidal granulomas in about 50% of patients with systemic sarcoidosis. Otherwise, histologic evaluation of any involved tissue may be considered.

Sarcoidosis in the Setting of Immunologic Abnormalities

Numerous reports document sarcoidosis occurring in patients with various forms of lymphoma, especially Hodgkin's disease ("sarcoidosis–lymphoma syndrome"). There are numerous reports documenting the appearance of sarcoidisis in association with IFN-α therapy. Cutaneous lesions (50% of patients), pulmonary findings, or both, as well as other features of sarcoidosis, occur in 5% of patients treated with IFN-α for hepatitis C. The addition of ribavirin may increase the risk. However, hepatitis C virus (HCV) infection alone may be associated with the development of sarcoidosis. Treatment

of human immunodeficiency virus (HIV) infection with highly active antiretroviral therapy (HAART) has led to the appearance of sarcoidosis or tattoo granulomas, apparently by enhancing the number and function of helper T-cells. Hematopoetic stem cell transplantation, both allogenic or autologous, has been associated with the appearance of pulmonary sarcoidosis. If the transplantation is performed for malignant disease, the presence of hilar adenopathy may be interpreted as recurrent or metastatic disease and inappropriate treatment may be given.

Differential Diagnosis

Granulomatous secondary syphilis may closely simulate sarcoidosis both clinically and histologically. Blau syndrome, an autosomal-dominant granulomatous disease, is similar to childhood sarcoidosis. It can be distinguished from sarcoidosis by the lack of pulmonary involvement. Granulomatous cutaneous T-cell lymphoma can usually be distinguished histologically and by the presence of pulmonary involvement in sarcoidosis.

Treatment

Numerous therapies have been reported as beneficial in cutaneous sarcoidosis, usually after anecdotal observation. There is virtually no information regarding what types of therapy are best for which of the various cutaneous manifestations. The cutaneous disease may spontaneously remit without treatment. Because most skin lesions are asymptomatic, the major indication for treatment is cosmetic (except for disfiguring facial lesions).

Systemic corticosteroids are virtually always beneficial in cutaneous sarcoidosis. Unfortunately, the doses required to control cutaneous disease may be too high (usually in excess of 15 mg/day) to be ideal for long-term use. For limited skin disease, intralesional injection of 2.5 to 5.0 mg/mL of triamcinolone acetonide suspension is very effective. For thinner lesions, superpotent topical steroids, topical tacrolimus, and UVA1 phototherapy may be effective. A trial of minocycline or doxycycline, up to 100 mg twice a day, may be considered in patients with skin lesions in whom systemic disease does not require treatment. Maximum response is reported to occur at 3 months of therapy.

Systemic corticosteroid therapy is indicated when there is acute systemic involvement with fever and weight loss, in active eye disease, in sarcoidal involvement of the myocardium, in active pulmonary disease with functional disability, in hypersplenism, in hypercalcemia, and in symptomatic CNS involvement.

Antimalarials, both chloroquine and hydroxychloroquine, have been used to treat extensive cutaneous sarcoidosis in doses of 250 mg/day or 200 to 400 mg/day, respectively. About three-quarters of patients appear to respond partially or completely. In some cases the associated pulmonary disease also improves. These agents may also be used to reduce the dose of systemic steroids required.

Methotrexate in doses of 15 to 25 mg/week is also efficacious and seems to help patients with severe lupus pernio or ulcerative sarcoidosis who are otherwise very difficult to treat. Methotrexate-induced hepatitis occurs in 15% of patients with sarcoidosis treated with methotrexate. Leflunomide may be used in analogous fashion to methotrexate and may be used in patients with gastrointestinal intolerance for methotrexate. Response rates are about 75%. The retinoids, principally isotretinoin, have been reported as beneficial in some patients, usually at doses of 0.5 to 1.0 mg/kg. Response is only seen after 6 or more weeks. Thalidomide, 50 to 200 mg/day, has led to improvement of the skin lesions after several months. It should *not* be used to treat pregnant patients, however, because of possible teratogenic effects to the fetus. Venous thrombosis may complicate thalidomide therapy, especially if doses above 100 mg/day are used. While azathioprine and cyclophosphamide had been used for refractory disease, mycophenolate mofetil, has shown efficacy in mucocutaneous disease and may be considered as an effective form of rescue and steroid-sparing therapy. The combination of thalidomide, an immunosuppressive agent, in combination with an antimalarial may be effective when these agents fail individually.

TNF is an important cytokine in the formation of granulomas. Not surprisingly, TNF inhibitors, primarily infliximab but also etanercept, have been reported to be effective in refractory cutaneous and systemic sarcoidosis.

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HISTIOCYTOSES

Certain syndromes that are well-defined clinically and histologically include the term *histiocyte* in their name. This terminology is less than ideal, since there is no cell called a "histiocyte." These disorders are characterized by infiltrates which contain either Langerhans cells (the X-type histiocytoses) or infiltrates of monocytes/macrophages (the non-X histiocytoses).

Zelger B, Burgdorf WHC: The cutaneous "histiocytoses." In: Advances in Dermatology, vol 17, ch 4. St Louis, Mosby, 2001.

Non-X Histiocytoses

Zelger and Burgdorf proposed classifying this group of disorders as the "xanthogranuloma family". Their classification scheme relies on the morphology of the monocyte/macrophage composing the lesion. With each variant, the lesions may be localized (as a single lesion or in the skin) or generalized (multiple, widespread lesions with the potential for systemic involvement). Current terminology tends to give each of these separate entitites its own designation. This ignores relationships of certain groups, such as juvenile xanthogranuloma (JXG) and Langerhans cell histiocytosis (LCH), both of which are proliferations of dendritic cells (Fig. 31-19). Benign cephalic histiocytosis, generalized eruptive histiocytosis, and xanthoma disseminatum occur along a spectrum of localized benign, to generalized but benign, to visceral and progressive disease of the same cell type histologically and immunohistochemically.

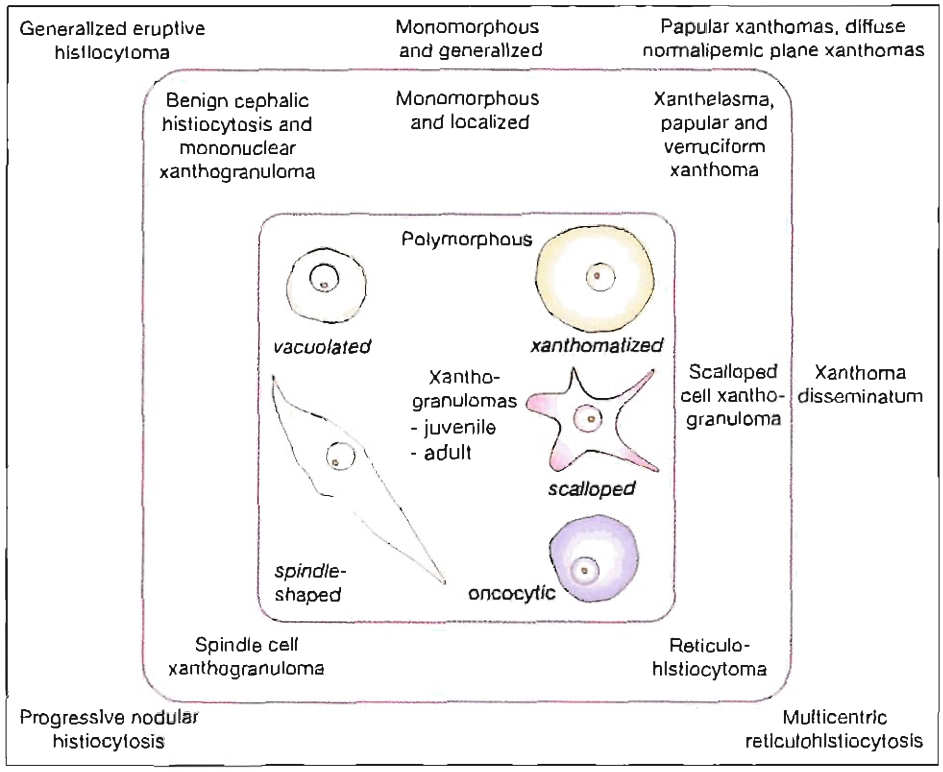

Fig. 31-19 Schematic drawing of unifying concept of non-X histiocytoses.

Juvenile Xanthogranuloma

Juvenile xanthogranuloma (JXG) is the most common non-LCH. Eighty percent of lesions occur before the age of 20. Between 5% and 17% are present at birth and 40% to 70% appear in the first year of life. In adults, lesions tend to occur in the late 20s to early 30s. JXG is 10 times more common in white than black persons, but occurs in all races. In childhood, JXG is slightly more common in males than females, but the gender distribution in adults is equal. Multiple cutaneous lesions affect male children much more commonly (12:1).

Ninety percent of cutaneous JXGs are solitary (Fig. 31-20). They begin as well-demarcated, firm, rubbery, round to oval dermal papules or nodules from 5 to 10 mm in diameter. Early lesions are pink to red with a yellow tinge and become tan–brown over time. Most lesions are asymptomatic. The head and neck are the most common locations, followed by the upper trunk and upper extremities. Lesions have been divided into three forms: small nodular (2–5 mm; Fig. 31-21); large nodular (5–20 mm; Fig. 31-22); and giant xanthogranuloma (>20 mm) types. The small-type lesions are more numerous than the large type. However, often one patient will have both types of lesions and the proposed increased risk for ocular involvement in the micronodular type and other internal involvement in the macronodular type has been refuted. Skin lesions regress spontaneously within 3 to 6 years in children. In adults, lesions are usually persistent. Hyperpigmentation, atrophy, or anetoderma may remain after lesions resolve.

Multiple atypical presentations have been described. These include hyperkeratotic nodules; macronodular tumors from 2 to 10 cm in diameter; clustered forms; flat, plaque-like lesions; and pedunculated lesions. Atypical sites of involvement include the genitalia, lips, palms, soles, earlobes, and fingers. The most common location after the dermis for JXGs

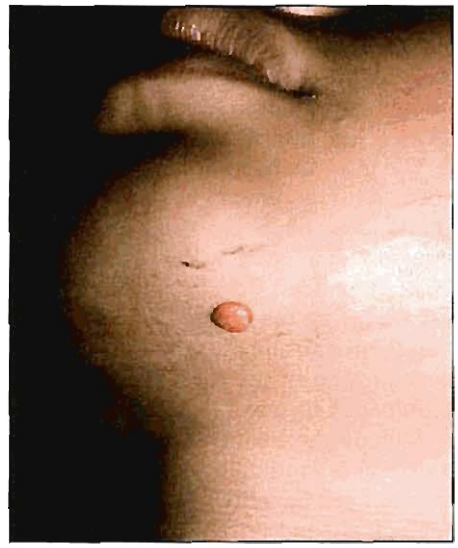

Fig. 31-20 Juvenile xanthogranuloma, solitary.

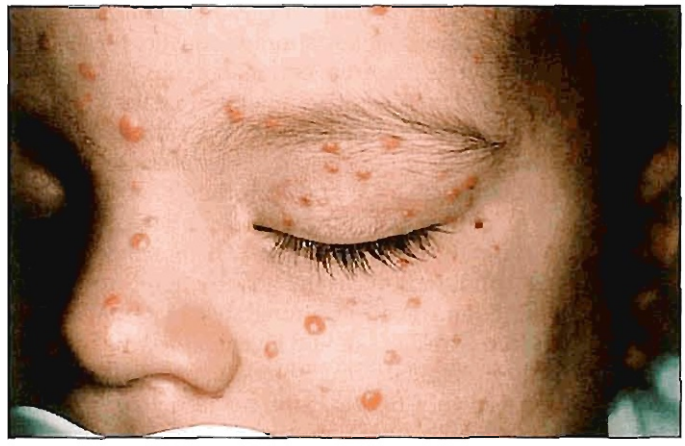

Fig. 31-21 Juvenile xanthogranuloma, multiple small nodular.

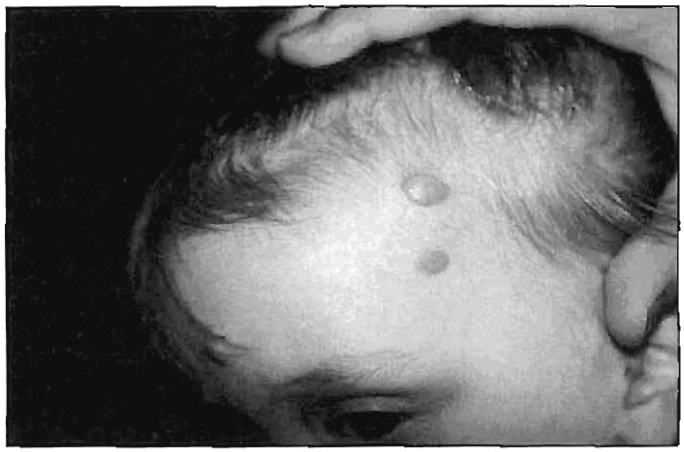

Fig. 31-22 Juvenile xanthogranuloma, multiple large nodular.

is the subcutaneous tissue, again most commonly on the head and neck. About 15% of JXGs present in this manner, usually as a solitary mobile mass up to 3 cm in diameter. Subcutaneous JXG most commonly appears before age 1 and often before age 3 months. Oral JXG may develop in infancy or childhood and is most frequently a solitary lesion of the tongue, lip, or palate.

Extracutaneous JXG is uncommon and occurs either as visceral involvement, in association with multiple cutaneous lesions (5% of JXG cases), or a solitary extracutaneous lesion (also 5% of JXG cases). Ocular involvement occurs in about 0.4% of children with multiple JXGs and 41% of children with ocular JXGs have skin lesions. Skin lesions appear after eye lesions in 45% of cases. Eye lesions usually occur during the first 2 years of life. The most common location is the iris, where JXG can present as a tumor, unilateral glaucoma, unilateral uveitis, with spontaneous hyphema, or as heterochromia iridis. The eyelid or posterior eye may also be involved. Ocular screening is recommended for all children with multiple cutaneous lesions before the age of 2 years.

Mass lesions of the nasal, orbital, and paranasal sinus region can occur and can cause erosion of the orbit and extend to the skull. Other extracutaneous sites and their presentations, in order of frequency, include the lung (respiratory distress and nodular opacities on chest radiograph), liver (hepatomegaly and rarely fatal giant cell hepatitis), testis (mass), and rarely, the CNS, kidney, spleen, and retroperitoneum. Other evaluations for extracutaneous JXGs are not indicated unless there are symptoms or findings suggesting their presence. Extracutaneous lesions also spontaneously regress. If surgical intervention is required, extracutaneous lesions tend not to recur, even if they are incompletely excised.

JXGs have been reported in association with neurofibromatosis (NF-1) and juvenile chronic myelogenous leukemia (JCML). JCML and NF-1 are known to be linked, but since JCML occurs in infancy or early childhood, often café-au-lait macules are the only findings of NF-1 at that time. Sometimes all three conditions affect the same patient, with males having a 3:1 predominance and commonly a maternal history of NF-1. Children with JXG should be examined for stigmata of NF-1. If these stigmata are found, especially in a boy with a maternal history of NF-1, the pediatrician should be alerted of the possible, although uncommon, occurrence of JCML. Rarely, JXG in childhood may be associated with mastocytosis. Multiple xanthogranulomas are rare in adults and for them to occur in an eruptive manner is quite unusual. Three such cases have been associated with hematologic malignancy (lymphocytic leukemia and monoclonal gammopathy).

Lesions appear histologically as nonencapsulated, but circumscribed, proliferations in the upper and mid-reticular dermis and may extend more deeply into the subcutaneous tissue or abut directly on the epidermis with no grenz zone. Epidermotropism does not occur. Classically it has been proposed that the histopathology varies in accordance with the age of the lesion. Very early lesions are composed of mononuclear cells with abundant amphophilic cytoplasm that is poorly lipidized or vacuolated. Later the cells become more vacuolated and multinucleated forms appear. In mature lesions, foam cells, multinucleated foam cells (Touton giant cells) and foreign-body giant cells are present. Touton giant cells are characteristic of JXG but not specific for it. The inflammatory infiltrate consists of lymphocytes, eosinophils, and neutrophils, and lacks plasma cells. Fibrosis occurs in the older lesions. The histology described above is characteristic of cutaneous JXGs. Soft-tissue and visceral JXGs present with more monomorphous cytology, may have very few of the characteristic Touton giant cells, and can have a prominent spindle cell appearance. Immunohistochemistry is especially valuable in confirming the diagnosis of extracutaneous JXG. The cells of JXG of all anatomic locations stain with factor XIIIa, vimentin, and CD68, rarely with CD1, and not with S-100.

It is noteworthy that the pattern of involvement by JXG and LCH are similar, with childhood onset, primary cutaneous involvement, and when visceral disease occurs, the liver, bone and lungs are commonly involved. Without histologic confirmation, isolated JXG of the bone would be most likely diagnosed as isolated LCH, a much more common condition. These clinical similarities between JXG and LCH may be explained by the fact that both diseases are caused by antigen-presenting dendritic cells. JXG is a proliferation of dermal dendrocytes and LCH is a proliferation of Langerhans cells. The clinical features favoring JXG include lack of crusting or scale and the distribution and uniformity of size of lesions. Histologic evaluation is definitive in difficult cases since JXGs are negative for the Langerhans cell marker CD1. Unlike LCH, JXGs are usually negative for S100, although a few S100-positive JXGs have been reported. Benign cephalic histiocytosis (BCH) may be difficult to distinguish both clinically and histologically, but in BCH lesions tend to be flatter and are mainly on the head and neck. Papular xanthoma can be distinguished histologically. Clinically, mastocytosis will urticate when scratched (Darier's sign) and can be distinguished histologically. Solitary JXG appearing in a child must be distinguished from a Spitz nevus, usually requiring a biopsy.

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Benign Cephalic Histiocytosis

BCH is a rare condition affecting boys and girls equally. The onset is between 2 and 34 months of age (rarely up to 5 years), with 50% of cases beginning between ages 5 and 12 months. The disease begins initially on the head in all cases, often the cheeks, eyelids, forehead, and ears. Lesions may later appear on the neck and upper trunk and less commonly more caudad. There are always multiple lesions, but often few in number (5–20), but can number more than 100. Individual lesions are slightly raised, reddish-yellow papules, 2 to 4 mm in diameter. Lesions may coalesce to give a reticulate appearance. The lesions cause no symptoms. The mucosa and viscera are not involved. Lesions spontaneously involute over 2 to 8 years, leaving behind hyperpigmented macules. Some view BCH as a localized childhood variant of generalized eruptive histiocytoma. Histologically, there is a diffuse dermal infiltration of monomorphous macrophages which do not stain with S-100 or CD1a.

Jih DM, et al: Benign cephalic histiocytosis: A case report and review. J Am Acad Dermatol 2002;47:908.

Generalized Eruptive Histiocytoma (Generalized Eruptive Histiocytosis)

The major characteristics of this rare disease are: 1) widespread, erythematous, essentially symmetrical papules, particularly involving the trunk and proximal extremities, and rarely the mucous membranes (there is no visceral involvement); 2) progressive development of new lesions over several years with eventual spontaneous involution to hyperpigmented macules; and 3) a benign histologic picture of monomorphous, vacuolated macrophages. Lesions appear in crops, but are not grouped. They are skin-colored, brown, or violaceous. Generalized eruptive histiocytoma (GEH) is rare in childhood. GEH may be difficult to distinguish from widespread BCH if indeed it is a separate condition. It is separated from xanthoma disseminatum by the lack of visceral disease, the benign course, and by the scalloped appearance of the macrophages in xanthoma disseminatum. GEH may rarely be associated with underlying malignancy, usually leukemia. Histologically, there is a dermal infiltrate of monomorphous vacuolated macrophages and mononuclear histiocytes. The GEH cells stain positively for vimentin, CD68, MAC387, and negatively for S-100, and CD1a. It has been proposed that GEH is an early indeterminate stage of various non-X histiocytoses, including indeterminate cell histiocytosis, multicentric reticulohistiocytosis, xanthogranuloma, and xanthoma disseminatum.

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Xanthoma Disseminatum (Montgomery Syndrome)

Xanthoma disseminatum (XD) is a rare, potentially progressive non-LCH that preferentially affects males in childhood or young adulthood. It is characterized by the insidious onset of small, yellowish-red to brown papules and nodules that are discrete and disseminated. They characteristically involve the eyelids and flexural areas of the axillary and inguinal folds, and the antecubital and popliteal fossae. Over years the lesions increase in number, forming coalescent xanthomatous plaques and nodules. About 50% of cases have mucous membrane involvement, most commonly of the oropharynx (causing dysphagia), larynx (causing dysphonea and airway obstruction), and conjunctiva and cornea (causing blindness). Diabetes insipidus (in 40%) and less commonly other forms of hypopituitarism occur from involvement of the pituitary fossa. CNS involvement with epilepsy, hydrocephalus, and ataxia can occur. In some cases, the disease may spontaneously involute.

The serum lipids are abnormal in 20% of cases, which may lead to confusion with hyperlipidemic xanthomatosis. Histologic examination of early lesions shows surprisingly nonfoamy, scalloped macrophages. Later lesions show xanthoma cells, Touton giant cells, and frequently, a mild inflammatory cell infiltrate of lymphocytes, plasma cells, and neutrophils. The macrophages stain with CD68 and factor XIIIa.

Disseminated xanthosiderohistiocytosis is a variant of XD in which there is a keloidal consistency to the lesions; they have annular borders, a cephalad distribution, and extensive iron and lipid deposition in the macrophages and connective tissue.

Progressive xanthoma disseminatum can produce considerable morbidity and can even be fatal. Therefore, aggressive therapy may be indicated. Cyclophosphamide has led to dramatic improvement in two of three patients so treated.

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Kavalec CC, et al: Xanthoma disseminatum. Arch Ophthalmol 1993;111:1428.
Seaton ED, et al: Treatment of xanthoma disseminatum with cyclophosphamide. Br J Dermatol 2004;150:346.

Progressive Nodular Histiocytosis

Progressive nodular histiocytosis is clinically characterized by the development of two types of lesions: superficial papules and deeper larger subcutaneous nodules. The larger lesions can be up to 5 cm in diameter and are associated with pain and ulceration. The eruption is diffuse and essentially symmetrical without predilection to the flexural areas. On the face, lesions may coalesce, giving the patient a leonine facies. New lesions progressively appear and spontaneous resolution does not occur. Most patients have no mucosal or visceral lesions, although one patient had a hypothalamic lesion leading to precocious puberty and growth hormone deficiency. Histologically, the superficial lesions show foamy macrophages and the deeper lesions a densely cellular proliferation of spindle-shaped histiocytes with multinucleated giant cells. Local excision may be used for symptomatic lesions.

Beswick SJ, et al: Progressive nodular histiocytosis in a child with a hypothalamic tumour. Br J Dermatol 2002;146:138.
Gonzalez A, et al: Progressive nodular histiocytosis accompanied by systemic disorders. Br J Dermatol 2000;143:628.
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Vadoud-Seyedi J, et al: Progressive nodular histiocytomas. Br J Dermatol 2000;143:678.

Papular Xanthoma

Papular xanthoma is a rare form of non-LCH that is poorly defined. It occurs in adults and children and in the latter may involute leaving anetoderma-like scars. The primary lesion is a small, yellow papule from 1 to 10 mm in diameter. There are usually multiple lesions that are generalized. The lesions have no tendency to merge into plaques and do not favor the flexors. There is no visceral involvement and no abnormalities are found on lipid profile examination. Histologically, there are aggregates of xanthomatized foamy macrophages in the dermis with Touton giant cells. Inflammatory cells are scant or absent.

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Hereditary Progressive Mucinous Histiocytosis in Women

Hereditary progressive mucinous histiocytosis is an autosomal-dominant or X-linked hereditary disorder described only in women. The skin lesions consist of a few to numerous skin-colored to red–brown papules up to about 8 mm in diameter that tend to appear on the face, arms, forearms, hands, and legs. Onset is in the second decade of life, with slow progression and no tendency to spontaneous involution. Visceral and mucosal lesions have not been reported. Histologically, in the mid-dermis there is a proliferation of spindle-shaped and epithelioid monocytes, with the later primarily in the upper dermis. Superficial telangiectatic vessels and increased mast cells are found. Abundant mucin is demonstrated by alcian blue staining, indicating the presence of acid mucopolysaccharides. This condition can be distinguished from the other non-LCHs by its familial pattern, lack of lipidized and multinucleated cells, and presence of mucin. Immunoperoxidase studies have been conflicting. The mononuclear cells in one case were factor XIIIa and CD68 positive and in another case were negative for these antigens.

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Reticulohistiocytosis

Two distinct forms of reticulohistiocytosis occur: reticulohistiocytoma and multicentric reticulohistiocytosis. The two forms have identical histology but distinct clinical manifestations.

Reticulohistiocytoma Reticulohistiocytoma usually occurs as a solitary, firm, dermal lesion of less than 1 cm in diameter. Multiple lesions may rarely occur and can be quite extensive and diffuse. Solitary lesions and multiple lesions without systemic involvement, in contrast to multicentric reticulohistiocytosis, have been described mainly in adult men and rarely in children.

Multicentric Reticulohistiocytosis Multicentric reticulohistiocytosis is a multisystem disease beginning usually around age 50 (range 6–86). It is twice as common in women as in men and affects all races. About 25% of reported cases have had an associated malignancy, but no specific type of malignancy is more prevalent. The skin lesions usually appear before the diagnosis of the malignancy, but synchronous behavior of the skin lesions and the underlying malignancy is rarely reported. Given the high frequency of underlying malignancy, however, an evaluation for underlying cancer should be undertaken in a patient with multicentric reticulohistiocytosis.

Clinically, there may be a few to a few hundred firm, skin-colored to red–brown papules and nodules, mostly 2 to 10 mm in diameter, but some reaching several centimeters in size (Fig. 31-23). These occur most frequently on the fingers and hands, with a tendency to cause paronychial lesions. In about half the cases, lesions will be arranged about nailfolds, giving a so-called "coral bead" appearance, which may be associated with nail dystrophy. The upper half of the body, including the arms, scalp, face, ears, and neck are also common sites. Ninety percent of patients have lesions on the face and hands. Characteristic are nodular and papular involvement of the pinnae and a symmetrical distribution of the lesions, especially over joints. The nodules on the arms,

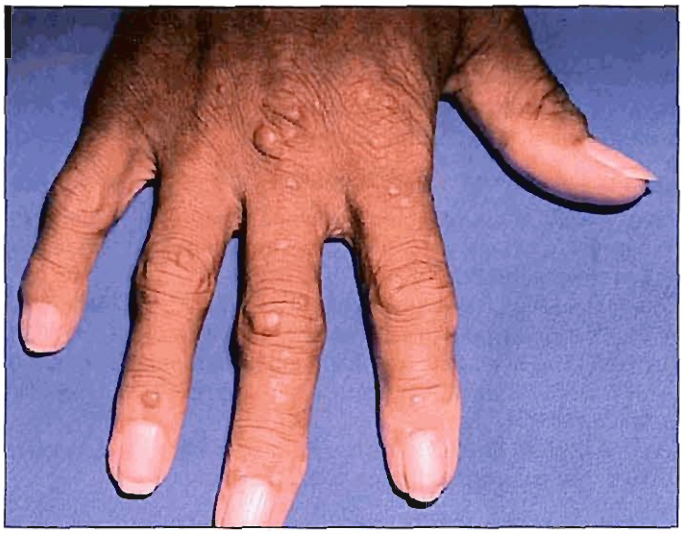

Fig. 31-23 Multicentric reticulohistiocytosis.

elbows, and knees may resemble rheumatoid nodules. Some patients may complain of pruritus.

Mucous membrane involvement is seen in half the cases and is most frequent on the lips and tongue; other sites are the gingiva, palate, buccal mucosa, pharynx, larynx, and sclera. One-third of cases have hypercholesterolemia and xanthelasma. Rheumatoid factor is negative.

Osteoarticular changes are the most important aspect of multicentric reticulohistiocytosis. In 40% of cases joint symptoms precede the appearance of the skin lesions and in 30% the skin and joint disease occurs simultaneously. The associated arthropathy is an inflammatory, symmetrical, polyarticular arthritis that can affect many joints, including the hands, knees, shoulders, wrists, hips, ankles, elbows, feet, and spine. The arthritis can be rapidly destructive and mutilating, with absorption and telescopic shortening of the phalanges and digits—doigts en lorgnette, opera-glass fingers. In older reports at least 50% of cases developed arthritis mutilans, but this has been reduced to about 12% with aggressive early treatment. The joint involvement may resemble rheumatoid arthritis and psoriatic arthritis. Weight loss and fever occur in one-third of patients.

Other organs and tissues may be involved, such as bone, muscle, lymph nodes, liver, myocardium, pericardium, pleura, and stomach. Myocardial involvement may be fatal. Gallium scans have been proposed as a screening method to assess the extent of disease. The clinical course varies. In many instances there is complete involution after about 8 years. The joint destruction is permanent, however, and is a cause of severe disability.

Histologically, the skin lesions are usually centered in the mid-dermis and tend to occupy much or all of the dermis. The infiltrating cells are mononuclear and multinucleate monocyte/macrophages. The giant cells are most characteristic with an abundant smooth, or slightly granular, eosinophilic or amphophilic "ground-glass" cytoplasm. Their cytoplasm is darker in the center than at the periphery. These cells stain positive for periodic-acid Schiff (PAS) after diastase digestion. The overlying epidermis may be thinned but is usually separated from the dermal process by a narrow zone of collagen (Grenz zone). Characteristically, there is polymorphous infiltrate of lymphocytes, neutrophils, eosinophils, and plasma cells within the lesions.

Given the aggressive nature of the arthritis, early and adequate treatment should be considered. However, associated malignancy is frequent and can be worsened by immunosuppressive therapy. The same would be true if there were underlying asymptomatic tuberculosis. Initially, the patient should be screened for these two conditions and they should be adequately treated if found. In patients free of neoplasia and tuberculosis, the treatment is individualized. Spontaneous remissions are common, making efficacy of treatment hard to determine. Initially, in mild cases, low-dose prednisone with antimalarials or low-dose methotrexate could be considered. In severe cases, more aggressive immunosuppressive therapy with a cytotoxic agent such as cyclophosphamide (Cytoxan), 1 to 2 mg/kg/day with or without corticosteroid treatment, could be considered. The lowest dose of cytotoxic should be used to maintain control of the arthritis and the medications discontinued as soon as possible. Alendronate and etanercept have been reported as effective in controlling the arthritis and improving the skin lesions. For patients with skin lesions only, therapy is not required. PUVA, antimalarials, topical nitrogen mustard, and low-dose methotrexate, alendronate, or etanercept could be considered if symptoms are severe.

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Indeterminate Cell Histiocytosis

Indeterminate cells are felt to represent dermal precursors of Langerhans cells. They are S-100 and CD1a positive, but do not contain Birbeck granules. Less than 50 cases of indeterminate cell histiocytosis have been described, half in one report. Children and adults are affected, with males outnumbering females. Solitary and multiple lesions may occur, and the color of lesions varies from yellow to red brown. Lesions may be papules, plaques or nodules from 3 mm to 10 cm in size. Visceral involvement of bone and conjunctiva are rare. Histologically, while the cells in these cases do stain with S-100 and at times with CD1a, the staining is never as intense as Langerhans cells. At times the infiltrating cells in non-LCH can be S-100 positive and weakly and focally CD1a positive. This has led Ratzinger *et al to suggest that* most cases reported as indeterminate cell histiocytosis are some form of non-LCH or sinus histiocytosis with lymphadenopathy, and indeterminate cell histiocytosis is not a distinct entity. Indeterminate cells may be found as a minor component of the dermal infiltrate in nodular scabies and rarely following pityriasis rosea. Severe cutaneous involvement in indeterminate cell histiocytosis has been treated with chemotherapeutic agents similar to those used for LCH including cyclophosphamide, etoposide, vinblastine, systemic corticosteroids, and 2-chlorodeoxyadenosine.

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Sea-Blue Histiocytosis

Sea-blue histiocytosis may occur as a familial inherited syndrome or as an acquired secondary or systemic infiltrative process. The characteristic and diagnostic cell is a histiocytic cell containing cytoplasmic granules that stain blue–green with Giemsa stain and blue with May-Gruenwald stain. The disorder is characterized by infiltration of these cells into the marrow, spleen, liver, lymph nodes, and lungs, as well as the skin in some cases. Skin lesions include papules, eyelid swelling, and patchy gray pigmentation of the face and upper trunk. Similar histologic findings have occurred in patients with myelogenous leukemia, adult Neimann-Pick disease (type B), and following the prolonged use of intravenous fat supplementation. The inherited form may be associated with neurologic symptoms, including ataxia, epilepsy, and dementia.

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X-TYPE HISTIOCYTOSES

This group of disorders is caused by infiltration of the skin, and in some cases other organs, by Langerhans cells. The spectrum of disease is similar to that seen in mastocytosis, with solitary, usually benign and autoinvoluting lesions, multicentric skin-limited disease, and visceral disease. In the LCHs, multicentric skin disease and systemic disease are common, and severe morbidity and mortality are unfortunately not uncommon.

Congenital Self-Healing Reticulohistiocytosis (Hashimoto-Pritzker)

Congenital self-healing reticulohistiocytosis (CSHR) is an autoinvoluting, self-limited form of LCH. CSHR is usually present at birth or appears very soon thereafter. It has been described in two forms: a solitary and a multinodular variant. Solitary or generalized lesions can affect any part of the cutaneous surface. Lesions range from 0.2 to 2.5 cm in diameter (Fig. 31-24). Lesions may grow postnatally. Exceptionally large tumors up to 8 cm in diameter can occur. At presentation the lesions can be papules or nodules with or

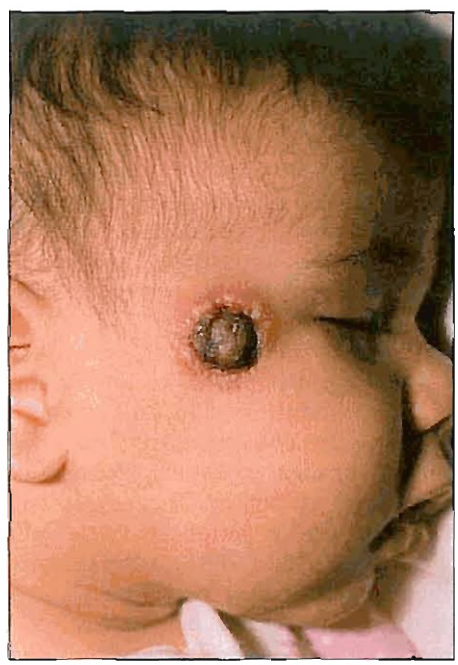

Fig. 31-24 Congenital self-healing reticulohistiocytosis, *solitary lesion.*

without erosion or ulceration. Individual lesions are red, brown, pink, or dusky. Lesions may rarely appear as hemorrhagic bullae. Lesions greater than 1 cm characteristically ulcerate as they resolve. Lesions are asymptomatic and spontaneously involute over 8 to 24 weeks, leaving atrophic scarring from the ulcerated nodules. Internal involvement is not found.

On histologic examination large mononuclear cells and multinucleated giant cells with ground-glass or foamy cytoplasm are present in the dermis and epidermis. Immunoperoxidase staining is positive for CD1, HLA-DR, and S-100. By electron microscopy 10% to 25% of cells have Langerhans cell granules. This histology is characteristic but cannot distinguish this entity from other forms of LCH, so a definitive diagnosis cannot be made histologically.

This is a proliferation of Langerhans cells. Because LCH with systemic involvement may present in identical fashion, systemic evaluation is recommended, including a physical examination, complete blood count, liver function tests, and bone survey. A liver–spleen scan and bone marrow biopsy should be considered.

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Langerhans Cell Histiocytosis (Histiocytosis X)

LCH, or histiocytosis X, is a disease characterized by proliferation of Langerhans cells. This group of disorders can involve many organ systems but affects primarily the bone, skin, lymph nodes, lungs, liver and spleen, endocrine glands, and nervous system. The separation of these conditions into separate entities—Letterer-Siwe disease, Hand-Schuller-Christian disease, and eosinophilic granuloma—is of historical interest only. Currently, the disease is classified by the number of organ systems involved (single or multisystem) (Box 31-1). This classification, as in staging cutaneous T-cell lymphoma, is flawed, since Langerhans cells circulate in the blood and small foci of involvement in internal organs may not be detected. The disease affects primarily children from 1 to 4 years of age, but can present from birth to the ninth decade. It is uncommon, with an incidence of between 4 and 40 per million children per year. It is less common in adults, and presents at an average age of 33 years. The range of clinical features of LCH in any organ is identical in children and adults, but the relative percentages of patients with multisystem disease versus single organ disease differs markedly. Localized disease appears more common in children, primarily as localized bone disease (eosinophilic granuloma of bone). In adults, multisystem disease is most common, and prognosis is better for localized versus multisystem disease, except for isolated pulmonary LCH which represents 15% of all adults with LCH and has the worst prognosis.

Box 31-1 Classification system for Langerhans cell histiocytosis (LCH)

1. Single organ involvement
   - Lung
   - Bone
   - Skin
   - Pituitary
   - Lymph node
   - Other sites
2. Multisystem disease
   - Multiorgan disease with lung involvement
   - Multiorgan disease without lung involvement
   - Multisystem histiocytic disorder

Alternative classification system (relating to old classification scheme)

- Acute disseminated LCH (multifocal, multisystem disease) = Abt-Letterer-Siwe
- Chronic multifocal LCH (multifocal, unisystem disease) = Hand-Schuller-Christian
- Chronic focal LCH (unifocal) = eosinophilic granuloma

The pathogenesis of LCH is unknown. There remains debate as to whether the infiltrating cells are truly neoplastic or simply reactive. It is clear that the infiltrating Langerhans cells are clonal. However, aneuploidy is infrequent and histologically the cells do not appear atypical as in lymphoma. These features have led to the suggestion that the proliferation of Langerhans cells is cytokine related. A family history of LCH is found in about 1% of childhood cases and a lesser percentage of adults. Associated lymphomas, solid tumors, and leukemias have occurred in patients with LCH, with acute lymphoblastic leukemia preceding the appearance of LCH and acute myeloblastic leukemia following it.

Skin Lesions About 10% of children have single-organ disease involving only the skin and 50% have skin involvement, making skin the most commonly involved organ in childhood LCH. Skin involvement occurs in 50% of adults with multisystem LCH, being slightly less common than pulmonary and bone lesions. Only 2% of adult patients with LCH have isolated skin disease. In children and adults, the pattern of skin disease does not predict the presence or extent of systemic disease. The most common form of skin disease in children is that described in Abt-Letterer-Siwe disease. The skin lesions are tiny red, red–brown, or yellow papules that are widespread but favor the intertriginous areas, behind the ears, and the scalp (Figs 31-25 and 31-26).

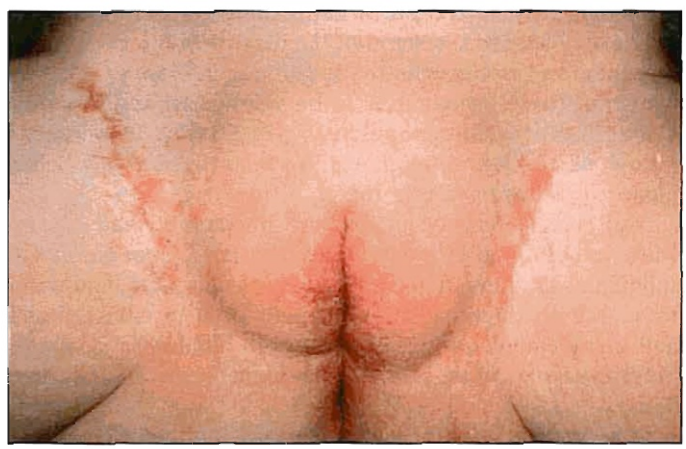

Fig. 31-25 Langerhans cell histiocytosis, erythematous eruption accentuated in the groin folds.

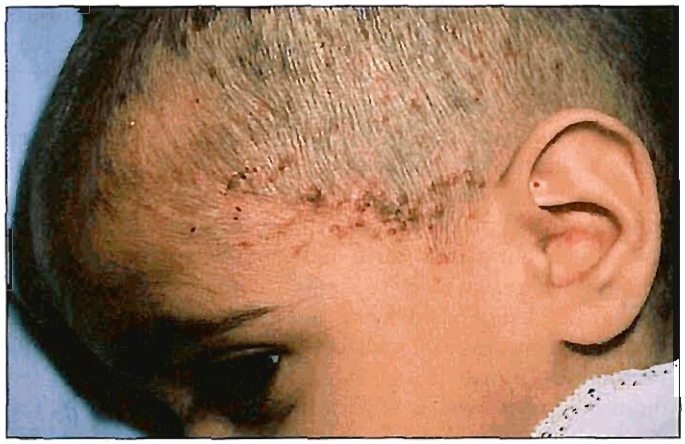

Fig. 31-26 Langerhans cell histiocytosis: seborrheic dermatitis-like eruption with hemorrhage.

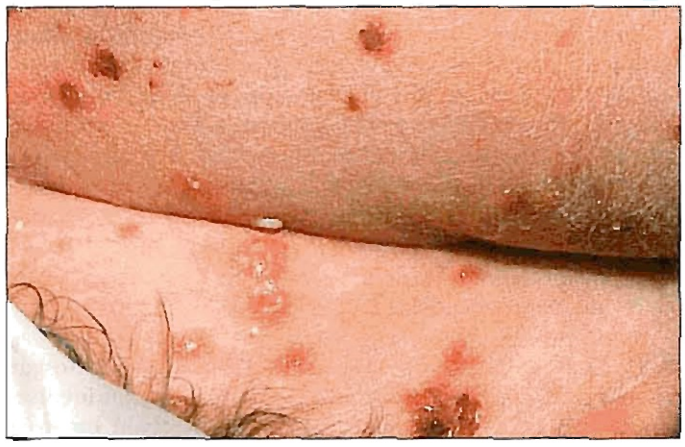

Fig. 31-27 Langerhans cell histiocytosis, bullous lesions.

There is a superficial resemblance to seborrheic dermatitis, but on careful inspection the lesions are individual papules and there is focal hemorrhage in the lesions. The papules are often folliculocentric. Lesions may erode or weep. In children this pattern frequently is associated with multisystem disease. In the rare adult cases, one-quarter have disease limited to the skin. A rare variant of this pattern of LCH is one in which vesicles appear (Fig. 31-27). This can occur in infants or adults. The vesicles are due to large intraepidermal collections of Langerhans cells and a Tzanck smear may lead to suspicion of the diagnosis. A less common presentation is with slightly larger papules up to 1 cm in diameter. These lesions tend to be yellow–red and resemble xanthomas or xanthogranulomas (Fig. 31-28). They can be numerous and widespread. A rare variant resembling lichen planopilaris has been reported.

Nail changes can occur, but are uncommon and can include longitudinal grooving, purpuric striae, hyperkeratosis, subungual thinning, deformities, loss of nail plate, and paronychia. Both fingernails and toenails may be affected and nail involvement has occurred in both children and adults. Most patients with nail involvement have multisystem disease.

LCH restricted to the genitalia is rare, but vulvar, inguinal, and perianal disease may be the initial manifestation of LCH. It tends to be painful and ulcerative, and may simulate hidradenitis suppurativa, since axillary and scalp involvement may also be present.

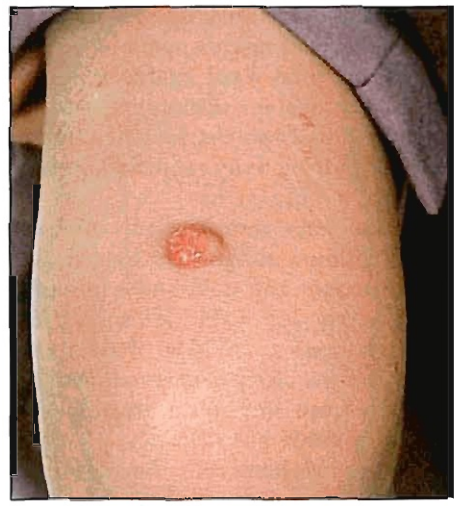

Fig. 31-28 Langerhans cell histiocytosis, xanthomatous nodule in a patient with diabetes insipidus.

Histologically, there is a dense dermal infiltrate of Langerhans cells. This can be superficial and immediately below the epidermis (in small papular and seborrheic-like lesions), folliculocentric, or deep and diffuse (in papular and nodular lesions). The Langerhans cells are recognized by their abundant, amphophilic cytoplasm and eccentric round or kidney bean-shaped nucleus. There is frequently exocytosis of the abnormal cells into the overlying epidermis. If this is extensive, macroscopic vesicles can be seen, and erosion can occur secondarily. The dermal infiltrate is accompanied by many other inflammatory cells, including neutrophils, eosinophils, lymphocytes, and plasma cells. Dermal edema and hemorrhage are characteristically present. In larger and older lesions the infiltrating histiocytic cells become foamy and fibrosis may be present. The histologic features of the Langerhans cells, such as nuclear atypia and mitotic indices, do not predict prognosis and are not reproducible. This makes those cases reported as "malignant" Langerhans cell tumor hard to interpret.

Immunohistochemistry is useful in confirming the diagnosis. The infiltrating cells in LCH are S-100 and CD1a positive. Electron microscopy will detect the presence of Birbeck granules. In older lesions and in some organ systems the number of cells staining with these markers and containing Birbeck granules is much diminished. The number of Birbeck granules and the presence of other intracellular structures, such as lamellar bodies, are not useful in classifying LCH cases.

Oral Mucosa Lesions The oral mucosa may be involved. Periodontal involvement is most common, affecting primarily the jaw (Fig. 31-29). Alveolar bone is lost with detachment of the teeth which on x-ray appear to be "floating." Palpable masses and gingival lesions should be looked for and a dental evaluation completed in all patients. Bilateral parotid swelling may occur.

Visceral Involvement The most commonly involved organ is the bone (Fig. 31-30). In various series between one- and two-thirds of pediatric patients and 12% of adult patients have disease limited to one or several bones. The lesions may be asymptomatic or cause pain. The skull is most commonly involved, followed by the long bones, then the

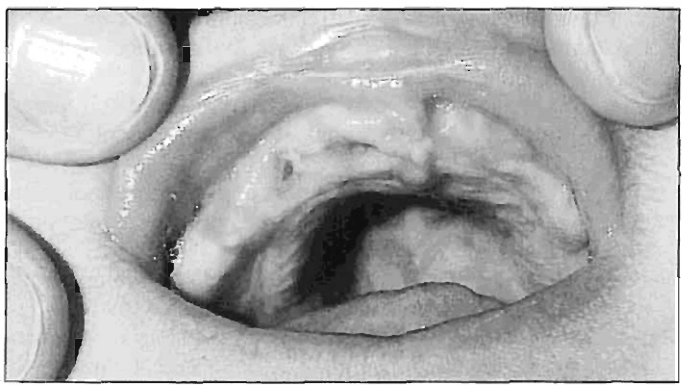

Fig 31-29 Langerhans cell histiocytosis, gingival lesions.

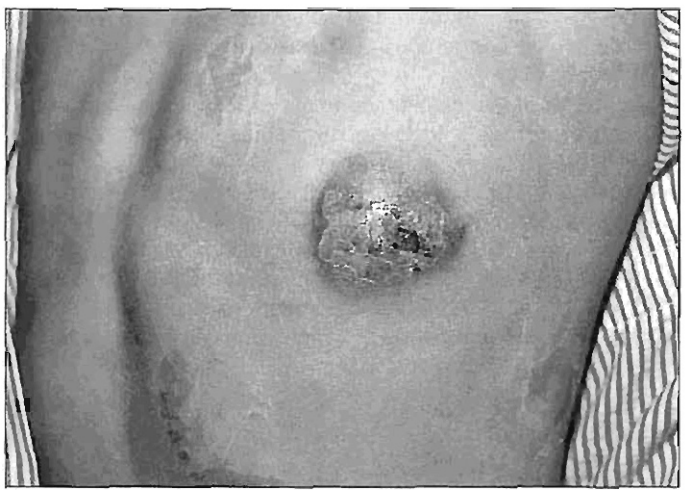

Fig. 31-30 Langerhans cell histiocytosis, eosinophilic granuloma of rib that eroded through to the skin.

flat bones. Bony lesions tend to occur in older children and young adults. Lesions are treated with curettage, intralesional corticosteroids, or radiation. Endocrine dysfunction occurs usually in the form of diabetes insipidus, which is more common in patients with bone disease of the skull and in patients with extensive disease.

Lymph nodes are characteristically involved, especially the cervical nodes. The bone marrow may be affected and the presence of pancytopenia is usually associated with a poor prognosis in childhood LCH. This may present as purpura in the skin.

The liver may be involved directly by infiltration with Langerhans cells or may be indirectly affected by enlarged nodes in the porta hepatis leading to obstructive disease. Either pattern can lead to biliary cirrhosis.

Pulmonary LCH occurs on average at age 33 years. A diffuse micronodular pattern on chest radiograph may progress to cyst formation (honeycomb lung), large bullae, and pneumothorax. More than 90% of adults with pulmonary LCH are smokers. Five-year survival is 88%.

Prognosis

In childhood LCH outcome is determined by the extent of involvement and, more importantly, the function of affected organs. Children younger than 2 years with multisystem disease have the worst prognosis, with a 37% mortality, as opposed to 16% for children over the age of 2 years. Early, initial response to multidrug chemotherapy in childhood multisystem LCH is an important predictor of survival, with 92% of responders and 11% of nonresponders after 6 weeks of treatment surviving. In adults, isolated disease, except pulmonary disease, has the best prognosis. Multisystem LCH in adults has a 5-year survival of 91.7%. Baseline and repeated evaluation are important. Lesions in one organ system may resolve while disease progresses in another organ. Skin lesions may spontaneously resolve, only for the disease to relapse, even years later, so patients must be followed regularly. In addition, if chemotherapeutic agents are used for treatment, a risk of secondary malignancies of less than 5% exists.

Differential Diagnosis

The diffuse small papular form is frequently misdiagnosed as seborrheic dermatitis. The yellow color of the lesions and the presence of hemorrhage in the small papules, if present, should suggest the diagnosis of LCH. Nodular lesions of scabies can closely simulate LCH. This includes the finding of Langerhans or indeterminate cells in the dermal infiltrate by electron microscopy and S100 and CD1a staining. The larger papules resemble juvenile xanthogranulomas and xanthomas. Erosive genital disease may simulate hidradenitis.

Treatment

Treatment is not always required. LCH may spontaneously remit, especially cases of isolated skin or bone disease. For disease limited to the skin, topical corticosteroids may be used. Topical nitrogen mustard 20% (as used for cutaneous T-cell lymphoma) is an effective nonsystemic approach. Some patients with superficial lesions have responded to PUVA. Thalidomide has been successful in doses from 50 to 300 mg/day in skin and genital disease, but associated visceral disease may not respond in parallel. Low-dose methotrexate 20 mg/week has been effective in treatment-resistant cutaneous disease. IFN-α, 3 MU three times a week, has cleared cutaneous lesions and improved visceral disease. Intralesional IFN can be effective. Radiotherapy is less effective for mucocutaneous disease than bone disease.

In multisystem disease of childhood, vinblastine and corticosteroids are the current standard for treatment. Cyclosporin, methotrexate, cytarabine, and 6-mercaptopurine can all be effective. Combination therapy may be used. In refractory cases, 2-chlorodeoxyadenosine has been successful. Etoposide is not currently recommended by the Histiocyte Society, due to concerns regarding secondary leukemias. Autologous or allogenic stem cell rescue has rarely been performed. Liver transplantation for end-stage liver disease resulting from LCH is complicated by an increased risk of acute rejection and, possibly, an increased risk of post-transplant lymphoproliferative disorder. Basiliximab may be used.

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CHAPTER

32 Cutaneous Lymphoid Hyperplasia, Cutaneous T-Cell Lymphoma, Other Malignant Lymphomas, and Allied Diseases

CUTANEOUS LYMPHOID HYPERPLASIA (LYMPHOCYTOMA CUTIS, LYMPHADENOSIS BENIGNA CUTIS, PSEUDOLYMPHOMA)

The term *cutaneous lymphoid hyperplasia* refers to a group of benign disorders characterized by collections of lymphocytes, macrophages, and dendritic cells in the skin. These processes can be caused by known stimuli (such as medications, injected foreign substances, infections, or the bites of arthropods) or they may be idiopathic. They may have a purely benign histologic appearance or resemble cutaneous lymphoma. If there is a histologic resemblance to lymphoma, the term *pseudolymphoma* was used in the past. Most cases contain a mixed population of T- and B-cells, but they may contain mostly T-cells. By standard techniques, most cases of cutaneous lymphoid hyperplasia will be found to lack clonality. Cases of monoclonal B- and T-cell cutaneous lymphoid hyperplasia do occur. Thus, a finding of monoclonality does not equate to the diagnosis of malignancy or lymphoma, nor does it predict biologic behavior. A subset of polyclonal or monoclonal (T- or B-cell) cutaneous lymphoid hyperplasias does progress to cutaneous B-cell and less commonly T-cell lymphoma. Even when the initial evaluation detects a T-cell rich infiltrate (>90%), which may be monoclonal, the lymphoma which eventuates from this form of cutaneous lymphoid hyperplasia may be B-cell. Thus, as in many cancer syndromes, cutaneous lymphoid hyperplasia represents the benign end of a spectrum of cutaneous lymphoid proliferation with cutaneous lymphoma at the other end and cases falling everywhere along that spectrum of progression. Unfortunately, current techniques cannot predict accurately which cases will progress.

Histologically, the cutaneous lymphoid hyperplasias also represent a spectrum of disease. At one end are cases that are benign in appearance. Intermediate cases are histologically atypical but with benign clinical behavior. (In the past, the term "pseudolymphoma" might have been used.) At the other end are cases that are histologically ambiguous, some of which may progress to lymphoma or represent lymphoma from the onset but which cannot reliably be diagnosed. Clonality studies for both T- and B-cell markers may show clonality for either or both in some cases of cutaneous lymphoid hyperplasia. The clonality studies do not correlate directly with cytologic features; cases with clonal T-cell gene rearrangement may progress to cutaneous B-cell or T-cell lymphoma; and both cases with and without clonality may progress to cutaneous B-cell lymphoma. This makes evaluation of some cutaneous lymphoid infiltrates very challenging. The clinician must provide the dermatopathologist with accurate and complete information and an adequate full thickness tissue sample to evaluate. Any change in clinical behavior or morphology may be an indication for repeat histologic, immunophenotypic, and immunogenetic evaluation to exclude the development of true cutaneous lymphoma. Lymphoid hyperplasias that occur in the setting of immunosuppression may behave aggressively, like lymphomas, but regress with the discontinuation of immunosuppression.

Two clinical patterns of cutaneous lymphoid hyperplasia exist. The nodular form consists of nodular and diffuse dermal aggregates of lymphocytes, macrophages, and dendritic cells. The clinical and histologic differential diagnosis is cutaneous B-cell lymphoma. The diffuse type is usually associated with drug exposure or photosensitivity (actinic reticuloid). Histologically it is to be distinguished from cutaneous T-cell lymphoma.

Cutaneous Lymphoid Hyperplasias (Nodular Pattern)

The nodular pattern of cutaneous lymphoid hyperplasia is the most common pattern. It usually presents in adults and is two to three times more common in women. It favors the face (cheek, nose, or earlobe) and the majority of cases present as a solitary or localized cluster of asymptomatic, erythematous to violaceous papules or nodules (Fig. 32-1). Less commonly, lesions may affect the trunk (36%) or extremities (25%). At times the lesions may coalesce into a plaque or be widespread in one region, in which case they present as miliary papules. Systemic symptoms are not present and except for rare cases with regional lymphadenopathy, there are no other physical or laboratory abnormalities. Etiologically, it is usually idiopathic, but can be caused by tattoos, *Borrelia* infections, herpes zoster scars, antigen

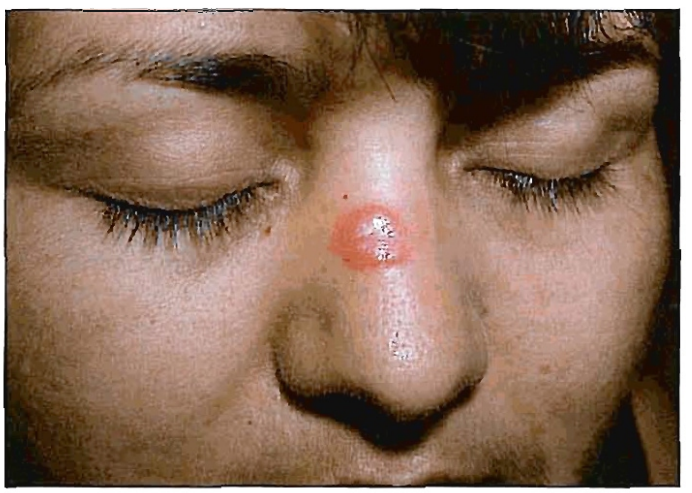

Fig. 32-1 Reactive lymphoid hyperplasia.

injections or acupuncture, and, in rare cases, drug reactions and persistent insect bite reactions. Lesions that result from a known stimulus tend to be localized to the site of the original process—tattoo, injection, or insect bite.

Borrelia-induced cutaneous lymphoid hyperplasia is an uncommon manifestation of this infection, occurring in 0.6% to 1.3% of cases reported from Europe. The lack of borrelial pseudolymphoma in the US compared with Europe may relate to the fact that there are different borrelial species in Europe, specifically *Borrelia afzeli*, that cause borreliosis. Lesions occur at the site of the tick bite or close to the edge of a lesion of erythema migrans. Lesions may appear up to 10 months after infection. Lesions may be multiple and favor the earlobes, nipple and areola, nose, and scrotal area and vary from 1 to 5 cm in diameter. Usually there are no symptoms, but associated regional lymphadenopathy may be present. Late manifestations of *Borrelia* infection are uncommon. The diagnosis is suspected by a history of a tick bite or erythema migrans, the location (earlobe or nipple), and the histologic picture. The diagnosis is confirmed by an elevated anti-*Borrelia* antibody (present in 50% of cases) and the finding of borrelial DNA in the affected tissue. The treatment is penicillin. Some cases progress to true lymphoma.

Histologic examination of nodular cutaneous lymphoid hyperplasia reveals a dense, nodular infiltrate that occupies primarily the dermis and lessens in the deeper dermis and subcutaneous fat, i.e. it is "top-heavy." The process is usually separated from the epidermis by a clear grenz zone. The infiltrate is composed chiefly of mature small and large lymphocytes, histiocytes, plasma cells, dendritic cells, and eosinophils. In the deeper portions, well-defined germinal centers are usually seen, with central large lymphoid cells with abundant cytoplasm and tingible body macrophages, and a peripheral cuff of small lymphocytes.

The clinical lesions may be nondescript and the differential diagnosis quite broad, usually mandating a biopsy. Amyloidosis, sarcoidosis, secondary syphilis, and lymphoma should be considered. Histologically, the primary differential diagnosis is cutaneous lymphoma. Histologic criteria and even immunophenotyping and immunogenetic analysis may not be sufficient to predict biologic behavior. Most cases are mixed B- and T-cell proliferations, but about 10% of cases are primarily T-cell infiltrates (>90% T-cells). CD30+ cells may be prominent, raising the concern about the development of a CD30+ lymphoproliferative disorder.

Because most lesions are asymptomatic, treatment is not required. If the process has been induced by a medication, use of the medication should be discontinued. Infection should be treated and localized foci of infection removed. Intralesional steroidal agents are sometimes beneficial, but lesions may recur in a few months. Potent topical steroids may also be tried for superficial lesions. Cryosurgery, thalidomide 100 mg/day for a few months, interferon (IFN)-α, laser ablation, or surgical excision can all be effective. Low-dose radiation therapy is usually very effective and may be used on refractory facial lesions that cannot be satisfactorily removed surgically. If monoclonality is detected in a localized lesion, complete removal and local radiation has been recommended, but there is no evidence this improves outcome, and lesions that are not initially monoclonal may also progress to lymphoma.

Cutaneous Lymphoid Hyperplasias (Bandlike and Perivascular Patterns)

Cutaneous lymphoid hyperplasias may histologically show a bandlike and perivascular dermal infiltrate, at times with epidermotropism. They may be idiopathic or caused by photosensitivity (formerly called *actinic reticuloid;* now called *chronic actinic dermatitis*), medications (usually anticonvulsants, but also many others), or contact dermatitis (so-called lymphomatoid contact dermatitis).

Clinically, these patients have lesions that clinically resemble mycosis fungoides: they have widespread erythema with scaling. Thicker plaques may occur as well and these cases are frequently caused by medications. The treatment is to stop any implicated medication. If stopping the medication is ineffective, topical and intralesional steroids, PUVA, and, for persistent localized lesions, radiotherapy may be considered.

The cytologic appearance of the atypical lymphocytes is usually adequate to identify cases of small cell lymphoma that may mimic lymphoid hyperplasia. Such lymphomas are usually of B-cell origin, so immunophenotyping is helpful. If T-cells are identified, immunogenetic studies to detect T-cell receptor clonal rearrangements should be considered. If monoclonality is identified, the case must be carefully evaluated for systemic involvement (including computed tomographic [CT] scans of the chest, abdomen, and pelvis, and perhaps a bone marrow biopsy). Distinguishing monoclonal T-cell lymphoid hyperplasia from small cell lymphoma may be very difficult.

Jessner Lymphocytic Infiltrate of the Skin

The existence of this entity has recently been challenged. Even the coauthors of the original paper feel their cases would now best be classified as a variant of lupus erythematosus. Clinically, Jessner is a persistent papular and plaque-like eruption that is photosensitive and occurs primarily on the face. Histologically there is a superficial and deep perivascular and periadnexal lymphocytic infiltrate. Interface dermatitis is absent. The infiltrating lymphocytes are suppressor T-cells (CD8+). It is distinguished from cutaneous lupus erythematosus by the absence of an interface dermatitis, lack of mucin, and negative direct immunofluorescence. Tumid lupus erythematosus has predominantly helper T-cells in the infiltrate. Since the spectrum of chronic cutaneous lupus erythematosus has expanded to include tumid lupus erythematosus and subacute cutaneous lupus erythematosus, however, the diagnosis of lupus erythematosus can now be made in cases lacking an interface dermatitis and with negative serologies and direct immunofluorescence. Polymorphous light eruption (PMLE) is distinguished from Jessner by having edematous papules and plaques that are more transient, and by the presence of dermal edema. In PMLE the infiltrating cells are CD8+. There may still exist true cases of lymphocytic infiltration of the skin. To clearly distinguish them from lupus erythematosus and PMLE, the lesions must contain predominantly CD8+ suppressor T-cells, lack dermal mucin and dermal edema, be fixed (not transient like PMLE), and patients must have negative direct immunofluorescence and serologic testing for lupus erythematosus. Both Jessner and chronic cutaneous lupus erythematosus can respond to antimalarials.

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CUTANEOUS LYMPHOMAS

Cutaneous lymphoma can be considered to be either primary or secondary. Primary cutaneous lymphomas are those that occur in the skin and where no evidence of extracutaneous involvement is found for some period after the appearance of the cutaneous disease. Cases of simultaneous skin and lymph node involvement (except for cases of mycosis fungoides with lymph node involvement) cannot always be absolutely classified as primary because the "origin" of the lymphoma cannot be determined. Secondary cutaneous lymphoma includes cases that have simultaneous or preceding evidence of extracutaneous involvement. These cases are best classified and managed as lymph node-based lymphomas with skin involvement. This conceptual separation is not ideal, but it has been important in developing classification schemes and determining prognosis in cutaneous lymphomas.

For many years classification of lymphomas has been based on their histologic appearance, and lesions from all organ systems were classified histomorphologically in an identical manner to lymphomas arising in lymph nodes. It had been recognized that these classification schemes have major shortcomings when applied to extranodal lymphomas. Specifically, they did not uniformly predict clinical behavior. New classification schemes have been developed that are specific for primary cutaneous lymphomas. In the following discussion, the classification scheme followed incorporates the EORTC, REAL, and WHO classifications.

Cutaneous lymphomas are classified based on their cell type of origin. There are B-cell lymphomas, T-cell lymphomas, true histiocytic lymphomas, and rarer types. Cell type is further classified by specific lymphoid markers associated with features of normal lymphocytes. Histologic features used in this classification system include cell size (large versus small) and differentiation features (follicular center cell, immunoblast, and so on). These features are supplemented by immunophenotypic markers such as CD30. Despite these major conceptual and diagnostic advances, the diagnosis and classification of cutaneous lymphomas can still be quite difficult. Because appropriate classification may be prognostically important, experienced dermatopathology consultation should be sought in cases of cutaneous lymphoma.

Primary Cutaneous T-Cell Lymphomas

A major insight into cutaneous lymphoma was the finding that the majority of lymphomas in the skin were of T-cell origin. This is logical, since T-cells normally traffic through the skin and are important in "skin-associated lymphoid tissue." Unfortunately, dermatologists frequently use the term *cutaneous T-cell lymphoma* synonymously with mycosis fungoides. Although mycosis fungoides represents the large majority of primary cutaneous T-cell lymphomas, it is not synonymous with cutaneous T-cell lymphoma. In fact, up to 30% of primary cutaneous T-cell lymphomas are not mycosis fungoides.

Because cutaneous Hodgkin's disease is very rare to nonexistent, the term *non-Hodgkin lymphoma* has little meaning when speaking of a lymphoma in the skin, because virtually all cutaneous lymphomas are "non-Hodgkin lymphomas." The term *non-Hodgkin lymphoma* may sometimes also be applied in cases of secondary cutaneous lymphoma. The following discussion is divided into mycosis fungoides and related conditions, Sézary syndrome, and lymphomatoid papulosis; and non-mycosis fungoides primary cutaneous T-cell lymphomas.

Mycosis Fungoides Mycosis fungoides is a malignant neoplasm of T-lymphocyte origin, almost always a memory T-helper cell. The incidence is 1 in 300,000 per year. Mycosis fungoides affects all races. In the US black persons are relatively more commonly affected than white persons. The condition is twice as common in males as in females.

Natural History

In general, mycosis fungoides is a chronic, slowly progressive disorder. It usually begins as flat patches (patch stage), which may or may not be histologically diagnostic of mycosis

fungoides (hence the term *premycotic*). This inability to diagnose early cases has more to do with the limits of diagnostic capabilities, rather than a transformation from some non-neoplastic (premycotic) condition to mycosis fungoides, and these cases are best considered mycosis fungoides from the onset. Pruritus, sometimes severe, is usually present at this stage. Over time, sometimes years, the lesions become more infiltrated, and the diagnosis is usually confirmed with repeated histologic evaluation. Infiltrated plaques occur eventually (plaque stage). In some cases tumors may eventually appear (tumor stage). Some patients may present with or progress to erythroderma. Most rarely, patients may present with tumors de novo, the so-called *d'emblée* form. With immunophenotyping, many of these cases are now recognized as non-mycosis fungoides CD30+ T-cell lymphomas. Eventually, in some patients, noncutaneous involvement is detected. This is most commonly first identified in lymph nodes. Peripheral blood involvement and visceral organ involvement may also occur.

In general, mycosis fungoides affects elderly patients and has a long evolution. For this reason, many patients die of other conditions rather than of mycosis fungoides. However, once tumors develop or lymph node involvement occurs, the prognosis is guarded and mycosis fungoides can be fatal. In most fatal cases the patient dies of septicemia. Early, aggressive chemotherapy in an attempt to "cure" mycosis fungoides is associated with excessive morbidity and mortality and is not indicated.

Evaluation and Staging

The North American Mycosis Fungoides Cooperative Group has developed a staging system. Because mycosis fungoides is a systemic disease from the onset (as lymphocytes naturally traffic throughout the body), concepts used for solid tumors such as tumor burden and metastasis cannot be readily applied. The TNMB system scores involvement in the skin (T), lymph node (N), viscera (M), and peripheral blood (B). Skin involvement is divided into less than 10% (T1), more than 10% (T2), tumors (T3), and erythroderma (T4). Node involvement is normal clinically and pathologically (N0), palpable but pathologically not mycosis fungoides (N1), not palpable but pathologically mycosis fungoides (N2), or clinically and pathologically involved (N3). Viscera and blood are either not involved (M0 and B0) or involved (M1 and B1). Stage IA is T1,N0,M0; stage IB is T2,N0,M0; stage IIA is T1–2,N1,M0; stage IIB is T3,N0–1,M0; stage IIIA is T4,N0,M0; stage IIIB is T4,N1,M0; stage IVA is T1–4, N2–3,M0; and stage IVB is T1–4,N0–3,M1. The "B" or blood status does not alter staging of the disease.

A staging work-up would include a complete history and physical examination, with careful palpation of lymph nodes and mapping of skin lesions; a complete blood cell count with assays for circulating atypical cells (*Sézary cells*); serum chemistries including renal and liver function tests with lactic dehydrogenase; a chest radiograph evaluation; and a skin biopsy. If lymph nodes are palpable, they should be examined histologically. Fine-needle aspiration is not an ideal mode of evaluation since early lymph node involvement may be localized to certain areas of the affected nodes, and architectural evaluation is often required to detect early lymph node involvement. If any abnormalities are detected through the above evaluations, they should be pursued. CT scans can be performed to assess chest, abdominal, and pelvic lymph nodes, and visceral organs. These are useful in patients with stage II–IV disease, but are not indicated in patients with stage IA disease. Whether patients with stage IB disease should undergo these tests is unknown.

The value of this staging system is confirmed in large series. Stage IA patients have a life-expectancy identical to a control population; only 8% to 9% progress to have more advanced disease; and only 2% die of their disease. By contrast, patients with T2 disease have a shorter survival time than control subjects (median survival of 11.7–15.6 years). Twenty-four percent of T2 patients progress to more advanced disease. T3 patients have a median survival of 3.2 to 8.4 years, and T4 patients of 1.8 to 3.7 years. Palpable adenopathy is associated with a median survival of only 7.7 years, whereas patients without adenopathy have a survival of 21.8 years. Lymphadenopathy, tumors, or cutaneous ulceration are cardinal prognostic factors; no patient dies without having developed one of them and patients with all three (in any order) survive a median of 1 year.

Clinical Features

In the early patch/plaque stage, the lesions are macular or slightly infiltrated patches or plaques varying in size from 1 to 5 cm or more. The eruption may be generalized or begin localized to one area and then spread. The lower abdomen, buttocks, upper thighs, and breasts of women are preferentially affected. The lesions may have an atrophic surface, or present as true poikiloderma with atrophy, mottled dyspigmentation, and telangiectasia. Poikiloderma vasculare atrophicans is now recognized as a clinical form of patch-stage mycosis fungoides. Likewise, large plaque parapsoriasis and rare cases of small-plaque parapsoriasis are early patch-stage lesions of mycosis fungoides (Fig. 32-2). Small-plaque parapsoriasis with poikilodermatous change is suspicious for mycosis fungoides, whereas typical digitate dermatosis probably never evolves into mycosis fungoides. "Invisible" mycosis fungoides is generalized skin involvement which is not visible to the naked eye, but can be documented histologically. With current diagnostic methods this can usually be confirmed. In general, the patch-stage lesions resemble an eczema, being round or ovoid, but annular, polycyclic, or arciform configurations can occur. Less common forms are the verrucous or hyperkeratotic form, the hypopigmented form (Fig. 32-3), lesions resembling a pigmented purpura, and the vesicular, bullous, or pustular form. The hypopigmented form seems to be more common in persons of color and is a common presentation for adolescents and children with mycosis fungoides.

In the plaque stage, lesions are more infiltrated and may resemble psoriasis, a subacute dermatitis, or a granulomatous dermal process such as granuloma annulare (Fig. 32-4). The palms and soles may be involved with hyperkeratotic, psoriasiform, and fissuring plaques. The infiltration of the plaques, at first recognized by light palpation, may be present in only a few of the lesions (Fig. 32-5). It is a manifestation of diagnostic importance. Different degrees of infiltration may exist even in the same patch and sometimes it is more pronounced peripherally, the central part of the plaque being depressed to the level of the surrounding skin. The infiltration becomes more marked and leads to discoid patches or extensive plaques, which may be as wide as 30 cm.

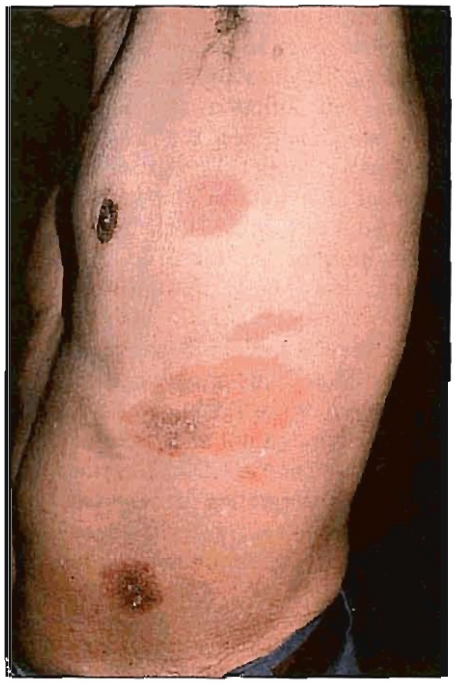

Fig. 32-2 Mycosis fungoides, patch stage, with small and large patches.

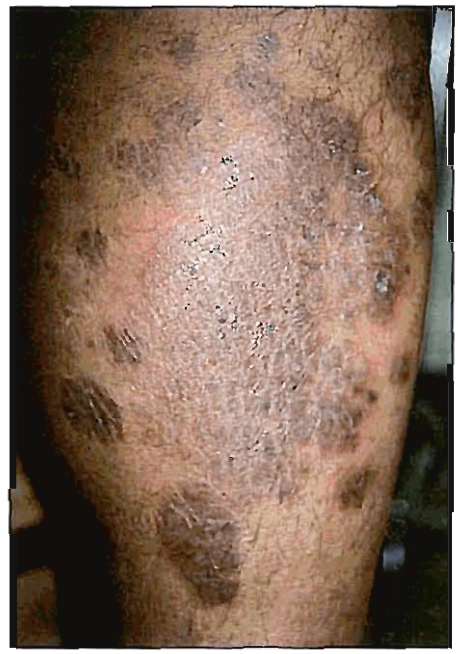

Fig. 32-4 Mycosis fungoides, patch/plaque stage.

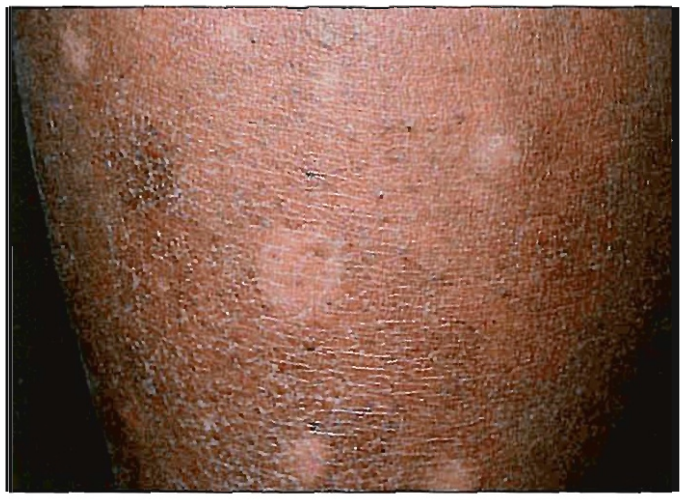

Fig. 32-3 Mycosis fungoides, hypopigmented patches.

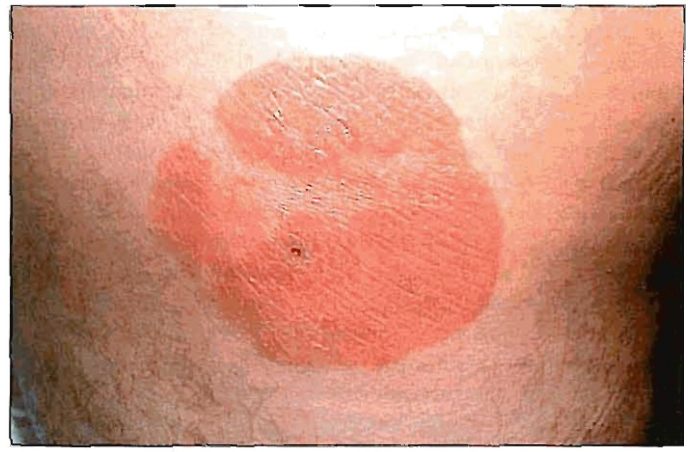

Fig. 32-5 Mycosis fungoides, plaque stage.

Eventually, through coalescence of the various plaques, the involvement becomes widespread, but there are usually patches of apparently normal skin interspersed. When the involvement is advanced, painful superficial ulcerations may occur. During this phase enlarged lymph nodes usually develop. They are nontender, firm, and freely movable.

The tumor stage is characterized by large, various sized and shaped nodules on infiltrated plaques and on apparently normal skin. These nodules have a tendency to break down early and to form deep oval ulcers, with bases covered with a necrotic grayish substance and with rolled edges. The lesions generally have a predilection for the trunk, although they may be seen anywhere on the skin or may involve the mouth and upper respiratory tract. Uncommonly, tumors may be the first sign of mycosis fungoides.

The erythrodermic variety of mycosis fungoides is a generalized exfoliative process, with universal redness. The hair is scanty, nails dystrophic, palms and soles hyperkeratotic, and at times there may be generalized hyperpigmentation. Erythroderma may be the presenting feature.

Alopecia Mucinosa. The infiltrating cells of mycosis fungoides can demonstrate a predilection to involve the hair follicle. This may be observed simply by folliculotropism of the cells (pilotropic or follicular mycosis fungoides) or by the appearance of follicular mucinosis. In all cases of follicular mucinosis, the histologic specimen should be carefully examined and the diagnosis of mycosis fungoides considered. Among patients older than 40 years of age who have follicular mucinosis, a large percentage will have mycosis fungoides or go on to develop it. However, the finding of a T-cell clone in lesions of follicular mucinosis without mycosis fungoides does not increase the likelihood of the development of cutaneous T-cell lymphoma.

Selective tropism of the cutaneous T-cell lymphoma cells to the sweat glands and ducts is termed syringotropic cutaneous T-cell lymphoma. It is often seen in conjunction with follicular involvement. Syringolymphoid hyperplasia may be seen in these cases histologically, and cases previously

termed syringolymphoid hyperplasia with alopecia are now considered to have cutaneous T-cell lymphoma. Clinically, the lesions present as discrete follicular and nonfollicular erythema along with alopecia, milia, and follicular cysts. The initial clinical diagnosis in such cases is often discoid lupus erythematosus. The prognosis in mycosis fungoides with adnexal involvement is as predicted by the staging system for other forms of mycosis fungoides.

Systemic Manifestations

Mycosis fungoides as a form of malignant lymphoma may progress to have visceral involvement. Lymph node involvement is most common; it predicts progression of the disease in at least a quarter of patients and reduces survival to about 7 years. Any other evidence of visceral involvement is a grave prognostic sign. An abnormal result on liver–spleen scan, chest radiograph or CT evaluation, abdominal or pelvic CT scans, or bone marrow biopsy is associated with a survival of about 1 year.

Pathogenesis

Mycosis fungoides is a neoplasm of memory helper T-cells in most cases. Rare cases of suppressor cell (CD8+) mycosis fungoides have been reported. These CD8+ cases may behave indolently, like mycosis fungoides, or aggressively. The later aggressive subset tends to present with plaques rather than patches. The events leading to the development of the malignant T-cells are unknown. It has been speculated that it is caused by chronic exposure to an antigen, but this has yet to be confirmed. Patients with atopic dermatitis appear to be at increased risk for the development of mycosis fungoides, suggesting that persistent stimulation of T-cells may lead to development of a malignant clone.

The inflammatory nature of the skin lesions has led to investigation of the interactions of the malignant T-cells and both keratinocytes and antigen-presenting cells (including Langerhans cells) in mycosis fungoides. Mycosis fungoides skin lesions have many features of skin that is immunologically "activated." Mycosis fungoides cells express cutaneous lymphocyte antigen (CLA), the ligand for E selectin, which is expressed on the endothelial cells of inflamed skin. This allows the malignant cells to traffic into the skin from the peripheral blood. CCR4, another homing molecule, is expressed on mycosis fungoides cells and the ligand for this receptor is on basal keratinocytes. Antigen-presenting cells are increased in mycosis fungoides lesions and have increased functional capacity to activate T-cells. There is increased expression of major histocompatibility complex (MHC) class II antigens on the surface of the antigen-presenting cells. Through cytokines, infiltration of neoplastic and reactive T-cells is increased. The pattern in early mycosis fungoides is more T-helper 1 (Th1)-like and the non-neoplastic infiltrating cells (tumor infiltrating lymphocytes [TILs]) may play a role in downregulating and controlling the neoplastic cells. There are more CD8+ cells in these early lesions and these TILs may control the malignant clone. In fact, mycosis fungoides patients with more than 20% CD8+ cells in their skin survive longer than those with less than 15%. In summary, early mycosis fungoides is a condition in which host immunity is intact and the host immune system effectively limits proliferation of the malignant T-cell clone. In more advanced mycosis fungoides and in Sézary syndrome, perhaps through interleukin (IL)-4 and -10, a Th2 environment exists. This downregulates suppressor cell function and allows the malignant clone to proliferate. In addition, the Th2-dominant environment reduces effective helper T-cell function, explaining the increased risk of infection and secondary cancer in patients with advanced cutaneous T-cell lymphoma. Correcting the aberrant immune response in advanced cutaneous T-cell lymphoma is the basis of some treatment approaches.

As mycosis fungoides advances, the number of circulating malignant T-cells increases. Standard cytologic evaluation (the Sézary preparation), even when enhanced by specific labeling techniques, is expensive and not very accurate. Use of standard laboratory tests, such as the CD4/CD8 ratio test, which increases as mycosis fungoides progresses, and assessment of the number of CD4+,CD7– or CD4+,CD26– circulating cells, which relatively specifically identify mycosis fungoides cells, yield indicators of tumor burden with advanced disease.

Histopathology

Perhaps more than in any other situation in dermatopathology, the ability to diagnose mycosis fungoides histologically closely correlates with the skill, training, and experience of the reviewing pathologist. When the clinician is considering a diagnosis of mycosis fungoides, if original histologic reports are nonconfirmatory or nonspecific, consultation with a skilled dermatopathologist should be strongly considered.

In patch-stage lesions there is a superficial perivascular and variably interstitial infiltrate of lymphocytes. There may be a band-like distribution of these cells and a few enter into the epidermis. This may produce the appearance of a vacuolar interface dermatitis with a large dark lymphocyte in every vacuole. The lymphocytes within the epidermis may be numerous or few in number, but are typically larger, darker and more angulated than those in the dermis. Papillary dermal fibrosis is typically present. The superficial perivascular lymphoid infiltrate that surrounds the postcapillary venule is typically more prominent above the vessel than below the vessel. (bear under-belly sign).

Plaques of mycosis fungoides show a more prominent superficial band-like lymphoid infiltrate and a deeper perivascular dermal component than patch-stage lesions. Papillary dermal fibrosis is more prominent and the subpapillary plexus is shifted downward. Epidermotropism is much more marked and is typically associated with very little spongiosis. This helps distinguish patch-stage mycosis fungoides from spongiotic dermatitis. Vesicular variants are an exception to this rule. In vesicular variants, spongiosis is prominent and results in intraepidermal and subcorneal vesiculation. Eosinophils are common in folliculotropic mycosis fungoides (with or without follicular mucinosis), but are uncommon in other forms of mycosis fungoides.

In thick plaques and tumors, epidermotropism may be substantially diminished. The diagnosis is confirmed by the presence of dense sheets of infiltrating lymphocytes in the dermis and subcutaneous fat. These cells may have cerebriform nuclei.

Cardinal features that should suggest a diagnosis of mycosis fungoides include the following:

- Solitary or small groups of lymphocytes in the basal cell layer
- Epidermotropism of lymphocytes with disproportionately scant spongiosis
- More lymphocytes within the epidermis than would normally be seen in an inflammatory dermatosis
- Lymphocytes in the epidermis larger than those in the dermis
- Lymphocytes in the stratum corneum and stratum granulosum
- Papillary dermal fibrosis with bundles of collagen arranged haphazardly
- Prominent folliculotropism or syringotropism of the lymphocytes, especially with intrafollicular mucin deposition (follicular mucinosis)

Features that should suggest a diagnosis of inflammatory dermatosis over mycosis fungoides include the following:

- Prominent upper dermal and papillary edema
- Marked epidermal spongiosis
- Accumulation of the intraepidermal inflammatory cells in flask-shaped collections with the top open to the stratum corneum

Immunohistochemistry is of some value in assessing mycosis fungoides. Mycosis fungoides cells characteristically are CD4+, but lose the CD7 and CD26 antigens, i.e. they are CD4+,CD7–,CD26–. This phenotype is very unusual for nonmalignant T-cells and thus is useful in evaluating biopsy specimens and peripheral blood lymphocytes. Loss of CD7 expression within the large dark lymphocytes in the epidermis, with normal expression in the benign recruited lymphocytes in the infiltrate below, suggests a diagnsosis of mycosis fungoides. DNA hybridization or a Southern blot test is frequently performed in equivocal cases to detect clonal rearrangement of the T-cell receptor (TCR). However, these data must be interpreted with caution; clonality does not confirm a diagnosis of malignancy. Benign processes may contain clonal TCR rearrangements. In early lesions of mycosis fungoides the number of infiltrating cells may be insufficient for a clone to be detected, so a negative test does not exclude the diagnosis of mycosis fungoides. Testing with fresh tissue is somewhat more sensitive than with fixed tissue using current methods. Similar techniques can be used to evaluate lymph nodes in mycosis fungoides patients. Lymph node involvement can be detected by these molecular methods, while the routine histologic evaluation yields normal results. Patients with more advanced disease are more likely to have clones in their lymph nodes and the presence of clonality is predictive of shorter survival.

Differential Diagnosis

In the early patch stage, mycosis fungoides may be difficult to diagnose. The skin lesions usually resemble a nondescript form of eczema with some scale. Interestingly, despite the itching, scratch marks and lichenification are usually absent. Mycosis fungoides presenting as papuloerythroderma of Ofuji is an obvious exception. The multiple morphologies of mycosis fungoides make the differential diagnosis vast. Plaque-like lesions may resemble subacute dermatitis or psoriasis. Tumors must be differentiated from other forms of lymphoreticular malignancy and metastases.

Treatment

Effective therapy that reliably prolongs survival has not yet been documented. Many forms of therapy induce remissions of variable length. The choice among them depends on extent of disease, the patient's overall health and physical status, the physician's experience and preference, and the availability of various options. Topical steroids, topical nitrogen mustard or 1,3-bis (2-chloroethyl)-l-nitrosourea (carmustine) (BCNU), bexarotene gel 1%, and PUVA (or narrow-band UVB) are generally good choices for stage IA, IB, and IIA disease. Total skin electron beam (TSEB) therapy can be used for refractory stage IIA and IIB cases. Single-agent chemotherapy or photophoresis can be used as initial management for stage III patients. Low-dose methotrexate may control the skin lesions of mycosis fungoides, but has been associated with the development of a secondary aggressive lymphoma in a few patients. Combinations of IFN-α, retinoids (bexarotene or isotretinoin), photophoresis, IFN-γ, skin-directed PUVA, sargramostim (granulocyte macrophage colony-stimulating factor), and perhaps IL-2, IL-12, and IFN-α may be effective in stage IV disease, and for patients who have failed the above therapies for stage IIB and III mycosis fungoides. Multiagent systemic chemotherapy is used much less commonly with the advent of immunomodulatory treatments for mycosis fungoides. It should only be considered when all other treatment options have failed. Treatment of early-stage disease is in general restricted to skin-directed treatments. More advanced disease is treated with different modalities at different institutions. Combinations of agents are often used and those combinations and their order of use vary from one institution to the next. In general, therapies that also enhance the patient's immune system are favored in patients with more advanced disease.

Topical Corticosteroids. The availability of superpotent class I topical corticosteroids has led to a reassessment of their possible role in the management of early (patch stage, T1 and T2) mycosis fungoides. Zackheim reported a 63% complete remission for patients with T1 disease and a total response rate of 94% in T1 patients. In T2 patients complete responses were only 25%, but total responses were 82%. The predominant side effect was a temporary and reversible suppression of the hypothalamic–pituitary axis in about 13% of patients. The responses were short-lived if therapy was stopped, but given the limited toxicity, this is not necessary in many patients. The adjunctive value of topical corticosteroids in T1 mycosis fungoides requires reappraisal because the response rates are similar to other modalities used for early mycosis fungoides and the toxicity is very low.

Topical Nitrogen Mustard. The contents of a 10 mg vial of mechlorethamine hydrochloride (Mustargen-MSD) are dissolved in 60 mL of tap water and applied to the entire skin surface, except the face, axillae, and genitalia, with a 2 inch paint brush or gauze pad. The last milliliter may be diluted to half strength or greater dilution for application to the face, axillae, and genitalia. Daily applications are made until complete clearing occurs, which usually takes several months or longer, and may be continued indefinitely. Such treatment leads to complete responses in 80% of patients with stage IA disease, 68% in patients with stage IB, 61% in stage IIA, 49% in stage IIB, and 60% in stage III patients. About 10% of patients obtain a durable and long-lasting

remission of over 8 years. The major side effects of topical nitrogen mustard (NH2) therapy is cutaneous intolerance, which occurs in almost 50% of patients, and allergic contact dermatitis, which occurs in 15%. Short (1 h) contact does not reduce this rate of sensitization. This can be reduced by the use of an ointment formulation, but response rates have been reported to be inferior with the ointment form. At least half of patients will relapse when therapy is stopped, but they frequently will respond again to NH2.

The duration of maintenance therapy after achieving remission is different in different centers. Some treat for an additional 6 months and others taper treatment over a year or more, or continue treatment indefinitely. In many centers, topical nitrogen mustard has been proven mainstay of therapy for patch- or plaque-stage mycosis fungoides without lymphadenopathy.

Topical BCNU (Carmustine). BCNU, 2 mg/mL in 150 mL aliquots, dissolved in ethanol, is dispensed to the patient. From this stock solution the patient takes 5 mL and adds it to 60 mL of water at room temperature. This is applied once a day to the whole body, sparing the folds, genitals, hands, and feet (if they do not have lesions). If the extent of disease is limited, only the affected areas are treated. The average treatment course is 8 to 12 weeks. If after 3 to 6 months the patient's condition is not responding, the concentration may be doubled and the treatment repeated for 12 weeks. For small or persistent lesions, the straight stock solution may be applied daily. Patients tolerate BCNU better than nitrogen mustard, contact sensitization is uncommon, and responses are more rapid. Complete blood counts should be monitored monthly during treatment, but marrow suppression occurs in less than 10% of patients treated with the low concentrations. Telangiectasia, which may be persistent and severe, can occur after prolonged BCNU therapy or following an adverse cutaneous reaction to the medication.

Ultraviolet Therapy. Both UVB (narrow or broad band) and PUVA (systemic or bath) have been effective in the management of mycosis fungoides. About 75% of patients with patch-stage disease will have a complete clinical remission with UVB therapy. Home therapy is successful. PUVA has been used more extensively and, because of its deeper penetration, it is perhaps better suited to the treatment of a disorder with a dermal component. Complete clearing is seen in 88% of patients with limited patch/plaque disease and in 52% of patients with extensive disease. Tumor-stage patients do not clear. Erythrodermic patients have poor tolerance for PUVA. Up to 50% of patients with a complete response to PUVA may have a remission of up to 10 years. Retinoids and IFN-α may be added to PUVA. Retinoids may reduce the total number of PUVA treatments required. Low-dose IFN-α plus PUVA may be used in patch-stage patients in whom topical therapy and PUVA alone are ineffective. The eximer laser may be used once or twice a week to deliver the phototherapy if the patient has a limited number of lesions. On average, 5 to 6 weeks of treatment is required and remissions up to 2 years or more can be achieved.

Extracorporeal photochemotherapy (photophoresis, ECP) is a therapeutic modality in which the circulating cells are extracted and treated with UVA outside the body; the patient ingests psoralen before the treatment. Complete responses are seen in a small percentage of mycosis fungoides patients, about 20%, and a partial response occurs in a similar percentage of patients. In the original reports the overall response rate for erythrodermic patients was 80%, but many of these patients failed to have at least the 50% clearing required to be considered a partial response. In one comparative trial, standard PUVA was significantly more effective than photophoresis alone and photophoresis was judged ineffective in plaque stage (T2) mycosis fungoides. ECP is now used in combination with other agents, especially IFN-α, and appears to have better efficacy. Insulin dependent diabetics respond poorly.

Radiation. TSEB therapy in doses in excess of 3000 Gy is very effective in the management of mycosis fungoides. Stage T1 patients have a 98% complete response; stage T2, 71%; stage T3, 36%; and stage T4, 64%. Long-term remissions occur in about 50% of T1 patients and 20% of T2 patients. Erythrodermic patients tolerate TSEB poorly; other modalities should be attempted initially. Because relapses are frequent, adjuvant therapy with a topical agent or PUVA can be considered if the patient relapses. The most common side effects of TSEB are erythema, edema, worsening of lesions, alopecia, and nail loss. Persistent hyperpigmentation and chronically dry skin are also problems after TSEB. Orthovoltage radiation may be used to control tumors or resistant thick plaques in patients whose conditions have been otherwise controlled with another modality.

Biologic Response Modifiers (Multimodality Immunomodulatory Therapy). The appearance of circulating malignant T-cells in mycosis fungoides may indicate failure of the host immune system to control the disease. Immunomodulatory agents are used in an attempt to enhance host immune function and gain control of the disease. It is often combined with treatments that increase malignant cell apoptosis, so that the "tumor antigens" released will be recognized and immunologically "attacked" by the host immune system. These immunomodulatory agents both activate antigen-presenting cells and enhance Th1 immune function directed against the malignant T-cell clone. IFN-α and -γ have been shown to have efficacy against mycosis fungoides. IFN-α is associated with a positive response in about 60% of patients and a complete response in 19%. If used as a single agent, toxicity is high and includes fever, chills, myalgias, neutropenia, and depression. Low-dose IFN-α and -γ treatments and granulocyte macrophage colony-stimulating factor are now used in an adjunctive fashion in combination with retinoid therapy, phototherapy, and other modalities. This is termed *multimodality immunomodulatory therapy*. IL-2 and -12 may be used in a similar fashion in the future.

Retinoids. Both isotretinoin and etretinate have efficacy in the treatment of mycosis fungoides. A clinical response is noted in about 44% of patients. Dosage of isotretinoin is about 1 mg/kg/day to start and may be increased up to 3 mg/kg/day as tolerated. Retinoids may be effective in stage IB (T2) patients, stage III patients, and as a palliative treatment in patients with stage IVA disease. Bexarotene (Targretin), a synthetic retinoid that is bound preferentially by the RXR (retinoid X receptor), is felt to work by inducing apoptosis in the malignant T-cells. It is available as a 1% topical gel and as an oral tablet. Topical therapy is used in patients with stage IA to IIA cutaneous T-cell lymphoma. Patients improve about 50% with this treatment. Oral bexarotene at a dose of 300 mg/m^2 also has a response rate

of about 50% in early-stage cutaneous T-cell lymphoma. This dose is complicated by hypercholesterolemia, marked hypertriglyceridemia (at times complicated by pancreatitis), central hypothyroidism, and leukopenia. It may be combined with PUVA and other forms of treatment at a lower dose.

Systemic Chemotherapy. For most forms of cancer, combinations of chemotherapeutic agents are given. In mycosis fungoides, however, multidrug chemotherapy often exacerbates the ongoing immune imbalance and may prevent the patient's immune system from attacking the malignant T-cells. For this reason, and due to the enhanced efficacy of combination immunomodulatory treatment regimens, systemic chemotherapy is now very uncommonly used for mycosis fungoides. Methotrexate in doses from 5 to 125 mg/week is effective for the management of T3 patients. In these patients, Zackheim et al demonstrated that 41% had a complete response, and an additional 17% a partial response, giving a total response of 58%. The median overall survival was 8.4 years and 69% of patients were alive at 5 years. For advanced mycosis fungoides, higher doses of methotrexate with citrovorum-factor rescue were successful in obtaining a response, which was then maintained with lower doses of methotrexate, not requiring rescue. Similarly, pentostatin, etoposide, fludarabine, and 2-chlorodeoxyadenosine have been used. Systemic chemotherapy beyond methotrexate, especially multiagent chemotherapy, is best managed by an oncologist. Systemic chemotherapy is only indicated in stage III and IVA patients who have failed all available immunoenhancing treatment protocols noted above.

Fusion Toxin. DAB389IL-2 is the fusion of a portion of the diphtheria toxin to recombinant IL-2. This selectively binds to cells expressing the IL-2 receptor and leads to their death. A series of mycosis fungoides cases that expressed the IL-2 receptor, demonstrated a response rate of 37%, including a complete response in 14% of cases. These patients had failed conventional therapies. Patients in stage I to III achieved response, but no patient with stage IV disease achieved a response. Fever, chills, hypotension, nausea, and vomiting were common and at high doses a vascular-leak syndrome occurred. This agent is reserved for advanced-stage patients who have failed other modalities.

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Pagetoid Reticulosis Localized epidermotropic reticulosis, Pagetoid reticulosis, or Woringer-Kolopp disease, is an uncommon lymphoproliferative disorder considered be a form of mycosis fungoides. Other terms suggested for these cases have been *acral mycoses fungoides* or *mycosis fungoides palmaris et plantaris*. In large mycosis fungoides clinics, such cases represent about 0.6% of all mycosis fungoides cases. Pagetoid reticulosis is divided into classic Woringer-Paget's, which usually describes solitary lesions, and cases with multiple lesions (Ketron-Goodman variant). The unique features of Woringer-Kolopp disease are clinical. The disease presents as a solitary lesion that is often located on an extremity and often has a keratotic rim. If there is more than a single lesion, often there is a propensity for lesions to involve both the palms and soles. Frequently, over months to years, the lesion gradually enlarges, reaching a size of greater than 10 cm. In some cases, the lesions spontaneously come and go over many years. Twenty percent of cases occur in patients who are younger than 15 years of age. The long duration without progression has been a clinical hallmark of Woringer-Kolopp disease. Histologically, there is prominent epidermotropism of lymphocytes, with many lining up in the basal cell layer. This histologic pattern correlates with strong αE–β7 and α4–β7 integrin expression by the infiltrating cells. This integrin expression is also seen in the epidermotropic cells of classic mycosis fungoides and contact dermatitis. In mycosis fungoides, most cases are CD4+, but in the acral mycosis fungoides cases they may be CD4+, CD8+, or negative for both. TCR gene rearrangements can be detected in many cases of Woringer-Kolopp disease. Therapeutically, local excision and radiation therapy have been "curative" in many cases. Topical and systemic PUVA have also proved effective. Local recurrence is possible.

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Sézary Syndrome Sézary syndrome is the leukemic phase of mycosis fungoides. The characteristic features are generalized erythroderma, superficial lymphadenopathy, and atypical cells in the circulating blood. Although patients with classic mycosis fungoides may progress to Sézary syndrome, usually patients with Sézary syndrome are erythrodermic from the onset. The skin shows a generalized or limited erythroderma of a typical fiery red color (Fig. 32-6). Associated features can include leonine facies, eyelid edema, ectropion, diffuse alopecia, hyperkeratosis of the palms and soles, and dystrophic nails. Some patients develop lesions identical to vitiligo, especially on the lower legs. The symptoms are those of severe pruritus and burning, with episodes of chills. Prognosis is poor, with an average survival of about 5 years.

Superficial lymphadenopathy is usually found in the cervical, axillary, and inguinal areas. Leukocytosis up to 30,000/mm^3 is usually present. In the peripheral blood, skin infiltrate, and lymph nodes, helper T-cells with deeply convoluted nuclei are found—the so-called Sézary cells.

Histologically, and by immunohistochemistry, there are no reproducible differences between cases of mycosis fungoides and Sézary syndrome. In a fair number of cases of the latter, the cutaneous histology may be nonspecific, showing a spongiotic dermatitis. Additional hematologic evaluation may be necessary to confirm the diagnosis in the erythroder-

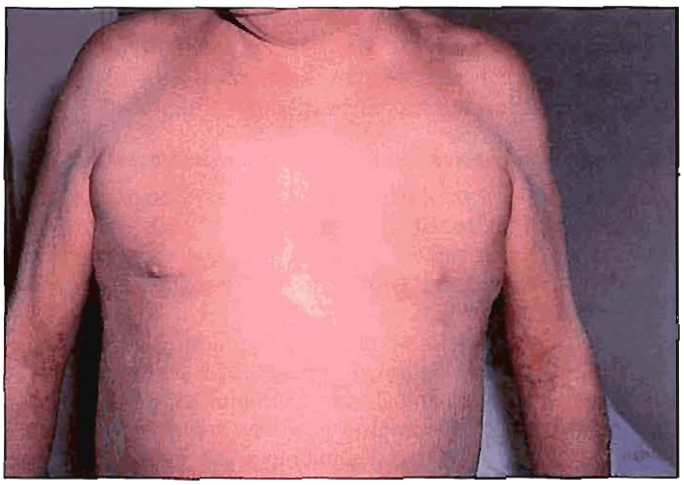

Fig. 32-6 Sézary syndrome.

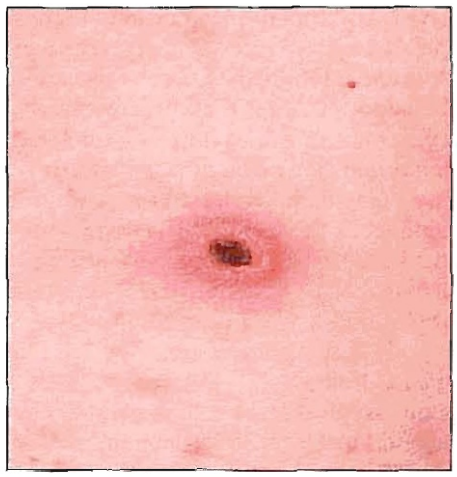

Fig. 32-7 Lymphomatoid papulosis.

nic patient. T-cell gene rearrangement studies are frequently used to confirm the diagnosis of Sézary syndrome. In addition, an increased CD4/CD8 ratio in the blood with an increase in the number of CD3+/CD4+/CD7–/CD26– circulating cells is suggestive of leukemic mycosis fungoides.

The erythroderma of Sézary syndrome must be distinguished from chronic lymphocytic leukemia (CLL), psoriasis, atopic dermatitis, photodermatitis, seborrheic dermatitis, contact dermatitis, drug reaction, and pityriasis rubra pilaris. This is done primarily by histopathologic and immunopathologic examination. In Sézary syndrome, the infiltrating T-cells in the skin have a Th2 phenotype and Th2 cytokines are produced by these cells. This explains the reduced delayed-type hypersensitivity, elevated IgE, and eosinophilia seen in these patients.

Sézary syndrome is difficult to treat. Low-dose methotrexate has a reasonable response rate of about 50% and an overall survival of 101 months, suggesting a survival benefit to its use. Photophoresis used in combination with other agents is effective in some patients, but the median survival time is only between 39 and 60 months (see above).

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Granulomatous Slack Skin Granulomatous slack skin is a rare variant lymphoma that typically presents in middle-aged adults and gradually progresses over years. It occurs more often in men. Lesions are erythematous, atrophic, bulky, infiltrated, pendulous, and redundant plaques in the axillae and groin. Histologically there is a lymphohistiocytic infiltrate extending though the dermis, into the subcutaneous fat. Focal collections of huge, multinucleated cells with 20 to 30 nuclei arranged in a wreath-like pattern are characteristic. Elastophagocytosis is prominent and elastic tissue is absent in areas of inflammation. Lymphocytes are also found within the multinucleate giant cells and are arranged around them. Epidermotropic lymphocytes are also seen. Immunohistologically, the cells are CD4+. T-cell gene rearrangements can be detected. In most patients, the condition evolves into mycosis fungoides, but about one-third of patients with granulomatous slack skin develop Hodgkin's disease after years to decades.

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Lymphomatoid Papulosis Lymphomatoid papulosis (LyP) is an uncommon, but not rare disorder. It occurs at any age, including childhood, but is most common in adults with a mean age of 44. In most typical cases, the lesions and course are very similar to that of Mucha-Habermann disease (pityriasis lichenoides et varioliformis acuta), except the lesions tend to be slightly larger, fewer in number, and have a greater propensity to necrosis (Fig. 32-7). Symptoms are usually minimal. The primary lesion is a red papule up to about 1 cm in diameter. The lesions evolve to papulovesicular, papulopustular, or hemorrhagic, then necrotic papules over days to weeks. Lesions typically heal spontaneously within 8 weeks, somewhat longer in larger lesions. Lesions are usually generalized, although cases limited to one anatomic region have been reported.

There may be crops of lesions or a constant appearance of a few lesions. In most patients, however, the condition tends to be chronic, and lesions are present most of the time if no treatment is given. The average number of lesions present at any one time is usually 10 to 20, but cases with more than 100 lesions occur. Lesions heal with varioliform, hyperpigmented, or hypopigmented scars. Cases previously reported as solitary, large nodules of lymphomatoid papulosis would now be classified as CD30+ large cell lymphomas or as overlaps between LyP and lymphoma, termed *borderline cases*.

The diagnosis of LyP is confirmed histologically. There is a dermal infiltrate that is wedge-shaped, patchy, and perivascular. In larger lesions the infiltrate may occupy the whole dermis. It may also be band-like. The infiltrate may involve the epidermis, with epidermotropism of inflammatory cells. As lesions evolve, epidermal necrosis and ulceration may occur. The dermal vessels may demonstrate fibrin deposition and more rarely, a lymphocytic "vasculitis." The dermal infiltrate is composed of lymphoid cells, eosinophils, neutrophils, and larger mononuclear cells. Atypical large or small lymphoid cells are present and may represent up to 50% of the infiltrate. Histologically, lesions have been classified into type A, type B, and type C lesions.

Type A lesions contain atypical large cells with abundant cytoplasm and prominent nuclei, with prominent eosinophilic nucleoli. If these cells contain two nuclei, they closely resemble Reed-Sternberg cells. In type B lesions, the atypical cells are smaller, with a smaller cerebriform, hyperchromatic nucleus. These resemble the atypical cells of mycosis fungoides. In both types of lesions, atypical mitotic figures may be observed. Immunophenotypically, the large atypical cells mark as T-cells, usually of the helper type. The atypical cells, especially those of the type A lesions, stain for the activation marker Ki-1 or CD30. Bcl-2 expression occurs in about 50% of cases. When clonal rearrangement studies are performed, clonal rearrangements may be found in up to 40% of LyP lesions, but this finding is not predictive of the behavior of that lesion or the case in general. Type C lesions overlap with primary cutaneous large cell lymphoma with no clear distinction between the two.

Lymphomatoid papulosis types A and B are associated with lymphoma. In the general literature this number is about 5% to 10%, but some reports have documented rates as high as 20%, and at the Univeristy of California at San Francisco (UCSF) up to 40% of cases of LyP have an associated lymphoma. The lymphoma may occur before, concurrently, or after the appearance of the LyP. In most cases, the LyP precedes the development of lymphoma, sometimes by a long period—up to 20 years. The associated lymphoma is most commonly mycosis fungoides (40%), a CD30+ T-cell lymphoma (30%), or Hodgkin's disease (25%). The lymphoma and LyP may behave quite independently. If the lymphoma is successfully treated and cleared, the LyP typically continues. Despite this independent behavior, the lymphoma and the LyP may contain the same clonal TCR gene rearrangement. Patients with pure type B lesions are much less likely to develop lymphoma than patients with type A lesions.

Therapy may not be necessary; there is no evidence that treatment of LyP prevents the development of secondary lymphoma. When any therapy is stopped, the LyP invariably returns. Therefore, patients only need to be treated if they are moderately symptomatic and the treatment has fewer potential complications than the benefits gained. Superpotent topical corticosteroids have been beneficial in some childhood cases. Topical bexarotene may abort early lesions, and oral bexarotene may suppress lesion formation. PUVA systemically or topically may be effective, although maintenance treatment is usually required. Both narrow- and broadband UVB may be effective. Of all the systemic agents, methotrexate gives the most dependable response, with up to 90% of LyP patients improving significantly. It is given in weekly doses similar to those used for rheumatoid arthritis—usually 7.5 to 15 mg/week. Higher doses may be required in some patients. Response is rapid. Some patients treated with methotrexate may have remissions of the LyP. In most, however, maintenance therapy is required.

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Pityriasis Lichenoides

Both the acute and chronic forms of pityriasis lichenoides are lymphocytic vasculitides. The lymphoid infiltrate may contain a clonal proliferation. However, progression to cutaneous lymphoma is rare.

Pityriasis Lichenoides et Varioliformis Acuta (Mucha-Habermann Disease) Pityriasis lichenoides et varioliformis acuta (PLEVA) is a disorder which usually appears suddenly in children or young adults. Individual lesions are erythematous macules, papules, or papulovesicles. Lesions tend to be brownish-red and evolve through stages of crusting, necrosis, and varioliform scarring. Lesions tend to appear in crops, and may number from a few to more than 100 (Figs 32-8 and 32-9). In general PLEVA patients have more and smaller lesions than patients with LyP. The trunk is favored, but even the palms and soles may infrequently be involved. The patient feels otherwise well. The natural history is benign, with spontaneous involution occurring over 1 to 3 years. In children diffuse cases resolved more quickly than cases than were purely central; cases with primarily peripheral lesions took almost twice as long to resolve.

Histologically, PLEVA is characterized by epidermal necrosis together with prominent hemorrhage and a dense perivascular infiltrate in the upper and mid dermis in a wedge-shaped pattern. Lymphocytic vasculitis may be seen.

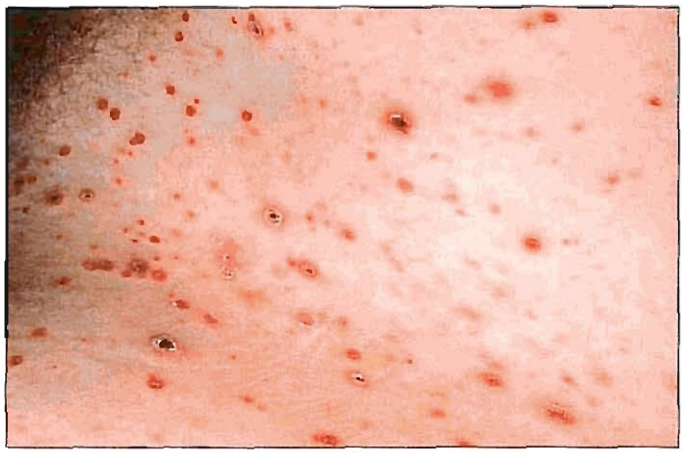

Fig. 32-8 Mucha-Habermann disease.

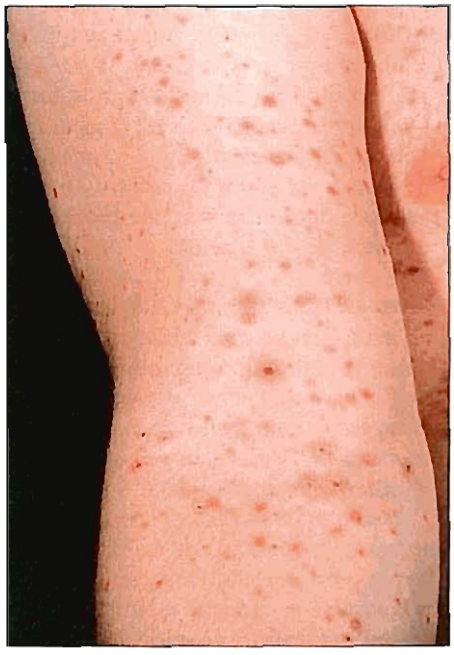

Fig. 32-9 Mucha-Habermann disease.

T-cell gene rearrangements may be detected, but the significance of that finding is unclear at this time. Treatment of PLEVA may include oral erythromycin or tetracyclines and phototherapy (UVB or PUVA). Topical tacrolimus may be effective. Low-dose methotrexate, 5.0 to 15 mg/week, may be required in severe cases.

An unusually severe form of PLEVA (febrile ulceronecrotic Mucha-Habermann disease) is characterized by the acute onset of diffuse, coalescent, large, ulceronecrotic skin lesions associated with high fever and constitutional symptoms. The condition may begin as typical as PLEVA, but the ulceronecrotic lesions usually begin to appear within a few weeks. Skin necrosis may be extensive, especially in the intertriginous regions. Associated symptoms include gastrointestinal and central nervous system (CNS) symptoms, pneumonitis, myocarditis, and even death (in adult cases). This condition favors boys who are 18 years of age or younger. This severe form of PLEVA usually lasts several months with successive outbreaks, then resolves or converts to more classic PLEVA. Treatment is systemic steroids and if response is limited, methotrexate. Dapsone may also be useful, for maintenance and as a steroid-sparing agent.

Pityriasis Lichenoides Chronica Pityriasis lichenoides chronica (PLC) is a chronic form of pityriasis lichenoides, related to PLEVA by its common histology. Lesions are erythematous, scaly macules and flat papules with very slow evolution. Lesions each last several months. This eventual resolution of lesions of PLC distinguishes it from guttate parapsoriasis which it may resemble clinically. Lesions of small plaque parapsoriasis do not spontaneously resolve. Lesions of PLC favor the lateral trunk and proximal extremities. Patients may have from 10 to 100s of lesions, but usually fewer than 50. Resolution may be with persistent areas of hypopigmentation which last for months to years. Unlike PLEVA, PLC tends to last for many years.

Histologically, the changes are similar to PLEVA, but much more subtle. A mild interface or perivascular lymphocytic infiltrate with overlying parakeratosis may be present. T-cell gene rearrangement studies may demonstrate monoclonality; however, the meaning of this finding is unclear at this time. Treatment with phototherapy (natural sunlight, UVB, UVA1 or PUVA) is most effective. Topical steroids or tacrolimus may be tried. No treatment is required.

Pityriasis lichenoides chronica is generally a benign disease. There are rare patients who have progressed to develop cutaneous T-cell lymphoma. The authors recommend that patients with PLC be followed regularly and changes in lesion morphology, including induration, erosion, atrophy, persistent erythema, or poikiloderma, should trigger repeat pathologic evaluation.

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Primary Cutaneous T-cell Lymphomas Other Than Mycosis Fungoides

Once a cutaneous lymphoma has been identified to be of T-cell origin and the diagnosis of mycosis fungoides and its variants has been excluded, the most important evaluation is

to determine the CD30-staining pattern. CD30 is a marker found on some activated, but not resting, T- and B-cells. It also marks the Reed-Sternberg cells of Hodgkin's disease. Monoclonal antibodies Ki-1 and Ber H2 are used to identify CD30 positivity. A cutaneous lymphoma is considered CD30+ if there are large clusters of CD30+ cells or more than 75% of the anaplastic T-cells are CD30+. Systemic CD30+ lymphoma with cutaneous involvement has a poor prognosis. Those that express anaplastic lymphoma kinase (ALK-1) associated with a 2:5 translocation have a somewhat better prognosis. Primary cutaneous large T-cell lymphomas that are CD30+ are typically ALK-1 negative, have a very good prognosis, and tend to run a relapsing course similar to that of lymphomatoid papulosis. Individual lesions respond to irradiation and the relapsing course may remit with low-dose methotrexate. Large cell lymphomas of the skin have similar histologic and clinical features, so immunophenotyping is essential for prognosis. Clonal TCR gene rearrangements are present in large cell T-cell lymphoma. The group of T-cell lymphomas that are not large cell and CD30+ are together classified in the WHO system as peripheral T-cell lymphomas.

CD56 is rapidly becoming the second most important immunophenotypic marker for cutaneous lymphomas. Four important variants of CD56+ cutaneous lymphomas have been identified: a subset of subcutaneous panniculitis-like T-cell lymphoma; natural killer (NK)/T-cell lymphoma; blastic NK cell lymphoma; and CD8+ aggressive epidermotrophic cytotoxic T-cell lymphoma.

Peripheral T-cell lymphoma is an heterogeneous grouping that includes primary cutaneous CD30+ nonanaplastic large cell lymphoma, primary cutaneous CD30– anaplastic and nonanaplastic large cell lymphoma, and primary cutaneous CD30– pleomorphic small/medium cell lymphoma.

CD30+ Cutaneous T-Cell Lymphoma (Primary Cutaneous Anaplastic Large Cell Lymphoma)

Clinically, these lymphomas present as solitary or localized skin lesions that have a tendency to ulceration (50%), spontaneous regression (25%), and relapse. These lymphomas are rare in children and occur with slightly greater frequency in males. Lesions are usually firm, red to violaceous tumors up to 10 cm in diameter (Fig. 32-10). Tumors may grow in a matter of weeks. There is no favored anatomic site.

Relapses in the skin are common, but the development of extracutaneous or lymph node involvement is uncommon. Lymph node involvement is associated with a poorer prognosis. The "pyogenic lymphoma" of the skin is a neutrophil-rich CD30+ lymphoma with skin lesions that clinically resemble Sweet syndrome, pyoderma gangrenosum, halogenoderma, leishmaniasis or deep fungal infection. IL-8 overexpression by the anaplastic CD30+ cells causes the neutrophilic infiltration. The number of neutrophils present may make histologic interpretation difficult. Cases with features of both lymphomatoid papulosis and CD30+ anaplastic T-cell lymphoma have been described, sometimes under the designation type C lymphomatoid papulosis. Histologically, there is a dense dermal nonepidermotropic infiltrate with atypical tumor cells with large nuclei with one or several prominent nucleoli and abundant cytoplasm. The malignant cells can be further characterized as anaplastic, pleomorphic, and immunoblastic, but this distinction may be difficult and has yet to be determined to be of prognostic or

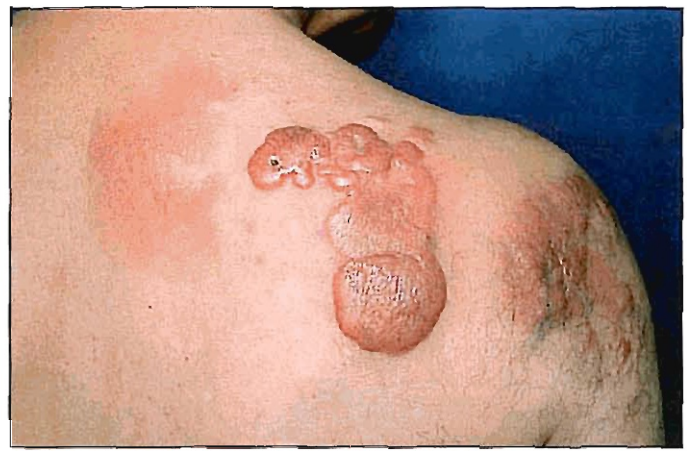

Fig. 32-10 Large cell anaplastic lymphoma.

therapeutic value. This form of primary cutaneous T-cell lymphoma has an excellent prognosis with a 5-year survival of 90%. Lesions are highly responsive to radiotherapy. Early individual lesions can even be surgically excised. Topical imiquimod has been therapeutically successful. Chemotherapy causes regression of lesions, but a rapid relapse usually occurs. Other than low-dose methotrexate, chemotherapy has little role in the treatment of this disease.

Secondary Cutaneous CD30+ Large Cell Lymphoma

CD30+ large cell lymphomas may arise in cases of mycosis fungoides, in patients with lymphomatoid papulosis, and in patients who have documented extracutaneous disease (secondary cutaneous anaplastic large cell lymphoma). Skin lesions of pyogenic lymphoma may be seen secondary to a pyogenic lymphoma of other organs. The prognosis is poor in patients who have extracutaneous disease preceding or near the time of cutaneous involvement. Among those with systemic disease, the expression of Alk-1 associated with a t(2;5) translocation is a favorable prognostic feature. Patients with lymphomatoid papulosis who develop cutaneous CD30+ lymphoma and who do not have systemic lymphoma or mycosis fungoides typically have an excellent prognosis. The prognosis for patients with mycosis fungoides who develop CD30+ anaplastic large cell lymphoma is poor.

Non-Mycosis Fungoides CD30– Cutaneous Large T-Cell Lymphoma

Non-mycosis fungoides CD30– cutaneous large T-cell lymphomas usually present as solitary or generalized plaques, nodules, or tumors of short duration. There is no preceding patch stage that distinguishes it from MF. The prognosis is poor, with a 5-year survival rate of 15%. The malignant cells are pleomorphic large or medium cell types or are immunoblastic. The cells may be cerebriform and epidermotropism may be present. Some cases previously called *d'emblée mycosis fungoides* are better classified in this group. Multiagent chemotherapy is recommended.

Pleomorphic T-Cell Lymphoma (Non-Mycosis Fungoides CD30– Pleomorphic Small/Medium Sized Cutaneous T-Cell Lymphoma)

This group comprises about 3% of all primary cutaneous lymphomas. Pleomorphic small/medium sized cutaneous T-cell lymphoma is distinguished from the large cell type

by having less than 30% large pleomorphic cells. It is distinguished from mycosis fungoides by clinical features (lack of patch or plaque lesions). These primary cutaneous lymphomas usually present with one or several red–purple papules, nodules or tumors (5 mm to 15 cm in size). Immunophenotypically, they are usually of helper T-cell origin and clonal rearrangements of the TCR gene are usually present. A CD4 versus a CD8 phenotype is associated with a more favorable prognosis, but a CD4/CD56 phenotype has a poorer prognosis. The presence of a mixed population of suppressor cells, B-cells, and histiocytes, usually favors the diagnosis of reactive lymphoid hyperplasia. The overall prognosis is intermediate, with a 5-year survival rate of 62%. The optimal therapy for this form of lymphoma has not been determined. Therapeutically, localized lesions have been treated with radiation therapy or surgical excision. Chemotherapy, retinoids, interferons, and monoclonal antibodies have been used in widespread or progressive disease.

Lennert Lymphoma (Lymphoepitheliod Lymphoma) Lennert lymphoma is a rare CD4+ systemic T-cell lymphoma. Cutaneous lesions occur in less than 10% of cases and present as papules, plaques, or nodules. The skin lesions may not represent lymphoma cutis because palisaded granulomatous and nonspecific dermal infiltrates may occur. The clinical and histologic appearance may resemble granuloma annulare very closely. The course is low-grade until the lymphoma transforms to a high-grade, large cell lymphoma.

Subcutaneous (Panniculitis-Like) T-Cell Lymphoma Clinically, patients are usually young adults who present with subcutaneous nodules, usually on the lower extremities, and are frequently diagnosed as having erythema nodosum or some other form of panniculitis. Weight loss, fever, and fatigue are common and may herald the onset of a rapidly progressive hemophagocytic syndrome which is often fatal. Extracutaneous involvement is rare, even in fatal cases. An indolent chronic course can also be seen, but even in these cases the prognosis is poor. This variant of lymphoma may also rarely be seen in childhood.

Histologically, there is a lace-like infiltration of the lobules of adipocytes, mimicking panniculitis, especially lupus profundus. A characteristic feature is rimming of neoplastic cells around individual adipocytes. The infiltrate contains primarily small cells with hyperchromatic, irregular nuclei and large anaplastic cells in varying proportions. The small cells are atypical, karyorrhexis is prominent, and mitotic figures are frequent. Benign histiocytes are present in large or small numbers and demonstrate erythrophagocytosis (bean-bag cells). Immunophenotypically, the neoplastic cells mark as T-cells (CD2+, CD3+). Most cases are derived from α/β T-cells and are CD56–. They have a less aggressive course. A subset of subcutaneous (panniculitis-like) T-cell lymphomas (SPTCLs) are derived from γ/δ T-cells and are CD56+. These cases have been misdiagnosed as lupus profundus or alopecia areata and histologically prominent dermal and even epidermal (interface) involvement may be seen. They have a more aggressive course. SPTCL may evolve from the benign variant of cytophagic histiocytic panniculitis, which may also have a hemophagocytic syndrome. The prognosis for a patient with SPTCL is poor, with a median survival of less than 3 years. Multiagent chemotherapy is recommended, at times with stem cell support. Denileukin diftitox (Ontak) was reported to produce a favorable response in one case.

Nasal/Nasal Type NK/T-Cell Lymphoma (Angiocentric Lymphoma) NK/T-cell lymphoma most frequently presents in extranodal tissue and is characterized by a high incidence of nasal involvement. It is more common in Asia, where it affects primarily women with a mean age of 40. In Korea it is reported to be the most common form of cutaneous lymphoma after mycosis fungoides. It is uncommon in the US. It presents clinically as dermal or subcutaneous papules or nodules that may ulcerate. Lesions are usually widespread and involve the lower extremities. A hydroa vacciniforme-type has been described in children in Mexico and in adults and children in Japan and Korea. Skin lesions are facial and extremity papulovesicles ulcerate and heal with scarring. Skin lesions are exacerbated by sun exposure and are reproduced with UVA irradiation.

Histologically, the dermis and subcutaneous fat are infiltrated with intermediate-sized, atypical lymphocytes, within and around the walls of small and medium sized vessels. Epidermotropism may be noted. The lymphoma cells express a spectrum of T- and NK-cell immunophenotypic markers, variably expressing CD2, CD3, CD4, CD8 and the NK-cell marker CD56. CD56 is not cell-lineage specific and a subset of CD56 cutaneous lymphoma cases are classified under the SPTCL category. Epstein-Barr virus is present in the NK variants and variably present in the T-cell variants. T-cell clonality is detected if the T-cell immunophenotype is present. The prognosis is poor.

Blastic NK-Cell Lymphoma The majority of patients are males, with a mean age of about 60 years. All patients present with multiple, rapidly expanding plaques and/or nodules on noncontiguous sites. Lesions are characteristically purple in color. The course is aggressive in most patients with rapid cutaneous relapse after chemotherapy with systemic involvement. Histologically, the cells infiltrate the dermis or subcutaneous fat, with a tendency for the neoplastic cells to "Indian file" in dermal collagen. There is usually a grenz zone below the epidermis. The lymphoma cells are small/medium to large blastic lymphocytes. Angiocentricity may be noted, but is not prominent. Immunophenotyping is CD4+, CD56+. MIB-1 shows a proliferation activity of greater than 50%. T-cell gene rearrangements are negative.

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Adult T-Cell Leukemia/Lymphoma

Infection with human lymphotropic virus type 1 (HTLV-1) may lead to acute T-cell leukemia/lymphoma (ATL) in 0.01% to 0.02% of infected persons. This virus is endemic in Japan, Southeast Asia, the Caribbean, Latin America, and equatorial Africa. ATL usually has an acute onset with leukocytosis, lymphadenopathy, and HOTS (hypercalcemia, osteolytic bone lesions, T-cell leukemia, and skin lesions). Lesions resemble mycosis fungoides, except patches are uncommon and plaques and nodules predominate. Histologically the skin lesions contain lichenoid infiltrates of medium sized lymphocytes with convoluted nuclei. Epidermotropism and involvement around and within adnexa occur. Granuloma formation may occur in the dermis. ATL cells are usually CD4+/CD7– and show T-cell gene rearrangements.

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CUTANEOUS B-CELL LYMPHOMA

Primary cutaneous B-cell lymphomas (Figs 32-11 and 32-12) occur less commonly than cutaneous T-cell lymphomas, but more frequently than generally believed (25% of cases of primary cutaneous non-Hodgkin lymphomas are B-cell in origin). Although the morphologic appearance of the malignant lymphocytes composing these primary cutaneous lymphomas is identical to lymphomas based in lymph nodes, they have a distinctly different clinical behavior and immunophenotypic profile. This renders the classification systems based on lymph node histology of limited benefit

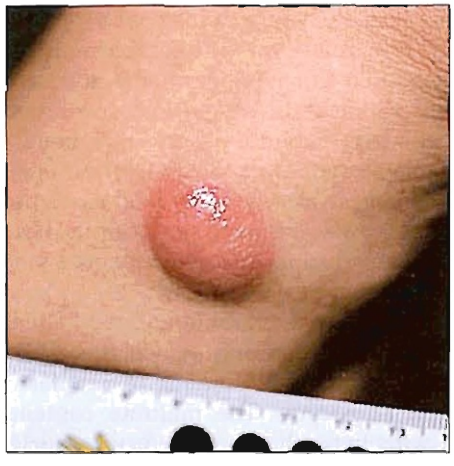

Fig. 32-11
Lymphoma, B-cell.

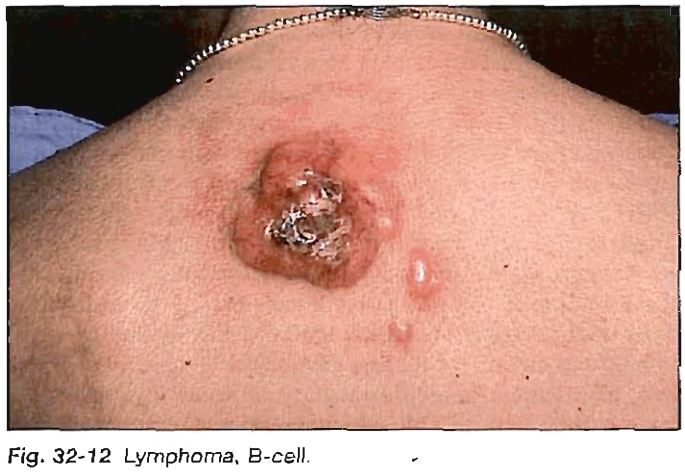

Fig. 32-12 Lymphoma, B-cell.

clinically in the diagnosis of primary cutaneous B-cell lymphomas. More simplified schemes have thus been proposed that apply to primary cutaneous lymphomas only. These new systems have not been universally adopted and some controversy exists regarding classification of some forms of cutaneous B-cell lymphoma. This is illustrated by the fact that some authors state that follicular center cell lymphoma is the most common form of primary cutaneous B-cell lymphoma, while others say marginal zone lymphoma is the most common.

The great majority of primary cutaneous B-cell lymphomas are composed of cells with the morphologic characteristics of the B-cells normally found in the germinal centers of lymph nodes. Classification schemes used primarily for lymph node-based lymphomas divide these lymphomas into multiple types based on histomorphology. Fewer distinctions are made for primary cutaneous B-cell lymphomas, since the behaviors of most of the lymphomas of follicular center cell origin are similar. Secondary cutaneous involvement can occur with all forms of B-cell lymphoma based primarily in lymph node or other sites. The clinical features are similar to those of primary cutaneous lymphoma, with violaceous papules or nodules. Typically, the histologic structure of secondary lesions in the skin is similar to that of the lymphoma at the site of origin, usually lymph nodes. The pattern in the skin may not, however, be sufficient to accurately classify the lymphoma, making lymph node biopsy necessary in most cases. In secondary cutaneous B-cell lymphomas the prognosis is, in general, poor. It is therefore critical to completely evaluate and stage any patient suspected of having primary cutaneous B-cell lymphoma to exclude involvement at another site. Primary large B-cell lymphoma of the leg also appears to have a relatively poor prognosis.

Diffuse Large B-Cell Lymphoma (Primary Cutaneous Large B-Cell Lymphoma)

This group of lymphomas is high-grade histologically, but when the disease is restricted to the skin, high-grade does not correlate with prognosis. High-grade follicular lymphoma and immunoblastic lymphoma may be classified in this category by some (WHO), but others (EORTC) favor grouping follicular center cell lymphomas of large cells and diffuse histology with follicular lymphoma. Clinically, lesions present as solitary or localized red or purple papules, nodules or plaques. In general, solitary or localized lesions are typical of primary disease and widespread lesions suggest secondary cutaneous involvement of primary nodal lymphoma. Lesions on the head and neck have an excellent prognosis. Lesions on the leg have a poorer prognosis with a 5-year survival of about 50% and are considered in some classifications as a separate entity. Histologically, a diffuse dermal infiltrate is composed of large centroblasts and immunoblasts. Round cell morphology is an adverse prognostic feature. Immunophenotypically, cells usually express CD19, CD20, and monotypic immunoglobin, and leg lesions express bcl-2. Secondary cutaneous involvement with nodal large B-cell lymphoma is associated with a poor prognosis.

Primary Cutaneous Follicular Lymphoma (Follicular Center Lymphoma, Follicular Center Cell Lymphoma)

Clinically, most patients present with single or multiple papules, plaques or nodules, with surrounding erythema, in one anatomic region. About two-thirds of cases present on the trunk, about one-fifth on the head and neck (the vast majority of these on the scalp), and about 15% on the leg. These lymphomas are more common in men than women. Males outnumber females 4:1 in trunk lesions, whereas women disproportionately have head and leg lesions. Untreated, the lesions gradually increase in size and number, but extracutaneous involvement is uncommon. The prognosis is excellent with 5-year survival with treatment approaching 100%. Secondary cutaneous involvement of systemic follicular lymphoma has a poor prognosis.

Histologically, the infiltrate is nodular or diffuse within the dermis and spares the epidermis. Follicular growth pattern with primary cutaneous follicular lymphoma is uncommon. In early lesions, the neoplastic cells are of smaller size and there is a substantial portion of normal T-cells surrounding and mixed with the neoplastic B-cells. Over time, the neoplastic B-cells become a more predominant portion of the infiltrate, the neoplastic cells are larger in size and tumor-infiltrating T-cells diminish. Immunophenotypically, the neoplastic cells stain with B-cell markers (CD20 and others) and are monotypic for immunoglobulin production, i.e. they stain for either κ or λ light chains, but not both. Immunoglobulin staining may be negative in tumorous lesions. Clonal rearrangement of the immunoglobulin gene can be demonstrated. The absence of expression of IgH/bcl-2 rearrangement, no adenopathy, and lack of involvement of the bone marrow excludes the presence of nodal follicular center lymphoma. Bcl-2 expression in cutaneous follicular lymphoma does not affect outcome, however. In contrast, nodal follicular lymphoma usually expresses bcl-2 and there is a t(14:18) translocation in more than 80% of cases.

Radiation therapy totaling 30 to 40 Gy and including all erythematous skin and a 2-cm margin of normal skin is very effective for lesions of the head and trunk. A combination of intralesional IFN-α 5 MU every 4 weeks and topical bexarotene gel 1% twice a day cleared one patient. Anthracycline-based chemotherapy or rituximab may be used for relapses. In Europe some cases of primary cutaneous follicular center cell lymphoma are associated with *Borrelia* infection and may arise in lesions of acrodermatitis chronica atrophicans.

Primary Cutaneous Marginal Zone Lymphoma (Primary Cutaneous Immunocytoma, Marginal Zone B-Cell Lymphoma, MALT Lymphoma)

These lymphomas present as solitary or multiple dermal or subcutaneous nodules or tumors primarily on the upper part of the body, trunk, or extremities. Widespread lesions suggest secondary skin involvement by systemic lymphoma. Women are affected more than men. Histologically, the infiltrate is nodular or diffuse and composed of small lymphocytes and cells showing plasma cell differentiation. The atypical cells are often located at the periphery of aggregates of reactive T- and B-cells. The lymphoma cells may contain "Dutcher bodies," intranuclear collections of immunoglobin. Initially, the malignant cells may represent a very small proportion of the infiltrate and the diagnosis of pseudolymphoma is made. Over time the "marginal zone" cells predominate and the germinal centers are diminished. Immunophenotypically, the cells are monotypic for immunoglobulin and are CD79+ and CD19+. Clonal immunoglobulin gene rearrangements can be demonstrated. The prognosis is excellent, with 5-year

survival close to 100%. Local radiation therapy or excision if lesions are few is recommended. In some *Borellia*-endemic areas in Europe up to one-third of cutaneous marginal zone lymphomas are associated with *Borrelia* infection.

Intravascular Large B-Cell Lymphoma (Malignant "Angioendotheliomatosis," Angiotropic Large Cell Lymphoma)

Clinically, these cases present with variable cutaneous morphologies, often very subtle and nonspecific. Some cases resemble classic lymphoma with violaceous papules or nodules. Other cases more closely resemble intravascular thrombotic disorders with livedo reticularis-like lesions or telangiectatic patches. Sclerotic plaques may also occur. Even normal skin when biopsied can be diagnostic. Patients often present with fever of unknown origin. CNS symptoms are prominent with progressive dementia or multiple cerebrovascular ischemic events which may precede the findings of lymphoma by many months. Histologically, the features are characteristic and diagnostic. Dermal and subcutaneous vessels are dilated and filled with large neoplastic cells. Focal extravascular accumulations may be seen. The neoplastic cells are CD20+ and CD79a+, and monotypic for immunoglobulin. Clonal immunoglobulin gene rearrangements may be detected. Despite the large number of intravascular cells in the skin and other affected organs, the peripheral blood smears and bone marrow may be normal histologically. The prognosis is very poor. Multiagent chemotherapy is recommended. Rare cases of intravascular lymphoma may be of T-cell origin.

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Plasmacytoma (Multiple Myeloma)

Cutaneous plasmacytomas, or localized neoplasms of plasma cells in the skin, are seen most commonly in the setting of myeloma. They are, however, rare, occurring in only 2% of myeloma cases. These cases are called *secondary cutaneous plasmacytoma*. They may also occur by direct extension from an underlying bone lesion. They may appear at sites of trauma, such as biopsies or intravenous catheters (inflammatory oncotaxis). Most commonly, secondary cutaneous plasmacytomas occur in the setting of advanced myeloma and the prognosis is poor. Less commonly, the skin lesions may be the initial clinical finding, leading to the diagnosis of myeloma. Histologically there are nodular and diffuse collections of plasma cells with varying degrees of pleomorphism and atypia. The degree of atypia may predict prognosis. The cells are monotypic for immunoglobin production and produce the same light chain as the myeloma. The immunoglobulin produced is most commonly IgG or IgA and rarely IgD or IgE. CD79 is positive, but CD19 and CD20 are negative.

In addition to plasmacytomas, patients with myeloma may develop a vast array of cutaneous complications. These include normolipemic plane xanthomas, amyloidosis, vasculitis, and calcinosis cutis. An unusual but characteristic skin finding in myeloma is multiple follicular spicules of the nose, forehead, cheeks and chin. They are yellowish and firm to palpation and can be removed without bleeding. Numerous small ulcerations may occur on the trunk. Both the spicules and ulcers contain an eosinophilic material composed of the abnormal monoclonal protein produced by the malignant cells. The spicules are *not* made of keratin. Similar cutaneous spicules composed of keratin can be seen in vitamin A deficiency, chronic renal failure, acquired immunodeficiency syndrome (AIDS), Crohn's, and other malignant diseases.

More rarely, solitary or multiple skin lesions may be seen with no evidence of involvement in any other tissue. They represent 4% of extramedullary plasmacytomas (EMP) and present as skin-colored or violaceous dermal or subcutaneous papules, nodules or plaques. EMPs are three-four times more common in men than women. The diagnosis of EMP requires a negative skeletal survey and no evidence of plasma cell proliferation in the bone marrow. The cutaneous lesions may produce a monoclonal protein. Such skin lesions are termed *primary cutaneous plasmacytomas*. The prognosis for isolated primary cutaneous plasmacytoma is excellent (>90% chance of 5-year survival) and progression to myeloma is uncommon. Neither the clinical nor histologic appearance of the cutaneous lesions predicts the course and their histologic appearance is identical to plasmacytomas seen in association with myeloma. Cutaneous plasmacytomas may occur following treatment of EMP at another site, as a secondary cutaneous recurrence. Rarely, soft-tissue extramedullary plasmacytomas may be associated with post-transplantation plasma cell dyscrasia. Anetoderma may show plasmacytoma on biopsy. A rare manifestation of a solitary plasmacytoma of bone is an overlying erythematous skin patch which may be 10 cm or more in diameter. The chest is the most common location. Lymphadenopathy is present and some of the patients have or develop POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes). This syndrome has been called adenopathy and extensive skin patch overlying a plasmacytoma, or AESOP.

The appropriate treatment of plasmacytomas is determined by the presence or absence of associated systemic disease. Solitary or paucilesional primary cutaneous plasmacytomas

have been treated successfully with local surgery and radiation therapy. Systemic chemotherapy may be required if these modalities fail. The treatment for secondary plasmacytomas and for patients with numerous primary cutaneous plasmacytomas is chemotherapy.

Cutaneous and Systemic Plasmacytosis

Cutaneous and systemic plasmacytosis occur largely in Asians, slightly favoring males. They typically occur between the ages of 20 and 55. These conditions are characterized by polyclonal proliferations of plasma cells and hyperglobulinemia and were originally considered variants of Castleman's disease. Cutaneous plasmacytosis affects only the skin but patients may have lymphadenopathy, and systemic symptoms of fever and malaise. Systemic plasmacytosis has involvement in two or more organ systems, usually, in addition to skin, the lung, bone marrow, and liver. Dyspnea may occur due to interstitial pneumonia. Uncommonly, cases of systemic plasmacytosis may progress to lymphoma. The course is chronic and benign and response to various cytostatic and immunosuppressive treatments has been poor. PUVA and topical tacrolimus have been reported effective for skin lesions. The skin lesions in cutaneous and systemic plasmacytosis are identical. They consist of multiple brown–red plaques, mostly of the central upper trunk, but also the face. Lesions range from 1 to 3 cm in diameter. They are often considered simply postinflammatory hyperpigmentation until they are palpated. Histologically they show a dense perivascular infiltrate of mature plasma cells, which stain for both κ and λ light chains (polyclonality). Elevated IL-6 has been reported in some patients.

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HODGKIN'S DISEASE

The vast majority of reports of cutaneous Hodgkin's disease actually represent type A lymphomatoid papulosis (LyP). These two diseases have a considerable number of overlapping features. The type A cells of LyP have similar morphology and share immunophenotypic markers with Reed-Sternberg cells. LyP can be seen in patients with Hodgkin's disease. Primary cutaneous Hodgkin's disease without nodal involvement is thus difficult to prove and is very, very rare, if it exists.

Most cases of Hodgkin's disease of the skin usually originate in the lymph nodes, from which extension to the skin is either retrograde through the lymphatics or by direct extension. Lesions present as papules or nodules with or without ulceration. Lesions resembling scrofuloderma may occur. Miliary dissemination to the skin can occur in advanced disease.

Nonspecific cutaneous findings are common in patients with Hodgkin's disease. Generalized, severe pruritus may precede by many months other findings of Hodgkin's disease or may occur in patients with a known diagnosis. Secondary prurigo nodules and pigmentation may occur as a result of scratching. An evaluation for underlying lymphoma should be considered in any patient with severe itching, no primary skin lesions, and no other cause identified for the pruritus.

Acquired ichthyosis, exfoliative dermatitis, and generalized and severe herpes zoster are other cutaneous findings in patients with Hodgkin's disease.

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MALIGNANT HISTIOCYTOSIS (HISTIOCYTIC MEDULLARY RETICULOSIS)

Most cases considered malignant histiocytosis in the past are now considered to be other forms of lymphoma or lymphomas with large components of reactive histiocytes. Very rare cases of true malignancies of histiocytes may still occur and can have cutaneous lesions, most characteristically erythematous nodules. Often, the bone marrow examination in these cases is initially normal, but cases are rapidly progressive and fatal and the bone marrow becomes involved.

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LEUKEMIA CUTIS

Clinical Features

Cutaneous eruptions seen in patients with leukemia may be divided into specific (leukemia cutis) and nonspecific lesions (reactive and infectious processes). Overall, about 30% of biopsies from patients with leukemia will show leukemia cutis. All forms of leukemia can be associated with cutaneous findings, but skin disease is more common in certain forms of leukemia. The vast majority of dermatologic manifestations are seen in patients with acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS). AML includes types M1 through M5. In AML and MDS patients, only about 25% of skin biopsies will show leukemia cutis, the remainder showing complications of the leukemia. These include infections, graft-versus-host disease, drug reactions, or the reactive conditions associated with leukemia that were formerly called *leukemids*. By contrast, in patients with acute lymphocytic leukemia (ALL), chronic myelogenous leukemia (CML), and CLL, about 50% of biopsies will show *leukemia cutis*.

Specific Eruptions

The most common morphology of leukemic infiltrations of the skin in all forms of leukemia is multiple papules or nodules (60% of cases) or infiltrated plaques (26%). These lesions are usually flesh-colored, erythematous, or violaceous (plum-colored) (Fig. 32-13). They are rubbery on palpation and ulceration is uncommon. Extensive involvement of the face may lead to a leonine facies.

Less common manifestations of leukemia cutis are subcutaneous nodules resembling erythema nodosum or panniculitis, arciform lesions (in juvenile CML), ecchymoses, palpable purpura, erythroderma, ulcerations (which may resemble pyoderma gangrenosum or venous stasis ulceration), and urticaria-like, urticaria pigmentosa-like (in ALL), and guttate psoriasis-like lesions. Rare manifestations are a lesion resembling Sister Mary Joseph nodule and cutaneous sarcoidal lesions. Myelogenous leukemia may be complicated by lesions resembling stasis dermatitis or chilblains. Gingival infiltration causing hypertrophy is common in and relatively unique to patients with acute myelomonocytic leukemia.

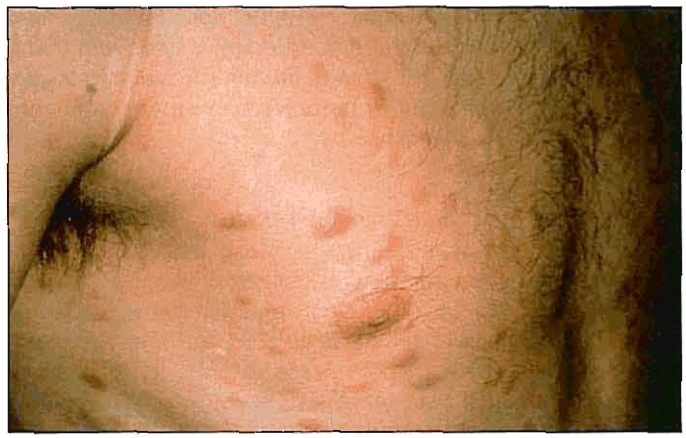

Fig. 32-13 Leukemia cutis.

Leukemia cutis most commonly occurs concomitant with the diagnosis of leukemia or following the diagnosis of leukemia. The skin may also be a site of relapse of leukemia after chemotherapy, especially in patients who present with leukemia cutis. Uncommonly, leukemia cutis may be identified while the bone marrow and peripheral blood are normal. These patients are classified as "aleukemic leukemia cutis," as they have normal bone marrow evaluations and no circulating blasts. These cases are often misdiagnosed as cutaneous lymphomas and undertreated. They eventually relapse with fullblown leukemia. Systemic involvement occurs within 3 weeks to 20 months (average 6 months). Leukemia cutis is a poor prognostic finding in patients with leukemia, with 90% of such patients having extramedullary involvement and 40% having meningeal infiltration.

The term congenital leukemia applies to cases appearing within the first 4 to 6 weeks of life. Leukemia cutis occurs in 25% to 30% of such cases, the vast majority being congenital myelogenous leukemia. The typical morphology is multiple, red or plum-colored nodules. In about 10% of cases of congenital leukemia cutis (or 3% of all cases of congenital leukemia), the skin involvement occurs while the bone marrow and peripheral blood are normal. Systemic involvement is virtually always identified in 5 to 16 weeks. Unlike other forms of leukemia, in congenital leukemia, cutaneous infiltration does not worsen prognosis. Congenital leukaemia cutis has been complicated by disseminated linear calcinosis cutis.

Granulocytic Sarcoma (Chloroma)

Granulocytic sarcomas are rare tumors of immature granulocytes. They occur in about 3% of patients with myelogenous leukemia. Granulocytic sarcoma is seen in four settings: in patients with known AML; in patients with CML

or MDS as a sign of an impending blast crisis; in undiagnosed patients as the first sign of AML; or after bone marrow transplantation as the initial sign of relapse. Most lesions occur in the soft tissues, periosteum, or bone. Skin lesions represent 20% to 50% of reported cases. They may be solitary or multiple. They appear as red, mahogany, or violaceous firm nodules with a predilection for the face, scalp, or trunk.

The name *chloroma* comes from the green color of fresh lesions, which can be enhanced by rubbing with alcohol; this is caused by the presence of myeloperoxidase. This appearance is variable, so the preferred term is now *granulocytic sarcoma*.

The diagnosis is not difficult if the diagnosis of leukemia has been established. Such patients are treated with appropriate chemotherapy. However, if the skin lesion is the initial manifestation of leukemia, and the blood and bone marrow are normal, the lesion may be misdiagnosed as a large cell lymphoma. The treatment of such patients is controversial, but most go on to develop AML within months, so chemotherapy is often given.

Hairy-Cell Leukemia

Skin involvement is rare in hairy-cell leukemia and violaceous papules and nodules, which are the characteristic morphology of other forms of leukemia cutis, are extremely rare in hairy-cell leukemia. Rather, often in the setting of a systemic mycobacterial infection or a drug reaction, a diffuse erythematous, nonpruritic eruption occurs. This may progress to erythroderma or a severe blistering eruption. Stopping the offending medication usually leads to resolution of the eruption. This is especially common in patients treated with 2-chlorodeoxyadenosine and allopurinol. The former treatment alone does not lead to these severe skin reactions, suggesting the allopurinol is the cause. Patients with hairy cell leukemia also develop lesions of pustular vasculitis of the dorsal hands, a neutrophilic dermatitis closely related to bullous Sweet syndrome. This is sometimes termed a "vasculitis" in the oncology literature.

Nonspecific Conditions Associated with Leukemia (Leukemids)

Leukemia and its treatment is associated with a series of conditions which may also be seen in patients without leukemia, but which are seen frequently enough in leukemic patients to be recognized as a complication of that condition or its treatment.

When a dermatologist or dermatopathologist is consulted to evaluate a patient with leukemia and skin lesions, the differential diagnosis usually includes four groups of conditions: drug reactions, leukemia cutis, an infectious complication, and a reactive condition. Drug reactions include all forms of reactions, but are most commonly erythema multiforme, morbilliform reactions, or acral erythema. Infections may present in many ways but are usually purpuric papules, pustules, or plaques if they are caused by bacteria or fungi. Ulceration is typical. Herpes simplex and herpes zoster should be considered in all erosive, ulcerative, or vesicular lesions. The reactive conditions include a group of neutrophilic dermatoses with considerable clinical overlap. These include Sweet syndrome, pyoderma gangrenosum, neutrophilic hidradenitis, and leukocytoclastic vasculitis. Transient acantholytic dermatosis and eosinophilic reactions resembling insect bites may occur, most commonly in patients with CLL. In CLL a pruritic and unremitting exfoliative erythroderma is a unique feature.

Evaluation of these patients must be complete and often extensive diagnostic tests and empiric treatment are pursued until the diagnosis is established. In the acute setting, a clinical diagnosis is made based on morphology. Possible infectious complications are covered by appropriate antibiotics, especially if the patient is febrile or the diagnosis of a herpes virus infection is made. Diagnostic tests are submitted, often including a skin biopsy. For herpes infections, a direct fluorescent antibody should be done, as the results are virus specific and rapid, so appropriate treatment can be given quickly. Once the diagnostic tests return, the therapy is tailored to the appropriate condition. Except for herpes infections, a skin biopsy is often required. If infection is considered, a portion of the biopsy should be sent for culture.

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CUTANEOUS MYELOFIBROSIS

Myelofibrosis is a chronic myeloproliferative disorder characterized by a clonal proliferation of defective multipotential stem cells in the bone marrow. Overproduction and premature death of atypical megakaryocytes in the bone marrow produce excess amounts of platelet-derived growth factor, a potent stimulus for fibroblast proliferation and collagen production. Extramedullary hematopoiesis (EMH) is a hallmark of myelofibrosis. Blast cells and committed stem cells escape the marrow in large numbers, enter the circulation, and form tumors of the same atypical clone in other organs, especially the spleen, liver, and lymph node. EMH in the skin of neonates is usually caused by intrauterine viral infections. In adults, cutaneous EMH has rarely been reported, characteristically associated with myelofibrosis. Skin lesions are dermal and subcutaneous nodules. Histologically, the cutaneous lesions are composed of dermal and subcutaneous infiltrates of mature and immature myeloid cells, erythroid precursors (in only half of cases), and megakaryocytic cells (which may predominate). There is marked production of collagen fibers in the cutaneous lesions by the mechanism described above. Myelofibrosis must be distinguished from CML, since both have elevated white blood cell counts with immature myeloid forms, defective platelet production and marrow fibrosis. Both may terminate in blast crisis and myelofibrosis may rarely convert to CML. CML is associated with the Philadelphia chromosome, whereas chromosomal abnormalities occur in 40% of myelofibrosis cases on various chromosomes.

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HYPEREOSINOPHILIC SYNDROME

Idiopathic hypereosinophilic syndrome (HES) is defined as eosinophilia with more than 1500 eosinophils/mm^3 for more than 6 months, with some evidence of parenchymal organ involvement; there must also be no apparent underlying disease to explain the hypereosinophilia and no evidence of vasculitis. Ninety percent of patients reported have been men, mostly between the ages of 20 and 50. Childhood cases are rare. Presenting symptoms include fever (12%), cough (24%), fatigue, malaise, muscle pains, and skin eruptions. Two pathogenic variants of HES have been defined: m-HES (myeloproliferative HES) and l-HES (lymphocytic HES). M-HES patients are overwhelmingly males, and anemia, thrombocytopenia, elevated serum B12 levels, mucosal ulcerations, splenomegaly, and endomyocardial fibrosis are the clinical features. Eosinophil clonality and interstitial deletion on 4q12 result in fusions of FIP1qL1 and PDGFRα genes, forming an F/P fusion protein displaying constituitive activity, are pathogenically related to m-HES cases. Increased mast cells and elevated tryptase levels with myeloid precursors in peripheral blood and myelofibrosis may be found, suggesting mast cells may be pathogenically related to this form of HES. Leukemia may develop in patients with m-HES. L-HES has been associated with circulating T-cell clones of CD4+ phenotype which secrete Th2 cytokines, especially IL-5. Females and males are equally affected by l-HES and cutaneous manifestations are observed in virtually all patients. Skin manifestations include urticaria, angioedema, pruritus, eczema, and erythroderma. Splinter hemorrhages and necrotic skin lesions are seen in some HES patients as well. Endomyocardial fibrosis is uncommon, but pulmonary and digestive symptoms are common. Some patients with l-HES are clinically identical to Gleich syndrome or episodic angioedema and hypereosinophilia. Over time some patients with l-HES will develop lymphoma.

Treatment is determined by classifying cases appropriately as m-HES or l-HES. M-HES patients may be treated with corticosteroids, hydroxyurea, IFN-α, and chemotherapeutic agents. Imatinib mesylate (Gleevac, 100 mg/day or less) can be highly effective for m-HES patients with the F/P mutation, as imatinib inhibits the phosphorylation of the F/P protein and leads to apoptosis of cells producing this protein. This has rapidly become first-choice treatment for this subset of patients. Response may be dramatic, with eosinophil levels, and skin and gastrointestinal manifestations clearing in days. For l-HES patients, systemic glucocorticoids, and perhaps IFN-α with glucocorticoids, can be used and are usually effective. Monoclonal anti-IL-5 antibody, cyclosporin A, anti-IL-2R-α, and CTLA-4-Ig may be treatment options. If lymphoma supervenes, intense chemotherapy and allogenic stem cell transplantation can be considered.

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ANGIOIMMUNOBLASTIC LYMPHADENOPATHY WITH DYSPROTEINEMIA (ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA)

Angioimmunoblastic lymphadenopathy with dysproteinemia (AILD) is an uncommon lymphoproliferative disorder. Patients are middle-aged or elderly and present with fever (72%), weight loss (58%), hepatomegaly (60%), polyclonal hyperglobulinemia (65%), and generalized adenopathy (87%). Pruritus occurs in 44% and a skin rash in 46%. The skin eruption usually is morbilliform in character, resembling an exanthem or a drug reaction. Petechial, purpuric, nodular, ulcerative, and erythrodermic eruptions have also been reported. In about 30% of cases the eruption is associated with the ingestion of a medication. The eruptions usually resolve with oral steroids, misleading the clinician to believe the eruption was benign.

Histopathologically, there is a patchy and perivascular dermal infiltrate of various types of lymphoid cells, plasma cells, histiocytes (enough to rarely give a "granulomatous" appearance), and eosinophils. The lymphoid cells are usually helper T-cells (CD4+). Some portion of the lymphoid cells is atypical in most cases, suggesting the diagnosis. Blood vessels are increased and the endothelial cells are prominent, often cuboidal. Unfortunately, these changes may not be adequate to confirm the diagnosis. However, clonal T-cell gene rearrangement is found in three-quarters of these skin lesions and is the same as the clone in the lymph node. Immunophenotyping of the skin lesions does not give a consistent pattern. At times the skin lesions will show leukocytoclastic vasculitis on biopsy. Lymph node biopsy is usually required to confirm the diagnosis and exclude progression to lymphoma.

AILD appears to develop in a stepwise fashion. Initially there is an immune response to an unknown antigen. This immune reaction persists, leading to oligoclonal T-cell proliferation. Monoclonal evolution may occur, eventuating in lymphoma (angioimmunoblastic lymphoma [AILD-L]). These are usually T-cell lymphomas, but B-cell lymphomas can also occur. In the case of AILD-L, skin lesions may contain the neoplastic cells (secondary lymphoma cutis). In up to 50% of cases multiple unrelated neoplastic cell clones have been identified. Clones identified in the skin may be different from clones found in lymph node. Trisomy 3 or 5, or an extra X chromosome, may be found. AILD is an aggressive disease, with mortality ranging from 48% to 72% in various series (average survival time is 11 to 60 months). The cause of death is usually infection. Epstein-Barr virus and human herpesviruses 6 and 8 have been implicated in AILD.

Treatment of AILD has included systemic steroids, methotrexate plus prednisone, combination chemotherapy, fludarabine, 2-chlorodeoxyadenosine, IFN-α, and cyclosporin. Early treatment with systemic steroids during an oligoclonal or prelymphomatous stage may induce a long-lasting remission. Asymptomatic patients may not be treated initially but must be watched very closely. More aggressive chemotherapy achieves better remission. Nonetheless, recurrence rates are high, and average survival is between 1 and 3 years.

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Sinus Histiocytosis with Massive Lymphadenopathy (Rosai-Dorfman Disease)

Sinus histiocytosis with massive lymphadenopathy (SHML), or Rosai-Dorfman disease, usually appears in patients in the first or second decade of life as a febrile illness accompanied by massive cervical (and commonly other) lymphadenopathy, polyclonal hyperglobulinemia, leukocytosis, anemia, and an elevated sedimentation rate. Males and black persons are especially susceptible. Extranodal involvement occurs in 40% of cases, with skin being the most common site. Ten percent of patients with SHML have skin lesions and 3% of patients have disease detectable only in the skin. The terms *cutaneous sinus histiocytosis* or *cutaneous Rosai-Dorfman disease* have been applied to these cases. Skin lesions consist of isolated or disseminated yellow–brown papules, pustules, or nodules; or macular erythema. Large annular lesions, resembling granuloma annulare, may occur. Most patients with cutaneous Rosai-Dorfman are older (40 to 60 years).

Histologically, there is a superficial and deep perivascular infiltrate of lymphocytes and plasma cells. Nodular and diffuse infiltration of the dermis by large, foamy histiocytes is present. A very important diagnostic feature is the finding of intact lymphocytes (and less commonly plasma cells) in the cytoplasm of the histiocytic cells. This is called *emperipolesis*. Foamy histiocytes may be seen in dermal lymphatics. The cutaneous histology in some cases may be very nonspecific (except for the finding of emperipolesis) and only on evaluation of lymph node or other organ involvement does the diagnosis become clear. Immunohistochemistry and electron microscopy may be very useful as the infiltrating cells are positive for CD4, factor XIIIa, and S-100, but do not contain Birbeck granules.

The cause of this condition is unknown, but numerous reports have identified human herpesvirus 6 in involved lymph nodes. The condition usually clears spontaneously, so no treatment is required. Numerous agents have been used therapeutically with variable success, but are only indicated if the condition puts the patient at risk for death or a significant complication (usually by compressing a vital organ).

Treatments have included radiation, systemic corticosteroids, and thalidomide. Single and multiagent chemotherapy is met with mixed to poor response. To treat skin lesions, cryotherapy, topical steroids, and intralesional steroids may be tried.

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POLYCYTHEMIA VERA (ERYTHREMIA)

Polycythemia vera (PCV) is characterized by an absolute increase of circulating red blood cells, with a hematocrit level of 55% to 80%. Leukocyte and platelet counts are also increased. The skin changes are characteristic. There is a tendency for the skin to be red, especially on the face, neck, and acral areas. The mucous membranes are engorged and bluish. The phrase "red as a rose in summer and indigo blue in winter" has been ascribed to Osler in describing PCV. Telangiectases, bleeding gums, and epistaxis are frequently encountered. Cyanosis, purpura, petechiae, hemosiderosis, rosacea, and koilonychia may also be present.

In 50% of patients with PCV, aquagenic pruritus occurs. In about two-thirds of patients this is of limited severity and does not require treatment. The pruritus is typically triggered after a bath or shower and the feeling induced may be itching, burning, or stinging. It usually lasts 30 to 60 min and is independent of the water temperature. Pruritus unassociated with water exposure may also occur. There is a concurrent elevation of blood and skin histamine. Pruritus is present in about 20% of patients at presentation and develops in the remaining 30% over the course of their disease. Patients with pruritus have lower mean corpuscular volumes and higher leukocyte counts. Some have suggested that iron deficiency plays a role in PCV-associated pruritus, so a ferritin level, and a trial of iron therapy, may be indicated. Platelet counts are no different between PCV patients who itch and those who do not.

The treatment of PCV-associated pruritus may be difficult. Initial therapy would include first- or second-generation H_1 antihistamines. Hydroxyzine was reported as the most effective antihistamine by a group of PCV patients. H_2 blockers can be added. Narrow-band UVB has been reported to be effective in 80% of patients. Topical therapy is of limited benefit. Phlebotomy may be useful in patients with elevated hematocrits. Paroxetine (Paxil) 20 to 60 mg/day may be dramatically effective.

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CHAPTER

33 Diseases of the Skin Appendages

DISEASES OF THE HAIR

Normal human hairs can be classified according to cyclical phases of growth. Anagen hairs are growing hairs, catagen hairs are those undergoing transition from the growing to the resting stage, and telogen hairs are resting hairs, which remain in the follicles for variable lengths of time before they fall out (teloptosis). The lag period between loss of the telogen hair and growth of a new anagen hair has been referred to as kenogen.

Anagen hairs grow for about 3 years (1000 days), with a range between 2 and 6 years. The follicular matrix cells grow, divide, and become keratinized to form growing hairs. As the matrix produces the hair shaft, it incorporates substances that may be useful in medical or forensic analysis. Catagen hairs are in a transitional phase, lasting 1 or 2 weeks, in which all growth activity ceases, with the eventual formation of the telogen "club" hair. Many apoptotic cells are present in the outer root sheath of the catagen hair as it involutes. Telogen club hairs are resting hairs, which continue in this state for 3 to 5 months (about 100 days) before they are released.

Among human hairs plucked from a normal scalp, 85% to 90% are anagen hairs and 10% to 15% are telogen hairs. Catagen hairs normally comprise less than 1% of scalp hairs. It has been estimated that the scalp normally contains about 100,000 hairs, and the average number of hairs shed daily is 100 to 150. The hair growth rate of terminal hairs is about 0.37 mm/day. Contrary to popular belief, neither shaving nor menstruation has any effect on hair growth rate. The average uncut scalp hair length is estimated to be 25 to 100 cm, although exceptional hairs may be as long as 170 cm (70 inches).

Human hair is also designated as lanugo, vellus, or terminal hair. Lanugo hair is the fine hair present on the body of the fetus. This is replaced by the vellus and terminal hairs. Vellus hairs are fine, usually light-colored, and have a narrow hair shaft thinner than the width of the inner root sheath. Terminal hairs are coarse, thick, and dark, except in blonds. Hair occurs on all skin surfaces except the palms, soles, labia minora, lips, nails, glans, and prepuce. Terminal hairs are commonly present on a man's face, chest, and abdomen, but vellus hairs usually predominate on these sites in women.

Causes of alopecia are generally divided into the broad categories of cicatricial and noncicatricial alopecia. The evaluation should take into account the patient's age and ethnicity. Examination of hair shafts can establish a diagnosis of trichodystrophy. Hair counts, hair pull, and hair pluck (trichogram) can establish the degree of hair shedding, the type of hairs that are shed, and the anagen-to-telogen ratio. Biopsies can also the determine anagen-to-telogen ratio, and provide information regarding the potential for regrowth as well as providing a diagnosis. Biopsies are particularly valuable in the evaluation of cicatricial alopecia. Often, a correct diagnosis hinges on a synthesis of clinical, histologic, serologic, and immunofluorescent data.

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Noncicatricial Alopecia

Alopecia Areata

Clinical Features

Alopecia areata (in French, *pelade*) is characterized by rapid and complete loss of hair in one or more round or oval patches, usually on the scalp, bearded area (Fig. 33-1), eyebrows, eyelashes, and less commonly, on other hairy areas of the body. Often the patches are from 1 to 5 cm in diameter. A few resting hairs may be found within the patches. Early in the course there may be sparing of gray hair, and white hairs are rarely affected. Sudden whitening of hair may represent widespread alopecia areata in a patient with salt and pepper hair. In about 10% of cases of alopecia areata, especially in long-standing cases with extensive involvement, the nails develop uniform pits that may form transverse or longitudinal lines. Trachyonychia, onychomadesis, and red or spotted lunulae occur, but less commonly.

Complete loss of scalp hair is referred to as alopecia totalis, and complete loss of all hair as alopécia universalis.

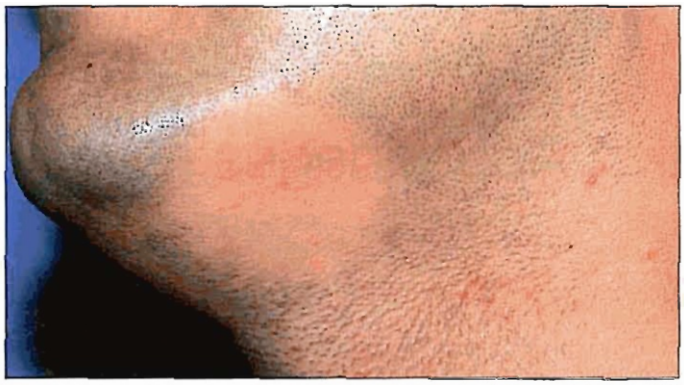

Fig. 33-1 Alopecia areata.

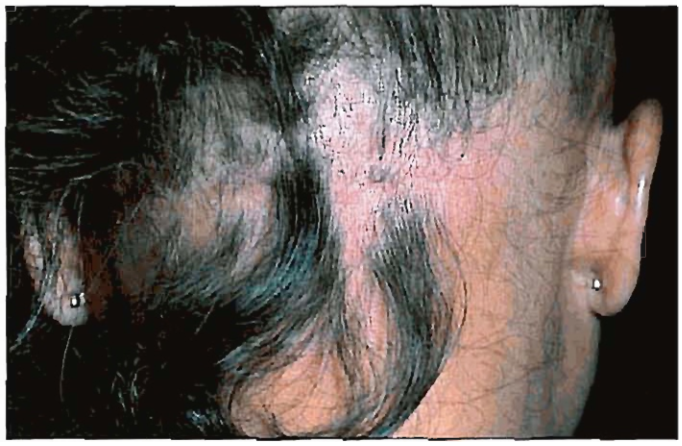

Fig. 33-2 Alopecia areata.

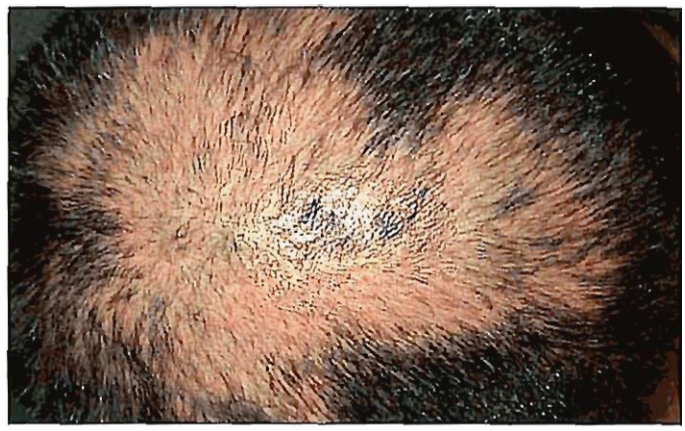

Fig. 33-3 Alopecia areata.

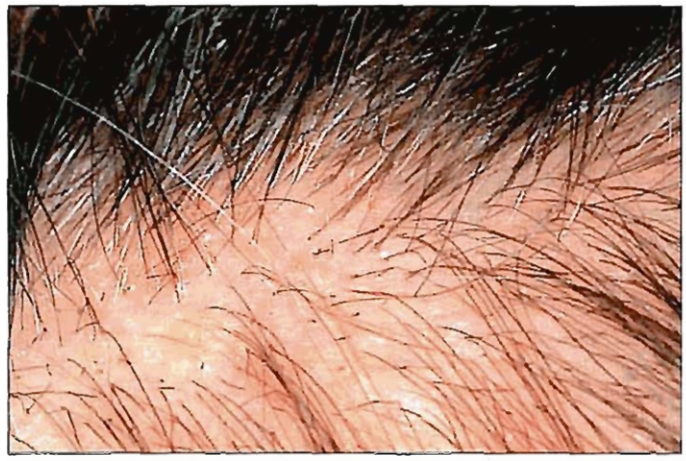

Fig. 33-4 Exclamation point hairs of alopecia areata.

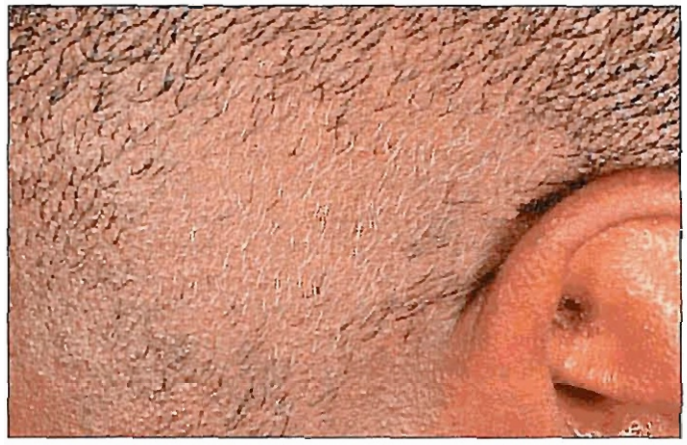

Fig. 33-5 Migratory poliosis.

In most cases, hair loss is confined to the scalp and is patchy in distribution. Loss may occur confluent along the temporal and occipital scalp (ophiasis) (Fig. 33-2) or on the entire scalp except for this area (sisaipho). Rarely, alopecia areata may present in a diffuse pattern that may mimic pattern alopecia (Fig. 33-3). Clues to the correct diagnosis include a history of periodic regrowth, nail pitting, and the presence of tapered fractures or *exclamation point* hairs (Fig. 33-4). Alopecia areata generally presents as an anagen effluvium, with an inflammatory insult to the hair matrix resulting in tapering of the hair shaft, and resulting in fracture of anagen hairs. As the hair miniaturizes or converts from anagen to telogen, the remaining lower portion of the hair rises above the level of the scalp, producing the exclamation point hair.

Alopecia areata is associated with a higher incidence than usual of atopic dermatitis, Down syndrome, lichen planus, and autoimmune diseases, such as systemic lupus erythematosus, thyroiditis, diabetes mellitus, myasthenia gravis, and vitiligo. However, most cases of alopecia areata occur without associated disease, and routine screening for these disorders is of little value unless prompted by signs or symptoms.

Migratory poliosis of the scalp may represent a forme fruste of alopecia areata. Patients with this disorder present with migrating circular patches of white hair (Fig. 33-5), but never loose hair. The histology resembles alopecia areata.

Etiologic Factors

The preponderance of evidence supports an autoimmune etiology. Oligoclonal and autoreactive T-lymphocytes are present in the peribulbar inflammatory infiltrate, and many patients respond to immune-modulating drugs. Affected alopecia areata scalp skin grafted onto nude mice with severe combined immunodeficiency demonstrates loss of infiltrating lymphocytes and hair growth. In this model, injecting T-lymphocytes with scalp homogenate can reproduce the alopecia. Follicular melanocytes substitute for scalp homogenates to produce alopecia areata in this model, providing evidence that follicular melanocytes are the targets for activated T-cells in this disease. This hypothesis is also

supported by the observations that white hair is rarely affected and regrowing hair is often depigmented.

In early alopecia areata, the perifollicular and intrafollicular inflammatory infiltrate is composed of activated CD4+ and CD8+ T-cells, together with macrophages and Langerhans cells. The early phase of hair loss appears to be mediated by type 1 cytokines, including interleukin (IL)-2, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α. The hair bulb normally represents an area of relative immune privilege during anagen, as evidenced by a very low level of expression of major histocompatibility complex (MHC) class Ia antigens. This immune privilege may prevent antigen recognition by autoreactive CD8+ T-cells. Alopecia areata may be related to collapse of this immune privilege.

Neuropeptides modify immune reactivity and may play a role in the disease. Heredity also plays a role. Overall, nearly 25% of patients have a positive family history; there are reports of twins with alopecia areata. Patients with "early onset, severe, familial clustering alopecia areata" have a unique and highly significant association with the HLA antigens DR4, DR11, and DQ7. The "later onset, milder severity, better prognostic" subsets of patients have a lower frequency of familial disease and do not share these HLA antigens.

Histology

In early disease there is a lymphoid infiltrate in the peribulbar area of anagen or early catagen follicles. Eosinophils may be present in the infiltrate, and lymphocyte-mediated damage to the bulb produces melanin pigment incontinence in the surrounding stroma. The hair structures enter an abnormal catagen phase, followed by telogen. During this phase, the presence of many catagen hairs and pigment casts within the follicular canal can cause histologic confusion with trichotillomania. In alopecia areata, the follicles eventually miniaturize, appearing as small dystrophic anagen hairs high in the dermis, often with a persistent lymphocytic peribulbar infiltrate. The presence of a peribulbar infiltrate helps to distinguish the miniaturized follicles of alopecia areata from those of androgenetic alopecia. Fibrous tract remnants beneath the miniaturized bulbs of alopecia areata may contain lymphoid cells, eosinophils, and melanin pigment. These findings are never present in trichotillomania or androgenetic alopecia. With time, the lymphocytes disappear, but focal eosinophils and pigment remain. Finally, only focal melanin pigment remains in the fibrous tract remnants. Hair fiber granulomas and scarring never occur. Every histologic feature of alopecia areata may be seen in syphilis. The presence of plasma cells is suggestive of syphilis, but plasma cells are lacking in about one-third of syphilis biopsies. Plasma cells may be present in biopsies from any form of inflammatory alopecia if the biopsy is taken from the occipital scalp, as this site readily recruits plasma cells.

Differential Diagnosis

The sharply circumscribed patch of alopecia with exclamation point hairs at the periphery and the absence of scarring are indicative of alopecia areata. Tinea capitis, androgenetic alopecia, early lupus erythematosus, syphilis, congenital triangular alopecia, alopecia neoplastica, and trichotillomania should be kept in mind when alopecia areata is considered. A biopsy will generally help to distinguish alopecia areata from these other entities, except syphilis which may be indistinguishable. In endemic areas of southwest Asia, *Pheidole* ants shear hair shafts during the night, resulting in overnight loss of clumps of hair. The resulting round patches of hair loss closely mimic alopecia areata.

Treatment

The natural course of the hair loss is highly variable. Some patches will regrow in a few weeks without any treatment. Various treatments can induce growth, but the inherent risks and cost must be weighed against the benefit of earlier regrowth. Arnold found, in his series of 63 consecutive responders to a follow-up questionnaire, that after reassurance only, hair had regrown in all but four patients after 1 year and in all but one after 2 years. The great majority had recovered in 3 months after their only office visit. Therefore, anecdotal reports of success must be interpreted carefully in the light of the high rate of spontaneous recovery.

Intralesional injections of corticosteroid suspensions are the treatment of choice for localized cosmetically conspicuous patches, such as those occuring in the frontal hairline or involving an eyebrow. Injections of triamcinolone, 2 to 10 mg/mL, are typically given intradermally or in the superficial subcutaneous tissue. Large volumes and higher concentrations of triamcinolone present a greater risk of atrophy. High-strength topical steroids may be used as first-line therapy, but are less reliable than injections. Several investigators have reported the use of pulsed oral corticosteroids in rapidly progressing or widespread disease. However, long-term treatment is frequently needed to maintain growth, and the attendant risks should be carefully weighed against the benefits. In a study of 66 patients aged 9 to 60 years, monthly methylprednisolone was administered at a dose of 500 mg/day during 3 days or 5 mg/kg twice a day over 3 days in children. More than 60% of patients with widespread patchy alopecia responded. Half of the patients with alopecia totalis had a good response, while a quarter of those with universal alopecia responded. Patients with ophiasic alopecia areata did not respond.

Induction of contact sensitivity to squaric acid dibutyl ester, dinitrochlorobenzene, and diphencyprone can be useful in refractory cases. In mice, contact immunotherapy is associated with a decrease in cutaneous activated T-cells, a reduction in intrafollicular CD8+ lymphocytes, and reduced expression of CD44v3+ and CD44v10+ cells. These results suggest that blockade of leukocyte trafficking and extravasation is an important mechanism of action. Topical or oral methoxsalen and ultraviolet A (PUVA) therapy are options for refractory or widespread lesions. Short contact topical anthralin 1% cream (applied for 15–20 min and then shampooed off) can be of benefit. Topical minoxidil may be combined with other treatments or utilized as a single agent. The 308-nm xenon chloride excimer laser (300–2300 mJ/cm^2/session) has been reported to produce regrowth after 11 and 12 sessions over a 9- to 11-week period.

AA can cause tremendous psychological stress. Education about the disease process, cosmetically acceptable alternatives (especially information about wigs), and research into innovative therapies should all be made available to the patient. In addition to the information conveyed by the dermatologist, an excellent resource is the National Alopecia Areata Foundation (NAAF): PO Box 150760, San Rafael,

CA 94915–0760, E-mail: NAAF@compuserve.com, website: www.alopeciaareata.com.

Prognosis

The tendency is for spontaneous recovery in patients who are postpubertal at onset. At first, the regrowing hairs are downy and light in color; later, they are replaced by stronger and darker hair with full growth. Predictors of a poor prognosis are the presence of atopic dermatitis, childhood onset, widespread involvement, ophiasis, duration of longer than 5 years, and onychodystrophy.

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Telogen Effluvium Telogen effluvium presents with excessive shedding of normal telogen club hairs. This excessive shedding of telogen hairs has several possible mechanisms. It most commonly occurs 3 to 5 months after the *premature* conversion of many anagen hairs to telogen hairs induced by surgery, parturition, fever, drugs, dieting, or traction. Local patches of early telogen conversion may be induced by papulosquamous diseases affecting the scalp. Alternatively, follicles may remain in *prolonged* anagen rather than normally cycling into telogen. This occurs during pregnancy. On delivery, many follicles are then released simultaneously into telogen, and shedding occurs 3 to 5 months later. Prolongation of telogen also occurs during pregnancy, and results in an initial wave of hair loss soon after delivery or heralding early termination of a pregnancy. Shortening of the anagen phase occurs in pattern (androgenetic) alopecia, and results in telogen effluvium. Normally, anagen lasts about 1000 days and telogen about 100 days. This results in a 10:1 ratio of anagen-to-telogen hairs in the scalp. With progression of pattern alopecia, anagen shortens, and the ratio of anagen-to-telogen hairs falls. A greater proportion of hairs are in telogen at any one time, resulting in a chronic increase in telogen shed. Administration of topical minoxidil may produce a telogen effluvium by premature termination of telogen necessary to initiate anagen in responding follicles. This causes early telogen release and a brief telogen effluvium.

Whatever the cause of the telogen loss, the hair is lost "at the root." Each hair will have a visible depigmented club-shaped bulb and will lack a sheath (Fig. 33-6). In most cases, loss is diffuse. Patients commonly have more than one mechanism for telogen hair loss. Patchy or diffuse telogen may be associated with papulosquamous diseases of the scalp. Perceptible thinning of the hair is more common in patients with preexisitng pattern alopecia. In patients with pattern alopecia, shortening of the hair cycle results in increased telogen shed. Superimposed papulosquamous disease, iron-deficiency or thyroid disease can result in even more telogen shed and accentuate the pattern loss.

Trichodynia is a common symptom in patients with telogen effluvium, as it is in pattern hair loss. Trichodynia

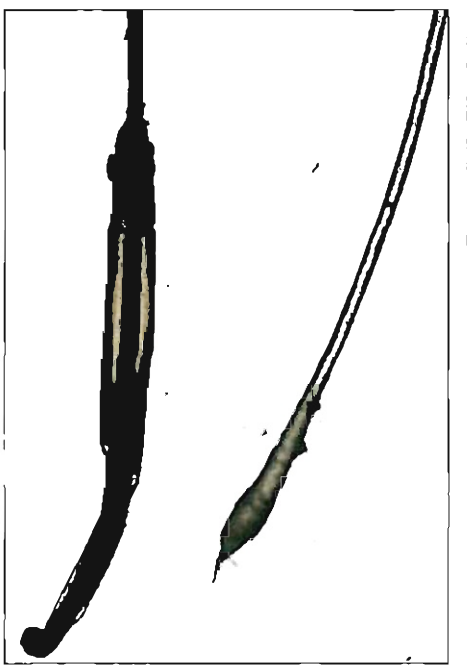

Fig. 33-6 Anagen and telogen hair (anagen hair has a pigmented bulb and is surrounded by a gelatinous root sheath; telogen hair has a nonpigmented bulb and lacks a root sheath).

often coexists with signs of depression, obsessive personality disorder, and anxiety.

Telogen shed may be estimated by the pull test: grasping 40 hairs firmly between thumb and forefinger, followed by a slow pull that causes minimal discomfort to the patient. A count of more than four to six club hairs is abnormal, but the result is influenced by recent shampooing (a count of two or three hairs being abnormal in a freshly shampooed scalp), combing, and the phase of telogen effluvium (whether it is resolving or entering a chronic phase). The clip test may also be useful: 25 to 30 hairs are cut just above the scalp surface and mounted. Indeterminate and telogen hairs are short and of small diameter. Many hairs of this type may be present in telogen effluvium or pattern alopecia. Trichogram evaluation (50 hairs plucked with a Kelly clamp with rubber drains over the teeth) can also provide information on the anagen-to-telogen ratio.

Age, sex, race, and genetic factors influence the normal average daily hair loss in an individual. A full head of hair numbers about 100,000; of these, approximately 100 to 150 are lost daily. In telogen effluvium, estimates of loss vary from 150 to more than 400. Patients may be instructed to collect and count the hair daily; however, they should make sure to collect all small hairs and those that come out in washing and in the bed, as well as those present on the comb or brush. When the pull test is positive, hair shed counts are not needed. An alternative is to collect all hairs lost during a 1-min combing session. For this technique, developed by Dr Jeffrey Miller, the patient combs for 1 min prior to shampooing on 3 consecutive days. The patient is instructed to comb from the vertex to the anterior hairline. The normal range of lost hairs with this technique is 10 to 15. Loss of more than 50 is common in telogen effluvium. Serial 1-min hair counts can be performed to monitor progress.

Telogen effluvium is commonly related to protein or other nutrient deprivation. Assessment of dietary habits and determination of iron saturation and ferritin are the simplest ways to determine nutritional status. Iron replacement is advisable if saturation or ferritin are low, but in one study iron replacement alone did not result in resolution of telogen effluvium. Iron may merely serve as a marker for overall nutritional status. Patients with evidence of deficiency should be given supplements to correct the identified deficiency and encouraged to eat a varied diet. Sources of blood loss, such as menstrual bleeding and gastrointestinal blood loss, should be investigated. Hypothyroidism, allergic contact dermatitis to hair dyes, and renal dialysis with secondary hypervitaminosis A may also be associated with telogen effluvium. Drug-induced telogen effluvium has been noted with the use of amphetamines, aminosalicyclic acid, bromocriptine, captopril, coumarin, carbamazepine, cimetidine, danazol, enalapril, etretinate, lithium carbonate, levodopa, metyrapone, metoprolol, propranolol, pyridostigmine, and trimethadione. Postnatal telogen effluvium of infants may occur between birth and the first 4 months of age. Usually, regrowth occurs by 6 months of age. Telogen counts by Kligman in six infants varied from 64% to 87%. He also found a tendency for the alopecia to occur in the male-pattern distribution. Idiopathic chronic telogen effluvium has been described by Whiting in a group of 355 patients (346 women and 9 men) with diffuse generalized thinning of scalp hair. Most were 30- to 60-years old, and their hair loss started abruptly, with increased shedding and thinning. There was a fluctuating course and diffuse thinning of the hair all over the scalp, accompanied by bitemporal recession. He found high telogen counts on horizontal sections of scalp biopsies and considers these patients to have a chronic form of telogen effluvium. This chronic form may respond to 5% minoxidil solution.

If a 4-mm punch biopsy is performed, 25 to 50 hairs are normally present for inspection in transverse (horizontal) sections. If more than 12% to 15% of terminal follicles are in telogen, this indicates a significant shift from anagen to telogen. Pattern (androgenetic alopecia) demonstrates miniaturization, variable hair shaft diameter, and an increased proportion of telogen hairs. Traction alopecia and trichotillosis (trichotillomania) result in an increased number of catagen and telogen hairs. Pigment casts, empty anagen follicles, trichomalacia, and catagen hairs help distinguish these entities from simple telogen effluvium.

No specific therapy is required for most patients with telogen effluvium. In the majority of cases the hair loss will stop spontaneously within a few months and the hair will regrow. The prognosis is good if a specific event can be pinpointed as a probable cause. Papulosquamous scalp disorders may precipitiate telogen hair loss and should be addressed. Iron and thyroid status should be determined if the course is prolonged or if history or physical examination suggest an abnormality. Patients should be encouraged to eat a balanced diet. In a mouse model, sonic stress can produce catagen. This model may be useful in the study of agents for the treatment of telogen effluvium.

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Anagen Effluvium Anagen effluvium usually results from hair shaft fracture. It is seen frequently following the

administration of cancer chemotherapeutic agents, such as the antimetabolites, alkylating agents, and mitotic inhibitors. These agents result in temporary shutdown of the hair matrix with resultant tapering of the shaft (Pohl-Pinkus constrictions). Trichograms reveal tapered fractures. Only anagen hairs are affected. The 10% of scalp hairs in telogen have no matrix and are unaffected. Severe loss is frequently seen with doxorubicin, the nitrosureas, and cyclophosphamide. When high doses are given, loss of anagen hairs becomes most apparent clinically in 1 to 2 months. The hair shafts are abruptly narrowed at the time of maximum drug effect, and when the very thin portion reaches the surface, the hair shafts all break at about the same time. With cessation of drug therapy, the follicle resumes its normal activity within a few weeks; the process is entirely reversible. It is apparent that mitotic inhibition merely stops the reproduction of matrix cells but does not permanently destroy the hair. A pressure cuff applied around the scalp during chemotherapy and scalp hypothermia have been reported to prevent such anagen arrest, but as the scalp may be a site of metastasis, it may be better not to spare the scalp from the effects of chemotherapy. Topical minoxidil has been shown to shorten the period of baldness by an average of 50 days.

In addition to the cytotoxic chemotherapeutic agents, various agents, such as INH, thallium, and boron may induce anagen effluvium. Anagen effluvium with tapered fractures also occurs in alopecia areata and syphilis. In these diseases, an inflammatory insult to the hair bulb results in Pohl-Pinkus contrictions and tapered fracture.

Anagen loss may also occur at the root. Loose anagen syndrome, described by Price in 1989, is a disorder in which anagen hairs may be pulled from the scalp with little effort. It occurs mostly in blond girls and usually improves with age. The syndrome appears to be related to a defect in the hair cuticle. Instead of anchoring the hair firmly, the cuticle simply folds back like a rumpled sock (Fig. 33-7), allowing the hair shaft to be extracted. Woolly hair can be associated with loose anagen hair syndrome. A keratin mutation, E337K in K6HF, was identified in three of nine families studied. Colobomas have also been associated with loose anagen hair.

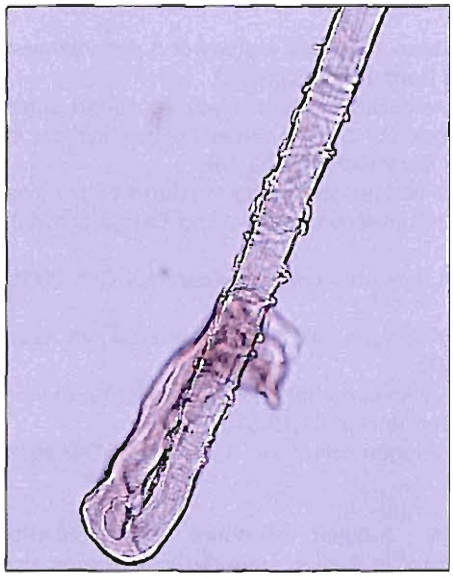

Fig. 33-7 Loose anagen hair with "rumpled sock" cuticle.

Anagens hairs may be easily extracted from active areas of lupus erythematosus and lichen planopilaris. They commonly lack the root sheath that normally surrounds a plucked anagen hair (Fig. 33-8). Anagen effluvium has also been described in lesions of pemphigus.

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Androgenetic Alopecia

Male-Pattern Baldness

Male-pattern alopecia or male-pattern androgenetic alopecia (common baldness) shows itself during the teens, 20s or early 30s with gradual loss of hair, chiefly from the vertex and frontotemporal regions. The process may begin at any time after puberty, and the presence of "whisker" or kinky hair may be the first sign of impending male-pattern alopecia. The anterior hairline recedes on each side, in the Geheimratswinkeln ("professor angles"), so that the forehead becomes high. Eventually the entire top of the scalp may become devoid of hair. Several patterns of this type of hair loss occur, but the most frequent is the biparietal recession with loss of hair on the vertex. The rate of hair loss varies among individuals. Sudden hair loss may occur in the 20s and then proceed relentlessly, though very slowly, for a number of years. The follicles produce finer and lighter hairs

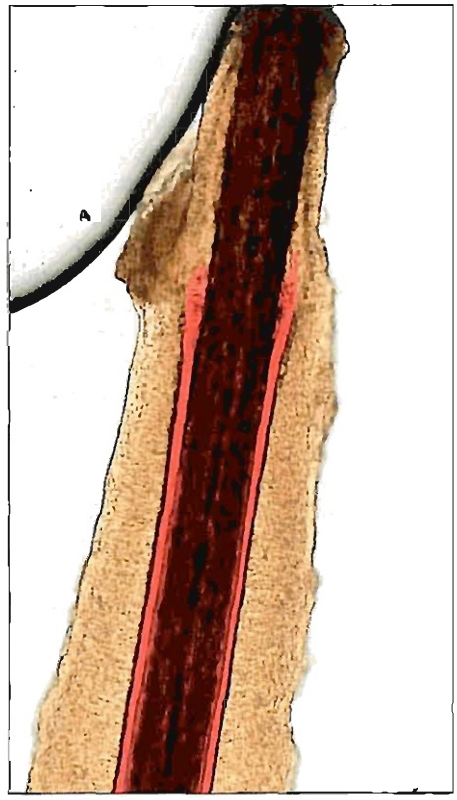

Fig. 33-8 Stain for citrulline demonstrates the inner root sheath (red) surrounded by an outer root in a plucked anagen hair from a normal scalp.

with each hair cycle until terminal hairs are eventually replaced by vellus hairs. During evolution of the process, hair shafts vary significantly in diameter. The parietal and occipital areas are usually spared permanently from this process of progressive miniaturization.

Early onset male pattern alopecia is related to the androgen receptor gene. There is no doubt that inherited factors and the effect of androgens such as dihydrotestosterone on the hair follicle are important. Arguments for regarding the inheritance as polygenic include the high prevalence, gaussian curve of distribution in the population, increased risk with number of affected relatives, increased risk in relatives of severely affected women compared with mildly affected, and greater import of an affected mother than an affected father. The possibility that the early-onset (before the age of 30) and later-onset (after the age of 50) forms may be inherited separately by single genes is also hypothesized.

Male-pattern alopecia is dependent on adequate androgen stimulation and appears to be related to the androgen receptor gene. Eunuchs do not develop baldness if they are castrated before or during adolescence. If they are given androgen therapy, baldness may develop. The 5-α reduction of testosterone is increased in the scalp of balding individuals, yielding increased dihydrotestosterone. Androgen-inducible TGF-β1 derived from dermal papilla cells appears to mediate hair growth suppression. In congenital 5-α-reductase deficiency, the type 2 isoenzyme is lacking and baldness does not occur. Pattern alopecia does occur in males with X-linked ichthyosis, indicating that steroid sulfatase is not critical for the production of alopecia.

Progressive shortening of the anagen phase of hair growth is noted as the hair shaft diameter decreases, so hairs are not only narrowing, but shorter. A higher proportion of telogen hairs in the affected area results in greater telogen shed. There may also be an increase in the duration of the lag phase between telogen and anagen (the kenogen lag phase).

Histologically, a decrease in anagen and increase in telogen follicles is present. Follicular miniaturization and variability in shaft diameter are noted. These features are particularly evident in transverse sections. Below the level of the miniatured or telogen follicle, a vascular or fibromucinous fibrous tract remnant is present. These appear numerous in cross-section. Many mast cells may be noted in the fibrous tract remnant, but inflammatory cells are absent. Sebaceous glands may be enlarged, and hair thinning may be associated with solar elastosis. Sparse lymphoid inflammation with spongiosis may be noted at the level of the follicular infundibulum. This may represent associated seborrheic folliculitis. A sparse lymphoid infiltrate may also be noted at the level of the hair bulge.

Miniaturized human hair follicles grafted onto immunodeficient mice can quickly regenerate and grow as well as or better than terminal follicles from the same individual. This suggests that even advanced pattern alopecia may be reversible. Unfortunately, available pharmacologic interventions produce little effect in advanced pattern alopecia.

Minoxidil, an oral hypotensive drug that causes hypertrichosis when given systemically, is available as topical solutions (Rogaine). Minoxidil promotes the survival of dermal papilla cells, prolongs anagen phase, and results in enlargement of shaft diameter. Clinically, apparent success is best in early cases (<10 years) of limited extent (<10-cm diameter bald area on the vertex) in whom pretreatment hair density is above 20 hairs/cm^2. Minoxidil is available without a prescription as a 2% or a 5% solution. With the 2% solution, 26% of men studied showed moderate-to-dense regrowth, while 33% showed minimal regrowth after 4 months. Studies show a 45% increase in hair weight with the 5% solution compared to the 2% solution. In those who respond, regrowth can occur as early as 2 months after the first application. Those who respond must continue to use minoxidil indefinitely to maintain a response.

Finasteride, a type 2 5α-reductase inhibitor, given as a 1-mg tablet daily, is effective in preventing further hair loss and in increasing the hair counts to the point of cosmetically appreciable results in men aged 18 to 41 with mild-to-moderate hair loss at the vertex, in the anterior midscalp, and the frontal region. It has been shown to stop hair loss in up to 90% of men for at least 5 years. Approximately 65% of men demonstrate hair regrowth. As with monoxidil, continued use of the product is required to sustain benefits. Hair patterning on the temples is not improved. It has been shown to lower dihydrotestosterone in the scalp and the serum of treated patients. Hair growth will be evident only after 6 months or more on the drug. If no effect is seen after 12 months, further treatment is unlikely to be of benefit. In one study, regimens that included finasteride were more effective than minoxidil alone, and therapeutic efficacy was enhanced by combining the two drugs. Short-term side effects related to finasteride are infrequent; however, the need to take this medication indefinitely suggests that study of long-term side effect profiles is critical. A prostate cancer prevention trial with a different dosage form of the same drug showed a decrease in the incidence of cancer. However, those cancers that did occur in the treatment group had a higher average Gleason score. Other treatments that show some promise in preliminary studies include fluridil (a topical antiandrogen that suppresses the human androgen receptor) and hormone-enriched topical cell culture medium. Hair transplantation using micrografts of hair follicles from the occipital area to the anterior scalp may satisfactorily recreate hairlines and give excellent cosmetic results.

Androgenetic (Pattern) Alopecia in Women

Women generally have diffuse hair loss throughout the apical scalp with the part wider anteriorly. There is typically sparing the frontal hairline, although a subset of women exhibits a "male" pattern of temporal recession. Although maintenance of the frontal hairline is the rule in women, a progressive decrease in hair density from the vertex to the front of the scalp does occur. The midline part is an important clinical clue, revealing a "Christmas tree pattern" of hair loss with the part tapering from the anterior to posterior scalp. Phototrichograms and measurement of shaft diameter can be used to assess female-pattern alopecia. The same basic changes—reduced hair density and diameter, and diminished anagen and increased telogen hair—occur in women as in men. Sebaceous gland hyperplasia may be present, but is less common than in men.

The cause is now believed to be a genetic predisposition with an excessive response to androgens. Both women and men with pattern alopecia have higher levels of 5α-reductase and androgen receptor in frontal hair follicles compared to

the levels in occipital follicles. Most women with pattern alopecia have normal menses and fertility. If other evidence of androgen excess is present, such as hirsutism, menstrual irregularities, or acne, or the onset is sudden, evaluation as outlined for hirsutism (see below) should be performed.

Topical minoxidil is of benefit. Although some data suggest that 5% minoxidil may be of greater benefit than 2% minoxidil, the data are mixed. Given the higher cost of 5% minoxidil, the 2% formulation may be the best choice for many women. Oral antiandrogens, including spironolactone and cyproterone acetate, have been used to treat androgenetic alopecia in women. In one study, cyproterone acetate was more effective than minoxidil when there were other signs of hyperandrogenism, hyperseborrhea, and menstrual abnormalities, and when the body mass index was high. When these other factors were absent, minoxidil was the more effective treatment.

Treatment with finasteride is of no benefit for most women, although the subset with temporal recession may show some benefit. Finasteride treatment is contraindicated in women who may become pregnant. Hair transplantation, wigs or interwoven hair may give satisfactory cosmetic results. In a pilot study, topical melatonin appeared to prolong anagen phase and may prove to be of some benefit. In some women, telogen effluvium may produce worsening of preexisiting pattern alopecia. Reversible causes of telogen effluvium, such as seborrheic dermatitis, nutrient deficiency, and thyroid disease, should be addressed.

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Trichotillomania (Trichotillosis) Trichotillomania is the compulsive practice of plucking hair from the scalp, brows or eyelashes. Typical areas are irregular patches of alopecia that contain hairs of varying length (Fig. 33-9). The scalp has a rough texture, resulting from the short remnants of broken-off hairs. Trichotillomania is seen mostly in girls under the age of 10, but boys, or adults of either sex, may engage in the practice also. Some patients relate exquisite pain localized to a follicle that can only be relieved by plucking the hair.

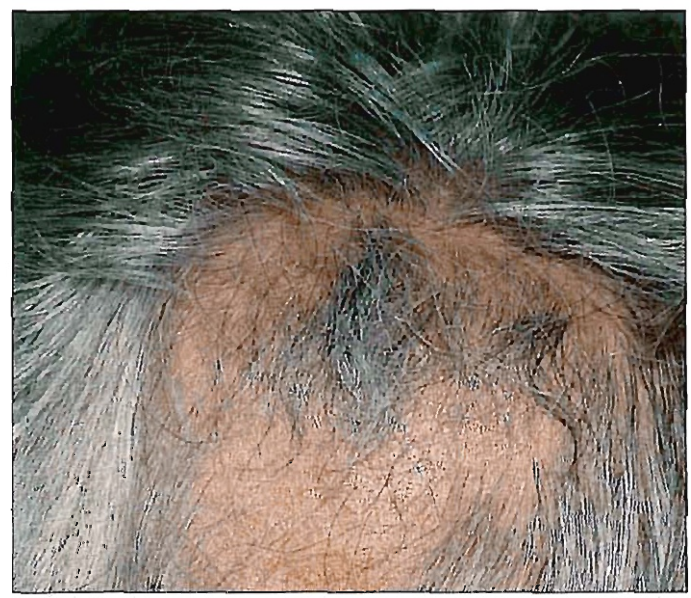

Fig. 33-9 Trichotillosis.

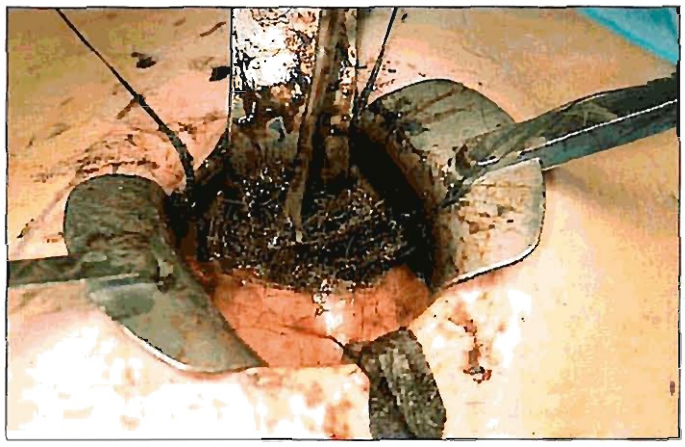

Fig. 33-10 Trichobezoar being extracted from the stomach of a patient with compulsive trichophagia. (Courtesy of Wilford Hall Air Force Medical Center Teaching File)

When speaking with a patient with characteristic areas of alopecia, it has been suggested that it be asked not *if* but rather *how* removal of the hair is done. If this fails to uncover a history of hair pulling, shaving a 3-cm^2 area in the involved part of the scalp will result in hairs too short for plucking, and normal regrowth in the "skin window" within 3 weeks. Finally, a biopsy, especially if cut horizontally, may demonstrate empty anagen follicles, catagen hairs, pigment casts within the infundibulum, trichomalacia, and hemorrhage. Alopecia areata shares many of these histologic features, and care must be taken to search for the presence of peribulbar lymphocytes or inflammatory cells within the fibrous tract remnants.

Trichotillomania is usually a manifestation of an obsessive–compulsive disorder, but may also be associated with depression or anxiety. It may be associated with compulsive swallowing of the plucked hairs (trichophagia), and may result in formation of a gastric bezoar (Fig. 33-10). Behavior modification, psychotherapy, and appropriate psychopharmacologic medication (such as serotonin-reuptake inhibitors) may be helpful.

Other Forms of Noncicatricial Alopecia Alopecia syphilitica may have a typical moth-eaten appearance on the occipital scalp (Fig. 33-11), a generalized thinning of the hair, or may resemble alopecia areata. Other areas such as the eyebrows, eyelashes, and body hair may be involved. The alopecia may be the first sign of syphilis.

Follicular mucinosis (alopecia mucinosa) most commonly occurs on the scalp or beard area and manifests as a boggy red plaque or hypopigmented patch with hair loss. Comedone-like lesions may exude mucin when expressed. Biopsy demonstrates deposition of mucin in the outer root sheath and sebaceous glands. The mucin stains as hyaluronic acid, rather than epithelial sialomucin. Primary cases (unassociated with underlying disease) usually occur as localized lesions of the head or neck. Young people are primarily affected. The secondary type is associated with mycosis fungoides-type cutaneous T-cell lymphoma or a chronic inflammatory skin disease. Lesions associated with mycosis fungoides are generally widespread and chronic, and occur in older patients.

Vascular or neurologic alopecia, most often of the lower extremities, may be seen in diabetes mellitus or atherosclerosis. In meralgia paresthetica there may be alopecia of the anesthetic area of the outer thigh.

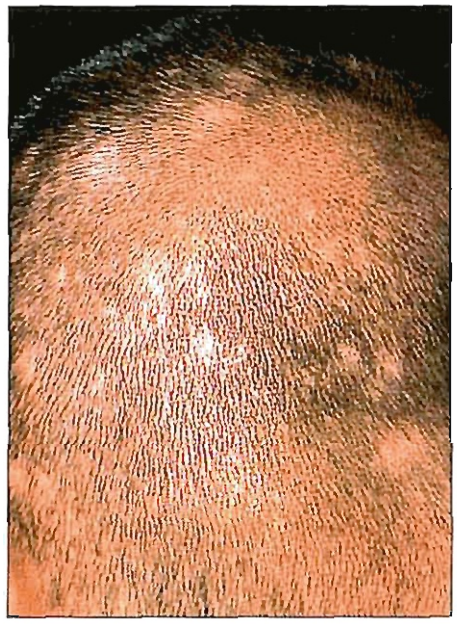

Fig. 33-11 Syphilitic alopecia. (Courtesy of Brooke Army Medical Center Teaching File)

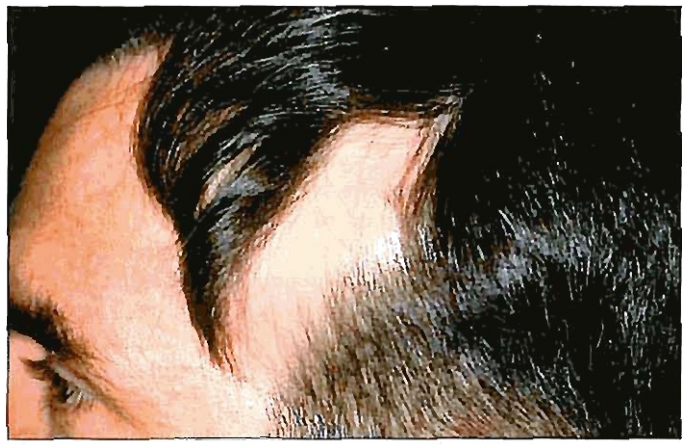

Fig. 33-12 Triangular alopecia. (Courtesy of Brooke Army Medical Center Teaching File)

Endocrinologic alopecia may occur in various endocrinologic disorders. In hypothyroidism the hair becomes coarse, dry, brittle, and sparse. The proportion of telogen hairs has been shown to be three to seven times higher than the normal 10%. In hyperthyroidism the hair becomes extremely fine and sparse. Oral contraceptives have been implicated in some instances of androgenetic alopecia. It develops in predisposed women who are usually taking androgenic progestogens. It is advisable to discontinue the androgen-dominant pill and substitute an estrogen-dominant oral contraceptive. Some women develop telogen effluvium 2 to 4 months after discontinuing anovulatory agents, which is analogous to postpartum alopecia.

Congenital alopecia occurs either as total or partial loss of hair, or a lack of initial growth, accompanied usually by other ectodermal defects of the nails, teeth, and bone. The hair is light and sparse, and grows slowly. Congenital triangular alopecia (Fig. 33-12) and aplasia cutis congenita are examples of congenital localized absence of hair, while hidrotic ectodermal dysplasia is an example of a

diffuse abnormality of hair associated with dental and nail changes.

Lipedematous alopecia consists of thickening of the scalp that gives the impression of thick cotton batting. The hair may be normal or shortened and sparse. Biopsy shows an increase in thickness of the subcutaneous fat and variable lymphoid inflammation. This disease appears to affect black persons primarily.

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Cicatricial Alopecia

Cicatricial alopecia appears as areas of hair loss with absence of follicular ostia (Fig. 33-13). Acute lesions may appear as erythematous plaques, perifollicular papules, keratotic follicular spines, or pustules. Deep inflammatory lesions may be boggy or may resemble noncicatricial areata clinically. The inflammatory nature of the lesion may only be evident on biopsy.

Discoid lupus erythematosus, lichen planopilaris, sarcoidosis, and folliculitis decalvans are the most common inflammatory causes of cicatricial alopecia. Chronic bacterial and fungal infections may produce inflammatory alopecia that mimicks primary scarring alopecia. For example, fungal folliculitis may mimic lupus erythematosus.

Biopsy can confirm the diagnosis and provide prognostic information regarding the potential for new growth. A 4-mm punch biopsy will provide the pathologist with an adequate specimen. Smaller specimens are of limited value. The punch should be placed parallel to the direction of hair growth to avoid transecting follicles, and the punch should be advanced to the deep subcutaneous fat. The biopsy site will typically bleed profusely, but a 4-mm wide strip of gel foam advanced into the defect will generally provide rapid hemostasis. Sutures are rarely necessary, and as the scar from a sutured biopsy site generally stretches back to the original dimensions of the biopsy, suturing provides little benefit to the patient.

Where to biopsy, how many biopsies to obtain, and how to process the tissue depends on the suspected diagnosis and the preference of the pathologist. In all cases, a pathologist experienced in the interpretation of scalp biopsies is an advantage. The pathologist may prefer vertical or transverse (horizontal) sectioning of the specimen. Each has advantages. Every follicular unit in the specimen will be demonstrated in transverse sections. Vertical sections are superior to demonstrate changes in the surface epidermis, dermoepidermal junction, superficial dermis, and subcutaneous fat. In general, the features of androgenetic (pattern) alopecia, telogen effluvium, and trichtillomania are better demonstrated in transverse (horizontal) sections through the specimen. Alopecia areata and syphilitic alopecia are well demonstrated in transverse sections if serial step sections are obtained to demonstrate deeper planes of section or if the block is cut horizontally in a bread-loaf fashion prior to embedding. They are equally well demonstrated with serial vertical sections through the block. Lupus erythematosus and lichen planopilaris are more easily demonstrated in serial vertical sections.

The diagnostic yield can be enhanced by pairing vertical and transverse sections. If two biopsies are done, one specimen can be bisected vertically for direct immunofluorescence (DIF) and hematoxylin and eosin (H&E) processing. It is most easily split by laying it on its side and bisecting it with a 15 blade pushed cleanly through the specimen in a single downward motion. Sawing at the specimen will not produce a satisfactory result. One-half of the bisected specimen is placed in formalin, and the other half in immunofluorescent media. The second specimen can be bisected for transverse sections in the clinic or left for the laboratory to bisect after processing. If it is to be bisected in the clinic, it should be placed on its side. The 15 blade should be pushed downward through the specimen in a single motion at the level of the mid-dermis. All pieces for vertical and transverse sections may be placed in a single bottle to be embedded in a single cassette.

In many forms of cicatricial alopecia, a biopsy of an active inflammatory lesion will be most diagnostic. In lupus erythematosus, the biopsy must be from a lesion of several months' duration in order to demonstrate hyperkeratosis, follicular plugging, basement membrane thickening (Fig. 33-14), and dermal mucin. Only biopsies from established lesions of lupus will demonstrate reliable immunofluorescence.

When biopsies of the most active area of alopecia have failed to yield a definite diagnosis, a biopsy from a scarred area may provide additional information. Scars show loss of elastic tissue with the Verhoff van Geison stain. The pattern

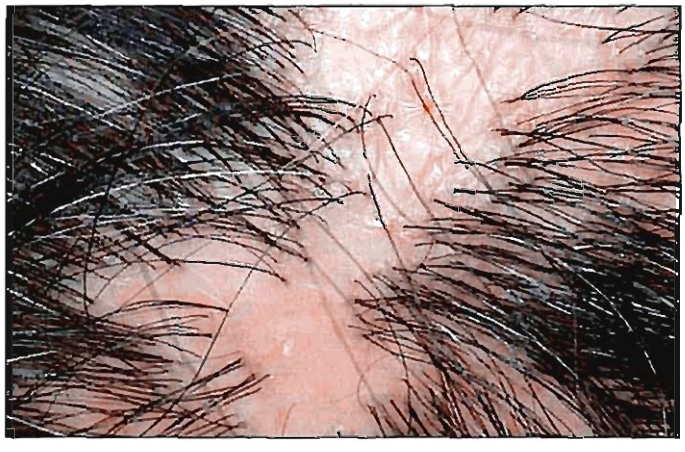

Fig. 33-13 Loss of follicular ostia in scarring alopecia.

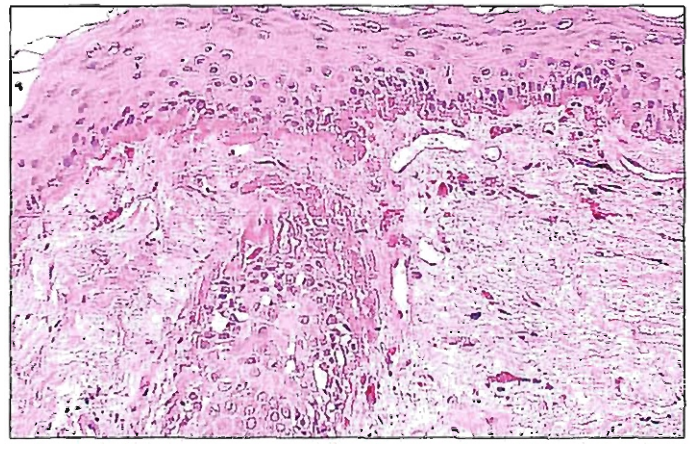

Fig. 33-14 Basement membrane thickening in lupus erythematosus (PAS stain).

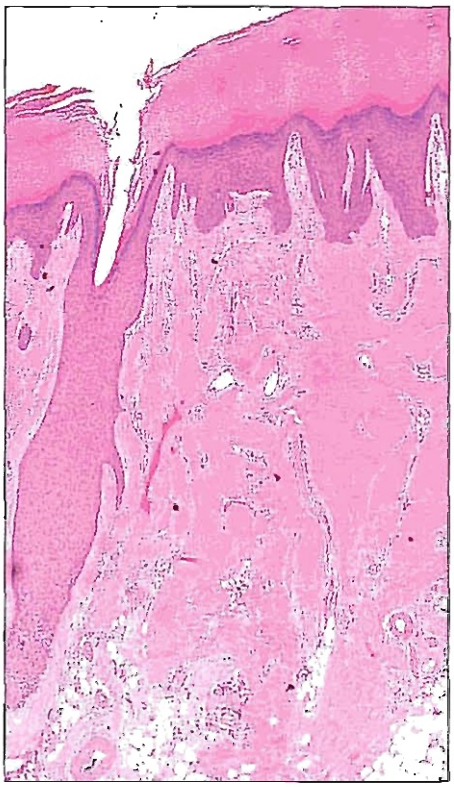

Fig. 33-15 Scarring alopecia (H&E stain).

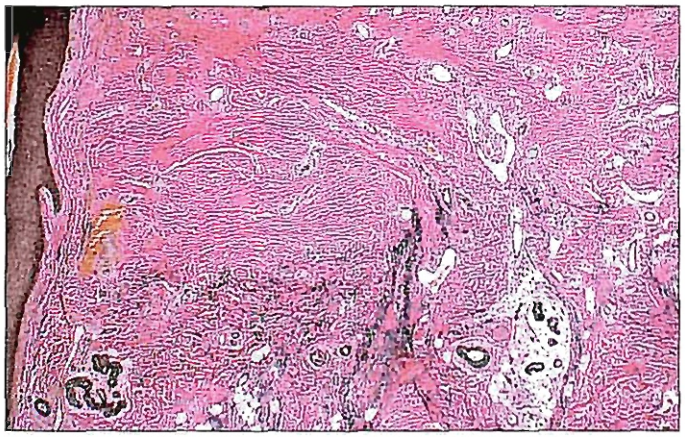

Fig. 33-16 Scarring alopecia (elastic stain). Normal elastic fibers (black) indicate the nonscarred portions of the dermis.

of elastic tissue loss is the "footprint" of the preceding inflammatory process (Figs 33-15 and 33-16). Lichen planopilaris and folliculitis decalvans both affect the infundibulum. Both result in wedge-shaped superficial dermal scars. Discoid lupus erythematosus results in scarring of both the follicular units and the intervening dermis. Morphea does not produce a scar, but rather hyalinization of collagen bundles with preservation of the elastic fibers. In idiopathic pseudopelade, the fibrous tract remnants are widened, but the elastic tissue sheath at the periphery of the fibrous tract is preserved.

Most patients with cicatricial alopecia experience gradual progression of the alopecia, and the prolonged course of the disease may lead to inappropriate therapeutic complacency. The progressive destruction of hairs will result in ever expanding areas of permanent alopecia. Therefore, cicatricial alopecia must be treated aggressively and early to avoid permanent disfigurement. Surgical revision of the hairless plaque is an option for stable end-stage alopecia, but unless the underlying disease is controlled, surgery may only lead to a flare of the underlying disease with progression of hair loss. Therapy may be forestalled by the inability to establish a definite diagnosis. To help guide therapy for patients who defy diagnosis, work groups of the North American Hair Research Society have proposed a classification scheme based on the type and pattern of inflammation. Some forms of destructive alopecia are lymphocyte mediated, while some are suppurative processes. The type of infiltrate and the portion of the pilosebaceous unit affected can be used to guide therapy. This classification system may also allow patients to enroll in clinical trials, even in the absence of a definite diagnosis.

Lymphoid-Mediated Disorders

Lupus Erythematosus

Chronic cutaneous lupus of the scalp (discoid lupus erythematosis [DLE]) is a common cause of cicatricial alopecia. In active disease, anagen hairs may be easily extracted from the involved area. Usually, erythema, atrophy, follicular plugging and mottled hyper- and hypo-pigmentation are present. Patients with chronic cutaneous lupus of the scalp may or may not have accompanying systemic lupus erythematosus (SLE) or skin lesions of DLE on other parts of the body. The external ear canal and concha should always be examined, as they are common sites for discoid lesions. Occasionally, alopecia occurs in a plaque of tumid lupus. Lupus panniculitis may occasionally result in alopecia in the absence of surface skin changes. SLE is often associated with discoid lesions of the scalp. Patients with SLE may also have short miniaturized "lupus hairs" on the anterior scalp.

Biopsy of early lesions of DLE is often nondiagnostic. Patchy lymphoid inflammation and perifollicular mucinous fibrosis may be the only histologic findings. Focal vacuolar interface dermatitis may or may not be noted. Active established lesions, present for several months, have a higher diagnostic yield. Active established lesions usually demonstrate hyperkeratosis, follicular plugging, vacuolar interface dermatitis, basement membrane zone thickening, pigment incontinence, and dermal mucin. Peri-vascular and -adnexal lymphoid infiltrates are patchy and involve the eccrine coil and fibrous tract remnants. Fibrous tract involvement creates dense vertical columns of lymphocytes. The underlying subcutaneous tissue may demonstrate nodular lymphoplasmacytic infiltrates and fibrin or hyaline rings around necrotic fat. Hypertrophic lesions of chronic cutaneous lupus erythematosus often demonstrate lichenoid dermatitis. DIF may be nonspecific, but active established lesions typically demonstrate a "full house" (continuous granular deposition of IgG, IgA, IgM, and C3) at the dermoepidermal junction. When present, this pattern is particularly helpful in distinguishing lichenoid hypertrophic lupus erythematosus from lichen planopilaris. Burn-out lesions of DLE demonstrate loss of elastic fibers throughout the dermis, which differs from the focal periinfundibular wedge-shaped scars of lichen planopilaris. In systemic lupus, there may be follicular atrophy associated with pronounced dermal mucinosis.

Chronic cutaneous lupus may respond to intralesional or potent topical corticosteroids, but systemic therapy is

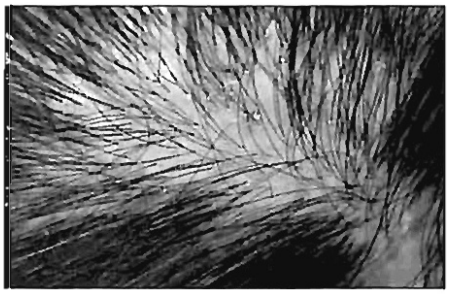

Fig. 33-17 Lichen planopilaris.

frequently required. Antimalarials, retinoids, dapsone, thalidomide, sulfasalazine, mycophenolate mofetil, and methotrexate have been used successfully. Topical tazarotene and topical calcineurin inhibitors are generally disappointing.

Lichen Planopilaris

Lichen planopilaris presents with perifollicular erythema (Fig. 33-17) and progressive scarring. Small follicular papules may be noted, or the lesion may resemble the ivory white irregular patches of pseudopelade. In some patients, typical polygonal flat-topped papules are present on the wrists and ankles, and lacy white lesions are noted on the oral and genital mucosa. Widespread follicular papules may be present on the trunk or extremities. In most patients, however, only the scalp is involved. Frontal fibrosing alopecia appears to be a variant of LPP. Most patients are older women with bandlike frontotemporal alopecia. Graham Little-Piccardi-Lassueur syndrome includes cicatricial alopecia on the scalp, keratosis pilaris in the skin of the trunk and extremities, and noncicatricial hair loss in the pubis and axillae. It has been described in association with complete androgen insensitivity syndrome, a condition that also presents with noncicatricial alopecia in the axillary and pubic hair.

Diagnostic biopsies demonstrate lichenoid interface dermatitis of the follicular unit and sometimes the intervening epidermis. The entire fibrous tract may be filled with cytoid bodies (Fig. 33-18). The changes commonly occur focally and may be best visualized with serial vertical sections. Perifollicular mucinous fibrosis is common and focal perifollicular lymphoid infiltrates tend to involve the infundibulum (the infiltrates of lupus erythematosus tend to involve the isthmus). DIF may be negative or may reveal cytoid bodies and shaggy linear fibrin at the dermoepidermal junction.

Lichen planopilaris responds to oral and intralesional corticosteroids. Topical corticosteroids may be adequate in a few patients, but the activity of the disease waxes and wanes, and slow progression should not lead to therapeutic complacency. Oral retinoids can be effective. Alternative therapies include the other oral agents used to treat lupus; however, there are fewer data regarding their use in lichen planopilaris. As in lupus, topical tazarotene and topical macrolactams are generally disappointing.

Hot Comb Alopecia and Central Centrifugal Cicatricial Alopecia

Hot comb alopecia was reported in the late 1960s as a scarring alopecia seen in black women who straightened their hair with hot combs for cosmetic purposes. It develops characteristically on the crown and spreads peripherally to form a large oval area of partial hair loss. The hot petrolatum used with the iron was thought to cause thermal damage to the hair follicle. However, Sperling et al reported a similar-appearing scarring alopecia in both men and women who did not report the use of hot combs. Some authors now regard hot comb alopecia, Sperling's disease (follicular degeneration syndrome), central centrifugal cicatricial alopecia (CCCA), and idiopathic pseudopelade to be one entity or overlapping entities that can be indistinguishable.

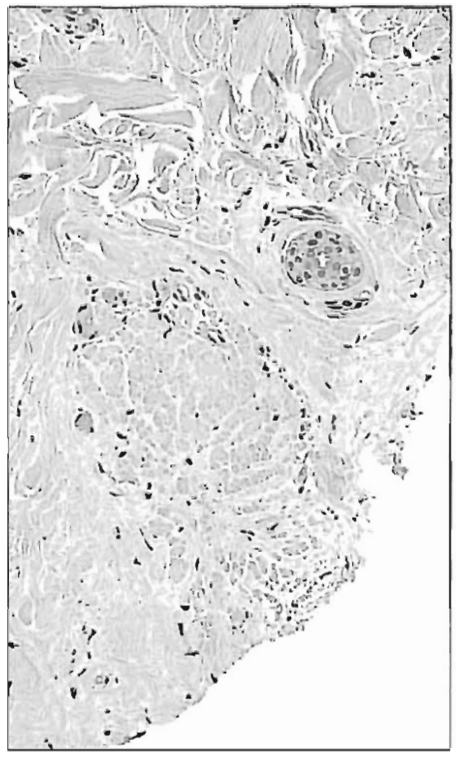

Fig. 33-18 Lichen planopilaris, note cytoid bodies completely fill the fibrous tract remnant.

CCCA is slowly progressive, usually begins in the crown, and advances to the surrounding areas. The term is often used as a broad category that includes cases once classified as hot comb alopecia, follicular degeneration syndrome, and central elliptical pseudopelade in white women. CCCA is seen most commonly in African American women, and shows significant overlap with other causes of cicatricial alopecia in this group. In particular, some will demonstrate crops of crusts at the periphery of the patches, a feature of folliculitis decalvans. Treatment of CCCA is difficult and often unsatisfactory. Discontinuation of chemical and heat processing, and reduction of traction are routinely recommended, but the effectiveness of these recommendations has yet to be substantiated. Cases with overlapping features of folliculitis decalvans may respond to long-term antibiotic therapy and topical corticosteroids. In such overlapping cases, the histology shows a lymphocytic infiltrate during the chronic stage, but periodic crops of pustules demonstrate a neutrophilic folliculitis.

Neutrophil-Mediated Disorders

Folliculitis Decalvans

Follicular decalvans presents with crops of pustules that result in cicatricial alopecia. Successive crops of pustules, crusts, or erosions lead to expansion of the alopecic patches. Staphylococci are sometimes cultured from the lesions, and some authors have suggested that folliculitis decalvans merely represents a chronic staphylococcal infection. It is

more likely that follicular destruction is the result of an abnormal suppurative immune response. Staphylococci and other organisms probably play a role in inciting the response. The lesions often respond to long-term treatment with tetracycline. The improvement may reflect the antineutrophil effects of the drug or its antimicrobial effects. Many patients also respond to other forms of antistaphylococcal therapy, but the lesions generally recur after the antibiotic is discontinued. Chronic antibiotic treatment generally results in a continued response. Some sustained responses have been noted after combination therapy with rifampin and clindamycin. Rifampin alone has been used, but may promote the emergence of resistance. Selenium sulfide shampoo and topical corticosteroids may be useful as adjunctive therapy. Oral retinoids, oral and topical fusidic acid, and oral zinc sulphate have sometimes produced sustained responses.

A variant of folliculitis decalvans occurs in African American patients who present with pseudofolliculitis of the beard, acne keloidalis nuchae, and scarring alopecia in the vertex and parietal scalp. The scalp demonstrates ingrown hairs, crops of pustules or crusts, and permanent scarring alopecia. While pseudofolliculitis barbae is generally accepted to be the result of ingrown hairs, the pathogenesis of acne keloidalis nuchae remains in question. Histologically, ingrown hairs are common in advanced lesions. Early lesions may not demonstrate the hair. Some patients merely develop small papules on the nape of the neck, while others develop pustules, crusts, and progressive alopecia. This latter group overlaps with folliculitis decalvans.

Acne Necrotica

Acne necrotica presents with discrete excoriated follicular papules in the scalp. Biopsy demonstrates an inflammatory crust and suppurative folliculitis. Usually there is no associated scarring alopecia, but occasional cases overlap with folliculitis decalvans.

Erosive Pustular Dermatitis of the Scalp

This often presents as expanding eroded patches with moist granulation tissue. The lesions often follow trauma or a surgical procedure and tend to be chronic and progressive. They do not respond to 10-day courses of antibiotics but may respond to sustained treatment, as for folliculitis decalvans. Some lesions have responded to tacrolimus or calcipotriene.

Dissecting Cellulitis (Perifolliculitis Capitis Abscessens et Suffodiens of Hoffman)

This often coexists with acne conglobata and hidradenitis suppurativa. It may also occur with folliculitis decalvans. The lesions are deep, boggy, and suppurative. They may respond to tetracyclines, retinoids, and intralesional corticosteroids.

Tufted folliculitis

Tufted folliculitis presents with doll's hair-like bundling of follicular units. It is seen in a wide range of scarring conditions, including chronic staphylococcal infection, chronic lupus erythematosus, lichen planopilaris, Graham-Little syndrome, folliculitis decalvans, acne keloidalis nuchae, immunobullous disorders, and dissecting cellulitis. Compound hairs (two or more hairs sharing a common infundibulum) occur physiologically on the scalp and legs. They are common in the occipital scalp. Recurrent staphylococcal infection is more common in patients with many compound hairs and commonly leads to tufted folliculitis.

Other Forms of Permanent Alopecia

Pseudopelade of Brocq

Also known as *alopecia cicatrisata*, this is a rare form of cicatricial alopecia in which destruction of the hair follicles produces multiple round, oval, or irregularly shaped, hairless, cicatricial patches of varying sizes. They are usually coin-sized and are white or slightly pink in color, with a smooth, shiny, marble-like or ivory, atrophic, "onion skin" surface. Interspersed in the patches may be a few spared follicles with hairs growing from them. A clinical inflammatory stage is completely absent. No pustules, crusts, or broken-off hairs are present. The onset is, as a rule, insidious, with one or two lesions appearing on the vertex. It affects females three times more commonly than males, and has a prolonged course. In advanced cases large irregular patches are formed by coalescence of some of the many small macules, a pattern referred to as "footprints in the snow." The alopecia is permanent and the disease is slowly progressive. Histologically, the majority of patients with clinical lesions of pseudopelade demonstrate true scarring (indicated by loss of elastic tissue) in a wedge-shaped pattern in the superficial dermis. The pattern is similar to that seen in lichen planopilaris and suggests that many cases classified as pseudopelade represent an end stage of lichen planopilaris. A subset of patients, however, demonstrates no perifollicular or interfollicular scarring at all. This subset has been called idiopathic pseudopelade. It shows significant clinical overlap with CCCA. In these patients, the dermis is contracted into a thin band of dense collagenous tissue. Elastic fibers are intact and quite thick as a result of elastic recoil related to dermal contraction. Fibrous tract remnants are wide and hyalinized with an intact elastic sheath. Lymphoid and neutrophilic inflammation is absent, but loss of the inner and outer root sheathes with subsequent hair fiber granuloma formation is noted. Sebaceous glands are decreased or absent, as they are in most forms of permanent alopecia. DIF is negative.

The end stage of many forms of cicatricial alopecia can resemble pseudopelade clinically, but, like lichen planopilaris, they demonstrate distinct patterns of elastic tissue loss in the dermis. Folliculitis decalvans is distinguished by periodic crops of pustules or crusts at the periphery of the alopecic patches. It produces superficial wedge-shaped scars similar to those of lichen planopilaris.

Topical and intralesional corticosteroids and long-term tetracycline in anti-inflammatory doses may be tried but are not often successful. The disease usually reaches an inactive end stage after many years.

Traction Alopecia

Traction alopecia occurs from prolonged tension on the hair, either from wearing the hair tightly braided or in a ponytail, pulling the hair to straighten it, rolling curlers too tightly, or from the habit of twisting the hairs with the fingers. Traction alopecia most commonly involves the periphery of the scalp, especially the temples and above the ears.

Sarcoidosis

Sarcoidosis of the scalp presents with diffuse or patchy hair loss. The involved scalp is often indurated and a raised peripheral border may be present. The lesions are often red–brown in color and may have an apple jelly appearance with diascopy. Biopsy reveals noncaseating granulomas. Treatment is as for other forms of sarcoidosis.

Pressure Alopecia

Pressure alopecia occurs in adults after prolonged pressure on the scalp during general anesthesia, with the head fixed in one position. It may also occur in chronically ill persons after prolonged bed rest in one position, which causes persistent pressure on one part of the scalp. It probably arises because of pressure-induced ischemia.

Tumor Alopecia

Tumor alopecia refers to hair loss in the immediate vicinity of either benign or malignant tumors of the scalp. Syringomas, nerve sheath myxomas, and steatocystoma multiplex are benign tumors that may be limited to the scalp and cause alopecia. Alopecia neoplastica is the designation given to hair loss from metastatic tumors, most often from breast or renal carcinoma.

Keratosis Pilaris Atropicans

Keratosis pilaris atropicans includes many forms of keratosis pilaris with cicatricial alopecia. Variants include keratosis pilaris atrophicans faciei, atrophoderma vermiculatum, keratosis follicularis spinulosa decalvans, and ichthyosis follicularis.

Keratosis pilaris atrophicans faciei (ulerythema ophryogenes, keratosis pilaris rubra atrophicans faciei, folliculitis rubra, lichen pilare, or xerodermi pilaire symmetrique de la face) begins in infancy as follicular papules with perifollicular erythema. Initially, the lesions are restricted to the lateral eyebrows. With time, they spread to involve the cheeks and forehead. There may be associated keratosis pilaris on the extremities and buttocks. The condition may also be associated with an atopic diathesis, ectodermal dysplasia, or Noonan syndrome.

Atrophoderma vermiculatum (acne vermoulanti, honeycomb atrophy, folliculitis ulerythema reticulata, ulerythema acneiforme, folliculitis ulerythematous reticulata, atrophodermia reticulata symmetrica faciei, atrophoderma reticulatum) presents with erythematous follicular papules on the cheeks in childhood. With time, the lesions develop into pit-like depressions (reticulate atrophy). Autosomal-dominant inheritance has been described. This condition generally spares the scalp and eyebrows.

Keratosis follicularis spinulosa decalvans is a rare X-linked disorder described by Siemens in 1926. The gene has been mapped to Xp21.2–p22.2. It begins in infancy with keratosis pilaris localized on the face, then evolves to more diffuse involvement. Progressive cicatricial alopecia occurs on the scalp, eyebrows, and sometimes eyelashes. The alopecia starts during childhood and active disease may remit during the early teenage years. Corneal and conjunctival inflammation, corneal dystrophy, and blepharitis occur, and photophobia is usually a prominent finding.

Ichthyosis follicularis also demonstrates extensive spiny follicular hyperkeratosis, permanent alopecia, and photophobia. Palmar plantar keratosis, nail deformities, atopy, and recurrent chilitis have been described.

Atrichia with Papular Lesions

Atrichia with papular lesions is a rare autosomal-recessive disorder with early onset of atrichia, followed by a papular eruption appearing within the first years of life. The condition has been linked to chromosome 8p21 and mutations have been detected in what is now referred to as the hairless gene. It is discussed in more detail in Chapter 27.

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HAIR COLOR

Melanin in the hair follicles is produced in the cytoplasm of the melanocytes. Organelles involved include the endoplasmic reticulum, ribosomes, and Golgi apparatus. Melanocytes producing hair pigment are associated with the hair matrix, and melanogenesis occurs only during anagen. This cyclic melanin synthesis distinguishes follicular melanogenesis from the continuous melanogenesis of the epidermis. With age, cyclic melanocytic activity in the follicular unit declines. By 40 years of age most individuals show evidence of graying. Graying results primarily from a reduction in tyrosinase activity within hair bulb melanocytes. Defective migration of melanocytes from a diminishing reservoir in the outer root sheath may play a role. Physiologic graying may also be related to reactive oxygen species-mediated damage to nuclear and mitochondrial DNA in bulbar melanocytes. The melanocortin 1 receptor gene (MCR1) is closely related to red hair, freckling, and sun-sensitivity.

The pigment in black and dark brown hair is composed of eumelanin, whereas in blond and red hair it is pheomelanin. In black hair the melanocytes contain the densest melanosomes. Brown hair differs only by its smaller melanosomes. Light brown hair consists of a mixture of the melanosomes of dark hair and the incomplete melanosomes of blond hair. Many of the melanosomes in blond hair develop only on the matrix fibers and not in the spaces between the fibers.

Red hair shows incomplete melanin deposits on the matrix fibers to produce a blotchy-appearing melanosome. Phaeomelanin is distinguished by its relatively high content of sulfur, which results from the addition of cysteine to dopaquinone along the biosynthetic pathway of melanin synthesis.

In gray hair (canities), melanogenic activity is decreased as a result of fewer melanocytes and melanosomes, as well as a gradual loss of tyrosinase activity. Graying of the scalp hair is genetically determined and may start at any age. Usually it begins at the temples and progresses with time. The beard usually follows, with the body hair graying last. Premature whitening of scalp hair is usually caused by vitiligo, sometimes without recognized, or actually without, lesions of glabrous skin.

Early graying (before age 20 in white or before age 30 in black persons) is usually familial; however, it may occur in progeria, Rothmund-Thomson syndrome, Böök syndrome, and Werner syndrome.

In poliosis, gray or white hair occurs in circumscribed patches. This may occur in Waardenburg syndrome and piebaldism, Tietze syndrome, Alezzandrini syndrome, neurofibromatosis, and tuberous sclerosis. Poliosis is also found in association with regressing melanoma, vitiligo, and Vogt-Koyanagi syndrome, and may be seen in alopecia areata when the new hairs grow. Migratory poliosis without hair loss may represent a forme-fruste of alopecia areata.

Green hair has been traced to copper in the water of a swimming pool. This occurs only in blond or light hair, and may be treated with topical EDTA, penicillamine-containing shampoos, or 1.5% aqueous 1-hydroxyethyl diphosphonic acid. Tars and chrysarobin stain light-colored hair brown.

Changes in hair color occur in various disorders. The hair is blond in phenylketonuria and homocystinuria. Light hair is also seen in oasthouse disease (familial methionine malabsorption), Menkes kinky hair syndrome, and albinism. In Griscelli and Chédiak-Higashi syndromes the hair has a silvery sheen. In kwashiorkor the hair assumes a red–blond color and may demonstrate periodic banding (flag sign, segmental heterochromia). Alternating light and dark bands may also occur in iron-deficiency anemia. In vitamin B_{12} deficiency and with interferon therapy, whitening may occur. The disorder has been called canities segmentata sideropenica. It responds completely to iron supplementation. Triparanol is associated with hypopigmented hair. Minoxidil (by changing vellus to terminal hairs) causes darkening of hair; another hypotensive agent, diazoxide, gives the hair a reddish tint. Chloroquine therapy may cause hair whitening, usually in redheads and blonds, not in brunettes. Pigmentation of the eyelashes and irides has been described with latanoprost.

Many black patients with acquired immunodeficiency syndrome (AIDS) have experienced softening, straightening, lightening, and thinning of their hair. Patients with human immunodeficiency virus (HIV)-1 infection may also experience elongated eyelashes and telogen effluvium.

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Lee WS, et al: Diffuse heterochromia of scalp hair. J Am Acad Dermatol 1996;35:823.
Mascaro JM Jr, et al: Green hair. Cutis 1995;56:37.
Santos Nogueira AC, et al. Hair color changes and protein damage caused by ultraviolet radiation. J Photochem Photobiol B 2004;74:109.
Van Neste D, et al. Hair cycle and hair pigmentation: dynamic interactions and changes associated with aging. Micron 2004; 35:193.

HAIR STRUCTURE DEFECTS

Examination of hairs for structural defects is greatly facilitated by a method devised by Shelley: putting a piece of double-stick tape on a microscope slide and aligning 5-cm segments of hair in parallel on it. Hairs are best examined under a dissecting microscope or polarized light. Gold-coating and scanning electron microscopy can also be done on hairs so mounted.

Dawber RP: An update of hair shaft disorders. Dermatol Clin 1996;14:753.
Rogers M: Hair shaft abnormalities. Part I. Australas J Dermatol 1995;36:179.
Rogers M: Hair shaft abnormalities. Part II. Australas J Dermatol 1996;37:1.
Whiting DA: Structural abnormalities of the hair shaft. J Am Acad Dermatol 1987;16:1

Hair Casts (Pseudonits)

Hair casts represent remnants of the inner root sheath. They often occur in great numbers and may mimic nits in the scalp. While nits are firmly cemented to the hair shaft, hair casts slide freely along the shaft. Taeb et al reviewed 36 published cases and distinguished two groups: girls between 2 and 8 years of age with diffuse involvement and no scalp disease, and children and adults with psoriasis, lichen planus, seborrheic dermatitis, or trichotillomania. Keipert made a similar distinction, separating a large group of cases with some keratinizing disorder of the scalp and dark, oddly shaped masses of keratin adherent to or surrounding the hairs, which he called parakeratotic hair casts; and lighter colored tubular casts, 2 to 4 mm long, which he called peripilar hair casts. Taeb et al found 0.025% tretinoin lotion effective.

Keipert JA: Hair casts. Arch Dermatol 1986;122:927.
Lam M, et al. Hair casts: a case of pseudonits. Cutis 1997; 60:251.
Taeb A, et al: Hair casts: a clinical and morphologic study. Arch Dermatol 1985;121:1009.

Pili Torti

Also known as *twisted hairs*, pili torti is a malformation of hair characterized by twisting of the hair shaft on its own axis (Fig. 33-19). The hair shaft is segmentally thickened, and light and dark segments are seen. Scalp hair, eyebrows, and eyelashes may be affected. The hairs are brittle and easily broken.

In the classic type, unassociated with other disorders, onset is usually in early childhood; by puberty, it has usually improved. Clinically, it may be associated with patchy alopecia and short, broken hairs. It usually follows a dominant inheritance pattern, though recessive and sporadic cases have been reported. Acquired cases have been described in young women with anorexia nervosa.

Pili torti may be seen with associated abnormalities. The Björnstad syndrome consists of congenital deafness of the cochlear type, with pili torti. Both autosomal-dominant and -recessive inheritance patterns have been described. Pili torti also may occur in citrullinemia (argininosuccinate synthetase deficiency), Menkes kinky hair syndrome, Bazex follicular atrophoderma syndrome, ectodermal dysplasias, Crandall syndrome (pili torti, nerve deafness, hypogonadism), Netherton syndrome (along with bamboo hair), with isotretinoin and etretinate therapy, in anorexia nervosa, and in trichothiodystrophy.

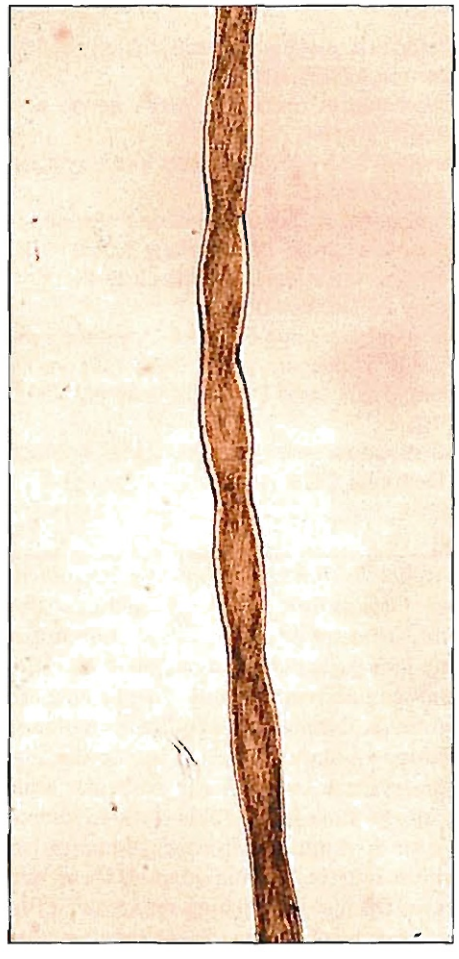

Fig. 33-19 Pili torti.

Laron syndrome is an autosomal-recessive disease with primary insulin-like growth factor 1 deficiency and primary growth hormone insensitivity. Affected children have sparse hair and frontal recession. Pili torti et canaliculi, tapered hair, and trichorrhexis nodosa have been noted.

Lurie R, et al: Laron syndrome (primary growth hormone insensitivity): a unique model to explore the effect of insulin-like growth factor 1 deficiency on human hair. Dermatology 2004;208:314.

Richards KA, et al: Three members of a family with pili torti and sensorineural hearing loss: the Björnstad syndrome. J Am Acad Dermatol 2002;46:301.

Sakamoto F, et al: Ultrastructural study of acquired pili torti-like hair defects accompanying pseudopelade. J Dermatol 2002; 29:197.

Selvaag E: Pili torti and sensorineural hearing loss. A follow-up of Björnstad's original patients and a review of the literature. Eur J Dermatol 2000;10:91.

Menkes Kinky Hair Syndrome

Pili torti, and often monilethrix and trichorrhexis nodosa, are all common in the hairs in this sex-linked recessively-inherited disorder. It has also been called steely hair disease, because the hair resembles steel wool. The characteristic ivory color of the hair appears between 1 and 5 months of age. Drowsiness, lethargy, convulsive seizures, and severe neurologic deterioration, and periodic hypothermia ensue with death at an early age. Hairs become wiry, sparse, fragile, and twisted about their long axes. Osteoporosis, and dental and ocular abnormalities are common. The skin is pale and the face pudgy, and the upper lip has an exaggerated "Cupid's bow" configuration. The occipital horn syndrome, primarily a connective tissue disorder, is a milder variant of Menkes syndrome.

Patients have a deficiency of serum copper and copper-dependent enzymes, resulting from mutations in the ATP7A gene. The gene encodes a trans-Golgi membrane-bound copper transporting P-type ATPase. Loss of this protein activity blocks the export of dietary copper from the gastrointestinal tract and causes the copper deficiency. Low serum copper and ceruloplasmin are characteristic, but are not seen in all patients. They are particularly variable in the first weeks of life. Other tests helpful for screening include the ratio of catechols, such as dihydroxyphenylalanine to dihydroxyphenylglycol. High levels of the catechols DOPA, dihydrophenylacetic acid, and dopamine, and low level of dihydroxyphenylglycol are characteristic. Studies of copper egress in cultured fibroblasts have also been used. Early detection allows for genetic counseling and the institution of copper histidine treatment, which is being studied and has shown promising results in some infants. Pamidronate treatment is associated with an increase in bone mineral density in children with Menkes' disease.

Gasch AT, et al: Menkes' syndrome: ophthalmic findings. Ophthalmology 2002;109:1477.

Gu YH, et al: Prenatal diagnosis of Menkes disease by genetic analysis and copper measurement. Brain Dev 2002;24:715.

Kanumakala S, et al: Pamidronate treatment improves bone mineral density in children with Menkes disease. J Inherit Metab Dis 2002;25:391.

Liu PC, et al: Rapid and robust screening of the Menkes disease/occipital horn syndrome gene. Genet Test 2002;6:255.

Poulsen L, et al: X-linked recessive Menkes disease: identification of partial gene deletions in affected males. Clin Genet 2002;62:449.

Turner Z, et al: Screening of 383 unrelated patients affected with Menkes disease and finding of 57 gross deletions in ATP7A. Hum Mutat 2003;22:457.

Uncombable Hair Syndrome

First reported in 1973 by Dupre et al as *cheveux incoiffable* (undressable hairs) and Stroud and Mehergan as *spun-glass hair*, the microscopic abnormality of a triangular cross-sectional appearance with a longitudinal groove gives the disease its other name, *pili triangulati et canaliculi*.

Clinically, the defect is noted in the first few years of life as dry, blond, shiny hair that stands straight out from the scalp and cannot be combed. On light microscopy it may appear quite normal when viewed lengthwise, but on horizontal sectioning and on scanning electron microscopy it shows the longitudinal grooves that make it abnormally rigid. These depressions are sometimes seen in unaffected persons so that 50% of hairs need to be affected to be clinically detectable.

Autosomal-dominant, -recessive, and sporadic forms have been described. Uncombable hair has been associated with angel-shaped phalango-epiphyseal dysplasia. It has also been seen in combination with retinal dystrophy, juvenile cataract, and brachydactyly. It has also been reported in a patient who acquired the abnormality at age 39 after an episode of diffuse alopecia treated with spironolactone. Although there are usually no associated ectodermal defects, isolated cases have been reported in which uncombable hair is one component of several clustered findings. Until more experience is available in the literature grouping of these cases into new syndromes is premature.

One of the Shelley's cases responded clinically (although without apparent change in the hair structure) to biotin 0.3 mg orally three times a day. Some cases improve spontaneously in late childhood.

Fritz TM, et al: Uncombable hair syndrome with angel-shaped phalango-epiphyseal dysplasia. Pediatr Dermatol 2000;17:21.

Hicks J, et al: Uncombable hair (cheveux incoiffables, pili trianguli et canaliculi) syndrome: brief review and role of scanning electron microscopy in diagnosis. Ultrastruct Pathol 2001;25:99.

Shelley WB, et al: Uncombable hair syndrome: observations on response to biotin and occurrence in siblings with ectodermal dysplasia. J Am Acad Dermatol 1985;13:97.

Monilethrix

Monilethrix, also known as *beaded hairs*, is a rare hereditary disease. It is characterized by dryness, fragility, and sparseness of the scalp hair, with fusiform or spindle-shaped swellings of the hair shaft separated by narrow atrophic segments. The hair tends to break at the delicate internodes. There is an occasional rupture at the node and longitudinal fissuring of the shaft, which also involves the nodes.

The disease is often associated with keratosis pilaris of the extensor surfaces, temples, and back of the neck. Hair on regions other than the scalp may be affected. Leukonychia

may occur. Inheritance of monilethrix is an autosomal-dominant trait. It has been described in association with Menkes syndrome. Several cases of monilethrix have been linked to the type II keratin gene cluster on chromosome 12q13. Causative heterozygous mutations of a highly conserved glutamic acid residue of the type II hair keratins hHb6 and hHb1 occur. Both hHb1 and hHb6 are largely coexpressed in cortical trichocytes of the hair shaft, confirming monilethrix is a disease of the hair cortex. There is no effective treatment. Improvement of the hair may occur during pregnancy, but after delivery the hair returns to its original state. Improvement may also occur with age and there may be seasonal improvement during the summer.

Djabali K, et al: Recurrent missense mutations in the hair keratin gene hHb6 in monilethrix. Clin Exp Dermatol 2003;28:206.

Horev L, et al: Monilethrix: mutational hotspot in the helix termination motif of the human hair basic keratin 6. Hum Hered 2000;50:325.

Horev L, et al: De novo mutations in monilethrix. Exp Dermatol 2003;12:882.

Muramatsu S, et al: Recurrent E413K mutation of hHb6 in a Japanese family with monilethrix. Dermatology 2003;206:338.

Trichorrhexis Nodosa

The affected hair shafts fracture easily and may have small white nodes arranged at irregular intervals. These nodes are the sites of fraying of the hair cortex. The splitting into strands produces a microscopic appearance suggestive of a pair of brooms stuck together end to end by their bristles. The hairs soon break at these nodes. The number of these nodes along one hair shaft varies from one to several, depending on its length. These fractured hairs are found mostly on the scalp, often in just a small area or areas, but other sites such as the pubic area, axillae, and chest may be involved.

Several categories or types of trichorrhexis nodosa have been described. Proximal trichorrhexis nodosa involves the proximal shafts of the hairs of black patients who traumatize their hair with styling or chemicals. The involved hairs break a few centimeters from the skin surface, resulting in patches of short hair. It appears to occur in genetically predisposed patients. Distal trichorrhexis nodosa affects primarily Asians and white patients, and occurs several inches from the scalp, and is associated with trichoptilosis, or longitudinal splitting, known as *split ends*. Acquired localized trichorrhexis nodosa is a common type in which the defect occurs in a localized area, a few centimeters across. A number of diseases accompany this type of trichorrhexis nodosa in which pruritus is a prominent symptom; scratching and rubbing may be the cause. Among such diseases are circumscribed neurodermatitis, contact dermatitis, and atopic dermatitis.

The occurrence of trichorrhexis nodosa in some patients with argininosuccinicaciduria has suggested an etiologic connection. Trichorrhexis nodosa has been described in Menkes kinky hair syndrome, Netherton syndrome, hypothyroidism, ectodermal dysplasia, the syndrome of intractable infant diarrhea, and trichothiodystrophy. Trichoschisis, a clean transverse fracture across the hair shaft, is more commonly present in trichothiodystrophy. The curly hair that may result from isotretinoin therapy has been attributed to extensive trichorrhexis nodosa. Because trauma may induce this hair shaft abnormality, the specificity of this finding in the above conditions may simply be fortuitous.

Treatment is directed toward the avoidance of trauma to the hair.

Landers MC, et al: Intractable diarrhea of infancy with facial dysmorphism, trichorrhexis nodosa, and cirrhosis. Pediatr Dermatol 2003;20:432.

Lurie R, et al: Trichorrhexis nodosa. Cutis 1996;57:358.

Silengo M, et al: Trichorrhexis nodosa and lip pits in autosomal dominant ectodermal dysplasia—central nervous system malformation syndrome. Am J Med Genet 1997;71:226.

Smith RA, et al: Localized trichorrhexis nodosa. Clin Exp Dermatol 1994;19:441.

Trichorrhexis Invaginata

Also known as *bamboo hair*, trichorrhexis invaginata is caused by intussusception of the hair shaft at the zone where keratinization begins. The invagination is caused by softness of the cortex in the keratogenous zone. The softness may be caused by inadequate conversion of –SH to S–S proteins in the cortex. The patient with bamboo hair will have nodose ball-and-socket deformities, with the socket forming the proximal and the ball part forming the distal portion of the node along the hair shaft. This type of hair is associated with Netherton syndrome. Occasionally, only the proximal half of the abnormality is seen; this has been called *golf tee hairs*.

Trichorrhexis invaginata associated with congenital ichthyosiform erythroderma or ichthyosis linearis circumflexa constitutes Netherton syndrome. Atopic manifestations and high IgE levels are commonly present. The bamboo hairs may be present not only on the scalp but also on the eyebrows, eyelashes, and rarely in other hairy areas. Hair sparsity is noted all over the body. The bamboo hairs may become normal within a few years. Other reported findings include pili torti, trichorrhexis nodosa, moniliform hairs, urticaria, angioedema, growth retardation, recurrent infections, multiple epithelial neoplasms, and mental retardation. An autosomal-recessive mode of inheritance has been suggested, although reported cases involving women far outnumber men. Pathogenic mutations have been identified in serine protease inhibitor Kazal-type 5 (SPINK5) on chromosome 5q32, a gene encoding lymphoepithelial Kazal-type-related inhibitor (LEKTI), a serine protease inhibitor involved in skin barrier formation and immunity. PUVA has been reported to help the circumflex linear ichthyosis while etretinate has been reported to both exacerbate and improve skin findings.

Menne et al reported the bamboo hair defect in very thin, probably vellus, hairs in a 7-year-old boy with short, thin, brittle scalp hairs and no eyebrows. They termed this a *canestick* deformity.

Bitoun E, et al: Netherton syndrome: disease expression and spectrum of SPINK5 mutations in 21 families. J Invest Dermatol 2002;118:352.

de Berker DA, et al: Golf tee hairs in Netherton disease. Pediatr Dermatol 1995;12:7.

Krasagakis K, et al: Early development of multiple epithelial neoplasms in Netherton syndrome. Dermatology 2003;207:182.

Menne T, et al: Canestick lesions of vellus hair in Netherton's syndrome. Arch Dermatol 1985;121:451.
Muller FB, et al: Genetic analysis of a severe case of Netherton syndrome and application for prenatal testing. Br J Dermatol 2002;146:495.

Pili Annulati (Ringed Hair)

Pili annulati is a peculiar disease in which the hair seems banded by alternating segments of light and dark color when seen in reflected light. The light bands are caused by clusters of abnormal air-filled cavities, which scatter light, and reduplicated lamina densa in the region of the root bulb.

Hair growth is normal in patients with pili annulati, although it is rarely associated with trichorrhexis nodosa-like breaks of the hair shaft. There are no other associated abnormalities of skin or other organ systems. It is inherited by autosomal-dominant mode, begins in infancy, and requires no treatment, since the spangled appearance of the hair is not unattractive (Fig. 33-20). The condition has been reported to disappear following recovery from alopecia totalis.

Feldmann KA, et al: Newly described weathering pattern in pili annulati hair shafts: a scanning electron microscopic study. J Am Acad Dermatol 2001;45:625.
Giehl KA, et al: Alterations in the basement membrane zone in pili annulati hair follicles as demonstrated by electron microscopy and immunohistochemistry. Br J Dermatol 2004; 150:722.
Green J, et al: Disappearance of pili annulati following an episode of alopecia areata. Clin Exp Dermatol 2002;27:458.

Pili Pseudoannulati

This anomaly of human hair mimics pili annulati. The two differ in that the light bands in pili annulati are caused by internal effects, whereas the bright segments in pili pseudoannulati are caused by reflection and refraction of light by flattened, twisted surfaces of hair. This latter type is a variant of normal hair.

Price VH, et al: Pseudo pili annulati. Arch Dermatol 1970;102:54.

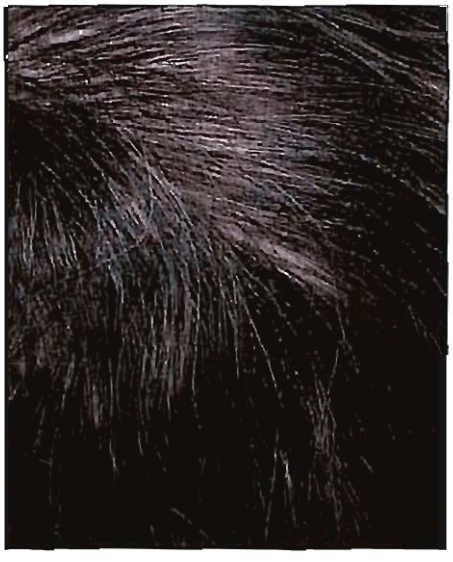

Fig. 33-20
Spangled hair of pili annulati.

Kinking Hair

Acquired progressive kinking of the hair, first described and named by Wise and Sulzberger in 1932, has a structural abnormality of kinking and twisting of the hair shaft at irregular intervals. The main recognized variant of this disorder begins in men in their late teens or early 20s on the frontotemporal or vertex regions, and then progresses to both the parietal and frontal areas. Usually straight, light brown hair becomes curly, frizzy, and lusterless.

When this occurs in the androgen-dependent areas of young men it is a precursor of male-pattern hair loss; usually these men have a strong family history of androgenetic alopecia. Treatment with topical minoxidil has not prevented development of hair thinning. "Whisker" hairs, the short dark hairs that grow anterior to the ears in young people who eventually develop androgenic alopecia, is felt to be a variant of acquired kinking of the hair.

Acquired hair kinking has been described in other clinical situations. Some reports detail prepubertal patients or women, as well as men, in whom kinking develops in non–androgen-dependent areas. In these reports alopecia has not developed, and the curly, frizzy hair may remain present or reverse to its previous condition.

Widespread kinking of the hair may be induced by drugs, notably retinoids, and it may also occur in patients with AIDS.

Tosti A, et al: Acquired progressive kinking of the hair: clinical features, pathological study, and follow-up of 7 patients. Arch Dermatol 1999;135:1223.
Tran JT, et al: What syndrome is this? Acquired progressive kinking of the hair. Pediatr Dermatol 2004;21:265.

Woolly Hair

Woolly hair is present at birth and is usually most severe during childhood, when it is often impossible to brush the hair. In adult life there is a variable amelioration in the condition. There is a clear distinction between the appearance of the affected and nonaffected members of a family. Both autosomal-dominant and -recessive inheritance have been described. Woolly hair nevus has partial scalp involvement by woolly hair, which has a markedly reduced diameter. Naxos' disease is an autosomal-recessive syndrome with arrhythmogenic right ventricular cardiomyopathy, diffuse nonepidermolytic palmoplantar keratoderma, and woolly hair. Hair abnormalities are a reliable marker for subsequent heart disease. The disease is caused by a mutation in the gene encoding plakoglobin. Carvajal syndrome is a familial cardiocutaneous syndrome consisting of woolly hair, palmoplantar keratoderma, and heart disease. It is caused by a recessive deletion mutation in desmoplakin.

Woolly hairs tend to unite into tight locks, whereas the hairs of black persons remain individual. The hair may not grow beyond a length of 12 cm, but may attain a normal appearance in adult life. In the familial group the eyebrows and hairs on the arms, legs, pubic, and axillary regions may be short and pale. There are no associated cutaneous or systemic diseases. A Dutch kindred has been described with premature loss of curly, brittle hair, premature loss of carious teeth, nail dystrophy, and acral keratoderma. It has been designated the curly hair-acral keratoderma-caries syndrome.

The microscopic findings of wooly hair include a decreased diameter, an ovoid shape on cross section, a pili torti-like twisting about a longitudinal axis, trichorrhexis nodosa, and pili annulati.

Alcalai R, et al: A recessive mutation in desmoplakin causes arrhythmogenic right ventricular dysplasia, skin disorder, and woolly hair. J Am Coll Cardiol 2003;42:319.

Kaplan SR, et al: Structural and molecular pathology of the heart in Carvajal syndrome. *Cardiovasc Pathol* 2004;13:26.

Protonotarios N, et al: Genotype–phenotype assessment in autosomal recessive arrhythmogenic right ventricular cardiomyopathy (Naxos disease) caused by a deletion in plakoglobin. *J Am Coll Cardiol* 2001;38:1477.

van Steensel MA, et al: Woolly hair, premature loss of teeth, nail dystrophy, acral hyperkeratosis and facial abnormalities: possible new syndrome in a Dutch kindred. Br J Dermatol 2001;145:157.

Whittock NV, et al: Compound heterozygosity for non-sense and mis-sense mutations in desmoplakin underlies skin fragility/woolly hair syndrome. J Invest Dermatol 2002;118:232.

Plica Neuropathica (Felted hair)

This is a curling, looping, intertwisting, and felting or matting of the hair in localized areas of the scalp. Predisposing factors include kinky hairs, changes in hair care, and a neurotic mental state. Plica polonica is an older name for this condition.

Ramanan C, et al: Plica neuropathica after using herbal soap. Int J Dermatol 1993;32:200.

Sarkar R, et al: "Plica neuropathica": matting of hair. Dermatology 2000;201:184.

Pseudofolliculitis Barbae

Pseudofolliculitis barbae are hairs that, after appearing at the surface, curve back and pierce the skin as ingrowing hairs. This results in inflammatory papules and pustules, which may scar. In severe cases large deforming keloids may result in the beard area. Pseudofolliculitis of the beard is seen in more than 50% of black men, who must sometimes give up shaving to alleviate the disorder. A single-nucleotide polymorphism, giving rise to a disruptive Ala12Thr substitution in the 1A α-helical segment of the companion layer-specific keratin K6hf appears to be partially responsible for the phenotype. White persons are uncommonly affected; however, shaving of the pubic hair will often result in pseudofolliculitis. Tenderness responds to mid-strength topical steroids. The use of clippers or chemical depilatories, glycolic acid lotion, and adjunctive antibiotic therapy may be helpful. Benzoyl peroxide 5%/clindamycin 1% gel has been shown effective in double-blind evaluation. Laser hair removal with the long-pulse Nd:YAG laser is suitable for a wide range of skin types. The diode laser has also been used.

Battle EF Jr, et al: Laser-assisted hair removal for darker skin types. Dermatol Ther 2004;17:177.

Bridgeman-Shah S: The medical and surgical therapy of pseudofolliculitis barbae. Dermatol Ther 2004;17:158.

Cook-Bolden FE, et al: Twice-daily applications of benzoyl peroxide 5%/clindamycin 1% gel versus vehicle in the treatment of pseudofolliculitis barbae. Cutis 2004;73(6 Suppl):18.

Garcia-Zuazaga J: Pseudofolliculitis barbae: review and update on new treatment modalities. Mil Med 2003;168:561.

Greppi I: Diode laser hair removal of the black patient. Lasers Surg Med 2001;28:150.

Perry PK, et al: Defining pseudofolliculitis barbae in 2001: a review of the literature and current trends. J Am Acad Dermatol 2002;46(2 Suppl):S113.

Weaver SM 3rd, et al: Treatment of pseudofolliculitis barbae using the long-pulse Nd:YAG laser on skin types V and VI. Dermatol Surg 2003;29:1187.

Winter H, et al: An unusual Ala12Thr polymorphism in the 1A alpha-helical segment of the companion layer-specific keratin K6hf: evidence for a risk factor in the etiology of the common hair disorder pseudofolliculitis barbae. J Invest Dermatol 2004;122:652.

Yamauchi PS, et al: Treatment of pseudofolliculitis barbae with the diode laser. J Cutan Laser Ther 1999;1:109.

Pili Multigemini

This rare malformation is characterized by the presence of bifurcated or multiple divided hair matrices and papillae, giving rise to the formation of multiple hair shafts within the individual follicles. It sometimes follows lines of Blaschko. Mehregan et al reported a patient with cleidocranial dysostosis and extensive pili multigemini over the heavily bearded chin and cheek areas. There is no treatment.

Cambiaghi S, et al: Scanning electron microscopy in the diagnosis of pili multigemini. Acta Derm Venereol 1995;75:170.

Mehregan AH, et al: Pili multigemini. Br J Dermatol 1999;100:315.

Pili Bifurcati

In this disorder, bifurcation is found in short segments along the shafts of several hairs. Each branch of the bifurcation is covered with its own cuticle. It has been seen in association with the trisomy 8 mosaic syndrome. Pili bifurcati differs from pili multigemini in which a single follicular matrix produces two different-sized hair shafts with separate cuticles that do not fuse again. Trichoptilosis is characterized by split distal ends that are never surrounded by a complete cuticle.

Camacho FM, et al: The different faces of pili bifurcati. A review. Eur J Dermatol 2000;10:337.

Trichostasis Spinulosa

Trichostasis spinulosa is a common disorder of the hair follicles that clinically gives the impression of blackheads (Figs 33-21 and 33-22), but the follicles are filled with funnel-shaped, horny plugs within which are bundles of vellus hairs (Fig. 33-23). The hairs are round at their proximal ends and shredded distally. The disease occurs primary on the nose and forehead, but may also occur on the trunk and be accompanied by pruritus.

Trichostasis spinulosa results from retention of telogen hairs, which are derived from a single hair matrix. It is primarily caused by a hyperkeratosis of the follicular infundibulum, which leads to a partial obstruction of the follicular orifice and thus does not permit shedding of small telogen hairs.

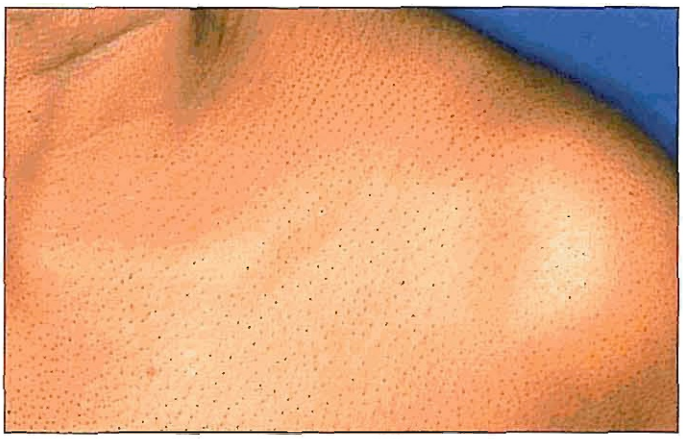

Fig. 33-21 Trichostasis spinulosa. (Courtesy of Richard Vinson, MD)

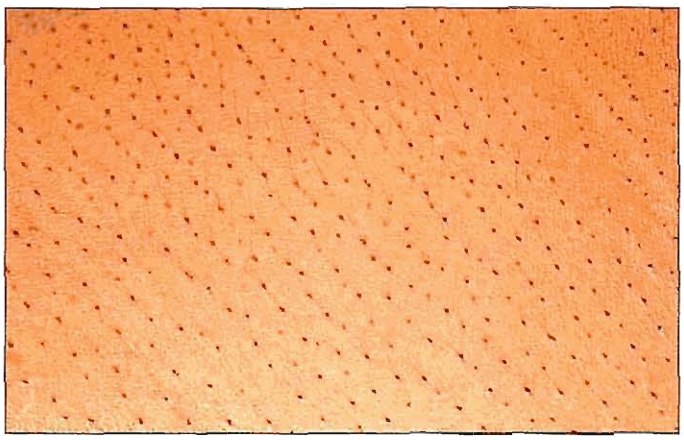

Fig. 33-22 Trichostasis spinulosa. (Courtesy of Richard Vinson, MD)

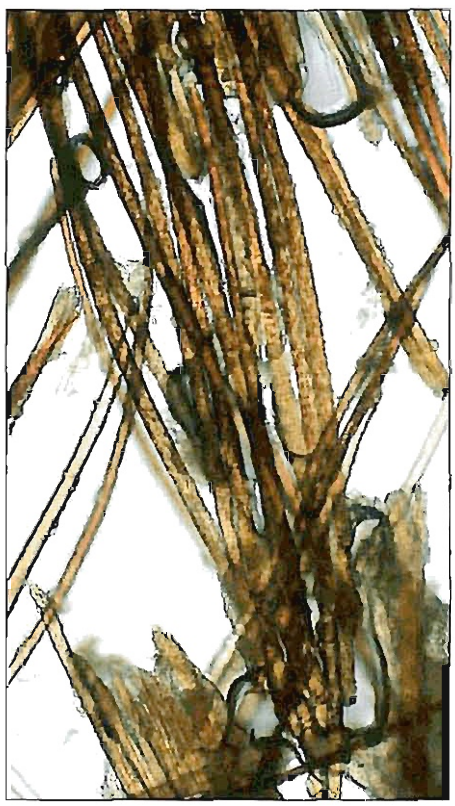

Fig. 33-23 Trichostasis spinulosa.

The plugs may be removed with hydroactive adhesive (Biore) pads. Keratolytics are also effective after using a wax depilatory. The pulsed diode laser has been used successfully, and application of 0.05% tretinoin solution, applied daily for 2 or 3 months, may also produce satisfactory results.

Elston DM, et al: Treatment of trichostasis spinulosa with a hydroactive adhesive pad. Cutis 2000;66:77.
Manuskiatti W, et al: Treatment of trichostasis spinulosa in skin phototypes III, IV, and V with an 800-nm pulsed diode laser. Dermatol Surg 2003;29:85.
Strobos MA, et al: Trichostasis spinulosa: itchy follicular papules in young adults. Int J Dermatol 2002;41:643.

Intermittent Hair-Follicle Dystrophy

Birnbaum et al reported a disorder of the hair follicle leading to increased fragility of the shaft, with no identifiable biochemical disturbance. The prevalence of this disorder is unknown.

Birnbaum PS, et al: Hereditable diseases of the hair. Dermatol Clin 1987;5:137.

Bubble Hair Deformity

Bubble hairs appear as areas of hair with altered texture. Fragility has been reported. The hairs may be curved or straight and stiff. Small, bubble-like defects are found within the hair shafts on light and electron microscopy. The condition is produced by overheating of wet hair with a malfunctioning hair dryer, analogous to the popping of popcorn. All damp hair will develop bubbles of gas when exposed to high heat.

Detwiler SP, et al: Bubble hair. J Am Acad Dermatol 1994;30:54.
Gummer CL: Bubble hair. Br J Dermatol 1994;131:901.

HYPERTRICHOSIS

Hypertrichosis is an overgrowth of hair not localized to the androgen-dependent areas of the skin. Several forms exist. The excessive hair growth can be managed with bleaching, trimming, shaving, plucking, waxing, chemical depilatories, and electrosurgical epilation. Laser treatment with long-pulse Nd:YAG, diode, ruby, long- and short-pulse alexandrite lasers, and intense pulsed light sources can be effective. Skin type must be considered when choosing a laser system. The greatest experience in dark skin types has been with the long-pulse Nd:YAG laser.

Localized Acquired Hypertrichosis

Dermal tumors, such as melanocytic nevi, smooth muscle hamartoma, meningioma, or Becker nevi, may have excessive terminal hair growth. Repeated irritation, trauma, occlusion under a cast, eczematous states, topical steroid use, linear melorheostotic scleroderma, lymphedema associated with filariasis, the Crow-Fukase (POEMS) syndrome, and pretibial myxedema may be other situations in which there is a localized increase in hair growth. Porphyrias generally show a localized hypertrichosis over the malar area, such as in porphyria cutanea tarda or variegate porphyria; however, in

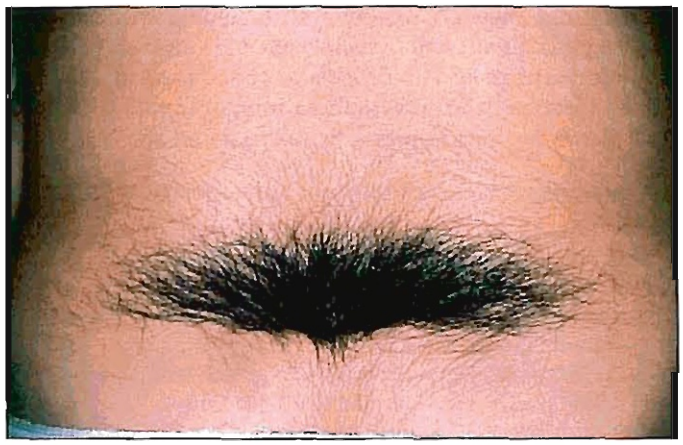

Fig. 33-24 Sacral hair tuft. (Courtesy of Brooke Army Medical Center Teaching File)

the Gunther variety of erythropoietic porphyria it may be generalized or more diffuse in nature.

Localized Congenital Hypertrichosis

Hypertrichosis cubiti (hairy elbows) consists of long vellus hair on the extensor surfaces of the distal third of the upper arm and the proximal third of the forearm bilaterally. It is a progressive, excessive growth of lanugo hairs that often begins in infancy; the hairs may reach a length of 10 cm. Later they become coarser, but regression has been observed during adolescence. There appears to be familial cases and a sporadic form. Short stature and some developmental abnormalities are present in some cases; however, there is no need for endocrine studies or other evaluation. The condition appears to be of cosmetic significance only.

Other causes of localized congenital hypertrichosis include congenital nevocytic nevi, anterior cervical hypertrichosis, and simple nevoid hypertrichosis. Localized hypertrichosis may be a sign of underlying spinal dysraphism when it occurs over the sacral midline (Fig. 33-24).

Generalized Congenital Hypertrichosis (Congenital Hypertrichosis Lanuginosa)

This rare type of excessive and generalized hairiness is a fully penetrant X-linked dominant trait. The entire body is covered with fine vellus hairs 2 to 10 cm long (Fig. 33-25). The scalp hair appears to be normal. Except for the palms and soles, all other areas are covered. Congenital hypertrichosis lanuginosa may be associated with dental anomalies and gingival fibromatosis. This type of hairiness has attracted considerable attention over the centuries. Hair removal by laser may be quite useful.

Other cases of congenital generalized hypertrichosis may be secondary to drug ingestion by the mother. The fetal hydantoin syndrome is characterized by hypertrichosis, depressed nasal bridge, large lips, a wide mouth, and a short, webbed neck. The fetal alcohol syndrome includes hypertrichosis, a small face, capillary hemangiomas, and physical and mental retardation. A case of generalized hypertrichosis and multiple congenital defects was reported by Kaler et al in a baby born to a mother who used minoxidil throughout pregnancy. Fetal valproate syndrome is characterized by generalized hypertrichosis, sparing the palms and soles,

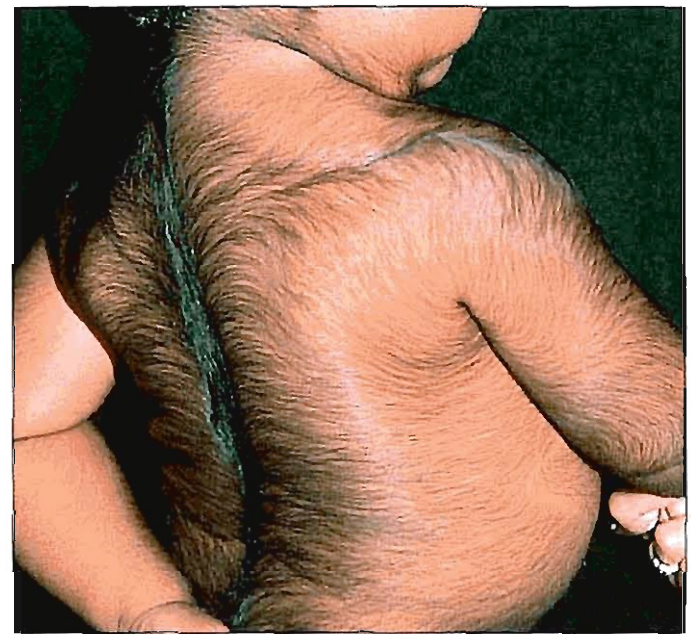

Fig. 33-25 Hypertrichosis lanuginose. (Courtesy of Brooke Army Medical Center Teaching File).

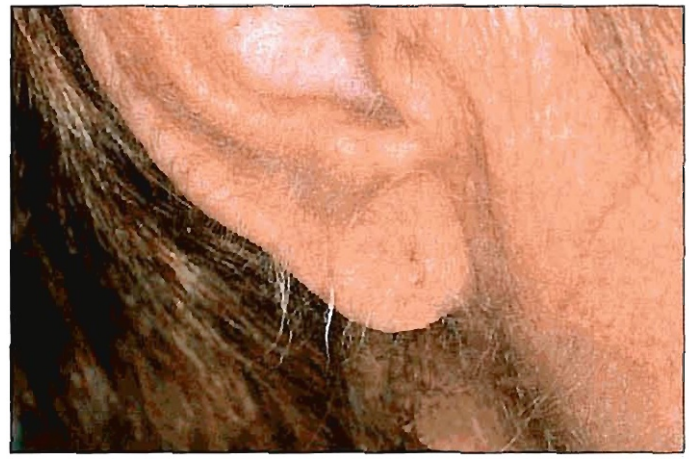

Fig. 33-26 Hypertrichosis lanuginose associated with an internal malignancy (malignant down).

coarse facies, gum hypertrophy, hypotonia, club feet and club hands, and abnormal dermatoglyphics.

Generalized or Patterned Acquired Hypertrichosis

These cases include those caused by acquired hypertrichosis lanuginosa, those associated with various syndromes, and those secondary to drug intake. Acquired hypertrichosis lanuginosa (Fig. 33-26) is an ominous sign of internal malignancy. Syndromes associated with increased hair growth include lipoatrophic diabetes, stiff skin syndrome, Down syndrome, Rubenstein-Taybi syndrome, Laband syndrome, Cornelia de Lange syndrome, Hurler syndrome, Morogu syndrome, leprechaunism, Winchester syndrome, the Schynzel-Giedier syndrome, and hypertrichosis with acromegalic features. Drugs associated with hypertrichosis include minoxidil, cyclosporin, diphenylhydantoin, diazoxide, streptomycin, penicillamine, corticosteroids, danazol, psoralens,

hexachlorobenzene, PUVA, topical bimatoprost, topical steroids, and topical androgens.

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HIRSUTISM

Clinical Features

Hirsutism is an excess of terminal hair growth in women in a pattern more typical of men. Androgen-dependent growth areas affected include the upper lip, cheeks, chin, central chest, breasts, lower abdomen, and groin. This altered growth pattern of the hair may be associated with other signs of virilization, which include temporal balding, masculine habitus, deepening of the voice, clitoral hypertrophy, and amenorrhea. Acne is an additional sign of hyperandrogenism.

Pathogenesis

When virilization accompanies hirsutism, especially when progression is rapid, a neoplastic cause is likely. In the absence of virilization, a neoplastic cause is extremely unlikely. Most medically significant hirsutism is related to the polycystic ovarian syndrome (PCOS, hyperinsulinemic hyperandrogenism with anovulation). In a study of 873 patients with medically significant hirsutism, PCOS was present in 82%. Idiopathic hirsutism was present in 4.7%, and 6.75% of the patients had elevated androgen levels and hirsutism with normal ovulation.

Ethnic variation should be considered when evaluating hirsutism. Women of Southwest Asian, Eastern European and Southern European heritage commonly have facial, abdominal, and thigh hair; whereas Asian and Indian women generally have little terminal hair growth in these areas.

In women, androgen biosynthesis occurs in the adrenal and ovary. Testosterone and the androgen precursor androstenedione are secreted by the ovary. The adrenal contributions are preandrogens: dehydroepiandrosterone (DHEA), DHEA sulfate, and androstenedione. They require peripheral conversion in the skin and liver to testosterone.

Testosterone is converted to dihydrotestosterone, the androgen that promotes androgen-dependent hair growth, in the hair follicle by 5-α-reductase. Receptor molecules in the end organ are necessary for binding and hormone action at that level. Because testosterone is normally bound to carrier molecules in the plasma at a 99% level, and it is the unbound testosterone that is active, the levels of free testosterone correlate with clinical evidence of androgen excess.

Hirsutism may result from excessive secretion of androgens from either the ovary or the adrenal gland. The excessive secretion may be from functional excesses or, rarely, from neoplastic processes. Ovarian causes include polycystic ovary syndrome (PCOS, Stein-Leventhial syndrome), and a variety of ovarian tumors, both benign and malignant. PCOS is defined by anovulation (fewer than nine periods a year or periods longer than 40 days apart) with clinical evidence of hyperandrogenism. Ovarian cysts are not required for the diagnosis, and laboratory and imaging studies are not required to establish the diagnosis. The pathogenesis of PCOS may relate to insulin resistance with resultant elevated insulin levels leading to ovarian overproduction of androgens. Prevalence rates of PCOS for black and white women in the US are 8.0% and 4.8%, respectively.

Ovarian tumors include unilateral benign microadenomas, arrhenoblastomas. Leydig cell tumors, hilar cell tumors, granular/theca cell tumors, and luteomas are rare causes of hirsutism. In tumor-associated hirsutism, the onset is usually rapid, occurs with other signs of virilization, and begins between the ages of 20 and 40.

Adrenal causes include congenital adrenal hyperplasia and adrenal tumors, such as adrenal adenomas and carcinomas. The adrenogenital syndrome or congenital adrenal hyperplasia (CAH) is an autosomal-dominant disorder that may result from deficiencies of the following enzymes: 21-hydroxylase (most common form), 11β-hydroxylase, or 3β-hydroxy steroid dehydrogenase. Onset is generally in childhood, with ambiguous genitalia, precocious growth, and virilism. Nonclassic (adult-onset) CAH may present with hirsutism.

Pituitary causes include Cushing's disease, acromegaly, and prolactin-secreting adenomas. Prolactin-secreting microadenomas have a 20% incidence of hirsutism and acne. Prolactin elevations may be seen in patients with PCOS. Other conditions in which prolactin levels may be elevated and that may lead to hirsutism include hypothyroidism, phenothiazine intake, and hepatorenal failure.

Other causes of hirsutism include the exogenous intake of androgens. End-organ hypersensitivity may be a mechanism in patients with a normal evaluation. Drugs such as minoxidil, diazoxide, corticosteroids, and phenytoin, which have been reported to cause hirsutism, generally cause hyper-

trichosis—a generalized increase in hair that is not limited to the androgen-sensitive areas.

Evaluation

Most hirsutism is related to ethnic heritage or PCOS. 21-Hydroxylase-deficient nonclassic adrenal hyperplasia, the hyperandrogenic insulin-resistant acanthosis nigricans syndromes, and androgen-secreting tumors are relatively uncommon causes. A careful history and physical examination are essential. The history should focus on onset and progression, virilization, menstrual and pregnancy history, and family/racial background. Physical examination may reveal signs of Cushing's disease, hypothyroidism, or acromegaly. Other signs to be evaluated are the distribution of muscle mass and body fat, clitoral dimensions, voice depth, and galactorrhea.

Laboratory evaluation is controversial. In the authors' opinion, testing is of value only when it affects management. If this is accepted, there is no mandatory *hormonal* testing for stable hirsutism in patients who have no signs of virilization. A diagnosis PCOS does not require laboratory confirmation. Determination of serum lipids and testing for glucose intolerance may be the most important laboratory evaluations in patients with PCOS as they have the greatest impact on management and long-term prognosis. When the history and physical examination suggest the possibility of a neoplasm, laboratory evaluation should include a total testosterone level. A dehydroepiandrosterone sulfate level is commonly performed if an adrenal cause is suspected. A 24-h urine cortisol is the gold standard for the diagnosis of Cushing's disease. Thyroid stimulating hormone (TSH), growth hormone, and somatomedin C levels are indicated if the history and physical examination suggest hypothyroidism or acromegaly.

Dexamethasone suppression tests are recommended by some authorities, but the results often do not affect management. A baseline 17-hydroxyprogesterone and adrenocorticotropic hormone (ACTH) stimulation test can screen for late-onset CAH, but steroid replacement has not been proved to result in better outcomes than empiric treatment with antiandrogens. Baseline 17-hydroxyprogesterone may be normal in some women with nonclassic 21-hydroxylase deficiency, and ACTH-stimuation may result in overdiagnosis of the syndrome. An exaggerated 17-hydroxyprogesterone response to ACTH stimulation is common in PCOS at a pharmacologic dose (250 μg) but not at a physiologic dose (1 μg) of ACTH. An ovarian origin of hirsutism can be identified by a buserelin test in 30% of patients with hirsutism and by dexamethasone in 22% of patients, but data proving that buserelin challenge results in better outcomes is lacking. A prolactin level will screen for prolactin-secreting tumors, but will also lead to further expensive testing in many patients ultimately diagnosed with PCOS. A prolactin level should be obtained in any patient with galactorrhea, but is of limited value as a routine screening test for patients with hirsutism alone.

If signs of acromegaly, Cushing's disease, or virilization are present clinically, referral to an endocrinologist is recommended. The presence of major menstrual irregularities is also an indication for referral to an endocrinologist or gynecologist. Although 90% of women with hirsutism have an elevated testosterone level, elevations above 200 ng/dL and rapid onset or progressive virilization suggest serious underlying disease. A major elevation in the DHEA sulfate level (>7000 ng/mL) suggests an adrenal neoplasm, and imaging of the adrenal gland is recommended. Many patients with late-onset congenital adrenal hyperplasia will have normal screening DHEAS. Patients with prolactin levels above 20 ng/mL should likewise be referred for further evaluation with a MRI or CT scan. Polymorphisms in the gene coding for sex hormone-binding globulin have been identified in some families with hirsutism, but such testing does not affect management.

Treatment

Various forms of mechanical, chemical, and laser epilation can be performed, as for hypertrichosis. Spironolactone with various oral contraceptives, cyproterone acetate plus ethyniloestradiol, gonadotropin-releasing hormone agonists such as leuprolide and nafarelin, flutamide, finasteride and topical eflornithine have been used successfully alone and in various combinations to treat hirsutism. The optimal combination and dosage remain to be determined. Finasteride at doses of 2.5 to 5 mg/day has been shown to decrease hair number and diameter in women with hirsutism. The combination of spironolactone (100 mg/day) plus finasteride (5 mg/day) has been shown to be superior to spironolactone (100 mg/day) alone. An analysis of the current literature suggested that spironolactone alone (100 mg/day) is superior to finasteride alone (5 mg/day) and low-dose cyproterone acetate alone (12.5 mg/day for the first 10 days of a cycle) in the treatment of hirsutism. As spironolactone is commonly used at a dose of 100 mg twice a day, further studies are needed comparing this higher dose with other modes of therapy. In a prospective, randomized study of Diane 35 (cyproterone acetate (CPA) [2 mg] and ethinyl estradiol [35 μg]), Diane 35 plus spironolactone, and spironolactone alone, all treatments were well tolerated. Combination therapy resulted in superior measured endocrine responses, but the authors concluded that spironolactone alone was the most cost-effective treatment. The choice of an oral contraceptive (OC) is also controversial. Third-generation OCs result in a significant increase in sex hormone-binding globulin and decrease in free testosterone, but both second- and third-generation OCs are clinically effective in treating hirsutism. When flutamide is used, initial treatment with 250 mg/day is followed by a long maintenance treatment period using 125 mg/day.

Insulin sensitizers are being studied in the treatment of hirsutism, particularly PCOS. The best data to date are for metformin. Metformin therapy has been shown to control menstrual cycles and improve fertility in women with PCOS. It causes a decline in testosterone and insulin levels. Oligomenorrheic women with an increased luteinizing hormone (LH)-to-follicle-stimulating hormone (FSH) ratio and lower testosterone levels respond best. Spironolactone (50 mg/day) was superior to metformin (1000 mg/day) in the treatment of hirsutism and menstrual cycle frequency in a study of 82 adolescent and young women with PCOS. Doses of 200 mg/day are commonly used to treat hirsutism. At this dose, menstrual irregularities induced by the drug are common, and it may be best used in combination with an OC pill. Yasmin, which contains the progestogen drosperinone has been shown to provide good cycle control for women with PCOS, with an improvement in acne but not in other

symptoms of the syndrome. Good correlation has been noted between an increase in ovulation frequency with clomiphene citrate and the chance of pregnancy in women with PCOS. Other options include the use of gonadotrophins and laparoscopic ovarian drilling. Infertility is best managed by a specialist is this field. Empiric treatment with an antiandrogen may be as good as steroid replacement for the management of hirsutism in patients with nonclassic CAH.

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TRICHOMYCOSIS AXILLARIS

One- to 2-mm discrete nodules attached firmly to the hair shafts of the axillary or pubic areas characterize trichomycosis. The color of the nodules may be yellow (Fig. 33-27), red or black. Hyperhidrosis of the affected regions is usually present. A yellowish discoloration of the axillae is sometimes noted. Large numbers of corynebacterium are present in the concretions.

Treatment with topical antibiotic preparations, such as topical clindamycin or erythromycin, or naftifine which has antibacterial properties, combined with any modality that will decrease the hyperhidrosis is effective, but shaving is faster.

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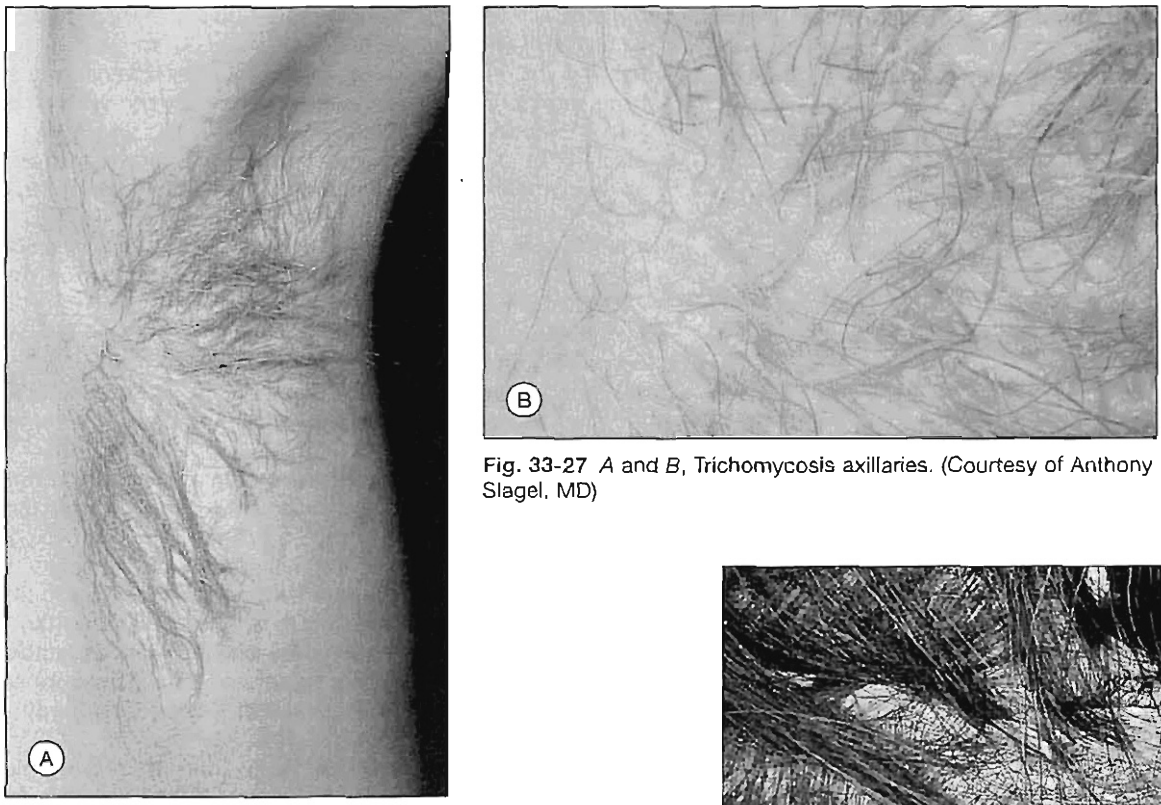

Fig. 33-27 *A* and *B*, Trichomycosis axillaries. (Courtesy of Anthony Slagel, MD)

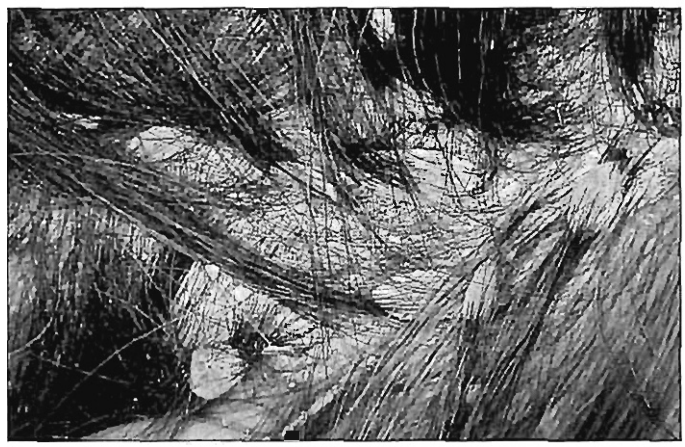

Fig. 33-28 Tinea amiantacea.

ASSOCIATED HAIR FOLLICLE DISEASES

Pityriasis Amiantacea (Tinea Amiantacea)

Thick, asbestos-like (amiantaceous), shiny scales on the scalp characterize pityriasis amiantacea. The silvery-white or dull gray crusting may be localized or, less often, generalized over the entire scalp. The proximal parts of the hairs are matted together by the laminated crusts (Fig. 33-28). There are no structural changes in the hair, but in some patches where the crusting is thick, there may be some purulent exudate under the crust and temporary alopecia such as occurs after some cases of furunculosis of the scalp.

The cause is most often a secondary infection occurring in seborrheic dermatitis or psoriasis. In a prospective study of 85 patients, psoriasis was documented in 35% and an eczematous process suggesting seborrheic dermatitis or atopic dermatitis occurred in another 35%. Tinea capitis was the eventual diagnosis in 13%. Staphylococcus was found in 96.5% compared with 15% of controls. The patient should shampoo daily or every other day with selenium sulfide suspension, or a tar or steroid-containing shampoo, for a couple of weeks. Prior application of peanut oil or a keratolytic a few hours before shampooing facilitates removal of the scales and crusts. With such debridement the secondary bacterial infection usually resolves without the need for oral antistaphylococcal therapy.

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Folliculitis Nares Perforans

Perforating folliculitis of the nose is characterized by small pustules near the tip of the inside of the nose. The lesion becomes crusted, and when the crust is removed it is found that the bulbous end of the affected vibrissa is embedded in the inspissated material. The affected hairs are typical of those occurring inside the nostril. *Staphylococcus aureus* may at times be cultured from the pustules. The hair should be removed and antibiotic ointment such as mupirocin applied.

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Acquired Perforating Dermatosis

Perforating folliculitis, *Kyrle's disease*, and *acquired perforating collagenosis*, are designations that have been supplanted by the more inclusive term *acquired perforating dermatosis*. The condition is not uncommon and is often associated with renal failure or diabetes or both. Between 4% and 10% of dialysis patients develop umbillicated dome-shaped papules on the legs, or less often on the trunk, neck, arms, or scalp, with variable itchiness (Fig. 33-29A). Early lesions may be pustular; late lesions resemble prurigo nodularis both clinically and histologically. There is a central hyper-

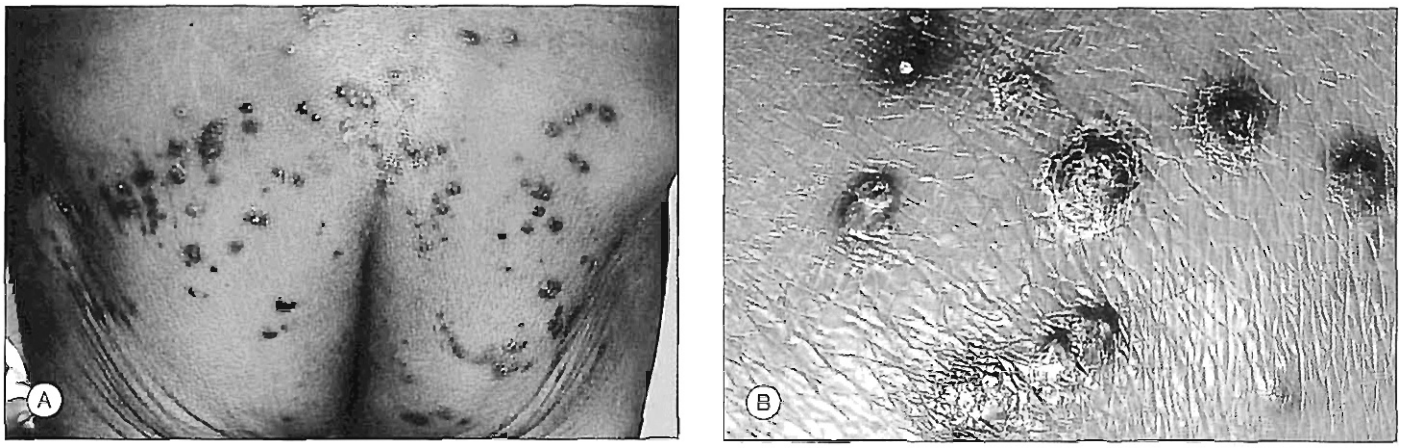

Fig. 33-29 *A* and *B*, Acquired perforating disease in uremia. (Courtesy of Curt Samlaska MD)

keratotic cone that projects into the dermis (Fig. 33-29B), so that when it is removed a pitlike depression remains. Usually the papules are discrete, but they may coalesce to form circinate plaques. Coalescing verrucous plaques are frequently seen, especially on the lower extremities. Koebner's phenomenon may also be observed, in which case plaques or elevated verrucous streaks are formed. The latter are seen primarily in the antecubital and popliteal spaces. Atrophic scars are seen on involution of these lesions.

Histologically, the epidermis becomes edematous, the granular layer disappears, and parakeratosis develops. Eventually the epidermis becomes atrophic, with disruption of the sites over the papillae. Through these sites necrobiotic connective tissue, degenerating inflammatory cells, and collagen bundles are extruded into a cup-shaped epidermal depression.

The condition is felt to be a response to trauma, usually the scratching or rubbing in response to the pruritus of the associated renal failure or dry skin. Other predisposing conditions reported include HIV infection, sclerosing cholangitis or other liver diseases, hypothyroidism, hyperparathyroidism, in areas of healed herpes zoster, and as a reaction to laser hair removal.

Ultraviolet treatment of either PUVA or UVB type helps the pruritus of renal disease and improves the perforating disorder. Hydration of the skin with a soaking tub bath in plain water followed immediately (without drying) by triamcinolone ointment is also useful. Topical retinoic acid (0.1% cream), allopurinol, doxycycline, isotretinoin, and etretinate have been effective in flattening lesions. HIV-infected patients may respond well to thalidomide. The disease may remit promptly after renal transplantation.

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Reactive Perforating Collagenosis

Reactive perforating collagenosis is an inherited condition characterized by pinhead-sized, skin-colored papules that grow to a diameter of 4 to 6 mm and develop a central area of umbilication in which keratinous material is lodged (Fig. 33-30). The discrete papules may be numerous and involve sites of frequent trauma such as the backs of the hands, forearms, elbows, and knees. The lesion reaches a maximum size of about 6 mm in 4 weeks and then regresses spontaneously in 6 to 8 weeks.

It is believed that this is caused by a peculiar reaction of the skin to superficial trauma. Koebnerization is often observed. Young children are most frequently affected. Most reports support an autosomal-recessive mode of inheritance; however, a family in which it appeared to be inherited by autosomal dominance has been reported.

No specific treatment is indicated, since the lesions involute spontaneously. Tretinoin 0.1% cream may be effective.

Kumar V, et al: Familial reactive perforating collagenosis. J Dermatol 1998;25:54.

Traumatic Anserine Folliculosis

Traumatic anserine folliculosis is a curious gooseflesh-like follicular hyperkeratosis that may result from persistent pressure and lateral friction of one skin surface on another. Such friction is often caused by habitual pressure of elbows, chin or jaw, or neck, often while watching television. Two-thirds of patients who develop this are atopic.

Padilha-Gonalves A: Traumatic anserine folliculosis. J Dermatol 1979;6:365.

Erythromelanosis Follicularis Faciei et Colli

Erythromelanosis follicularis faciei et colli is an erythematous pigmentary disease involving the follicles. A reddish-

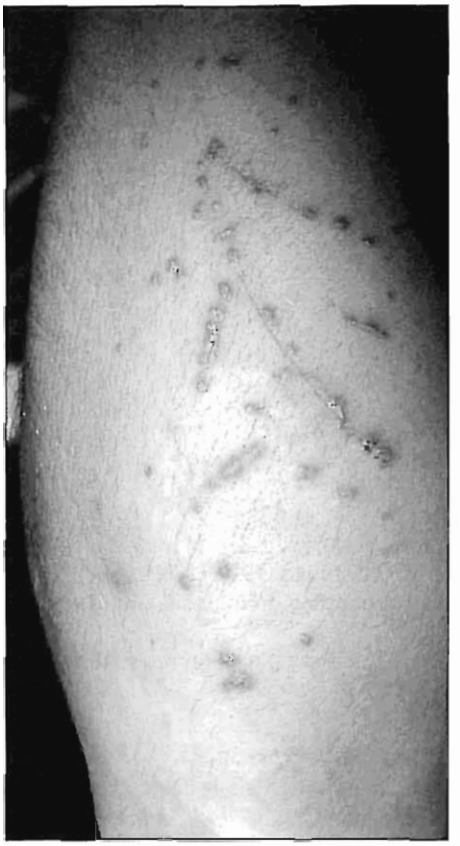

Fig. 33-30 Reactive perforating collagenosis.

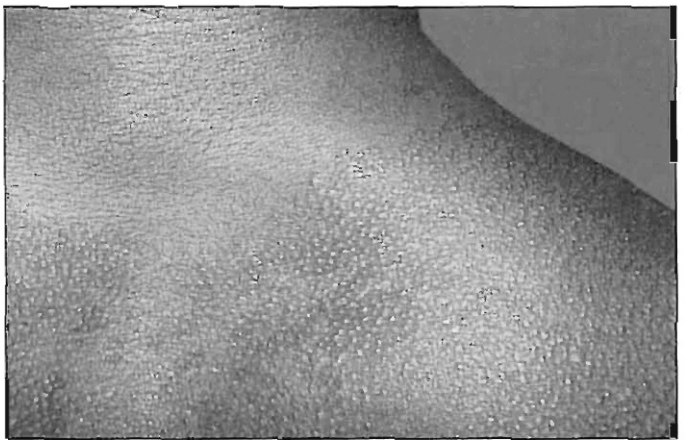

Fig. 33-31 Disseminated infuldibulofolliculitis.

brown, sharply demarcated, symmetrical discoloration involves the preauricular and maxillary regions. At times the pigmentation may be blotchy. In addition, follicular papules and erythema are present. Under diascopic pressure the reddish-brown area, containing telangiectases, becomes pale and the light brown pigmentation becomes more apparent. Pityriasiform scaling and slight itching may occur. Keratosis pilaris on the arms and shoulders is frequently found. It preferentially affects Asian patients.

Histologically, a slight hyperkeratosis occurs, with epidermal hyperpigmentation and dilation of the upper dermal vessels. The hair follicles may be enlarged in the infundibular area and the sebaceous glands may be hypertrophic. A lymphocytic infiltration surrounds the adnexa.

Kim MG, et al: Quantitiative histopathologic findings of erythromelanosis follicularis faceie et colli. J Cutan Pathol 2001; 28:160.

Sodaify M, et al: Erythromelanosis follicularis faciei et colli. Int J Dermatol 1994;33:643.

Disseminate and Recurrent Infundibulofolliculitis

Hitch and Lund described a disseminate follicular eruption on the torso of a black man that involved all the pilosebaceous structures (Fig. 33-31). The lesions were irregularly shaped papules pierced by a hair. They likened the eruption to cutis anserina viewed through a magnifying glass. The eruption is mildly pruritic at times, and is chronic, with recurrent exacerbations. The papules are uniform, 1 or 2 mm in diameter, and involve all the follicles in the affected areas, which are usually the upper trunk and neck, though the entire trunk and proximal extremities may be involved. Rarely, pustules may occur.

Histologically, the infundibular portion of the follicles is chiefly affected, and the lesions are inflammatory rather than hyperkeratotic. Edema, lymphocytic and neutrophilic infiltration, and slight fibroblastic infiltration surround the affected follicles.

Treatment with isotretinoin or PUVA may be effective.

Aroni K, et al: Disseminate and recurrent infudibulofolliculitis: response to isotretinoin. J Drugs Dermatol 2004;3:434.

Heymann WR: Infundibulofolliculitis of the neck. Cutis 2002; 70:178.

Ravikumar BC, et al: Disseminate and recurrent infundibulofolliculitis: response to psoralen plus UVA therapy. Int J Dermatol 1999;38:75.

Lichen Spinulosus

Lichen spinulosus (keratosis spinulosa) is a disease chiefly of children and is characterized by minute filiform horny spines, which protrude from follicular openings independent of any papules. The spines are discrete and grouped. The lesions appear in crops and are symmetrically distributed over the trunk, limbs, and buttocks (acne corne). There is a predilection for the neck, buttocks, abdominal wall, popliteal spaces, and the extensor surfaces of the arms. Little or no itching is present.

Histologic evaluation shows simple inflammatory changes and follicular hyperkeratosis. The lesions may respond to keratolytics and emollients, such as salicylic acid, lactic acid, or urea gels or ointments. Tretinoin is another alternative. The lesions tend to involute at puberty.

Friedman SJ: Lichen spinulosus. J Am Acad Dermatol 1990; 22:261.

Stricklling WA, et al: Spiny eruption on the neck. Arch Dermatol 2000;136:1165.

Tilly JJ, et al: Lichenoid eruptions in children. J Am Acad Dermatol 2004;51:606.

DISORDERS OF THE SWEAT GLANDS

Hyperhidrosis

Hyperhidrosis, or excessive sweating, may be localized to one or several areas or it may be more generalized. True generalized hyperhidrosis is rare, and even hyperhidrosis caused by systemic diseases is usually accentuated in certain regions.

Palmoplantar Hyperhidrosis (Emotional Hyperhidrosis) This type of hyperhidrosis is usually localized to the palms, soles or/or axillae (Fig. 33-32), and may be worse during warm temperatures. Patients with palm and sole hyperhidrosis may also have axillary hyperhidrosis, but only 25% of patients with axillary hyperhidrosis have palmoplantar hyperhidrosis. The hands may be cold and show a dusky hue. The soggy keratin of the hyperhidrotic soles is frequently affected by pitted keratolysis and has a foul odor. Sweating may be intermittent; in these cases anxiety, stress, or fear may trigger it. When sweating is constant, usually emotion is not as important.

This type of sweating can be autosomal-dominantly inherited. Its onset is in childhood for the palmar type and adolescence for axillary disease. It tends to improve with age. Sweating typically ceases during sleep.

Gustatory Hyperhidrosis Certain individuals regularly experience excessive sweating of the forehead, upper lip, perioral region, or sternum a few moments after eating spicy foods, tomato sauce, chocolate, coffee, tea, or hot soups. Gustatory sweating may be idiopathic or caused by hyperactivity of the sympathetic nerves (Pancoast tumor or postoperatively), sensory neuropathy (diabetes mellitus or subsequent to zoster), parotitis or parotid abscess, and surgery or injury of the parotid gland (auriculotemporal syndrome of von Frey). Frey syndrome occurs in one-third or more of patients following parotid surgery. Fortunately, only 10% of affected patients require treatment.

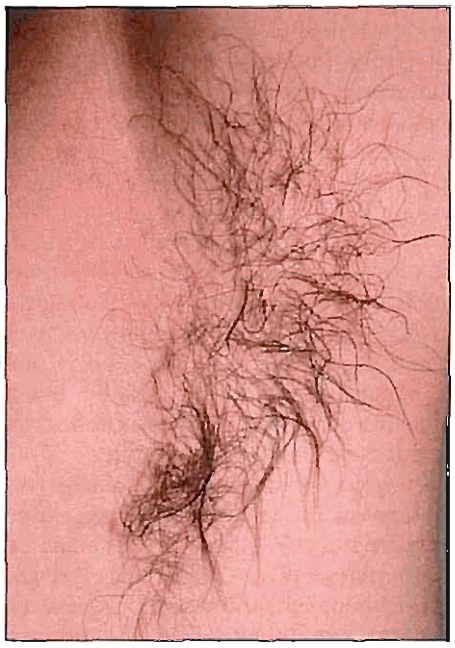

Fig. 33-32 Axillary hyperhidrosis.

Other Localized Forms of Hyperhidrosis Localized sweating can occur over lesions of blue rubber bleb nevus, glomus tumors, hemangiomas (sudoriferous hemangioma), and in POEMS syndrome, Gopalan syndrome, complex regional pain syndrome, as a result of spinal cord tumors (especially when unilateral palmar hyperhidrosis is the complaint), and pachydermoperiostosis.

Generalized Hyperhidrosis Febrile diseases, vigorous exercise or a hot, humid environment, such as a tropical milieu, may induce generalized hyperhidrosis. Hyperthyroidism, acromegaly, diabetes mellitus, pheochromocytoma, hypoglycemia, salicylism, substance abuse, lymphoma, pregnancy, and menopause may also produce generalized hyperhidrosis. Additional causes of hyperhidrosis include concussion, Parkinson's disease, other disturbances of the sympathetic nervous system, and metastatic tumors producing a complete transection of the spinal cord.

Treatment

The therapy of generalized hyperhidrosis is aimed at treating the underlying systemic disease. Virtually all cases of hyperhidrosis seen by dermatologists are of the palmoplantar or axillary types, and the treatments discussed below relate primarily to these conditions.

Topical Medication. Topical aluminum chloride or aluminum chlorhydroxide are the most commonly used agents for hyperhidrosis. For the axillae, application of a 10% to 35% solution nightly to a very dry axilla (blown dry with a hair dryer) is usually very effective. To limit irritation, lower concentrations should be tried first. Also, it should be washed off in 6 to 8 h. Occlusion is usually not required. Baking soda may be used instead of deodorant. In palmar hyperhidrosis the application of aluminum chloride nightly, alone or occluded with plastic gloves, has produced good results for some patients but is less effective than the same technique in the axilla. If topical treatment is effective when performed nightly, the frequency may be reduced to as little as once or twice a week with continued benefit. Topical formaldehyde and glutaraldehyde, which can sensitize and tan the skin respectively, are not routinely recommended.

Iontophoresis. Iontophoresis with plain tap water is an alternative for patients for whom topical treatments fail. It is frequently effective, using either a Drionic device or a Fischer unit. Treatments generally require 20- to 30-min sessions each day or twice a day. Once response has occurred, treatments may be used intermittently (as little as once every 2 weeks) for maintenance. Use of glycopyrrolate 0.01% and aluminum chloride 2% in the iontophoresis medium may hasten the response.

Botulinum Toxin. Injection of Botox (botulinum A toxin) into 4 cm^2 areas on the palms, soles, or axillae dramatically reduces sweating at the treated areas to at least 25% and often to less than 10% of baseline rates. Complications are rare but include some grip weakness when higher doses are used in the palms. This problem, the expense, and the painful injections limit its use in the palms and soles especially. The hypohidrosis continues for an average of 7 months, with some patients continuing to have substantial benefit at 16 months after one injection. Repeated injections generally do not lose efficacy and result in similar response and complication rates. This form of treatment should be offered

to all patients who fail topical treatments before surgical modalities are considered. Frey syndrome remits for 1 to 1.5 years in nearly every patient treated. This treatment may be considered for other rare forms of localized hyperhidrosis. Myobloc (botulinum toxin B) is also effective, but with more limited duration of response.

Internal Medication. The use of anticholinergic agents such as Pro-Banthine or glycopyrrolate may be helpful. The dosage of each is regulated by the patient's tolerance and response. Often, sweating is suppressed just as anticholinergic side effects reach intolerable levels, and this approach has to be abandoned. Side effects of acetylcholine-blocking agents may also cause or aggravate such conditions as glaucoma and convulsions. The effects on sweating generally last 4 to 6 h, and many patients prefer to use the medication to ensure dryness for special occasions only rather than as continuous treatment. Other agents reported to reduce localized hyperhidrosis include diltiazem and clonidine.

Surgical Treatment. Axillary hyperhidrosis may be effectively controlled by excision of the most actively sweating portion of the axillary skin, followed by undercutting and subcutaneous resection of the sweat glands for 1 to 2 cm on each side of the elliptical excision. This procedure is virtually always effective. Alternatively liposuction removal may be used. The most important preoperative consideration is the accurate mapping of the most active sweating areas of the axillae. The responsible eccrine glands are not necessarily located in the same areas as the axillary hair and are often in a reasonably limited area. Mapping may be performed with cobalt chloride or starch iodide.

Upper thoracic sympathectomy has been found to be effective in excessive palmar sweating when all other measures have failed. Sympathetic denervation of the upper extremities is performed via endoscopy by resection of the second thoracic sympathetic ganglion. Acute surgical complications occur in less than 2% but include chronic pain, infection, pneumothorax, hemothorax, bleeding, pneumonia, and even death. Sweating of the hands is stopped completely. Only two of three patients are satisfied, however, since compensatory and gustatory hyperhidrosis occurs in more than two-thirds of patients. This may be severe and as debilitating as the original problem. Horner syndrome may rarely result. Endoscopic thoracic sympathetic block at T4 is being evaluated as another alternative.

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Dumont P, et al: Long term results of thorascopic sympathetectomy for hyperhidrosis. Ann Thorac Surg 2004; 78:1801.

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Seline PC, et al: Cutaneous metastases from a chondroblastoma initially presenting as unilateral palmar hyperhidrosis. J Am Acad Dermatol 1999;40:325.

Ueyama T, et al: Thoracoscopic sympathertic surgery for hand sweating. Ann Thorac Cardiovasc Surg 2004;10:4.

Anhidrosis (Hypohidrosis)

Anhidrosis is the absence of sweating. Hypohidrosis, or reduced sweating, is part of the spectrum of these disorders. Dysfunction in any step in the normal physiologic process of sweating can lead to decreased or absent sweating. It may be localized or generalized. Generalized anhidrosis occurs in anhidrotic ectodermal dysplasia, miliaria profunda (tropical asthenia), Sjögren syndrome, hereditary sensory neuropathy (type IV) with anhidrosis, and in some patients with diabetic neuropathy, and multiple myeloma. Drugs such as quinicrine, topiramate, and zonisamide may cause hypohidrosis. Atopic dermatitis is frequently associated with reduced sweating and pruritus when sweating is triggered. Patients with psoriasis may have similar symptoms, but less frequently.

Anhidrosis with pruritus is a rare syndrome of young adults. Severe itching occurs whenever they are stimulated to sweat. No sweat is delivered to the skin surface, but when the body temperature is raised about 0.5° C, fine papules appear at each eccrine orifice. The associated pruritus is so severe that patients feel completely incapacitated and distracted. Cooling immediately resolves the symptoms. This may represent one form of tropical asthenia. The natural history is unknown, but spontaneous resolution may occur after several years. These patients are frequently misdiagnosed as having cholinergic urticaria. A patient with acquired anhidrosis was shown to have obsruction of the coiled ducts with an amorphous eosinophilic substance.

Segmental anhidrosis may be associated with tonic pupils (Holmes-Adie syndrome); this is called *Ross syndrome*. Patients have heat intolerance and segmental areas of anhidrosis on the trunk, arms, or legs. Loss of deep tendon reflexes in the arms, trunk, and legs is consistently seen. Compensatory segmental hyperhidrosis of functionally intact areas may occur. A selective degeneration of the cholinergic sudomotor neurons is the hypothesized abnormality.

Anhidrosis localized to skin lesions occurs regularly over plaques of tuberculoid leprosy. This is also true of segmental vitiligo (but not generalized type), in the hypopigmented streaks of incontinentia pigmenti, in lesions of syringolymphoid hyperplasia with alopecia and anhidrosis, and on the face and neck of patients with the rare Bazex's syndrome

consisting of follicular atrophoderma, basal cell carcinomas, and hypotrichosis, an X-linked dominant disorder.

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Sommer C, et al: Selective loss of cholinergic sudomotor fibers causes anhidrosis in Ross syndrome. Ann Neurol 2002; 52:247.
Thami GP, et al: Acquired idiopathic generalized anhidrosis. Clin Exp Dermatol 2003;28:262.

Bromidrosis

Also known as *fetid sweat* and *malodorous sweating*, bromidrosis is chiefly encountered in the axillae. Bacterial decomposition of apocrine sweat, producing fatty acids with distinctive offensive odors is considered to be the cause. Often, patients who complain of offensive axillary sweat actually have no offensive odor; the complaint represents a delusion, paranoia, phobia, or a lesion of the central nervous system. Intranasal foreign body and chronic mycotic infection in the sinuses are additional causes. True bromidrosis is usually not recognized by the patient.

Fish odor syndrome should be considered in patients presenting with complaints of offensive odor. It is caused by excretion of trimethylamine (which smells like rotten fish) in the eccrine sweat, urine, saliva, and other secretions. This chemical is produced from carnitine and choline in the diet and is normally metabolized in the liver. An autosomal-dominant defect in the ability to metabolize trimethylamine because of a defect in flavin-containing monooxygenase 3 is the cause of this syndrome. Dietary reduction of foods high in carnitine and choline is beneficial.

Antibacterial soaps and many commercial deodorants are quite effective in controlling axillary malodor. Frequent bathing, changing of underclothes, shaving of the axillae, and topical application of aluminum chloride (Drysol) are all helpful measures. Surgical removal of the glands is possible, as in axillary hyperhidrosis, but this is very rarely indicated.

Plantar bromidrosis is produced by bacterial action on eccrine sweat-macerated stratum corneum. Hyperhidrosis is the chief associated factor, and pitted keratolysis is often present. Careful washing with an antibacterial soap and the use of dusting powders on the feet are helpful in eliminating bromidrosis. Use of topical antibiotics, such as clindamycin, may be beneficial. Previously described measures to control plantar hyperhidrosis should be instituted.

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Park DH: Treatment of axillary bromhidrosis with superficial liposuction. Plast Recontr Surg 1999;104:1580.
Ruocco V, et al: Fish-odor syndrome. Int J Dermatol 1995;34:92.

Chromhidrosis

Chromhidrosis, or colored sweat, is an exceedingly rare functional disorder of the apocrine sweat glands, frequently localized to the face or axilla. It has been less often noted on the abdomen, chest, thighs, groin, genitalia, and lower eyelids. The colored sweat may be yellow (most common), blue, green, or black. The colored secretion appears in response to adrenergic stimuli, which cause myoepithelial contractions. Colored apocrine sweat fluoresces and is caused by lipofuscin.

Eccrine chromhidrosis is caused by the coloring of the clear eccrine sweat by dyes, pigments, or metals on the skin surface. Examples are the blue–green sweat seen in copper workers and the "red sweat" seen in flight attendants from the red dye in the labels in life-vests. Brownish staining of the axillae and undershirt may occur in ochronosis. Bile secretion in eccrine sweat occurs in patients with liver failure and marked hyperbilirubinemia. Small, round, brown or deep-green macules occur on the palms and soles.

Barankin B, et al: Bilateral facial apocrine chromhidrosis. J Drugs Dermatol 2004;3:184.
Kanzaki T, et al: Bile pigment deposition at sweat pores of patients with liver disease. J Am Acad Dermatol 1992;26:655.
Wenzel FG, et al: Nonneoplastic disorder of the eccrine glands. J Am Acad Dermatol 1998;38:1.

Fox-Fordyce Disease

Fox-Fordyce disease is rare, occurring mostly in women during adolescence or soon afterward. It is characterized by conical, flesh-colored or grayish, intensely pruritic, discrete follicular papules in areas where apocrine glands occur (Fig. 33-33). The axillae and areolae are the primary sites of involvement, but the umbilicus, pubes, labia majora, and

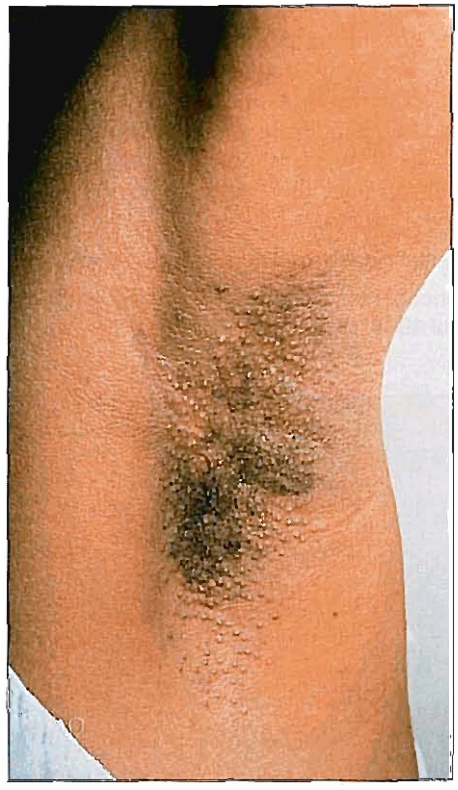

Fig. 33-33 Fox-Fordyce disease.

perineum may be affected. Apocrine sweating does not occur in affected areas, and hair density may be decreased. In some cases there is no itching. Ninety percent of cases occur in women between the ages of 13 and 35, but the disease may present postmenopausally or in males. Pregnancy invariably leads to improvement.

Histologically, Fox-Fordyce disease is characterized by obstruction of the follicular ostia by orthokeratotic cells. An inflammatory infiltrate of lymphocytes surrounds the upper third of the hair follicles and upper dermal vessels. There is an associated spongiosis of the infundibulum at the site of entrance of the apocrine duct into the hair follicle. In one case, detached apoeccrine cells obstructed the duct.

Treatment of Fox-Fordyce disease is difficult, and no form of therapy is universally effective. Estrogen therapy, usually in the form of oral contraceptive pills, is most uniformly effective. Topical tretinoin, topical and intralesional steroids, topical clindamycin solution, isotretinoin, and UV phototherapy have all been effective in small numbers of patients. Excision or liposuction-assisted curettage may be successful in axillary sites.

Chae KM, et al: Axillary Fox-Fordyce disease treated with liposuction-assisted curettage. Arch Dermatol 2002;138:452.

Ghislain P-D, et al: Itchy papules of the axillae. Arch Dermatol 2002;138:259.

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Granulosis Rubra Nasi

Granulosis rubra nasi is a rare familial disease of children, occurring on the nose, cheeks, and chin. It is characterized by diffuse redness, persistent hyperhidrosis, and small dark red papules that disappear on diascopic pressure. The tip of the nose is red or violet. There may be a few small pustules. Hyperhidrosis precedes the erythema (Fig. 33-34). The tip of the nose is cold and is not infiltrated. The disease disappears spontaneously at puberty without leaving any traces. The cause is unknown. Histologically, blood vessels are dilated and there is an inflammatory infiltrate about the sweat ducts.

Treatment is with local preparations for relief of the inflammation, and reassurance that with puberty there is usually involution of the process.

Wenzel FG, et al: Nonneoplastic disorder of the eccrine glands. J Am Acad Dermatol 1998;38:1.

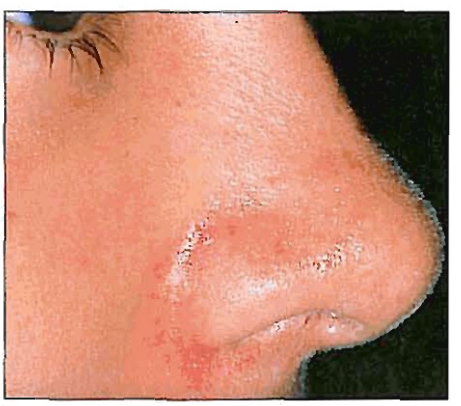

Fig. 33-34 Early granulosa rubra nasi.

Hidradenitis

Hidradenitis is a term used to describe diseases in which the histologic abnormality is primarily an inflammatory infiltrate around the eccrine glands. This group includes neutrophilic eccrine hidradenitis and idiopathic plantar hidradenitis (recurrent palmoplantar hidradenitis).

Neutrophilic Eccrine Hidradenitis Ninety percent of patients with neutrophilic eccrine hidradenitis (NEH) have a malignancy. It has been described primarily in patients with acute myelogenous leukemia; however, other leukemias, lymphomas, and uncommonly solid tumors may be present. It usually begins about 10 days after the start of chemotherapy. While the majority of patients have been treated with cytarabine, it has not been uniformly linked to any chemotherapeutic agent and may occur in patients who have not been treated. Granulocyte colony-stimulating factor (G-CSF), imatinib mesylate, zivoduvine, acetaminophen, and various antibiotics have also been implicated as triggers for this neutrophilic dermatosis.

The lesions are typically erythematous and edematous papules and plaques of the extremities, trunk, face (periorbital), and palms (in decreasing frequency). Pigmentatiom, purpura, or pustules may be present within the papules and plaques. Fever and neutropenia are often present. Histologically, there is a dense neutrophilic infiltrate around and infiltrating eccrine glands. Necrosis of sweat glands may be present, with or without the inflammatory infiltrate. Syringosquamous metaplasia may occur. This finding can also occur in fibrosing alopecia, in burn scars, adjacent to various nonmelanoma skin cancers and ischemic and surgical ulcers, in alopecia mucinosa, and in ports of radiation therapy.

The lesions may recur with repeated courses of chemotherapy, but many do not. Lesions resolve over 1 to 4 weeks (average, 10 days). Nonsteroidal anti-inflammatory drugs or oral corticosteroids may hasten the healing. Prophylactic administration of dapsone prevented recurrence in one patient.

Infectious neutrophilic hidradenitis may present as a recurrent, pruritic, papular eruption. *Serratia, Enterobacter cloacae*, *Nocardia*, and *S. aureus* have been implicated, and appropriate antibiotics for bacterial agents are curative. Multiple HIV-infected patients have developed neutrophilic eccrine hidradenitit. The diagnosis is confirmed by histologic evaluation and culture of affected tissue (surface cultures may not be adequate).

Recurrent Palmoplantar Hidradenitis Recurrent palmoplantar hidradenitis is primarily a disorder of healthy children and young adults. Lesions are primarily painful, subcutaneous nodules on the plantar surface, resembling erythema nodosum. Rarely, palmar lesions also occur. In some children *Pseudomonas* infection may be the cause (Pseudomonal hot foot, see Chapter 14). Children may present refusing to walk because of plantar pain. The condition is typically recurrent, and may be triggered by exposure to wet shoes or cold, damp weather. The use of oral and topical steroidal preparations may be beneficial.

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Crawford GH, et al: Erythematous facial plaques in a patient with leukaemia. Arch Dermatol 2003;139:531.
Hurt MA, et al: Eccrine squamous syringometaplasia. Arch Dermatol 1990;126:73.
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DISEASES OF THE NAILS

Several general references are available that review a wide spectrum of nail changes.

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Telfer NR: Congenital and hereditary nail disorders. Semin Dermatol 1991;10:2.

Nail-Associated Dermatoses

Numerous dermatoses are associated with characteristic, sometimes specific, nail changes. Many are considered elsewhere.

Lichen Planus of Nails The reported incidence of nail involvement in lichen planus varies from less than 1% to 10%. Lichen planus of the nails may occur without skin changes, but 25% with nail disease will have lichen planus at other locations. Although it may occur at any age, most commonly it begins during the fifth or sixth decade of life. The various nail changes are irregular longitudinal grooving and ridging of the nail plate, thinning of the nail plate, pterygium formation (Fig. 33-35), shedding of the nail plate with atrophy of the nailbed, subungual keratosis, longitudinal erythronychia (red streaks), and subungual hyperpigmentation. The plate may be markedly thinned, and at times distinct papules of lichen planus may involve the nailbed. Twenty-nail dystrophy (trachyonychia) may be the sole manifestation of lichen planus.

The histologic changes of lichen planus may be evident in any individual nail constituent or a combination of them. The one most frequently involved is the matrix.

Treatment is mostly unsatisfactory. Intralesional injection of corticosteroids may be of help in some patients. Digital nerve blocks should be considered before infiltration of the matrix or nailbed. Topical corticosteroids under polyethylene occlusive dressings are usually inadequate. Oral prednisone

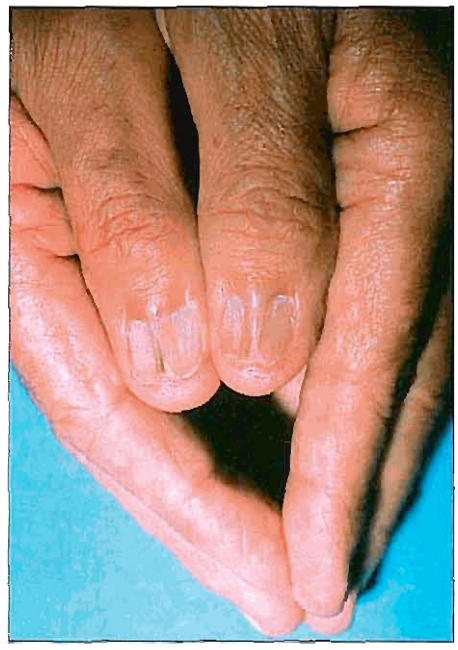

Fig. 33-35 Pterigium caused by lichen planus. (Courtesy of Lawrence Lieblich, MD)

(0.5–1 mg/kg for 3 weeks) or oral retinoids in combination with topical steroids applied to the involved sites have been successful in some patients. Tosti et al reported that typical lichen planus of the nails in children responded to 0.5 to 1 mg/kg/month of intramuscular triamcinolone acetonide given for 3 to 6 months, until the proximal half of the nail was normalized. Only two patients recurred during the follow-up period. While twenty-nail dystrophy was not treated, they spontaneously improved; those with idiopathic atrophy of the nails were unchanged. (See Chapter 12 for additional therapeutic considerations.)

De Berker, et al: Localized longitudinal erythronychia. Arch Dermatol 2004;140:1253.
Kato N, et al: Isolated lichen planus of the nails treated with etretinate. J Dermatol 1993;20:577.
Perez Oliva N, et al: Lichen planus of the nails. Cutis 1993; 52:171.
Scheinfeld NS: Trachyonychia: a case report and review of manifestations, associations, and treatments. Cutis 2003;71:299.
Tosti A, et al: Nail lichen planus: clinical and pathologic study of twenty-four patients. J Am Acad Dermatol 1993;28:724.
Tosti A, et al: Nail lichen planus in children: clinical features, response to treatment and long term follow-up. Arch Dermatol 2001;137:1027.

Psoriatic Nails Nail involvement in psoriasis is common, with reported incidences varying from 10% to 78%. Older patients, those with active exacerbations of disease, and in many studies patients with psoriatic arthritis are more likely to express nail abnormalities. In the nail plate there may be pits (Fig. 33-36), or much less often, furrows or transverse depressions (Beau's lines), crumbling nail plate, or leukonychia, with a rough or smooth surface. Splinter hemorrhages are found in the nailbed, with reddish discoloration of a part or all of the nailbed, and horny masses. In the hyponychium, yellowish–green discoloration may occur in the area of onycholysis. Many studies find patients with psoriatic arthritis will often have psoriatic nail changes.

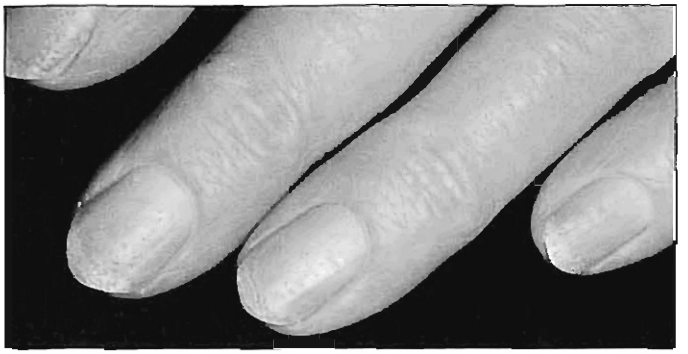

Fig. 33-36 Pitting caused by psoiasis.

The severity of nail disease may correlate with the severity of skin and joint disease. Pustular psoriasis may produce onycholysis, with lakes of pus in the nailbed or in the perionychial areas. Rarely, anonychia may result. Other papulosquamous diseases may affect the nails like psoriasis, with the exception of nail pitting. Reiter's disease, pityriasis rubra pilaris, Sézary syndrome, and acrokeratosis paraneoplastica produce as a rule hypertrophic nails with subungual hyperkeratosis.

Successful systemic treatment of psoriasis will usually also improve or clear the nail changes. Methotrexate, PUVA, cyclosporin, the biologics, or acitretin may be effective. Psoriatic nail disease may be only one area involved; the eventual treatment options selected depend on the degree of cutaneous and nail involvement. (See Chapter 10 for additional information and therapeutic options.) All local therapies have limitations, and the condition is frequently mistaken for onychomycosis. Intralesional injection of triamcinolone acetonide suspension, 3 to 5 mg/mL, with a 30-gauge needle is frequently helpful. Digital nerve block facilites adequate injection. Topical 5-fluorouracil (5-FU) applied to the proximal nailfold has been reported to be effective. It is best to avoid the free edge of the nail when applying 5-FU as it may cause distal onycholysis. Topical cyclosporin and topical tazarotene 0.1% gel have also been reported to be helpful. Topical calcipotriol improves about 50% of patients with localized pustular psoriasis of the nails and may be used as a maintenance treatment after successful intervention with systemic retinoids.

Cannavo SP, et al: Treatment of psoriatic nails with topical cyclosporin. Dermatology 2003;206:153.

de Jong EM, et al: Psoriasis of the nails associated with disability in a large number of patients: results of a recent interview with 1,728 patients. Dermatology 1996;193:300.

Piraccini BM, et al: Pustular psoriasis of the nails. Br J Dermatol 2001;144:1000.

Salomon J, et al: Psoriatic nails: a prospective clinical study. J Cutan Med Surg 2003;7:317.

Scher RK, et al: Tazarotene 0.1% gel in the treatment of fingernail psoriasis. Cutis 2001;68:355.

Williamson L, et al: Extended report: nail disease in psoiatic arthritis. Rheumatology (Oxf) 2004;43:790.

Darier's Disease Longitudinal, subungual, red or white streaks, associated with distal wedge-shaped subungual keratoses, are the nail signs diagnostic for Darier-White disease. Keratotic papules on the dorsal portion of the nailfold clinically may resemble acrokeratosis verruciformis, but histologically have features of Darier's disease. Other nail findings include splinter hemorrhages and leukonychia. All of these findings are less pronounced on the toenails.

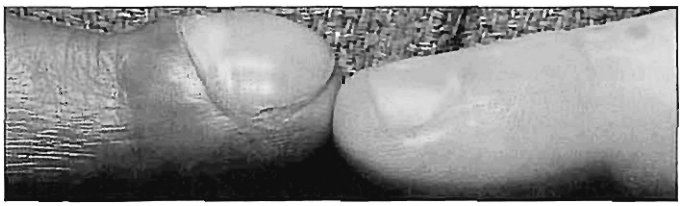

Fig. 33-37 Clubbing. (Courtesy of Lawrence Lieblich, MD)

De Berker DA, et al: Localized longitudinal erythronychia. Arch Dermatol 2004;140:1253.

Clubbing

Clubbing is divided into two types: idiopathic and acquired, or secondary. The changes occur not only in the nails but also in the terminal phalanges. The nails bulge and are curved in a convex arc in both transverse and longitudinal directions, like a watch crystal. The eponychium is thickened. The angle formed by the dorsal surface of the distal phalanx and the nail plate (Lovibond's angle) is approximately 160°; however, with clubbing this angle is obliterated and becomes 180° or greater (Fig. 33-37). The soft tissues of the terminal phalanx are bulbous, resembling drumsticks. These tissues are mobile when pressure is applied over the matrix.

Idiopathic clubbing is either of the isolated dominantly inherited type or of the pachydermoperiostosis type with its associated findings. Secondary (acquired) clubbing is usually a consequence of pulmonary, cardiac, thyroid, hepatic, or gastrointestinal disease. Typically, there is periostitis, with periosteal new bone formation in the phalanges, metacarpals, and distal ulna and radius. This is called *hypertrophic osteoarthropathy* and is responsible for the painful clubbing. It typically occurs in men with bronchogenic carcinoma. Unilateral or asymmetrical clubbing may also occur, reported in cases of Takayasu arteritis and sarcoidosis. Solitary clubbing may be associated with a digital mucous cyst.

Kaditis AG, et al: Takayasu's arteritis presenting with unilateral digital clubbing. J Rheumatol 1995;22:2346.

Myers KA, et al: The rational clinical examination. Does this patient have clubbing? JAMA 2001;286:1972.

Richter T, et al: Idiopathic clubbing of the fingers, pathogenetic mechanisms and differential etiologic diagnosis. Hautarzt 1994;45:866.

Shell Nail Syndrome

Cornelius et al described a shell nail in association with bronchiectasis. The nail resembles a clubbed nail, but the nailbed is atrophic instead of being a bulbous proliferation of the soft tissue.

Cornelius CE: Shell nail syndrome. Arch Dermatol 1969;100:118.

Koilonychia (Spoon Nails)

Spoon nails are thin and concave, with the edges everted so that if a drop of water were placed on the nail, it would

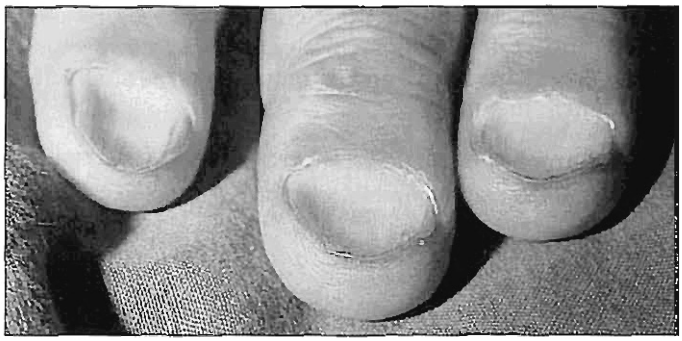

Fig. 33-38 Koilonychia.

not run off (Fig. 33-38). Koilonychia may result from faulty iron metabolism and is one of the signs of Plummer-Vinson syndrome, as well as of hemochromatosis. Spoon nails have been observed in coronary disease, syphilis, polycythemia, and acanthosis nigricans. Familial forms are also known to occur.

Other associations include psoriasis, lichen planus, Raynaud's disease, scleroderma, acromegaly, hypothyroidism and hyperthyroidism, monilethrix, palmar hyperkeratoses, and steatocystoma multiplex. A significant number of cases are idiopathic. Manual trauma in combination with cold exposure may result in seasonal disease. Sherpas are Tibetan people living in the Nepalese Himalayas who often serve as porters on mountain-climbing expeditions. Chronic cold exposure, in combination with hypoxemia, may contribute to the frequency with which koilonychia is observed among them.

Gao XH, et al: Familial koilonychia. Int J Dermatol 2001;40:290.

Murdoch D: Koilonychia in Sherpas. Br J Dermatol 1993; 128:592.

Congenital Onychodysplasia of the Index Fingers

Congenital onychodysplasia of the index fingers is defined by the presence of the condition at birth, index finger involvement (unilateral or bilateral), variable distortion of the nail or lunula, and polyonychia, micronychia, anonychia, hemionychogryphosis, or malalignment (Fig. 33-39). It may also involve adjacent fingers, such as the middle fingers and thumbs. An underlying bone dysplasia may be present beneath the involved nail. Cases have occurred in an autosomal-dominant pattern; other proposed causes include in utero ischemia or exposure to teratogens.

De Smet L: Congential oncychodystroplasia of the index finger. Genet Couns 2000;11:37.

Prais D, et al: Prevalence and new phenotypic and radiologic findings in congenital onychodysplasia of the index finger. Pediatr Dermatol 1999;16:201.

Twenty-Nail Dystrophy (Trachyonychia)

All 20 nails may become opalescent, thin, dull, fragile, and finely longitudinally ridged (and as a result, distally notched) at any age from 1½ years to adulthood, although it is most commonly diagnosed in children. It can be idiopathic or caused by alopecia areata, psoriasis, lichen planus, atopy, ichthyosis vulgaris, or other inflammatory dermatoses.

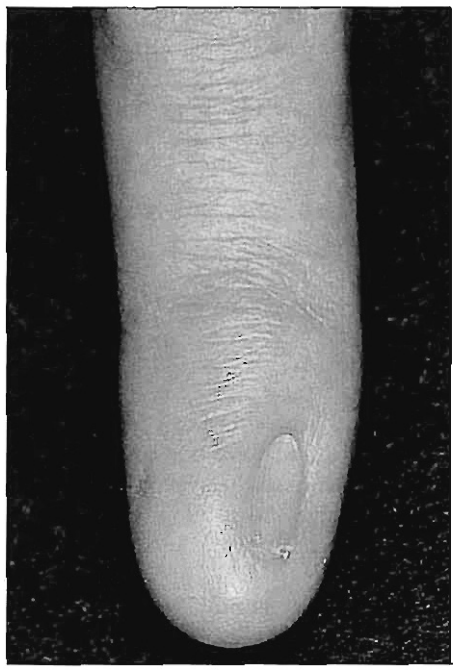

Fig. 33-39 Congenital onychodystrophy of the index finger. (Courtesy of James Fitzpatrick, MD)

Familial forms exist. In some cases spongiosis may be found on nail biopsy. Trachyonychia has also been reported associated with autoimmune processes such as selective IgA deficiency, vitiligo, and graft-versus-host disease. Thus, twenty-nail dystrophy is caused by a heterogenous group of inflammatory conditions. Childhood cases may resolve spontaneously by the time the patient is 20 to 25 years of age.

Grover C, et al: Longitudinal nail biopsy: utility in 20-nail dystrophy. Dermatol Surg 2003;29:1125.

Jerasutus S, et al: Twenty-nail dystrophy: a clinical manifestation of spongiotic inflammation of the nail matrix. Arch Dermatol 1990;126:1068.

Scheinfeld NS: Trachyonychia: a case report and review of manifestations, associations, and treatments. Cutis 2003;71:299.

Tosti A, et al: Idiopathic trachyonychia (twenty-nail dystrophy): a pathological study of 23 patients. Br J Dermatol 1994;131:866.

Onychauxis

In onychauxis the nails are thickened but without deformity (simple hypertrophy). Simple thickening of the nails may be the result of trauma, acromegaly, Darier's disease, psoriasis, or pityriasis rubra pilaris. Some cases are hereditary.

Treatment involves periodic partial or total debridement of the thickened nail plate by mechanical or chemical (40% urea paste) means. Matricectomy and nail ablation are options, as they are in onychogryphosis, congentital nail dystrophies, and chronic painful nails such as recalcitrant ingrown toenails or splits within the medial or lateral third of the nail.

Baran R, et al: Matricectomy and nail ablation. Hand Clin 2002; 18:696.

Bartolomei FJ: Onychauxis. Clin Podiatr Med Surg 1995;12:215.

Onychogryphosis

Hypertrophy may produce nails resembling claws or a ram's horn. Onychogryphosis may be caused by trauma or periph-

eral vascular disorders but is most often caused by neglect (failure to cut the nails for very long periods). It is most commonly seen in the elderly.

Some recommend avulsion of the nail plate with surgical destruction of the matrix with phenol or the CO_2 laser, if the blood supply is good.

Baran R, et al: Matricectomy and nail ablation. Hand Clin 2002; 18:696.
Mohrenschlager M, et al: Onychogryphosis in elderly persons. Cutis 2001;68:233.

Onychophosis

A common finding in the elderly, onychophosis is a localized or diffuse hyperkeratotic tissue that develops on the lateral or proximal nailfolds, within the space between the nailfolds and the nail plate. It may involve the subungual area, as a direct result of repeated minor trauma, and most frequently affects the first and fifth toes.

The use of comfortable shoes should be encouraged. The areas involved should be debrided and treated with keratolytics. Emollients are also helpful.

Cohen PR, et al: Geriatric nail disorder. J Am Acad Dermatol 1992;26:521.

Anonychia

Absence of nails, a rare anomaly, may be the result of a congenital ectodermal defect, ichthyosis, severe infection, severe allergic contact dermatitis, self-inflicted trauma, Raynaud phenomenon, lichen planus, epidermolysis bullosa, or severe exfoliative diseases. Permanent anonychia has been reported as a sequel of Stevens-Johnson syndrome. It may also be found in association with congenital developmental abnormalities, such as microcephaly, and wide-spaced teeth (autosomal-recessive inheritance), the autosomal-dominant Cooks syndrome (bilateral nail hypoplasia of digits 1 through 3, the absence of nails of digits 4 and 5 of the hands, total absence of all toenails, and absence or hypoplasia of the distal phalanges of the hands and feet), DOOR syndrome (deafness, onychoosteodystrophy, mental retardation), and the glossopalantine syndrome (abnormal mouth, tongue being attached to the temporomandibular joint).

Al Hawsawi K, et al: Anonychia congenital totalis. Int J Dermatol 2002;41:397.
Nevin NC, et al: Anonychia and absence/hypoplasia of distal phalanges (Cooks syndrome): report of a second family. J Med Genet 1995;32:638.
Ozdemir O, et al: Total anonychia congenita. Genet Couns 2004; 15:43.
Pall A, et al: Twenty-nail anonychia due to lichen planus. J Dermatol 2004;31:146.

Onychoatrophy

Faulty underdevelopment of the nail may be congenital or acquired. The nail is thinned and smaller. Vascular disturbances, epidermolysis bullosa, lichen planus, Darier's disease, multicentric reticulohistiocytosis, and leprosy may cause onychatrophy. It is also seen in congenital syndromes such as Apert, Goltz, Turner, Ellis van-Creveld, nail–patella, dyskeratosis congenital, cartilage-hair hypoplasia, progeria, hypohidrotic ectodermal dysplasia, incontinentia pigmenti, popliteal web, trisomy13 and trisomy 18, and as a side effect of etretinate therapy.

Al Hawsawi K, et al: Anonychia congenital totalis. Int J Dermatol 2002;41:397.

Onychomadesis

Onychomadesis is a periodic idiopathic shedding of the nail beginning at its proximal end. The temporary arrest of the function of the nail matrix may cause onychomadesis. Neurologic disorders, peritoneal dialysis, and cutaneous T-cell lymphoma, Kawasaki's disease, pemphigus vulgaris, drug allergy, and keratosis punctata palmaris et plantaris have been reported causes. It may appear as a periodic finding in runners. Immobilization from casting for fractures may cause onychomadesis and pyogenic granuloma formation. Medications such as antineoplastic agents and retinoids may cause onychomadesis also.

Mehra A, et al: Idiopathic familial onychomadesis. J Am Acad Dermatol 2000;43:349.
Piraccini BM, et al: Drug-induced nail abnormalities. Am J Clin Dermatol 2003;4:31.
Tosti A, et al: Onychomadesis and pyogenic granuloma following cast immobilization. Arch Dermatol 2001;137:231.

Beau's Lines

Beau's lines are transverse furrows that begin in the matrix and progress distally as the nail grows (Fig. 33-40). They are ascribed to the temporary arrest of function of the nail matrix. Although usually found to be bilateral, unilateral Beau's lines may occur. Various systemic and local traumatic factors may cause this. Some are childbirth, measles, paronychia, acute febrile illnesses, and drug reaction. When the process is intermittent the nail plate may resemble corduroy. They may result from almost any systemic illness or major injury, such as a broken hip. Shelley "shoreline" nails appear to be a very severe expression of essentially the

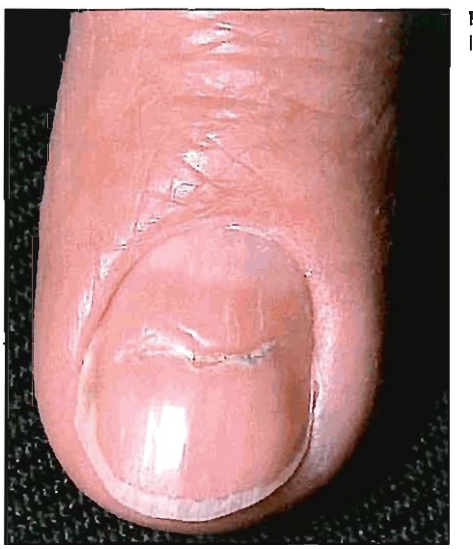

Fig. 33-40 Beau's lines.

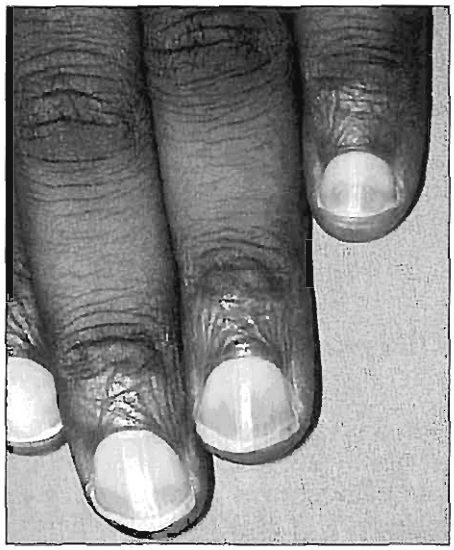

Fig. 33-41 Half and half nails.

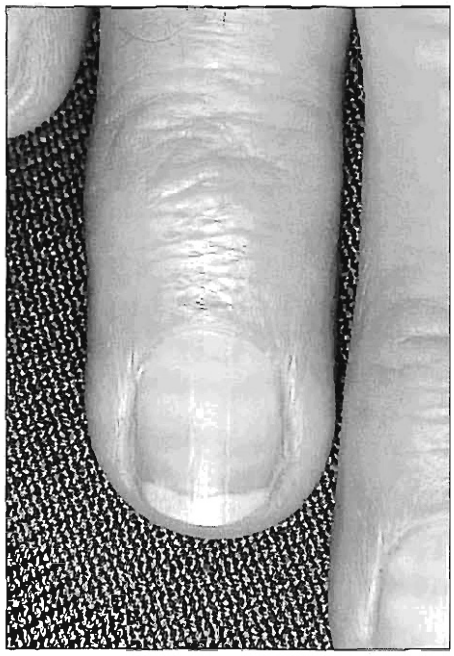

Fig. 33-42 Meuhke's lines.

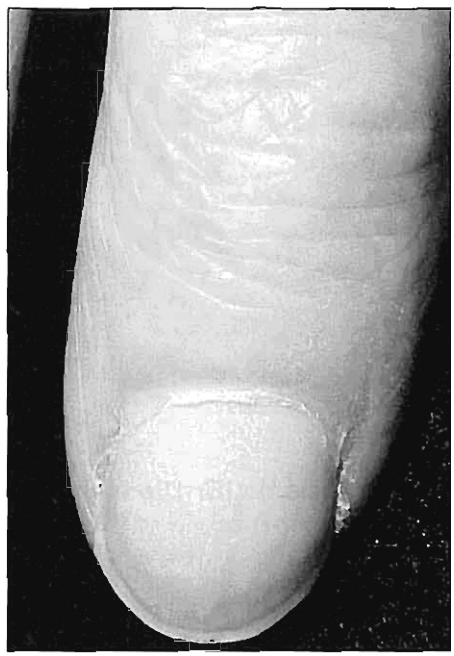

Fig. 33-43 Terry nails.

same transient growth arrest. They have been reported in all 20 nails of a newborn.

Koh B-K, et al: Transverse nail ridging (Beau's lines) and rough nails after bone marrow transplantation. Int J Dermatol 2004; 43:77.

Piraccini BM, et al: Drug-induced nail abnormalities. Am J Clin Dermatol 2003;4:31.

Half and Half Nails

Half and half nails show the proximal portion of the nail white and the distal half red, pink, or brown, with a sharp line of demarcation between the two halves (Fig. 33-41). Seventy percent of hemodialysis patients and 56% of renal transplant patients have at least one type of nail abnormality. Absence of lunla, splinter hemorrhage, and half and half nails were significantly more common in hemodialysis patients, while leukonychia was significantly more common in transplant patients.

Saray Y, et al: Nail disorders in hemodialysis patients and renal transplant recipients: a case control study. J Am Acad Dermatol 2004;50:197.

Muehrcke's Lines

Muehrcke described narrow white transverse bands occurring in pairs as a sign of chronic hypoalbuminemia. The lines may resolve when serum albumin is raised to or near normal (Fig. 33-42). Unlike Mees' lines, the disturbance appears to be in the nailbed, not in the nail plate. Similar lines have been reported in patients with normal albumin levels who are receiving chemotherapy. In a case of unilateral Muehrcke's lines associated with trauma, it was suggested that edema effects this change by inducing microscopic separation of the normally tightly adherent nail from its bed.

Alam M, et al: Muehrcke's lines in a heart transplant recipient. J Am Acad Dermatol 2001;44:316.

Fawcett RS, et al: Nail abnormalities: clues to systemic disease. Am Fam Physician 2004;15:1417.

Feldman SR, et al: Unilateral Muehrcke's lines following trauma. Arch Dermatol 1989;125:133.

Mees' Lines

Mees described single or multiple white transverse bands in 1919 as a sign of inorganic arsenic poisoning. They have also been reported in thallium poisoning, septicemia, dissecting aortic aneurysm, parasitic infections, chemotherapy, and both acute and chronic renal failure.

Hall AH: Chronic arsenic poisoning. Toxicol Lett 2002;128:69.

Hepburn MJ, et al: Mees' lines in a patient with multiple parasitic infections. Cutis 1997;59:321.

Quecedo E, et al: Mees' lines: a clue for the diagnosis of arsenic poisoning. Arch Dermatol 1996;132:349.

Uede, K, et al: Skin manifestations in acute arsenic poisoning from the Wakayama curry-poisoning incident. Br J Dermatol 2003;149:757.

Terry Nails

In Terry nails the distal 1 to 2 mm of the nail shows a normal pink color (Fig. 33-43), the entire nail plate or proximal end has a white appearance as a result of telangiectases in the nailbed. These changes have been noted in 25% of hospitalized patients, most commonly those with cirrhosis, chronic congestive heart failure, and adult-onset diabetes, and in very elderly patients.

Holzberg M, et al: Terry's nails: revised definition and new correlations. Lancet 1984;1:896.

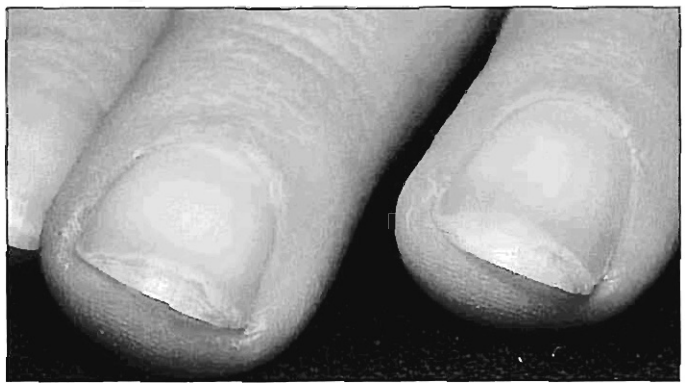

Fig. 33-44 Onychoschizia.

Onychorrhexis (Brittle Nails)

Brittleness with breakage of the nails may result from excessive strong soap and water exposure, nail polish remover, hypothyroidism, anorexia or bullemia, or after oral retinoid therapy. It affects up to 20% of the population. Fragilitas unguium (nail fragility) is part of this process. In a series by Hochman et al of 35 patients treated with B-complex vitamin biotin, 63% showed clinical improvement. The nail plate thickness in patients treated with biotin increases in thickness by 25%. Daily application of white petrolatum may also be helpful.

Hochman LG, et al: Brittle nails: response to daily biotin supplementation. Cutis 1993;51:303.

Scher RK, et al: Brittle nails. Semin Dermatol 1991;10:21.

Uyttendaele H, et al: Brittle nails: pathogenesis and treatment. J Drugs Dermatol 2003;2:48.

Onychoschizia

Splitting of the distal nail plate into layers at the free edge (Fig. 33-44) is a very common problem among women and represents a dyshesion of the layers of keratin, possibly as a result of dehydration. Longitudinal splits may also occur.

Nail polish should be discontinued; nail buffing can be substituted. Frequent application of emollients may be helpful. Biotin has also been shown to be effective in doses up to 2.5 mg/day.

Wallis MS, et al: Pathogenesis of onychoschizia (lamellar dystrophy). J Am Acad Dermatol 1991;24:44.

Stippled Nails

Small, pinpoint depressions in an otherwise normal nail characterize this type of nail change. This may be an early change seen in psoriasis. Stippled nails are also seen with some cases of alopecia areata, in early lichen planus, psoriatic or rheumatoid arthritis, chronic eczematous dermatitis, perforating granuloma annulare, and in some individuals with no apparent disease. The deeper, broader pits are more specific for psoriasis or Reiter syndrome. The pitting in alopecia areata tends to be shallower and more regular, suggesting a "Scotch plaid" (tartan) pattern.

Tosti A, et al: Prevalence of nail abnormalities in children with alopecia areata. Pediatr Dermatol 1994;11:12.

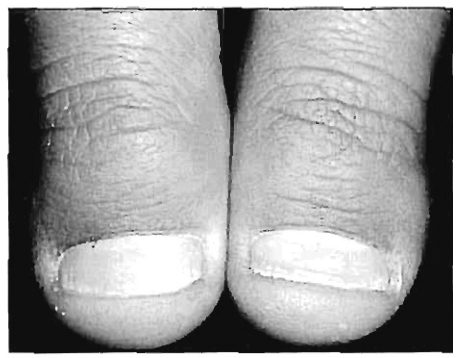

Fig. 33-45 Raquet nails.

Racquet Nails (Nail en Raquette)

In racquet nails, the end of the thumb is widened and flattened, the nail plate is flattened as well, and the distal phalanx is abnormally short (Fig. 33-45). Racquet nails occur on one or both thumbs and are apparently inherited as an autosomal-dominant trait.

Baran R, et al: Baran and Dawber's diseases of the nails and their management. Oxford: Blackwell Scientific, 2001.

Chevron Nail (Herringbone Nail)

This entity appears to be a rare transient fingernail ridge pattern of children. The ridges arise from the proximal nailfold and converge in a V-shaped pattern toward a midpoint distally.

Parry EJ: Chevron nail/herringbone nail. J Am Acad Dermatol 1999;40:497.

Zaiac MN, et al: Chevron nail. J Am Acad Dermatol 1998;38:773.

Hapalonychia

Softened nails result from a defect in the matrix that makes the nails thin and soft so that they can be easily bent. This type of nail change is attributed to malnutrition and debility. It may be associated with myxedema, rheumatoid arthritis, anorexia, bullemia, leprosy, Raynaud phenomenon, oral retinoid therapy, or radiodermatitis.

Baran R, et al: Baran and Dawber's Diseases of the nails and their management. Oxford: Blackwell Scientific, 2001.

Platonychia

The nail is abnormally flat and broad. It may be seen as part of an autosomal-dominant condition in which multiple nail abnormalities are present in many members of a large family.

Hamm, H, et al: Isolated congenital nail dysplasia: a new autosomal dominant condition. Arch Dermatol 2000;136:1239.

Nail–Patella Syndrome (Hereditary Osteoonychodysplasia, Fong Syndrome)

Nail–patella syndrome comprises numerous anomalies and is characterized by the absence or hypoplasia of the patella and congenital nail dystrophy. Triangular lunulae are characteristic (Fig. 33-46). Other bone features are thickened scapulae, hyperextensible joints, radial head abnormalities, and posterior iliac horns. The skin changes may also include

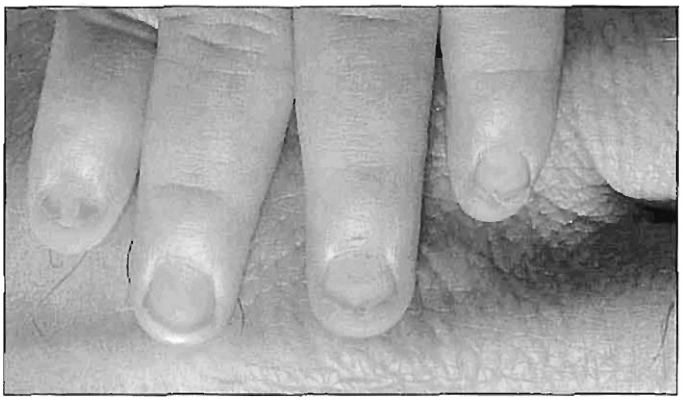

Fig. 33-46 Nail–patella syndrome. (Courtesy of Marshall Guill, MD)

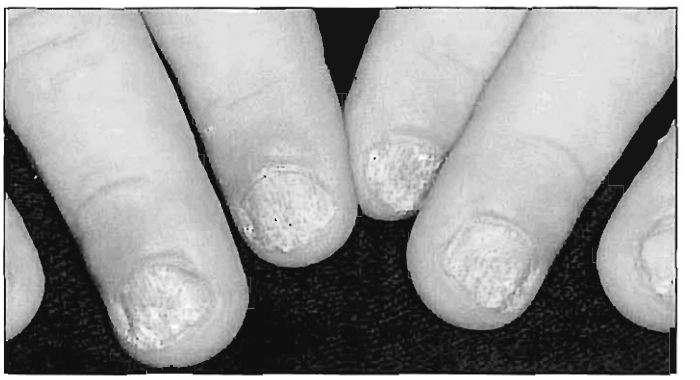

Fig. 33-47 Onychophagia.

webbing of the elbows. Eye changes such as cataracts and heterochromia of the iris may also be present. Hyperpigmentation of the pupillary margin of the iris ("Lester iris") is a characteristic finding in about half the cases. These patients may exhibit glomerulonephritis with urinary findings of albuminuria, hematuria, and casts of all kinds, especially hyaline casts. They may be predisposed to developing hemolytic–uremic syndrome. Forty percent of patients have renal dysplasia, and 25% suffer from renal failure. It is an autosomal-dominant trait localized to chromosome 9q34.1. Limb and kidney defects seen in L1M-homeodomain protein Lmx1b mutant mice are similar to those present in patients with nail–patella syndrome. Mutations of the human LMX1B gene result in this syndrome.

Bongers EM, et al: Nail–patella syndrome. Overview on clinical and molecular findings. Pediatr Nephrol 2002;17:703.

Buddin D, et al: What syndrome is this? Nail–patella syndrome. Pediatr Dermatol 2002;19:454.

Schulz-Butulis BA, et al: Nail-patella syndrome 2003;49:1086.

Sweeney E, et al: Nail patella syndrome. J Med Genet 2003; 40:153.

Onychophagia

Nail biting (Fig. 33-47) is a common compulsive behavior that may markedly shorten the nail bed, sometimes damages the matrix, and leads to pterygium formation. It is a difficult habit to cure.

If there is strong motivation, habit reversal training with awareness training, competing response training, and social support may help. Psychopharmacologic intervention with medications, such as fluoxetine, or hypnosis are other options.

Stein DJ, et al: Dermatology and conditions related to obsessive–compulsive disorder. J Am Acad Dermatol 1992;26:237.

Twohig MP, et al: Evaluating the efficacy of habit reversal: comparison with a placebo control. J Clin Psychiatry 2003;64:40.

Onychotillomania

Onychotillomania is a compulsive neurosis in which the patient picks constantly at the nails or tries to tear them off. Like oncyhophagia, this obsessive–compulsive disorder may be treated by biofeedback, cognitive–behavioral methods, hypnosis, or psychopaharmacologic agents.

Inglese M, et al: Onychotilloomania. Cutis 2004;73:171.

Shenefelt PH: Biofeedback, cognitive–behavioral methods and hypnosis in dermatology. Dermatol Ther 2003;16:114.

Onycholysis

Onycholysis is a spontaneous separation of the nail plate, usually beginning at the free margin and progressing proximally. Rarely, the lateral borders may be involved, with spread confined to these. Less often separation may begin proximal to the free edge, in an oval area 2 to 6 mm broad, with a yellowish-brown hue ("oil spot"); this is a lesion of psoriasis, as is often the case with ordinary onycholysis. The nail itself is smooth and firm with no inflammatory reaction. Underneath the nail a discoloration may occur from the accumulation of bacteria, most commonly *Pseudomonas*, or yeast, most commonly *Candida*. Color changes, such as green, a result of pyocyanin from *Pseudomonas*, black, or blue may be seen. One or more nails may be affected.

Onycholysis is noted most commonly in women, probably secondary to traumatically induced separation. It is common in patients with hand dermatitis. Keratinization of the distal nailbed, chronic exposure to irritants, untreated dermatitis, and secondary infection with *Candida albicans* are potential reasons for the failure of the nail to reattach itself.

Systemic causes are many: hyper- and hypo-thyroidism, pregnancy, porphyria, pellagra, and syphilis. Onycholysis has also been associated with atopic dermatitis, eczema, lichen planus, congenital abnormalities of the nails, trauma induced by clawing, pinching, stabbing (manicuring), and foreign-body implantation. It may be caused by mycotic, pyogenic, or viral (herpes) infections. Women should be checked for vaginal candidiasis, because that anatomic location may be the source of the infection opportunistically invading and aggravating onycholysis. Chemical causes may include the use of solvents, nail polish base coat, nail hardeners containing formalin derivatives, artificial fingernails, and allergic or irritant contact dermatitis from their use. Rarely, photo-onycholysis may occur during or soon after therapy with tetracycline derivatives, psoralens, fluoroquinolones, or chloramphenicol, and subsequent exposure to sunlight. Chemotherapeutic agents and systemic retinoids may induce onycholysis. On rare occasions it may be a sign of metastasis. Autosomal-dominant hereditary forms are also known.

Trauma and chemical irritants should be completely avoided and the nailbed should be kept completely dry. The

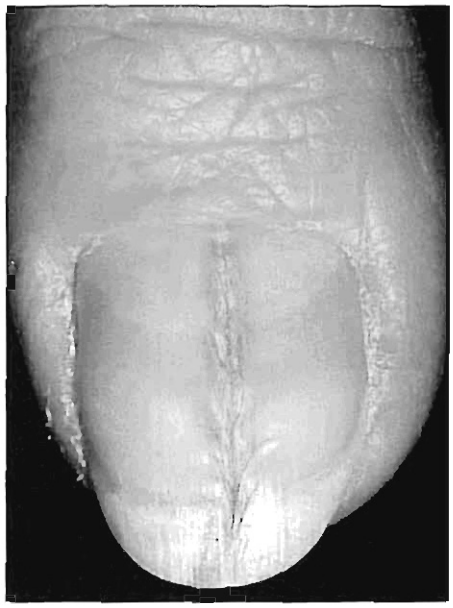

Fig. 33-48 Median nail dystrophy.

affected portion of the nail should be kept clipped away. Drying by exposing the nailbed in this way will rid the area of *Pseudomonas* and assist greatly in eliminating *Candida*. For additional treatment options, refer to the text on the specific cause (see Chapter 14 for *Pseudomonas*, Chapter 15 for *Candida*, and Chapter 10 for psoriasis).

Baran R, et al: Photoonycholysis. Photodermatol Photoimmunol Photomed 2002;18:202.

Daniel CR III, et al: Managing simple chronic paronychia and onycholysis with ciclopirox 0.77% and an irritant-avoidance regime. Cutis 2004;73:81.

Daniel CR III: Onycholysis: an overview. Semin Dermatol 1991; 10:34.

Daniel CR III, et al: Chronic paronychia and onycholysis: a thirteen-year experience. Cutis 1996;58:397.

Lambert D, et al: Distal phalangeal metastasis of a chondrosarcoma presenting initially as bilateral onycholysis. Clin Exp Dermatol 1992;17:463.

Piraccini BM, et al: Drug-induced abnormalities. Am J Clin Dermatol 2003;4:31.

Median Nail Dystrophy (Dystrophia Unguis Mediana Canaliformis, Solenonychia)

Median nail dystrophy consists of longitudinal splitting or canal formation in the midline of the nail. The split, which often resembles a fir tree, occurs at the cuticle and proceeds outward as the nail grows (Fig. 33-48). Trauma has been suspected of being the chief cause; however, many of these cases will persist for years even with scrupulous avoidance of trauma. The deformity may result from a papilloma or glomus tumor in the nail matrix, forcing the production of a structure like a tube (solenos) distal to it. Familial cases and an onset with isotretinoin therapy are other associations.

Griego RD, et al: Median nail dystrophy and habit tic deformity: are they different forms of the same disorder? Int J Dermatol 1995;34:799.

Sweeney SA, et al: Familial median canaliform nail dystrophy. Cutis 2005;75:161.

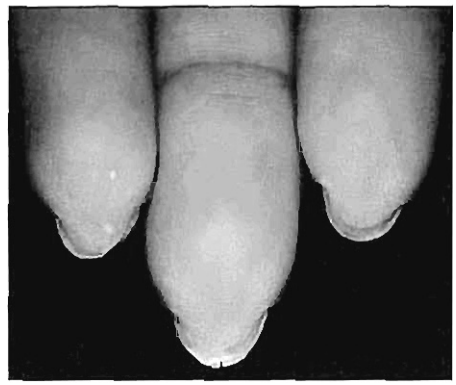

Fig. 33-49 Ptyrigium inversus ungium.

Pterygium Unguis

Pterygium unguis forms as a result of scarring between the proximal nailfold and matrix. The classic example is lichen planus. It has been reported to occur as a result of sarcoidosis and Hansen's disease. Peripheral circulatory disturbances may also be causative.

Richert BJ, et al: Pterygium of the nail. Cutis 2000;66:343.

Pterygium Inversum Unguis

Pterygium inversum unguis is characterized by adherence of the distal portion of the nailbed to the ventral surface of the nail plate (Fig. 33-49). The condition may be present at birth or acquired and may cause pain with manipulation of small objects, typing, and close manicuring of the nail. It is a condition resulting from the extension of the zone of the nailbed that normally contributes to the formation of the nail plate. This eventually leads to a more ventral and distal extension of the hyponychium. The most common forms of pterygium inversum unguis are the acquired secondary forms caused by systemic connective tissue diseases, particularly progressive systemic sclerosis and systemic lupus erythematosus. If a curved nail is present on the fourth toe only as a congenital lesion, this is an entity unto itself and occurs as an autosomal-recessive trait.

Caputo R, et al: Pterygium inversum unguis: report of 19 cases and review of the literature. Arch Dermatol 1993;129:1307.

Yotsumoto S, et al: Curved nail of the fourth toe. J Am Acad Dermatol 1999;40:123.

Hangnail

Hangnail is an overextension of the eponychium (cuticle), which becomes split and peels away from the proximal or lateral nailfold. These lesions are painful and annoying, so that persistent cuticle biting frequently develops. Trimming these away with scissors is the best solution. The use of emollient creams to keep the cuticle soft is also recommended.

Lee HJ, et al: Minor cutaneous features of atopic dermatitis in South Korea. Int J Dermatol 2000;39:337.

Pincer Nails

Pincer nails, trumpet nails, or omega (from the shape of the Greek letter) nails are alternative terms for a common

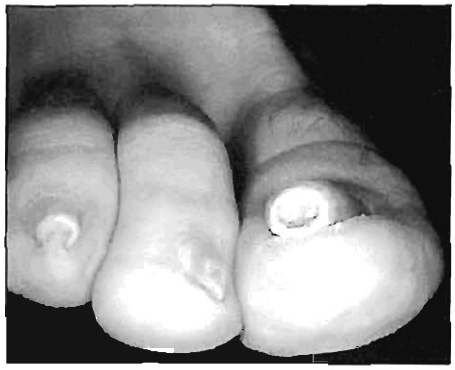

Fig. 33-50 Pincer nails.

toenail disorder in which the lateral edges of the nail slowly approach one another, compressing the nailbed and underlying dermis (Fig. 33-50). It may less often occur in the fingernails and is surprisingly usually asymptomatic. It may be an autosomal-dominantly inherited condition or acquired after trauma, Kawasaki's disease or use of β-blockers.

Some treatment success has been obtained with the use of commercial plastic braces after flattening of the nail. Urea ointment under occlusion, or chemical matricectomy with phenol and surgical nailbed repair has also been reported to be effective.

Bostanci S, et al: Pincer nail deformity: inherited and caused by a beta-blocker. Int J Dermatol 2004;43:316.

Kim KD, et al: Surgical pearl: nail plate separation and splint fixation—a new non-invasive treatment of pincer nails. J Am Acad Dermatol 2003;48:791.

Onychocryptosis (Unguis Incarnatus, Ingrown Nail)

Ingrown toenail is one of the most frequent nail complaints. It occurs chiefly on the great toes, where there is an excessive lateral nail growth into the nailfold, leading to this painful, inflammatory condition. The lateral margin of the nail acts as a foreign body and may cause exuberant granulation tissue. Unguis incarnatus may be caused by wearing improperly fitting shoes and by improper trimming of the nail at the lateral edges so that the anterior portion cuts into the flesh as it grows distally. Drugs such as isotretinoin, lamivudine, and indinavir may induce periungual granulation tissue mimicking onychocryptosis.

Treatment in mild cases with insertion of a cotton pad, dental floss or a flexible plastic tube beneath the distal corner of the offending nail may make surgery unnecessary. When surgical intervention is necessary, simple removal of the lateral portion of the nail plate can produce significant relief. Another simple operation involves removal of the overhanging lateral nailfold so that the nail does not cut into it. When healed, the nail edge resembles that of the thumb, and an excellent functional result occurs. The nail is not altered, since it is not touched. With the patient under local anesthesia (and with use of a rubber band tourniquet or infiltration of the proximal nailfold for hemostasis), a linear incision is made at the edge of the lateral nailfold perpendicular to the nail plate. A convex incision is made in a curvilinear plane parallel to the nailbed to meet the initial incision. The involved wedge of tissue is removed. The lateral flap is then approximated by one or two sutures and a petrolatum gauze dressing is applied. Healing is complete in 10 to 14 days.

Partial or complete nail avulsion with ablation of the nail matrix will prevent recurrence. Ablation can be accomplished surgically, with phenol, 10% sodium hydroxide, or with a CO_2 laser. When phenol is used, the proximal nailfold should be incised and reflected to avoid burning the nailfold. As an alternative, it can be left in place and injected with a corticosteroid to reduce the subsequent inflammation. Liquid nitrogen spray to the area of tissue and nail involved for a freeze time of 20 to 30 s has been successful in some patients, but may be painful and is reserved for patients in whom other surgical approaches are not appropriate.

Akasakal AB, et al: Decompression for the management of onychocryptosis. J Dermatolog Treat 2004;15:108.

Andreassi A, et al: Segmental phenolization for the treatment of ingrowing toenails. J Dermatolog Treat 2004;15:179.

Rounding C, et al: Surgical treatments for ingrowing toenails. Cochrane Database Syst Rev 2000;CD001541.

Kim YJ, et al: Nail-splinting technique for ingrown nails. Dermatol Surg 2003;29:745.

Ozdemir E, et al: Chemical matricectomy with 10% sodium hydroxide for the treatment of ingrowing toenails. Dermatol Surg 2004;30:26.

Persichetti P, et al: Wedge excision of the nail fold in the treatment of ingrown toenail. Ann Plast Surg 2004;52:617.

Woo S-H, et al: Surgical pearl: nail edge separation with dental floss for ingrown toenails. J Am Acad Dermatol 2004;50:939.

NAIL DISCOLORATIONS

Leukonychia or White Nails

Four forms of white nails are recognized: leukonychia punctata, leukonychia striata, leukonychia partialis, and leukonychia totalis. The punctate variety is common in completely normal persons with otherwise normal nails. Symmetrical sympathetic punctate leukonychia in contralateral or adjacent nails following a current episode of traumatic leukonychia has been described. Leukonychia striata (Fig. 33-51) may be hereditary or of traumatic or systemic origin. Partial leukonychia may occur with tuberculosis, nephritis, Hodgkin's disease, chilblains, metastatic carcinoma, or leprosy, or be idiopathic.

Leukonychia totalis may be hereditary and is of a simple autosomal-dominant type. It may also be associated with typhoid fever, leprosy, cirrhosis, ulcerative colitis, nail biting, use of emetine, cytostatic agents, and trichinosis. Leukonychia may result from abnormal keratinization, with persistence of keratohyalin granules in the nail plate.

A syndrome comprising leukonychia totalis, multiple sebaceous cysts, and renal calculi in several generations has been reported. Other reports have linked total leukonychia with deafness, or with koilonychia; however, it is most often inherited or is an isolated finding.

Claudel CD, et al: Idiopathic leukonychia totalis and partialis in a 12-year-old patient. J Am Acad Dermatol 2001;44:379.

Zaun H: Leukonychias. Semin Dermatol 1991;10:17.

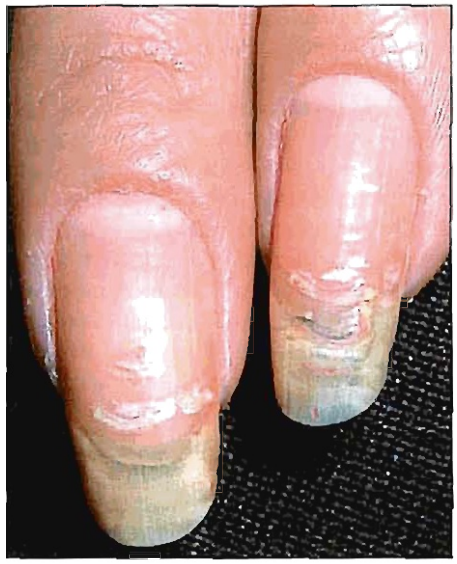

Fig. 33-51
Leukonychia striata.

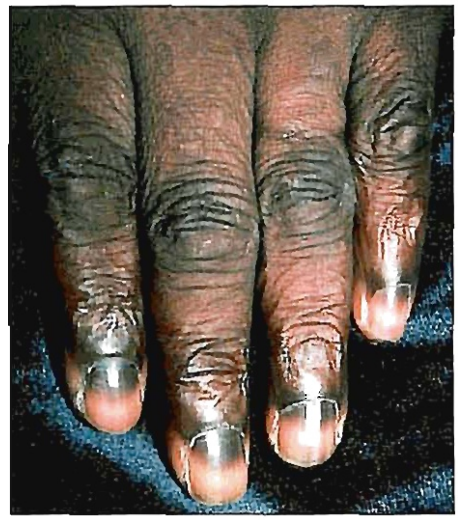

Fig. 33-52
Zidovudine-induced hyperpigmentation of the nail.

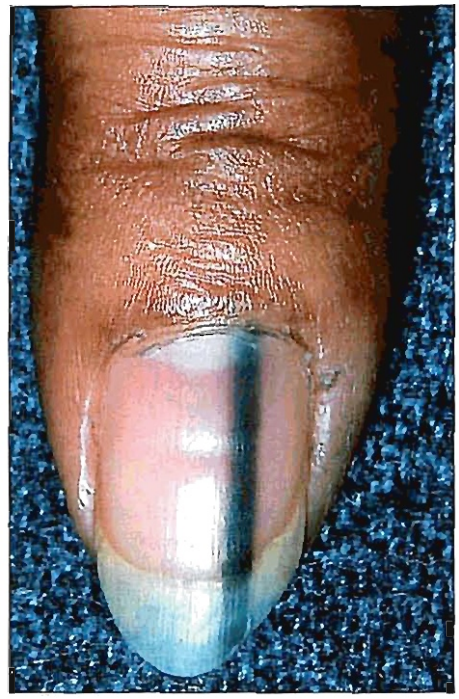

Fig. 33-53
Longitudinal melanonychia.

Longitudinal Erythronychia

Longitudinal red bands in the nail plate that commence in the matrix and extend to the point of separation of the nail plate and nailbed may occur on multiple nails with inflammatory conditions such as lichen planus or Darier's disease. When only a localized single or bifid streak is present, this may signal a benign or malignant tumor of the matrix. The fingernails of middle-aged persons are most commonly affected, with the thumbnail being most frequently involved. There may be a distal keratosis seen, as with Darier, human papilloma virus (HPV) infection, or a squamous cell carcinoma. Excision of this distal keratosis, however, usually does not result in cure or diagnostic findings; biopsy of the affected matrix is necessary. Since this may lead to a scar with a permanent split of the nail plate, observation may be indicated. As in longitudinal melanonychia, if the band broadens over time, then an excisional biopsy is indicated.

de Berker DAR, et al: Localized longitudinal erythronychia. Arch Dermatol 2004;140:1253.

Melanonychia

Black or brown pigmentation of the normal nail plate is termed *melanonychia*. It may be present as a normal finding on many digits in black patients, as a result of trauma, systemic disease, or medication, or as a postinflammatory event from such localized events as lichen planus or fixed-drug reaction.

Longitudinal black or brown banding of the nails has been reported to occur in 77% to 96% of black persons and 11% of Asians. It is a rare finding in white children; however, it is not uncommon in white adults. In a series by Duhard the prevalence of melanonychia was 12.6 in 100 in a white hospitalized population, and 1.4 in 100 in 4400 white clinic-based patients. The risk increased with age, the peak occurring between ages of 56 and 65.

Pigmentation of the nails may occur with acanthosis nigricans, Addison's disease, Peutz-Jeghers syndrome, vitamin B_{12} deficiency, after adrenalectomy for Cushing syndrome, as a part of Laugier-Hunziker syndrome (pigmentation of the nails associated with buccal and lip hyperpigmentation), with PUVA or ionizing radiation treatment, and as a drug-induced melanocyte activation with such medications as chemotherapy, antimalarials, minocycline, zidovudine (Fig. 33-52), or gold. Friction may cause longitudinal pigmented bands in the toenails, and subungual hemorrhage or black nail caused by *Proteus mirabilis* or *Trichophyton rubrum* may enter into the differential diagnosis of a dark nail.

When only one nail is affected by melanonychia striata (a single longitudinal band of brown or black color [Fig. 33-53]) a tumor of the nail matrix is the most important consideration. The location in the matrix can be inferred from the location of the pigment in the nail plate when viewed on end. Dorsal nail-plate pigmentation results from a proximal matrix lesion. Ventral nail-plate pigmentation is the result of a lesion in the distal matrix. Leaute-Labreze et al, Goettmann-Bonvallot et al, and Tosti et al found longitudinal melanonychia that appeared in children to be benign in nature, and it is recommended that since an ungual melano-

cytic band can appear at an age when other nevi appear, surgical excision should be undertaken only in the event of progressive change.

Tosti et al studied 100 white adult patients with a single band of longitudinal melanonychia of unknown cause. Biopsies revealed melanocytic hyperplasia in 65, nevi in 22, melanocytic activation in 8, and melanoma in 5. Whereas they were unable to ascertain any clear clinical criteria that would exclude melanoma, they recommended a 3-mm biopsy of any white adult with the appearance of a longitudinal band of pigment in one nail without a clear relation to a definite cause. They excised all melanoma, nevi or melanocytic hyperplasia lesions. Retracting the proximal nailfold to expose the origin of the streak at the matrix allows selection of the best biopsy site.

Melanoma is most likely to be present if the longitudinal band is enlarging in width, if dermoscopy reveals a brown coloration of the background and the presence of irregular longitudinal lines, or if there is periungual extension of brown–black pigmentation onto the proximal or lateral nailfold (Hutchinson's sign). The latter is not pathognomonic, however, as Bowen's disease may produce this appearance, and pigmentation of the nail matrix and proximal nailbed may reflect through the nailfold (pseudo-Hutchinson's sign).

Aste N, et al: Nail pigmentation produced by hydroxyurea. J Am Acad Dermatol 2002;47:146.

Baran R, et al: Hutchinson's sign. J Am Acad Dermatol 1996; 34:87.

Duhard E, et al: Prevalence of longitudinal melanonychia in the white population. Ann Dermatol Venereol 1995;122:586.

Goettmann-Bonvallot S, et al: Longitudinal melanonychia in children. J Am Acad Dermatol 1999;41:17.

Haneke E, et al: Longitudinal melanonychia. Dermatol Surg 2001;27:580.

Hernandez-Martin A, et al: Longitudinal, transverse, and diffuse nail hyperpigmentation induced by hydroxyurea. J Am Acad Dermatol 1999;41:333.

Lambiase MC, et al: Bowen disease of the nail bed presenting as longitudinal melanonychia: detection of human papillomavirus type 56 DNA. Cutis 2003;72:305.

Leaute-Labreze C, et al: Longitudinal melanonychia in children: a study of eight cases. Arch Dermatol 1996;132:167.

Ledbetter LS, et al: Melanonychia associated with PUVA therapy. J Am Acad Dermatol 2003;48:S31.

Piraccini BM, et al: Drug-induced nail abnormalities. Am J Clin Dermatol 2003;4:31.

Perrin C, et al: Longitudinal melanonychia caused by *Trichophyton rubrum*: histochemical and ultrastructural study of two cases. J Am Acad Dermatol 1994;31:311.

Ronger S, et al: Dermoscopic examination of nail pigmentation. Arch Dermatol 2002;138:1327.

Sau P, et al: Pigmantation of the nail bed and periungual area. Arch Dermatol 1994;130:204.

Smith DF, et al: Longitudinal melanonychia. Arch Dermatol 2003; 139:1209.

Tomizawa K: Early malignant melanoma manifested as longitudinal melanonychia. Br J Dermatol 2000;143:431.

Tosti A, et al: Nail matrix nevi. J Am Acad Dermatol 1996;34:765.

Green Nails

When onycholysis is present, a green discoloration may occur in the onycholytic area as a result of an infection with *Pseudomonas aeruginosa* (see Chapter 14). The color change may also occur as transverse green stripes. The stripes are ascribed to intermittent episodes of infection. Green nails may also result from copper in tap water.

Agger WA, et al: *Pseudomonas aeruginosa* infections of intact skin. Clin Infect Dis 1995;20:302.

Staining of the Nail Plate

Nicotine, dyes (including hair dyes and nail polish), potassium permanganate, mercury compounds, hydroquinone, elemental iron, mepacrine, photographic developer, anthralin, chrysarobin, glutaraldehyde, or resorcin may cause nail-plate staining. This is only a partial list; a complete listing is given in the article by Jeanmougin et al. A helpful diagnostic maneuver to distinguish nail-plate staining from exogenous sources and nail-plate pigmentation from melanin or endogenous chemicals is to scrape the surface of the nail plate several times firmly with a glass slide or scalpel blade. Exogenous stains frequently scrape off completely if the agent has not penetrated the entire nail plate. If the stain follows the curvature of the lunulae, it is probably endogenous; if it follows the curvature of the proximal and lateral nailfolds, it is exogenous.

Coulson IH: "Fade out" photochromonychia. Clin Exp Dermatol 1993;18:87.

Jeanmougin M, et al: Nail dyschromia. Int J Dermatol 1983;22:279.

Olsen TG, et al: Contact exposure to elemental iron causing chromonychia. Arch Dermatol 1984;120:102.

Red Lunulae

Dusky erythema confined to the lunulae has been reported in association with alopecia areata. Twenty percent of patients with systemic lupus erythematosus have been reported to have this abnormality. It may also be seen in patients on oral prednisone for severe rheumatoid arthritis or dermatomyositis, in cardiac failure, cirrhosis, lymphogranuloma venereum, psoriasis, vitiligo, chronic urticaria, lichen sclerosus et atrophicus, CO_2 poisoning, chronic obstructive pulmonary disease, twenty-nail dystrophy, and reticulosarcoma. The cause may be vascular congestion.

Bergner T, et al: Red lunulae in severe alopecia areata. Acta Derm Venereol 1992;72:203.

Cohen PR: Red lunulae: case report and literature review. J Am Acad Dermatol 1992;26:292.

Wollina U, et al: Lupus erythematosus-associated red lunula. J Am Acad Dermatol 1999;41:419.

Spotted Lunulae

This distinctive change occurs with alopecia areata.

Cohen PR: The lunula. J Am Acad Dermatol 1996;34:943.

Shelley WB: The spotted lunula: a neglected nail sign with alopecia areata. J Am Acad Dermatol 1980;2:385.

Purpura of the Nail Beds

Purpura beneath the nails usually results from trauma. Causes of toe involvement include physical pressure on the toes, such as that seen in surfboarding by a windsurfer trying

to maintain his balance, or exogenous pressure exerted from poorly fitting shoes. It may simulate a melanoma if the patient does not communicate the acuteness at onset.

Adams BB: Dermatologic disorders of athletes. Sports Med 2002;32:309.

Pierson JC, et al: Pen push purpura: iatrogenic nail bed hemorrhages in the intensive care unit. *Cutis* 1993;51:422.

Blue Nails

A blue discoloration of the lunulae is seen in argyria and cases of hepatolenticular degeneration (Wilson's disease). The blue color in the latter is probably related to the changes in the copper metabolism by the patient. It has also been reported in hemoglobin M disease and hereditary acrolabial telangiectases.

Lunular blue color, as well as blue discoloration of the whole nailbed, occurs with some therapeutic agents, especially 5-FU, minocycline, imipramine, mepacrine and other antimalarials, hydroxyurea, phenothalein and azidothymidine. Blue discoloration may also result from subungual hematoma and melanotic whitlow. Mepacrine and other antimalarials may stain the nails blue. Blue nails are a normal variant finding in blacks.

Glaser DA, et al: Blue nails and acquired immunodeficiency syndrome: not always associated with azidothymidine use. Cutis 1996;57:243.

Piraccini BM, et al: Drug-induced nail abnormalities. Am J Clin Dermatol 2003;4:31.

Yellow Nail Syndrome

The yellow nail syndrome is characterized by marked thickening and yellow to yellowish-green discoloration of the nails often associated with systemic disease, most commonly lymphedema and compromised respiration. The nails are typically over-curved both transversely and longitudinally, grow very slowly (<0.2 mm/week), are often subject to onycholysis, and lose both lunulae and cuticles (Fig. 33-54). Lymphedema, pleural effusions, chronic pulmonary infections, and chronic sinusitis most commonly precede the nail changes. Other less frequent associated conditions include autoimmune disorders, immunodeficiency states, the use of gold or D-penicillamine, and malignancies. In the latter cases, treatment of the underlying lymphoma or solid tissue tumor has resulted in improvement of the nail findings. Clinical responses have been shown with taking 800 IU/day of D-α-tocopherol and topical vitamin E solution. Itraconazole, alone or in combination with vitamin E, and oral zinc supplementation have also been used with success in individual cases.

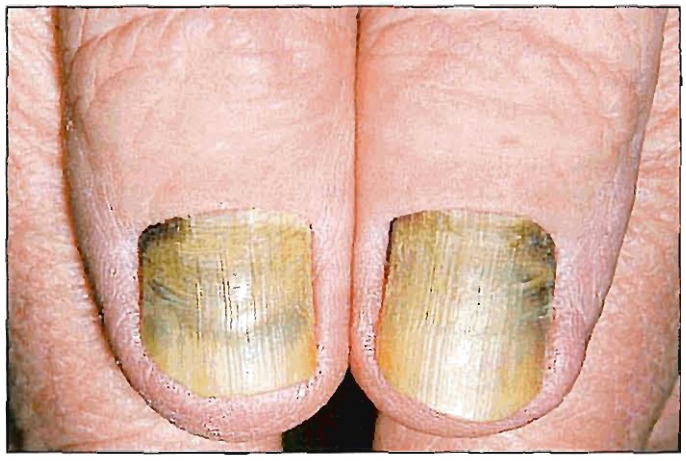

Fig. 33-54 Yellow nail syndrome.

Arroyo JF, et al: Improvement of yellow nail syndrome with oral zinc supplementation. *Clin Exp Dermatol 1993;18:62.*

De Coste SD, et al: Yellow nail syndrome. J Am Acad Dermatol 1990;22:608.

Ginarte M, et al: Yellow nail syndrome and lung lymphoma. *Clin* Exp Dermatol 2004;29:432.

Tosti A, et al: Systemic Itraconazole in the yellow nail syndrome. Br J Dermatol 2002;146:1067.

Williams HC, et al: Successful use of topical vitamin E solution in the treatment of nail changes in yellow nail syndrome. Arch Dermatol 1991;127:1023.

NEOPLASMS OF THE NAILBED

Various benign and malignant neoplasms may occur in or overlying the nail matrix and in the nailbed. Signs heralding such neoplasms are paronychia, ingrown nail, onycholysis, pyogenic granuloma, nail-plate dystrophy, longitudinal erythronychia, bleeding, and discolorations. Symptoms of pain, itching, and throbbing may also occur with various neoplasms.

Benign tumors of the nails include verruca, pyogenic granuloma, fibromas, nevus cell nevi, myxoid cysts, angiofibromas (Koenen tumors), and epidermoid cysts. Pyogenic granuloma-like lesions may occur during treatment with isotretinoin, lamivudine or indinavir. Glomangioma is readily recognized by exquisite tenderness in the nailbed. Enchondroma of the distal phalanx has been described. It often presents as a paronychia. Subungual exostoses may also present as an inflammatory process, but more commonly resemble a verruca or fibroma at the start. Most of these are on the great toe, and radiographic evaluation will aid in the diagnosis of these last two entities. Tender swelling of the distal finger with nail distortion and radiographic evidence of solitary lytic changes can be caused by intraosseous epidermoid cysts.

Squamous cell carcinoma of the nailbed is uncommon, and often mistaken for a pyogenic granuloma initially. Radiographs may reveal lytic changes in the distal phalanx. Metastases are rare. Mohs surgery is the treatment of choice. Bowen's disease may occur here, and on more than one digit; often the condition occurs secondary to HPV infection (Fig. 33-55). When keratoacanthoma occurs, there is often

Fig. 33-55 Bowen's disease.

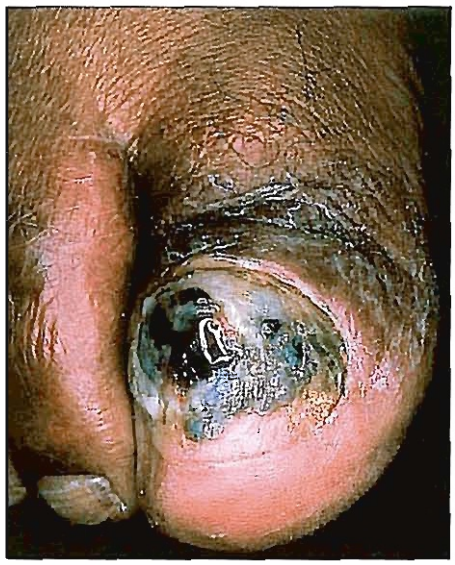

Fig. 33-56 Subungual melanoma.

lysis of underlying bone, which fills in after excision of the tumor.

Subungual melanoma (Fig. 33-56) is frequently diagnosed late in the course of growth, since it simulates onychomycosis or subungual hematoma, with which it is confused. Amelanotic melanoma may occur and may be mistaken for granuloma pyogenicum. Although melanoma is rare among Japanese, periungual and subungual melanoma is more frequently found in Japanese than in other ethnic populations. Discussion of melanoma in this location may be found in Chapter 30 and in the melanonychia section of this chapter.

Chang SE, et al: Metastastic squamous cell carcinoma of the nailbed: a presenting sign of lung cancer. Br J Dermatol 1999 141:939.

Davis DA, et al: Subungual exostosis: case report and review of the literature. Pediatr Dermatol 1996;13:212.

de Berker DAR, et al: Localized longitudinal erythronychia. Arch Dermatol 2004;140:1253.

Finley RK III, et al: Subungual melanoma: an eighteen-year review. Surgery 1994;116:96.

Guarneri C, et al: Solitary asymptomatic nodule of the great toe. Int J Dermatol 2005;44:245.

Horton S, et al: Erythematous nodule on the nail bed. Arch Dermatol 1999;135:1113.

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CHAPTER

34 Disorders of the Mucous Membranes

Lesions on the mucous membranes may be more difficult to diagnose than lesions on the skin, and not merely because they are less easily and less often seen. There is less contrast of color and greater likelihood of alterations in the original appearance because of secondary factors, such as maceration from moisture, abrasion from food and teeth, and infection. Vesicles and bullae rapidly rupture to form greyish erosions, and the epithelium covering papules becomes a soggy lactescent membrane, easily rubbed off to form an erosion. Grouping and distribution are less distinctive in the mouth than on the skin, and not infrequently it is necessary to establish the diagnosis by observing the character of any associated cutaneous lesions or by noting subsequent developments.

Bork K, et al: Diseases of the Oral Mucosa and Lips. Philadelphia: WB Saunders, 1996.

Eversole LR: Clinical Outline of Oral Pathology. Philadelphia: JB Lippincott, 2002.

Rogers RS III (ed); Diseases of the mucous membranes. Dermatologic Clinics, Jan 2003.

CHEILITIS

Cheilitis Exfoliativa

The term *cheilitis exfoliativa* has been used to designate a primarily desquamative, mildly inflammatory condition of the lips, of unknown cause, and also a clinically similar reaction secondary to other disease states. The former is a persistently recurring lesion that produces scaling and sometimes crusting; it most often affects the upper lip. The recurrent exfoliation leaves a temporarily erythematous and tender surface.

In the latter form, the lips are chronically inflamed and covered with crusts that from time to time tend to desquamate, leaving a glazed surface on which new crusts form. Fissures may be present, and there may be burning, tenderness, and some pain. The lower lip is more often involved, with the inflammation limited to the vermilion part. The cheilitis may be secondary to seborrheic dermatitis, atopic dermatitis, psoriasis, retinoid therapy, pyorrhea, long-term actinic exposure, or the habit of lip licking (Fig. 34-1). Uncommonly, the initial or only manifestation of atopic dermatitis may be a chronic cheilitis. Irritating or allergenic substances in lipsticks, dentifrices, and mouthwashes may be causative factors. Dyes in lipsticks may photosensitize. Candidiasis may be present. Cheilitis may be part of the Plummer-Vinson syndrome or Sjögren syndrome. Cheilitis is not uncommon in patients with AIDS, and is a known common complication of protease inhibitor therapy. These and other uncommon causes of cheilitis are discussed in more detail within the specific entities.

The only uniformly effective treatment is the elimination of causes when they can be found. Topical tacrolimus ointment, pimecrolimus cream, or low strength corticosteroid ointments and creams are usually helpful. If the underlying etiology is determined, specific therapy may be instituted. When there are fissures, petrolatum or zinc oxide ointment may be useful.

Casariego Z, et al: Eruptive cheilitis. Med Oral 2001;6:19.

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Allergic Contact Cheilitis

The vermilion border of the lips is much more likely to develop allergic contact sensitivity reactions than is the oral mucosa. Allergic cheilitis is characterized by dryness, fissuring, edema, crusting, and angular cheilitis.

Over 90% of patients are women and over half of the reactions are due to lipsticks. While patch testing will reveal a relevant positive in approximately 25% to 30% of patients, about one in five will only react to their own product. It may

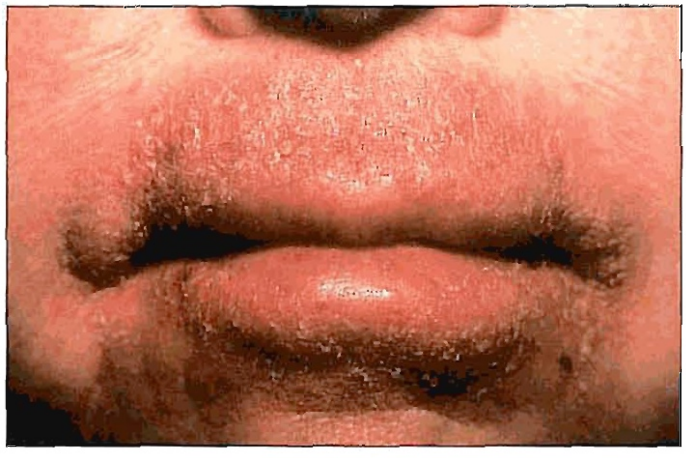

Fig. 34-1 Cheilitis secondary to lip licking.

result from use of topical medications, dentifrices and other dental preparations, antichap agents, lipsticks, and sunscreen-containing lip balms; from contact with cosmetics, nail polish, rubber, and metals; or from eating foods such as mangoes. Exotic or occupational causes may occur, such as an allergic response to cane reed among saxophonists or clarinetists.

Treatment includes discontinuation of exposure to the offending agent and administration of topical tacrolimus, pimecrolimus or corticosteroid preparations.

Chan EF, et al: Contact dermatitis to foods and spices. Am J Contact Dermat 1998;9:71.
Engasser PG: Lip cosmetics. Dermatol Clin 2000;18:641.
Francalanci S, et al: Multicentre study of allergic contact cheilitis from toothpastes. Contact Dermatitis 2000;43:216.
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Strauss RM, et al: Allergic contact cheilitis in the UK. Am J Contact Dermat 2003;14:75.

Actinic Cheilitis

Actinic cheilitis is an inflammatory reaction of the lips to chronic excessive sunlight exposure over many years. The lower lip, which is usually the only one involved, becomes scaly, fissured, and at times eroded and swollen; leukoplakia and even squamous cell carcinoma may develop (Fig. 34-2). Painful erosions may occur; actual ulceration is very rare unless carcinoma has developed. Hereditary polymorphous light eruption can resemble chronic actinic cheilitis, but it has no malignant potential.

Avoiding sun exposure and the use of sunscreen containing lip pomades suffice to minimize further damage. A biopsy should be performed on any suspicious, thickened areas that persist; preferably, a shave technique should be used to avoid scarring.

Cryosurgical treatment may be effective, particularly for localized lesions. In cases with diffuse involvement, application of topical 5-fluorouracil (5-FU), imiquimod, or photodynamic therapy using 5-aminolevulinic acid may be curative. Treatment with a CO_2 laser or electodessication may be required for severe disease and provides excellent results. The latter is a less expensive ablative therapy, but takes longer to heal (23 days compared to 14 with the laser). Should this treatment fail, vermilionectomy of the lower lip may be necessary. Excision of the exposed vermilion mucous membrane with advancement of the labial mucosa to the skin edge of the outer lip is effective, but this is performed less frequently since the advent of laser therapy. Refer to Chapter 29 for more information on actinic cheilitis.

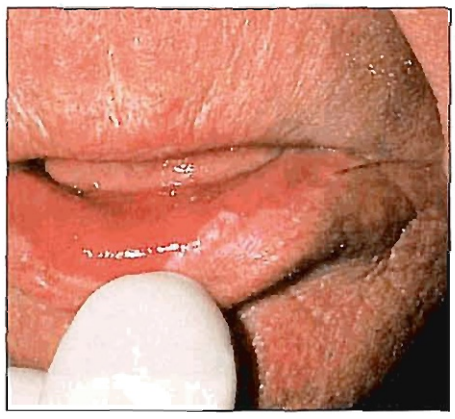

Fig. 34-2 Actinic cheilitis.

Dufresne RG Jr, et al: Actinic cheilitis: a treatment review. Dermatol Surg 1997;23:15.
Kaugers GE, et al: Actinic cheilitis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999;88:181.
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Sartorres Nieto M, et al: Surgical management of actinic cheilitis. Med Oral 2001;6:205.
Smith KJ, et al: Topical 5% imiquimod for the therapy of actinic cheilitis. J Am Acad Dermatol 2002;47:497.
Stender IM, et al: Photodynamic therapy with 5-aminolevulinic acid in the treatment of actinic cheilitis. Br J Dermatol 1996; 135:454.
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Cheilitis Glandularis

Cheilitis glandularis is characterized by swelling and eversion of the lower lip, patulous openings of the ducts of the mucous glands, cysts, and general enlargement of the lips (Fig. 34-3). Mucus exudes freely to form a gluey film that dries over the lips and causes them to stick together during the night. When the lip is palpated between the thumb and index finger, the enlarged mucous glands feel like pebbles beneath the surface. The lower lip is the site of predilection.

In general, two types are recognized, namely, cheilitis glandularis simplex and cheilitis glandularis apostematosa. (*Apostematosa* means "with abscess formation.") The latter type probably stems from the simplex form by the development of infection. Cheilitis glandularis is a chronic inflammatory reaction that is due to an exuberant response to chronic irritation, atopic, factitious, or actinic damage.

On biopsy, there is a moderate histiocytic, lymphocytic, and plasmocytic infiltration in and around the glands. Some believe it to be a disorder of ductal ectasia. Cheilitis glandularis has been reported to eventuate in squamous cell carcinoma, but these cases may be attributed to chronic sun exposure, which frequently precedes cheilitis glandularis.

Treatment depends on the nature of the antecedent irritation; in most cases, treatment as described for actinic cheilitis is appropriate. Surgical debulking may be necessary. Intralesional triamcinolone may be beneficial in some cases.

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Stoopler ET, et al: Cheilitis glandularis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003;95:312.
Verma S: Cheilitis glandularis. Br J Dermatol 2003;148:362.

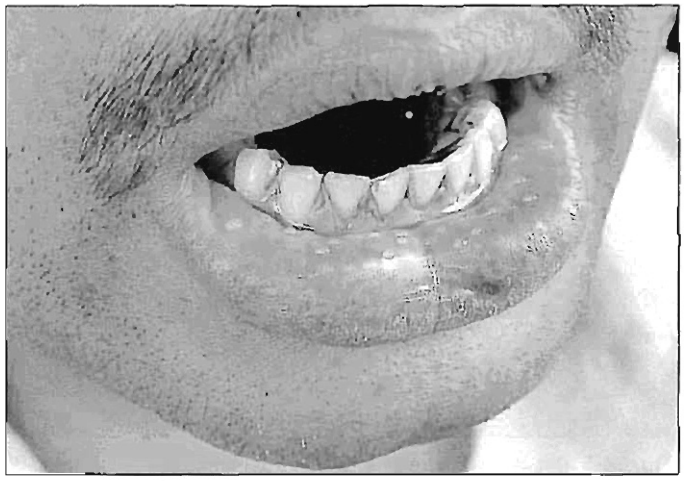

Fig. 34-3 Cheilitis Glandularis (Courtesy Dr Shyam Verma).

Angular Cheilitis

Angular cheilitis is synonymous with *perlèche*. Fissures radiate downward and outward from the labial commissures. It is an intertriginous dermatitis caused by excessive wetness or dryness. It is often complicated with secondary infection by *Candida albicans* or *Staphyloccocus aureus*.

The disease usually occurs in elderly people who wear dentures, but it may develop simply from an overhanging of the upper lip and cheek, and recession and atrophy of the alveolar ridges in old age. Measuring the facial dimensions with a ruler and tongue blade will help with objective assessment of the importance of decreased vertical facial dimension in the development of perlèche. If the distance from the base of the nose to the lower edge of the mandible is 6 mm or more less than the distance from the center of the pupil to the parting line of the lips, the vertical dimension is decreased. In these circumstances, drooling is usually a factor. In children, angular cheilitis occurs commonly in thumb suckers, gum chewers, and lollipop eaters. Other inciting factors include riboflavin deficiency, anorexia nervosa, Down syndrome, intraoral candidiasis, especially in patients with diabetes, acquired immune deficiency syndrome (AIDS), or chronic mucocutaneous candidiasis, Sjögren syndrome, drug-induced xerostomia, and atopic dermatitis.

Opening the "bite" by improving denture fit, capping teeth, replacing lost teeth, or increasing denture height, combined with topical use of nystatin and iodochlorhydroxyquin (Vioform) in hydrocortisone ointment, is usually effective when the condition is associated with anatomically predisposing factors. Stubborn cases typically respond to a slightly stronger corticosteroid, such as desonide, in combination with a topical anticandidal agent. Injection of collagen or insertion of Softform implants to obliterate the angular creases may be beneficial. Therapy for underlying diseases should be maximized. If *S. aureus* is present mupirocin ointment may be needed. Excision of the region, followed by a rotating flap graft, is another therapeutic option, but surgery should not be the first treatment tried.

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Smith AJ, et al: *Staphylococcus aureus* in the oral cavity. Br Dent J 2003;20:701.

Strumia R, et al: Skin signs in anorexia nervosa. Dermatology 2001;203:314.

Zegarelli DJ: Fungal infections of the oral cavity. Otolaryngol Clin North Am 1993;26:1069.

Plasma Cell Cheilitis

This is also referred to as *plasma cell orificial mucositi* or when the gingival is the site of involvement, *plasma cell gingivitis*. It is characterized by a sharply outlined, infiltrated, dark red plaque with a lacquer-like glazing of the surface of the involved area.

This lesion has the same lesion microscopic features as Zoon balanitis plasmacellularis. There is plasma cell infiltration in a bandlike pattern. Plasma cell cheilitis is not a response that is specific for any stimulus but rather represents a reaction pattern to any one of a variety of stimuli. Successful therapies include application of topical tacrolimus ointment or clobetasol propionate ointment twice a day.

Plasmoacanthoma Plasma cell cheilitis and plasmoacanthoma have been reported in the same patient and are believed to represent a spectrum of the same disease. Plasmoacanthoma is a verrucous tumor with a plasma cell infiltrate involving the oral mucosa, particularly along the angles. *C. albicans* has been found within the tissue, suggesting that it may be implicated as a cause of this disease.

Kaur C, et al: Plasma cell mucositis. J Eur Acad Dermatol Venereol 2001;15:566.

Rocha N, et al: Plasma cell cheilitis. J Eur Acad Dermatol Venereol 2004;18:96.

van de Kerkhof PC, et al: Co-occurrence of plasma cell orificial mucositis and plasmoacanthoma. Dermatology 1995;191:53.

Drug-Induced Ulcer of the Lip

Painful or tender well-defined ulcerations without induration on the lower lip may heal after withdrawal of oral medications. The causative drugs may be phenylbutazone, chlorpromazine, phenobarbital, methyldopa, or thiazide diuretics.

Solar exposure appears to be a predisposing causative influence; in some cases this reaction may represent a fixed drug photoeruption. On rare occasions, fixed drug eruptions may also involve the lip; usually the culprit is naproxen or one of the oxicams (Fig. 34-4).

Mackie BS: Drug-induced ulcer of the lip. Br J Dermatol 1967; 79:106.

Ozkaya-Bayazit E: Specific site involvement with fixed drug eruptions. J Am Acad Dermatol 2003;49:1003.

Other Forms of Cheilitis

Several diseases discussed elsewhere may affect the lips, including lichen planus, lupus erythematosus, atopic dermatitis and psoriasis. A high percentage of patients with Down syndrome have cheilitis of one or both lips. Lip biting may be a factor.

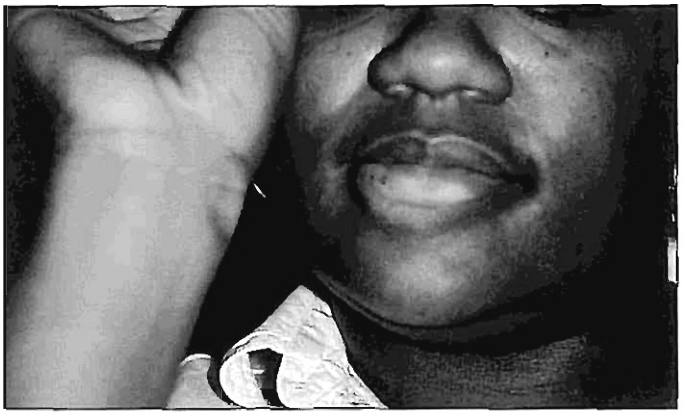

Fig. 34-4 Fixed drug eruption.

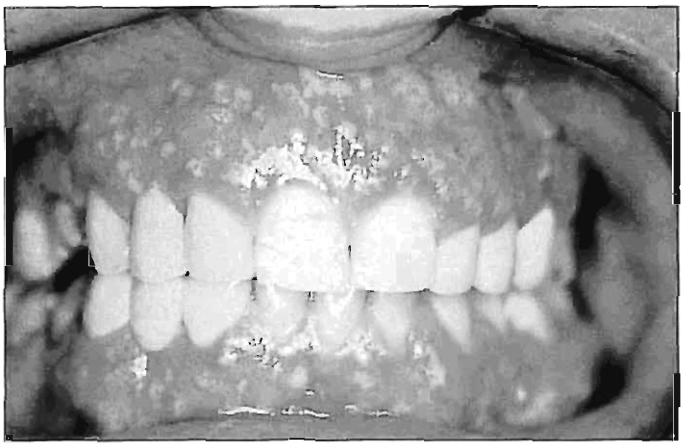

Fig. 34-5 Pyostomatitis vegetans. (Courtesy of Charles Casima, MD)

ORAL AND CUTANEOUS CROHN'S DISEASE

Crohn's disease is a chronic granulomatous disease of any part or parts of the bowel, to which the names *terminal ileitis, regional enteritis, ileocolitis, segmental colitis,* and *granulomatous colitis* have also been given. Patients with Crohn's disease may develop inflammatory hyperplasia of the oral mucosa, with metallic dysgeusia and gingival bleeding.

Reported typical changes include diffuse oral swelling, focal mucosal hypertrophy and fissuring (cobble-stoning), persistent ulceration, polypoid lesions, indurated fissuring of the lower lip, angular cheilitis, granulomatous cheilitis, or pyostomatitis vegetans. Oral involvement occurs in 10% to 20% of cases of Crohn's disease, and 90% have granulomas on biopsy. Males with early-onset disease are most often affected. Concomitant involvement of the anal and esophageal mucosa is common.

Many cases of Crohn's disease with other cutaneous manifestations have been reported, notably pyoderma gangrenosum (more closely associated with ulcerative colitis) and erythema nodosum, polyarteritis nodosa, pellagra, pernicious anemia, an acrodermatitis-like eruption, urticaria, and necrotizing vasculitis. Direct extension to perianal skin may occur.

Metastatic Crohn's disease denotes noncaseating granulomatous skin lesions in patients with Crohn's disease. In the absence of bowel involvement, the diagnosis cannot be made. Genital swelling, leg ulceration, pyogenic granuloma-like lesions of the retroauricular skin, or erythematous nodules, plaques, or ulcers in other locations are the morphologic appearances seen.

Treatment of the gastrointestinal manifestations with sulfasalazine, systemic corticosteroids, infliximab or immunosuppressive medications can improve the cutaneous findings. Several delivery systems use only the active ingredient of sulfasalazine, mesalamine. These include Asacol, Pentasa, Rowasa, and olsalazine, and they may be useful in treating the skin involvement of Crohn's disease. A mouthwash containing triamcinolone acetonide, tetracycline, and lidocaine may provide symptomatic and objective improvement. Budesonide, a well-absorbed oral corticosteroid that has a high rate of first-pass metabolism in the liver, has been shown to be effective in treating Crohn's disease while causing fewer long-term side effects. Cyclosporin, azathioprine, and oral metronidazole have also been shown to be effective as first-line agents. Mycophenolate mofetil and methotrexate may also be considered. Cutaneous ulcerated granulomas and erythematous plaques caused by Crohn's disease may respond to high-potency topical corticosteroids or tacrolimus ointment. Curettage and zinc by mouth have resulted in healing in several reported patients. Dietary manipulation is another measure that can be helpful in select individuals. The course is often prolonged over several years.

Al-Hussaniani AA, et al: Crohn's disease and cheilitis. Can J Gastroenterol 2003;17:445.

Dupuy A, et al: Oral Crohn disease. Arch Dermatol 1999; 135:439.

Gilson RT, et al: Metastatic Crohn's disease. J Am Acad Dermatol 1999;41:476.

Oskay T, et al: Metastatic Crohn's disease in a child. Clin Exp Dermatol 2005;30;358.

Sciubba JJ, et al: Orofacial granulomatosis. J Oral Pathol Med 2003;32:576.

Schwab RA, et al: Multiple cutaneous ulcerations. Arch Dermatol 1993;129:1607.

PYOSTOMATITIS VEGETANS

Pyostomatitis vegetans, an inflammatory stomatitis, is most often seen in association with ulcerative colitis but may also occur in other inflammatory bowel diseases, such as Crohn's disease. Edema and erythema with deep folding of the buccal mucosa characterize it, together with pustules, small vegetating projections, erosions, ulcers, and fibrinopurulent exudates (Fig. 34-5). Eroded pustules fuse into shallow ulcers, resulting in characteristic "snail-track" ulcers. It has also been associated with sclerosing cholangitis. Several cases have been reported without any underlying systemic disorder.

Histologically, there are dense aggregates of neutrophils and eosinophils. At times, crusted erythematous papulopustules that coalesce into asymmetrical annular plaques may occur with or after the oral lesions. The associated skin lesions favor the axilla, groin, and scalp. Topical corticosteroids may be effective; systemic steroids or infliximab, however, are usually necessary.

Ayangco L, et al: Pyostomatitis vegetans as an early sign of reactivation of Crohn's disease. J Periodontol 2002;73:1512.

Bens G, et al: Successful treatment with infliximab and methotrexate of pyostomatitis vegetans associated with Crohn's disease. Br J Dermatol 2003;149:181.
Hegargty AM, et al: Pyostomatitis vegetans. Clin Exp Dermatol 2004;29:1.
Mehravaran M, et al: Pyodermatitis-pyostomatitis vegetans. Br J Dermatol 1997;137:266.
Ruiz-Roca JA, et al: Pyodermatitis vegetans. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;99:447.

CHEILITIS GRANULOMATOSA

Miescher in 1945 reported six cases of swelling of the lips with progressive changes resulting in permanent macrocheilia. Cheilitis granulomatosa is characterized by a sudden onset and progressive course terminating in chronic enlargement of the lips. Usually the upper lip becomes swollen first: several months may elapse before the lower lip becomes swollen. Usually only enlargement is present, without ulceration, fissuring, or scaling. The swelling remains permanently. It may be a part of the Melkersson-Rosenthal syndrome when associated with facial paralysis and plicated tongue.

The cause is unknown. Histologically, it is characterized by an inflammatory reaction of lymphocytes, histiocytes, and plasma cells and tuberculoid granulomas consisting of epithelioid and Langerhans giant cells. In the differential diagnosis, solid edema, angioedema, cheilitis glandularis, sarcoidosis, oral Crohn's disease, infectious granulomas, and Ascher syndrome must be considered. This may be the presenting sign in a patient who will develop Crohn's disease or sarcoidosis at a later time.

Treatment with intralesional injections of corticosteroids is sometimes successful. In the firmly established case, surgical repair of the involved lip through a mucosal approach and in some cases, concomitant intralesional steroid treatment give best results. Other anecdotally effective medications include tetracyclines, hydroxychloroquine, clofazimine, and sulfasalazine.

Oliver DW, et al: Lip reduction cheiloplasty for Miescher's granulomatous macrocheilitis in childhood. Clin Exp Dermatol 2002;27:129.
Van der Waal RI, et al: Cheilitis granulomatosa. Int J Dermatol 2002;41:225.
Venable CE, et al: Persistent swelling of the lower lip. Arch Dermatol 1988;129:1705.

MELKERSSON-ROSENTHAL SYNDROME

Melkersson in 1928 and Rosenthal in 1930 described a triad consisting of recurring facial paralysis or paresis, soft nonpitting edema of the lips, and scrotal tongue.

Attacks usually start during adolescence, with permanent or transitory paralysis of one or both facial nerves, repeated migraine attacks, and recurring edema of the upper lip, cheeks, and occasionally the lower lip and circumoral tissues. Swelling of the skin and mucous membranes of the face and mouth is the dominant finding and the most important diagnostic feature (Fig. 34-6). In order of frequency, the swelling occurs first on the upper lip, then the lower lip, and then other regions.

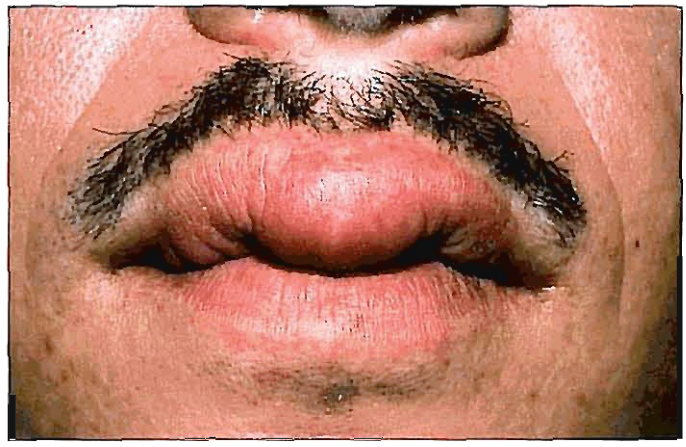

Fig. 34-6 Melkersson-Rosenthal syndrome. (Courtesy of Curt Samlaska, MD)

Extrafacial swellings appear on the dorsal aspect of the hands and feet, and in the lumbar region. The pharynx and respiratory tract may be involved, with thickening of the mucous membrane. The relapsing condition produces an overgrowth of connective tissue, edema, atrophy of the muscle fibers, and inflammatory infiltrates, with permanent deformities of the lips, cheeks, and tongue.

The cause is unknown. The association at times with megacolon, otosclerosis, and craniopharyngioma supports the theory of a neurotrophic origin. It may be familial.

Histopathologic evaluation shows a tuberculoid type of granuloma with lymphedema and a banal perivascular infiltrate. In the differential diagnosis, a number of diseases characterized by edema of the lips, must be considered. Ascher syndrome consists of swelling of the lips with edema of the eyelids (blepharochalasis) and is inherited. Melkersson-Rosenthal syndrome must also be differentiated from the acute swellings produced by angioedema, trauma, and infections of all sorts. Lymphangioma, hemangioma, neurofibroma, and sarcoidosis are some of the diseases to be considered on a clinical basis.

Melkersson-Rosenthal syndrome is frequently seen in an incomplete form, and other granulomatous diseases may present as swellings of the lips or oral–facial tissues. It is worthwhile to consider these as a group called *orofacial granulomatosis* so that various underlying disease states or etiologic factors will not be missed when evaluating such patients. Oral Crohn's disease, patients who will develop typical Crohn or sarcoidosis in the future, cheilitis granulomatosa, sarcoidosis, granulomatous infiltrates associated with tooth infections, and patients with food or contact allergic reactions should all be considered.

There is no satisfactory treatment, although intralesional injections of corticosteroids may be beneficial. Decompression of the facial nerve may be indicated in those patients with recurrent attacks of facial palsy. Surgery alone or combined with intralesional steroid injections may be more successful than either alone. Odontogenic infection has been reported to initiate this condition and antibiotic therapy for this may lead to remission. Clofazimine, thalidomide, and prednisone combined with minocycline or tetracycline have been reported to improve individual patients.

Camacho F, et al: Treatment of Miesher's cheilitis granulomatosa in Melkersson-Rosenthal syndrome. J Eur Acad Dermatol Venereol 2001;15:546.
Mignogna MD, et al The multiform and variable patterns of onset of orofacial granulomatosis. J Oral Pathol Med 2003; 32:200.
Rogers RS III: Melkersson-Rosenthal syndrome and orofacial granulomatosis. Dermatol Clin 1996;14:371.
Rogers RS III. Granulomatous cheilitis, Meldersson-Rosenthal syndrome, and orofacial granulomatosis. Arch Dermatol 2000;136:1557.
Stein SL, et al: Melkersson-Rosenthal syndrome in children. J Am Acad Dermatol 1999;41:746.

FORDYCE'S DISEASE (FORDYCE SPOTS)

Fordyce spots are ectopically located sebaceous glands, clinically characterized by minute orange or yellowish pinhead-sized macules or papules in the mucosa of the lips, cheeks, and, less often, the gums. Similar lesions may occur on the areola, glans penis, and labia minora. Prominent lip involvement may result in a lipstick-like mark left on the rim of a glass mug after consuming a hot beverage (Meffert's sign). Involvement of the labial mucosa with pseudoxanthoma elasticum may simulate Fordyce spots.

Because the anomaly is asymptomatic and inconsequential, treatment should be undertaken only if there is a significant cosmetic problem. CO_2 laser or isotretinoin are therapeutic options.

Elston DM, et al: Fordyce spots. Cutis 2001;68:24, 49.
Massmanian A, et al: Fordyce spots on the glans penis. Br J Dermatol 1995;133:498.
Monk BE: Fordyce spots responding to isotretinoin therapy. Br J Dermatol 1993;129:355.
Ocampo-Candiani J, et al: Treatment of Fordyce spots with CO_2 laser. Dermatol Surg 2003;29:869.

STOMATITIS NICOTINA

Also known as *smoker's keratosis* and *smoker's patches*, stomatitis nicotina is characterized by distinct umbilicated papules on the palate. The ostia of the mucous ducts appear as red pinpoints surrounded by milky white, slightly umbilicated asymptomatic papules. The intervening mucosa becomes white and thick and has a tendency to desquamate in places, leaving raw, beefy red areas. Ulceration and the formation of aphthous ulcers may occur.

This condition is attributed to heavy smoking in middle-aged men, although it has also been reported in nonsmokers who habitually drink hot beverages. Heat may be the causative event. Indeed, the most severe cases are associated with the type of tobacco use that produces intense heat—pipe and reverse smoking.

Treatment consists of abstaining from the use of tobacco or ingestion of hot liquids.

Mirbod SM, et al: Tobacco-associated lesions of the oral cavity. J Can Dent Assoc 2000;66:252.
Rossie KM, et al: Thermally induced nicotine stomatitis. Oral Surg Oral Med Oral Pathol 1990;70:597.

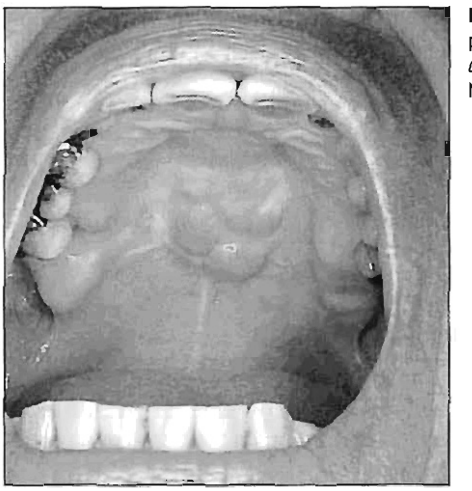

Fig. 34-7 Torus palantinus. (Courtesy of James Fitzpatrick, MD)

Taybos G: Oral changes associated with tobacco use. Am J Med Sci 2003;326:179.

TORUS PALATINUS

Torus palatinus is a bony protuberance in the midline of the hard palate, marking the point of junction of the two halves of the palate (Fig. 34-7). It is asymptomatic. Exostosis also commonly occurs in the floor of the mouth, involving the inner surface of the mandible.

Cagirankaya LB, et al: Is torus palatinus a feature of a well-developed maxilla? Clin Anat 2004;17:623.
Piera-Navarro N, et al: Clinical evaluation of hard tissue proliferations of the mouth. Med Oral 2002;7:97.

FISSURED TONGUE

Also known as *furrowed tongue*, *scrotal tongue* or *lingua plicata*, fissured tongue is a congenital and sometimes familial condition in which the tongue is generally larger than normal and there are plicate superficial or deep grooves, usually arranged so that there is a longitudinal furrow along the median raphe, reminiscent of scrotal rugae (Fig. 34-8).

Fissured tongue is seen in Melkersson-Rosenthal syndrome and in most patients with Down syndrome. Individual case reports have been seen in association with pachyonychia congenita, pemphigus vegetans, and Cowden syndrome. Geographic tongue occurs together with fissured tongue in 50% of patients, and both may appear in the setting of pustular psoriasis.

The condition gives rise to no difficulty, and treatment is not necessary, except that the deep furrows should be kept clean by use of mouthwashes.

Byrd JA, et al: Glossitits and other tongue disorders. Dermatol Clin 2003;21:123.
Leston JM, et al: Oral mucosa. Cutis 2002;69:215.

GEOGRAPHIC TONGUE

Geographic tongue is also known as *lingua geographica*, *transitory benign plaques of the tongue*, *glossitis areata exfoliativa*, and *benign migratory glossitis*. In some patients it is a manifestation of atopy, and in others, of psoriasis. However, in most it is an isolated finding.

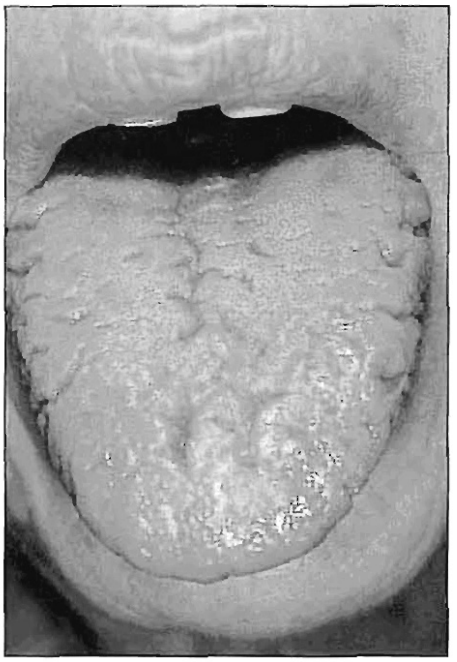

Fig. 34-8 Fissured tongue. (Courtesy of James Fitzpatrick, MD)

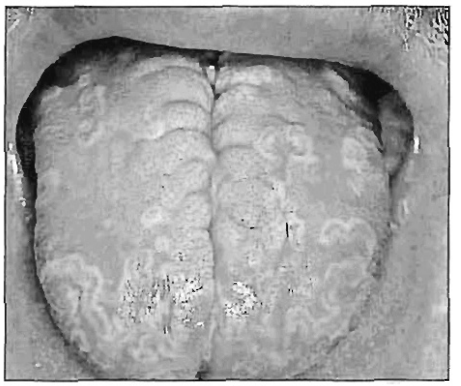

Fig. 34-9 Annulus migrans.

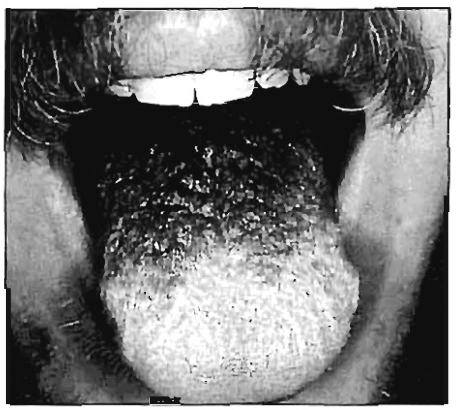

Fig. 34-10 Black hairy tongue.

The dorsal surface of the tongue is the site usually affected. Geographic tongue begins with a small depression on the lateral border or the tip of the tongue, smoother and redder than the rest of the surface. This spreads peripherally, with the formation of sharply circumscribed ringed or gyrate red patches, each with a narrow yellowish-white border, making the tongue resemble a map. The appearance changes from day to day; patches may disappear in one place and manifest themselves in others. The disease is characterized by periods of exacerbation and quiescence. The lesion may remain unchanged in the same site for long periods. The condition is frequently unrecognized because it produces no symptoms except for the occasional complaint of glossodynia.

There are two clinical variants of geographic tongue. In one type, discrete, annular "bald" patches of glistening, erythematous mucosa with absent or atrophic filiform papillae are noted. Another type shows prominent circinate or annular white raised lines that vary in width up to 2 mm. The clinical appearance and histopathologic findings of the tongue lesions in pustular psoriasis, reactive arthritis (Reiter syndrome), and geographic tongue are identical; when occurring with psoriasis or reactive arthritis, the name *annulus migrans* has been suggested for this entity (Fig. 34-9). It has been reported to be acquired in patients with AIDS or as a result of lithium therapy.

Histologically, the main features are marked transepidermal neutrophil migration with the formation of spongiform pustules in the epidermis and an upper dermal mononuclear infiltrate.

Although treatment is not usually necessary, a 0.1% solution of tretinoin solution (Retin-A) applied topically has produced clearing within 4 to 6 days.

Assimakopoulos D, et al: Benign migratory glossitis or geographic tongue. Am J Med 2002;113:751.

Byrd JA, et al: Glossitits and other tongue disorders. Dermatol Clin 2003;21:123.

BLACK HAIRY TONGUE

Black or brown hairy tongue occurs on the dorsum of the tongue anterior to the circumvallate papillae, where black, yellowish, or brown patches form, consisting of hairlike intertwining filaments several millimeters long (Fig. 34-10). The "hairs" result from a benign hyperplasia of the filiform papillae of the anterior two-thirds of the tongue, resulting in retention of long conical filaments of orthokeratotic and parakeratotic cells. It occurs far more frequently in men than in women.

Black hairy tongue may be associated with several conditions that may be predisposing factors in its causation: excessive smoking, use of oral antibiotics, and presence of *Candida* on the surface of the tongue.

This lesion may be differentiated both clinically and histologically from oral hairy leukoplakia, which is seen in human immunodeficiency syndrome (HIV)-infected patients. Hairy leukoplakia is usually seen on the lateral surface of the tongue in at first corrugated patches, then with time as solid white plaques that are adherent. Microscopic examination reveals acanthosis, parakeratosis, irregular projections of keratin, and vacuolated keratinocytes with Epstein-Barr virus present within them.

A toothbrush may be used to scrub off the projections, either alone, with 1% to 2% hydrogen peroxide, or after application of Retin-A gel, 40% aqueous solution of urea, or papain (meat tenderizer). Such predisposing local factors as smoking, antibiotics, and oxidizing agents should be eliminated, if possible, and scrupulous oral hygiene should be maintained.

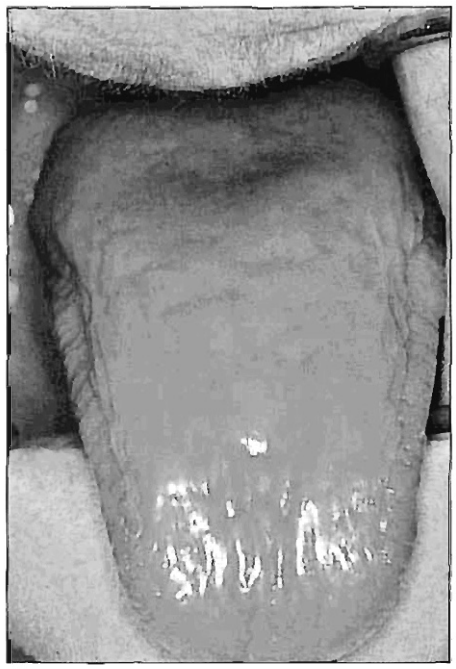

Fig. 34-11 Smooth tongue in Plummer-Vinson syndrome.

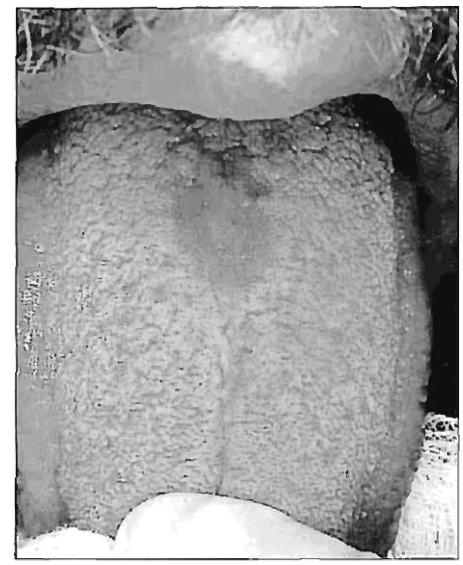

Fig. 34-12 Median rhomboid glossitis. (Courtesy of James Fitzpatrick, MD)

Heymann WR: Psychotropic agent-induced black hairy tongue. Cutis 2000;66:25.

Manabe M, et al: Architectural organization of filiform papillae in normal and black hairy tongue epithelium. Arch Dermatol 1999;135:177.

Newman CC, et al: Images in clinical medicine: black hairy tongue. N Engl J Med 1997;337:897.

Taybos G: Oral changes associated with tobacco use. Am J Med Sci 2003;326:179.

SMOOTH TONGUE

Also known as *bald tongue* or *atrophic glossitis*, the smooth glossy tongue is often painful and results from atrophy of the filiform and eventually the fungiform papillae (Fig. 34-11). When present with vitamin B_{12} deficiency it has been termed *Moeller* or *Hunter glossitis*. It begins with the tip and lateral surfaces of the tongue becoming intensely red, well-defined irregular patches in which the filiform papillae are absent or thinned and the fungiform papillae are swollen. The disease is chronic and the patches are painful and sensitive so that eating may be difficult and taste impaired. With time the entire tongue becomes smooth and a leukoplakia may result. Treatment is directed against pernicious (macrocytic) anemia. With specific vitamin B_{12} therapy, there will be improvements in the appearance and sensitivity of the tongue.

Atrophic glossitis is also a distinctive sign of pellagra; it results from a deficiency of niacin or its precursor, tryptophan. The sides and tip of the tongue are erythematous and edematous, with imprints of the teeth. Eventually, the entire tongue assumes a beefy-red appearance. Small ulcers appear, and all the mucous membranes of the mouth may be involved. Later the papillae become atrophied to produce a smooth, glazed tongue, as seen in pernicious anemia. Burning or pain in the ulcers may be present. Increased salivary flow early in the disease may lead to drooling and angular cheilitis. In malabsorption syndrome, riboflavin deficiency, anorexia nervosa, alcoholism, and sprue similar changes may be noted. Vitamin B complex is curative.

Patients with iron-deficiency anemia, alone or when combined with esophageal webs (Plummer-Vinson syndrome), folic acid deficiency, syphilis, amyloidosis, celiac disease, *Sjögren syndrome*, and Riley-Day syndrome may all manifest smooth tongue.

Atmatzidis K, et al: Plummer-Vinson syndrome. Dis Esophagus 2003;16:154.

Byrd JA, et al: Glossitits and other tongue disorders. Dermatol Clin 2003;21:123.

Itoh I, et al: Taste disorder involving Hinter's glossitis following total gastrectomy. Acta Otolaryngol 2002;546(Suppl):159.

Prousky JE: Pellagra may be a rare secondary complication of anorexia nervosa. Altern Med Rev 2003;8:180.

ERUPTIVE LINGUAL PAPILLITIS

Lacour and Perrin first described this acute, self-limiting inflammatory stomatitis in 1997. It affects children of both sexes equally with a mean age of onset of 3½ years. It has a seasonal distribution with the majority of cases occurring in the spring. Fever (40%), difficulties in feeding (100%), and intense salivation (60%) are common symptoms. The tongue examination reveals inflammatory hypertrophy of the fungiform papillae on the tip and dorsolateral sites. Additional signs include submandibular or cervical adenopathy (40%) and angular cheilitis (10%). Associated skin eruptions have not been described. Spontaneous involution occurs in a mean of 7 days with a range of 2 to 15 days. Recurrence is noted in 13%. It is felt to be the result of a viral infection, and the 50% transmission among family members further supports this theory.

Brfannon RB, et al: Transient lingual papillitis Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003;96:187.

Lacour JP, et al: Eruptive familial lingual papillitis. Pediatr Dermatol 1997;14:13.

Roux O, et al: Eruptive lingual papillitis with household transmission. Br J Dermatol 2004;150:299.

MEDIAN RHOMBOID GLOSSITIS

Median rhomboid glossitis is characterized by a shiny oval or diamond-shaped elevation, invariably situated on the dorsum in the midline immediately in front of the circumvallate papillae (Fig. 34-12). The surface is abnormally red and smooth. In some instances a few pale yellow papules surmount the elevation. On palpation the lesion feels slightly firm, but it usually causes no symptoms. It persists indefinitely with little or no increase in size. There is no relationship to cancer.

It may result from abnormal fusion of the posterior portion of the tongue, but it is nearly always chronically infected with *Candida*. If there is palatal inflammation above the inflamed part of the tongue, AIDS should be suspected and an HIV test obtained. Histologically, the changes are those of a simple, chronic inflammation with fibrosis, and usually with fungal hyphae in the parakeratin layer. Treatment with oral antifungals, such as itraconazole, may lead to improvement.

Bae GY, et al: A case of median rhomboid glossitis. J Dermatol 2003;30:423.
Gauchia Moreno R, et al: A painless mass on the tongue of a young man. Arch Dermatol 1999;135:593.
McNally MA, et al: Conditions peculiar to the tongue. Dermatol Clin 1996;12:257.

EOSINOPHILIC ULCER OF THE ORAL MUCOSA

Eosinophilic ulcer occurs most commonly on the tongue, but may occur anywhere in the oral mucosa. It is characterized by an ulcer with indurated and elevated borders that is usually covered by a pseudomembrane. It develops rapidly, most commonly on the posterior aspect of the tongue, and spontaneously resolves in a few weeks. A traumatic cause has been postulated for this benign, self-limited disorder. The histopathologic findings show a predominantly eosinophilic infiltrate in company with some histiocytes and neutrophils.

In some multifocal, recurrent cases, CD30+ cells have been reported. These patients may have the oral counterpart of primary cutaneous CD30+ lymphoproliferative disease. HIV-infected patients may develop ulcerations of the oral mucosa, resulting from a variety of infectious agents, such as herpes simplex virus (HSV), candidiasis, and histoplasmosis. However, 5 of the 16 patients they reported had no evidence of infection and simply showed eosinophilic infiltrates below the ulcer.

Liang GS, et al: An evaluation of oral ulcers in patients with AIDS and AIDS-related complex. J Am Acad Dermatol 1993; 29:563.
Mezei MM, et al: Eosinophilic ulcer of the oral mucosa. J Am Acad Dermatol 1995;33:734.
Rosenberg A, et al: Primary extranodal CD30-positive T-cell non-Hodgkin's lymphoma of the oral mucosa. Int J Oral Maxillofac Surg 1996;25:57.
Velez A, et al: Eosinophilic ulcer of the oral mucosa. Clin Exp Dermatol 1997;22:154.

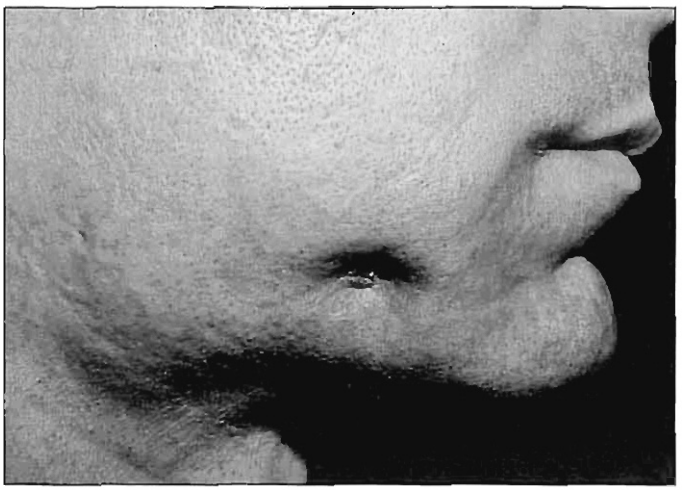

Fig. 34-13 Ondontogenic sinus.

CAVIAR TONGUE

William Bean gave the picturesque name *caviar tongue* to the purplish venous ectasias so commonly found on the undersurface of the tongue after the age of 50. They are attributed to elastic tissue deterioration with aging and may be associated with Fordyce angiokeratomas of the scrotum. Phleboliths or thrombophlebitis may occasionally complicate this condition.

Kocsard E, et al: The histopathology of caviar tongue. Dermatologica 1970;140:318.

CUTANEOUS SINUS OF DENTAL ORIGIN (DENTAL SINUS)

In dental (or odontogenous) sinus, chronic periapical infection about a tooth produces a burrowing, practically asymptomatic, occasionally palpable, cordlike sinus tract that eventually appears beneath the surface of the gum, palate, or periorificial skin. It forms a fistulous opening with an inflamed red nodule at the orifice. It may appear anywhere from the inner ocular canthus to the neck but is most often seen on the chin or along the jawline (Fig. 34-13). Bilateral involvement has been reported. Dental radiography is diagnostic. Pyogenic granuloma, actinomycosis, squamous cell carcinoma, osteomyelitis of the mandible, congenital fistulas, the deep mycoses, and foreign body reactions must be considered in the differential diagnosis.

Treatment requires the removal of the offending tooth or root canal therapy of the periapical abscess.

Cantatore JL, et al: Cutaneous dental sinus tract, a common misdiagnosis. Cutis 2002;70:264.
Gulec AT, et al: Cutaneous sinus tract of dental origin. Int J Dermatol 2001;40:650.
Johnson BR, et al: Diagnosis and treatment of cutaneous facial sinus tracts of dental origin. J Am Dent Assoc 1999;130:832.
Mittal N, et al: Management of extra oral sinus cases. J Endod 2004;30:541.
Palacio JE, et al: Unusual recurrent facial lesion. Arch Dermatol 1999;135:593.
Tavee W, et al: An unusual presentation of a cutaneous odontogenic sinus. Arch Dermatol 2003;139:1659.

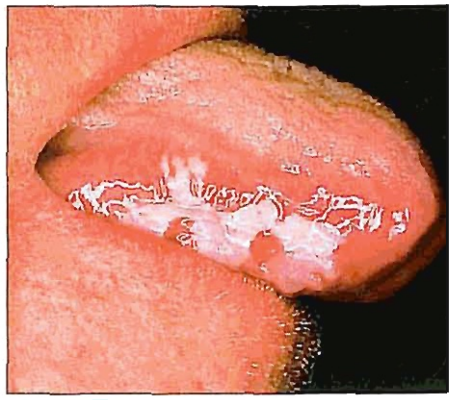

Fig. 34-14 Benign oral leukoplakia. (Courtesy of James Fitzpatrick, MD)

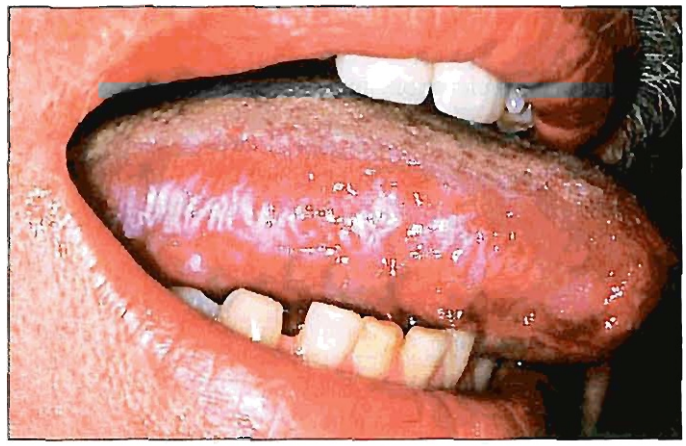

Fig. 34-15 Oral hairy leukoplakia of HIV.

NEOPLASMS

Many tumors may involve the oral cavity. Most are discussed elsewhere in this book, and several are uncommon entities that affect specialized oral structures, such as the many subtypes of benign and malignant proliferations that occur in the major and minor salivary glands. These will not be covered further here, and only a few selected neoplasms will be presented.

Leukoplakia

Clinical Features

Leukoplakia presents as a whitish thickening of the epithelium of the mucous membranes, occurring as lactescent superficial patches of various shapes and sizes that may coalesce to form diffuse sheets (Fig. 34-14). The surface is generally glistening and opalescent, often reticulated, and may even be somewhat pigmented. The white pellicle is adherent to the underlying mucosa and attempts to remove it forcibly cause bleeding. At times it is a thick, rough, elevated plaque The lips, gums, cheeks, and edges of the tongue are the most common sites, but the lesion may arise on the anus and genitalia. Leukoplakia is found chiefly in men over the age of 40.

Biopsy of these white lesions may reveal orthokeratosis or parakeratosis with minimal inflammation, or there may be evidence of varying degrees of dysplasia. There is a benign form that is usually a response to chronic irritation and that has very little chance of conversion into the precancerous dysplastic form. Premalignant leukoplakia, with atypical cells histologically, is present in only about 10% to 20% of leukoplakia. Unfortunately, clinically it is not possible to predict which lesions will be worrisome histologically, except that if ulceration, red areas or erosions are scattered throughout, the lesion is most likely precancerous. Therefore, biopsy is indicated.

When the lesion occurs on the lip, leukoplakia is closely related to chronic actinic cheilitis, which consists of a circumscribed or diffuse keratosis, almost invariably on the lower lip. It is preceded by an abnormal dryness of the lip and may be caused by smoking (especially pipe smoking) or chronic sun exposure. This type of leukoplakia is distinguished from squamous cell carcinoma of the lip by the absence of infiltration, from lichen planus and psoriasis of the lips and mouth by the absence of lesions elsewhere, and from lupus erythematosus by the absence of telangiectases. Biopsy is necessary, however, to fully differentiate these conditions.

Intraoral leukoplakia appears to progress to squamous cell carcinoma in not more than 1% per year. In time, an extensive, thick, white pellicle may cover the tongue or oral mucosa. In old lesions the epithelium may be desquamated and there may be fissures or ulcerations. Such changes are associated with more or less hyperemia and tenderness, and with a tendency to bleed after slight trauma. If transformation to carcinoma occurs, it generally follows a 1- to 20-year lag time, with the exception that immunosuppressed transplant patients may have a rapid course of transformation.

Oral hairy leukoplakia is a term used to describe white, corrugated plaques that occur primarily on the sides of the tongue of patients with acquired immunodeficiency syndrome (AIDS) (Fig. 34-15). This is a virally-induced lesion, discussed in Chapter 19, which has a characteristic histology.

Leukoplakia of the vulva usually occurs in obese women after menopause as grayish white, thickened, pruritic patches that may become fissured and edematous from constant rubbing and scratching. Secondary infection with edema, tenderness, and pain may occur. It is differentiated from lichen planus by the absence of discrete, rectangular or annular flat papules of violaceous hue in the mucosa outside the thickened patches, about the anus or on the buccal mucosa. Lichen planus may involve the skin as well as the mucocutaneous areas. Leukoplakia of the vulva is most frequently confused with lichen sclerosus et atrophicus and other vulval atrophies. On the penis, though leukoplakia may occur, a similar precancerous process called *erythroplasia* (of Queyrat) is usually seen instead.

Etiology

Numerous factors are involved in the cause of leukoplakia. It may develop as a result of tobacco smoking, use of smokeless tobacco, areca or betel nut chewing, reverse smoking, alcohol, poorly fitting dentures, sharp and chipped teeth, or improper oral hygiene. Extensive involvement of the lips and oral cavity with leukoplakia may exist for years without any indication of carcinoma. On the other hand, small inflamed patches may be the site of a rapidly growing tumor, which, with relatively insignificant local infiltration, may involve the cervical lymphatics. Carcinoma in leukoplakia usually begins as a localized induration, often about a fissure, or as a warty excrescence or a small ulcer. There is a 6% to 10% transformation rate of intraoral leukoplakia into squamous cell carcinoma. The red lesions of leukoplakia (erythroleukoplakia)

have a much higher risk of malignant degeneration than uniform white lesions.

The degree of epithelial atypia correlates with increased labeling with ^{3}H-thymidine and may be considered in staging the risk of developing malignancy. Aneuploid leukoplakia has a high rate of transformation into aggressive squamous cell carcinoma, and the cancers derived from them are more likely to be lethal.

Treatment

It must be remembered that cancer develops frequently on histologically dysplastic leukoplakia so that its complete removal should be the goal in each case—first by conservative measures, then by surgery or destruction, if necessary. The use of tobacco should be stopped, and proper dental care obtained. Fulguration, simple excision, cryotherapy, and CO_2 laser ablation are effective methods of treatment. Medical therapies that have been the subject of randomized clinical trials may lead to temporary resolution of the lesions, but relapses and adverse effects are common and there is no evidence they prevent the transformation to malignancy.

Leukoplakia with Tylosis and Esophageal Carcinoma

Leukoplakia associated with tylosis and esophageal carcinoma is extremely rare but may occur.

Epidermization of the Lip

Relatively smooth leukokeratosis of the lower vermilion, blending evenly into the skin surface distally and having a steep, sharp, irregular proximal margin, may easily be mistaken for precancerous leukoplakia clinically. Histologically, it shows only hyperkeratosis, without parakeratosis or cellular atypia. A shallow shave excision suffices to cure it and to rule out precancerous leukoplakia; no fulguration is required.

Erythroplakia

The term *erythroplakia* is applied to leukoplakia that has lost (or has not developed) the thick keratin layer that makes leukoplakia white; it is the usual pattern in mucocutaneous junctions. A focal red patch with no apparent cause should be suspected of being precancerous when found on the floor of the mouth, soft palate, or buccal mucosa, or under the tongue (Fig. 34-16). Histologically, there is cellular atypia, pleomorphism, hyperchromatism, and increased mitotic figures. Carcinoma in situ or invasive carcinoma is found in 90% of lesions.

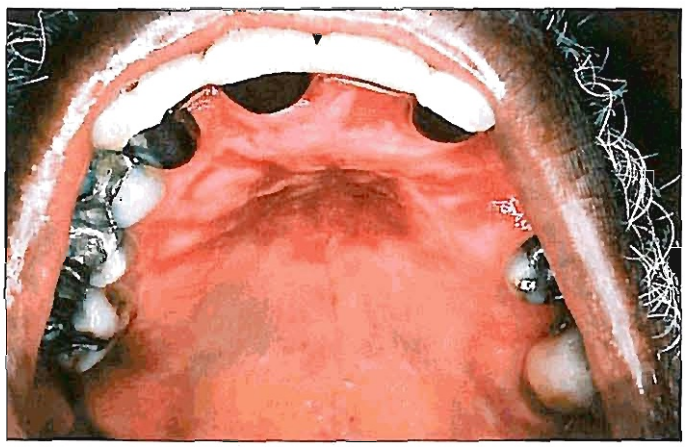

Fig. 34-16 Erythroplakia. (Courtesy of James Fitzpatrick, MD)

Oral Florid Papillomatosis

Oral florid papillomatosis was originally described by Rock and Fisher in 1960 as a confluent papillomatosis covering the mucous membranes of the oral cavity. The distinctive picture is that of a white mass resembling a cauliflower, covering the tongue and extending onto the other portions of the mucous membranes, including the oropharynx, larynx, and trachea. Usually there is no lymphadenopathy.

The course of the disease is progressive. Some lesions eventuate in squamous cell carcinoma, whereas others continue for many years, the patient dying of some intercurrent disease. Oral florid papillomatosis should be regarded as a verrucous carcinoma, which has been defined as a distinctive, slowly growing fungating tumor representing a well-differentiated squamous cell carcinoma in which metastases occur very late or not at all. The histologic features are those of papillomatosis, acanthosis, and varying degrees of dysplasia of the epithelium, without disruption of the basement membrane. It is reasonable to expect the eventual development of epidermoid carcinoma in most patients. Esophageal involvement and keratotic papules of the extremities may occur. In the differential diagnosis, leukoplakia, proliferative verrucous leukoplakia, candidiasis, acanthosis nigricans, and condyloma acuminatum should be considered. Treatment recommended is surgical excision; however, it is often followed by recurrence and spread. Recombinant interferon-α 2a in combination with a CO_2 laser has also been used.

Proliferative Verrucous Leukoplakia

Proliferative verrucous leukoplakia is a slowly progressive condition that begins as multifocal sites of hyperplasia of the oral mucous membranes and proceeds to thicken and enlarge until squamous cell carcinoma results. Women outnumber men 4:1. Initially flat, usually white patches are present, but the lesions relentlessly become warty exophytic masses. The patches may involve the lips and chin. Seventy percent develop squamous cell carcinoma (most frequently of the palate and gingiva), with 40% of the total dying of proliferative verrucous leukoplakia-associated carcinoma. It has been associated with human papillomavirus (HPV)-16 infection, but it remains to be proven whether this is the primary cause. Treatment is difficult because of the multifocal nature of the lesions. Aggressive early surgical therapy is best. Many patients develop recurrence after only a short interval. Laser treatment or photodynamic therapy should be considered primary options.

Squamous Cell Carcinoma

Squamous cell carcinoma is the most common oral malignancy, comprising 2% to 3% of all new cancers. With nearly 30,000 yearly cases in the US, it is the tenth most common malignancy. It occurs primarily in older men. The most frequent sites are the lower lip, tongue, soft palate, and floor of the mouth (Fig. 34-17). Squamous cell carcinoma of the lip develops from actinic damage with 95% of the cases involving the lower lip. Intraoral lesions frequently develop from leukoplakia, erythroplakia, at sites of frequent irrita-

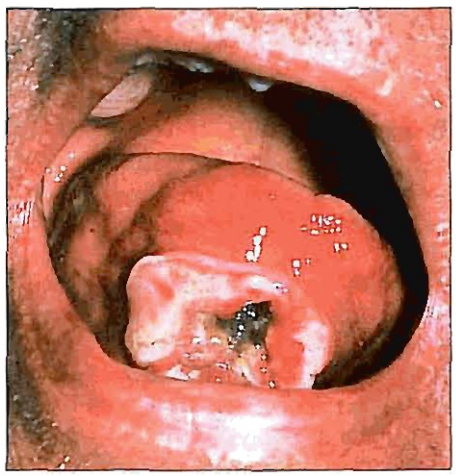

Fig. 34-17 Oral squamous cell carcinoma.

tion, or long-standing mucosal inflammatory disease such as ulcerative lichen planus. About 20% of oral squamous cell cancers have an associated focus of leukoplakia; these tend to be diagnosed at a less advanced stage than those where no associated leukoplakia exists. Verrucous carcinomas occur in the oral mucosa as they do on the skin. Tobacco smoking, the use of smokeless tobacco, areca or betel nut chewing, reverse smoking, and the use of alcohol are risk factors for the development of intraoral squamous cell carcinoma. They may also complicate xeroderma pigmentosa (the tip of the tongue), dyskeratosis congenita, dystrophic epidermolysis bullosa, erosive lichen planus, and oral submucous fibrosis. Unfortunately, the survival rate has remained at 50% for many years because it is often discovered late, after it has metastasized to the cervical lymph nodes. Exfoliative cytology is a practical and accurate aid to oral cancer screening.

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Ishii J, et al: Management of oral leukoplakia by laser surgery. J Clin Laser Med Surg 2004;22:27.

Ishii Y, et al: Oral florid papillomatosis and leukoplakia of the esophagus associated with keratoderma and showing transepidermal elimination. J Dermatol 1994;21:974.

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Svirsky JA, et al: Computer-assisted analysis of the oral brush biopsy. Compend Contin Educ Dent 2001;22:99.

Thoma G, et al: Risk factors for multiple oral premalignant lesions. Int J Cancer 2003;107:285.

Trivedy CR, et al: The oral health consequences of chewing areca nut. Addict Biol 2002;7:115.

van der Hem PS, et al: The results of CO_2 laser surgery in patients with oral leukoplakia: a 25 year follow up. Oral Oncol 2005;41:31.

Acquired Dyskeratotic Leukoplakia

James and Lupton reported a patient with acquired dyskeratotic leukoplakia, which manifested as distinctive white plaques on the palate, gingivae, and lips (Fig. 34-18). There were similar lesions of the genitalia of the patient. Histologically, there was a unique finding of clusters of dyskeratotic cells in the prickle-cell layer in all affected sites.

Aggressive laser treatment was followed by recurrence. Use of etretinate afforded some improvement, but the condition continues unabated after 15 years.

James WD, et al: Acquired dyskeratotic leukoplakia. Arch Dermatol 1988;124:117.

White Sponge Nevus

The mouth, vagina, or rectum may be the site of this spongy, white overgrowth of the mucous membrane, with acanthosis,

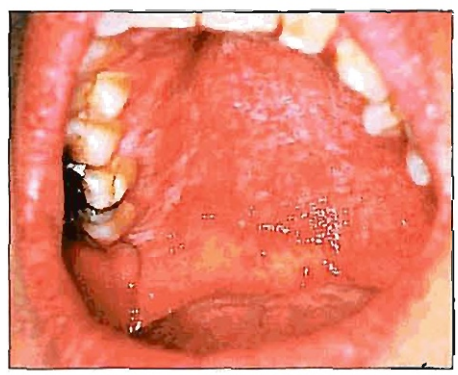

Fig. 34-18 Oral dyskeratotic leukoplakia.

vacuolated prickle cells, and acidophilic condensations in the cytoplasm of keratinocytes, which have been shown by electron microscopy to be aggregated tonofilaments. The buccal mucosa is the most common site of involvement. There are no extramucosal lesions. There is no treatment. Progression of the disorder generally stops at puberty. The disease is inherited as an autosomal-dominant disorder. A mutation in the mucosal keratin pair K4 and K13 has been identified as the inherited defect. HPV-16 DNA has been identified in some patients, the significance of which remains to be determined. Antibiotics, particularly tetracycline, give significant improvement.

Cox MF, et al: Human papillomavirus 16 DNA in oral white sponge nevus. Oral Surg Oral Med Oral Pathol 1992;73:476.
de Tomas MJ, et al: White sponge nevus. Med Oral 1999;4:494.
Iwanczak F, et al: Clinical quiz: white sponge nevus. J Pediatr Gastroenterol Nutr 2004;38:151.
Lim J, et al: Oral tetracycline rinse improves symptoms of white sponge nevus. J Am Acad Dermatol 1992;26:1003.

Melanocytic Oral Lesions

A wide variety of melanocytic lesions appear on the mucous membranes. Nevi of the oral mucosa in general are very uncommon. Among the melanocytic nevi of the cellular type, the intramucosal type is the most frequent, with the compound nevus next and the junction nevus occurring only rarely. Ephelis, lentigo, blue nevus, and labial melanotic macules are other types of focal hyperpigmentation. Ephelides darken on sun exposure and are usually limited to the lower lip. The blue nevus has dendritic cells in the submucosa. Lentigines show acanthosis of rete ridges on biopsy. Oral melanotic macules are solitary, sharply demarcated, flat, pigmented lesions that occur chiefly in young women, do not change on sun exposure, and show only acanthosis and basal-layer melanin on biopsy.

Oral melanoacanthoma is a simultaneous proliferation of keratinocytes and melanocytes. It is most commonly observed in young black patients (average age, 23) on the buccal mucosa. It seems to be a reactive process, usually following trauma and resolving spontaneously in 40% of patients.

Melanoma occurs rarely, mostly in older patients. It is recognized by being larger than the usual benign pigmented lesion, more irregular in shape, with a tendency to ulcerate and bleed. A peripheral areola of erythema and satellite pigmented spots may be present. There is a striking predilection for palatal (or, less often, gingival) involvement. The overall prognosis is poor (<5% survival at 5 years), because the lesions are usually deeply invasive by the time they are discovered. Whereas oral nevi are uncommon, biopsy of solitary pigmented oral lesions is indicated when the clinical diagnosis is uncertain.

Buchner A, et al: Relative frequency of solitary melanocytic lesions of the oral mucosa. J Oral Pathol Med 2004;33:550.
Casiglia J, et al: A comprehensive review of oral cancer. Gen Dent 2001;49:72.
Cebrian Carretero JL, et al: Melanoma of the oral cavity. Med Oral 2001;6:371.
Gaeta GM, et al: Oral pigmented lesions. Clin Dermatol 2002; 20:286.
Hicks MJ, et al: Oral mucosal melanoma. Oral Oncol 2000; 36:152.
Horlick HP, et al: Mucosal melanotic macule, reactive type. J Am Acad Dermatol 1988;19:786.
Maize JC: Mucosal melanosis. Derm Clin 1988;6:283.
Medina JE, et al: Current management of mucosal melanoma of the head and neck. J Surg Oncol 2003;83:116.
Sexton FM, et al: Melanotic macules and melanoacanthomas of the lip. Am J Dermatopathol 1987;9:438.

Oral Melanosis

Pigmentation of the oral cavity tends to occur most frequently in black persons. In other races, the darker the skin, the more mucosal pigmentation may be expected. Oral melanosis may occur with Albright syndrome, Peutz-Jeghers syndrome, Carney complex, Laugier-Hunziker disease, and Addison's disease, or rarely, as an idiopathic process with no associated disease.

James et al reported a patient with inflammatory acquired oral hyperpigmentation that first occurred at age 30 with numerous distinct pigmented macules, similar to those seen in Peutz-Jeghers syndrome. However, the condition progressed rapidly to a diffuse oral hyperpigmentation (Fig. 34-19). This appeared to be caused by an undefined inflammation, and slow partial resolution occurred after several years of observation.

In the differential diagnosis of oral hyperpigmentation, these other entities should be included. The amalgam tattoo is a focal, brownish-blue macule incurred from fragments of dental silver or amalgam being implanted into the gums (Fig. 34-20). Heavy-metal poisoning may also induce such

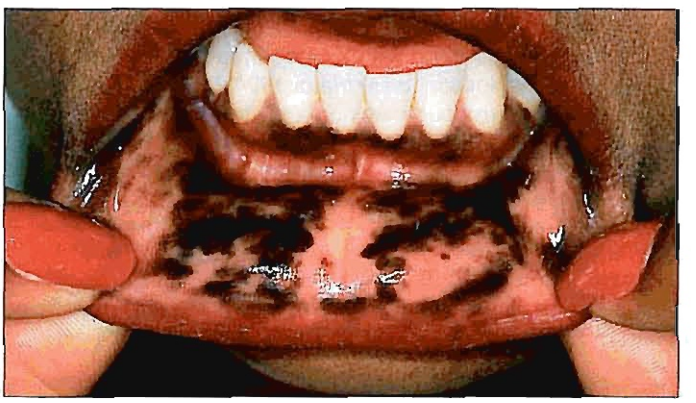

Fig. 34-19 Oral melanosis.

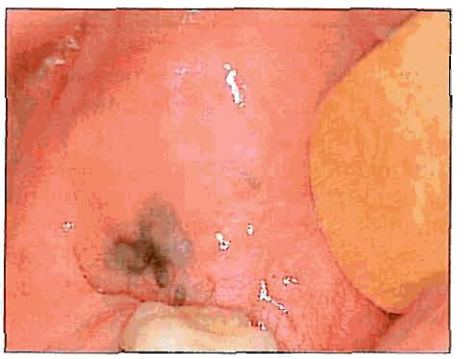

Fig. 34-20 Amalgum tattoo.

lesions. Bismuth, lead, and cis-platinium may produce a pigmented line along the gums near their margin. A multitude of medications will cause pigmentation. Amodiaquine, chloroquine, oral contraceptives, phenothiazines, phenolphthalein, quinacrine, quinidine, thallium, tobacco and zidovudine are among the most common of these.

Abdollahi M, et al: A review of drug-induced oral reactions. J Contemp Dent Pract 2003;15:10.
James WD, et al: Inflammatory acquired oral hyperpigmentation. J Am Acad Dermatol 1987;16:220.
Leanane P, et al: Oral pigmentation. J Eur Acad Dermatol Venereol 2000;14:448.

Osseous Choristoma of the Tongue

Osseous choristoma of the tongue presents as a nodule on the dorsum of the tongue containing mature lamellar bone without osteoblastic or osteoclastic activity. This does not recur after simple excision.

Supiyaphun P, et al: Lingual osseous choristoma. J Med Assoc Thai 2000;83:564.

Peripheral Ameloblastoma

This is a neoplasm of the gingivae, which appears most often on the lower jaw. Basal cell carcinoma can be simulated histologically; however, this does not occur intraorally; those reported are examples or ameloblastoma.

Hope L, et al: Peripheral ameloblastoma. J Oral Maxillofac Surg 2001;59:811.
Collangettes D, et al: Oral florid papillomatosis. Eur J Cancer B Oral 1993;29B:81.
Ishii Y, et al: Oral florid papillomatosis and leukoplakia of the esophagus associated with keratoderma and showing transepidermal elimination. J Dermatol 1994;21:974.
Schwartz RA: Verrucous carcinoma of the skin and mucosa. J Am Acad Dermatol 1995;32:1.

TRUMPETER'S WART

Trumpeter's wart is a firm, fibrous, hyperkeratotic, pseudoepitheliomatous nodule on the upper lip of a trumpet player. A similar callus may grow on the lower lip of trombone players.

Fisher AA: Dermatitis in a musician. Cutis 1998;62:214, 261.

EPULIS

The term *epulis* means any benign lesion situated on the gingiva. The majority of these are reactive processes that display varying degrees of fibrosis, inflammation, and vascular proliferation on biopsy.

Giant cell epulis (peripheral giant cell granuloma) is a solitary, bluish-red, 10- to 20-mm tumor occurring on the gingiva between or about deciduous bicuspids and incisors. They may be induced by dental implants. Similar lesions may occur in the autosomal-dominantly inherited syndrome, *cherubism*. Histologically, they resemble giant cell tumor of the tendon sheath.

Bischof M, et al: Peripheral giant cell granuloma associated with a dental implant. Int J Oral Maxillofac Implants 2004;19:295.

Pyogenic Granuloma

Pyogenic granuloma is an exuberant overgrowth of granulation tissue, frequently occurring in the oral cavity, most often involving the gingiva. It may also occur on the buccal mucosa, lips, tongue, or palate. It is a red to reddish-purple, soft, nodular mass that bleeds easily and grows rapidly, but is usually not painful. When it develops during pregnancy it is called *pregnancy tumor* or *granuloma gravidarum*.

Harris MN, et al: Lobular capillary hemangiomas. J Am Acad Dermatol 2000;42:1012.

GRANULOMA FISSURATUM

Granuloma fissuratum is a circumscribed, firm, whitish, fissured, fibrous granuloma occurring in the labioalveolar fold. The lesion is discoid, smooth, and slightly raised, about 1 cm in diameter. The growth is folded like a bent coin so that the fissure in the bend is continuous on both sides with the labioalveolar sulcus. Symptoms are slight. It is an inflammatory fibrous hyperplasia that usually results from chronic irritation caused by poorly fitting dentures. In the dental literature it is called *epulis fissuratum*, particularly when there is a deep cleft traversing the lesion. Treatment is by surgical extirpation, CO_2 laser ablation, or electrodesiccation after biopsy.

Gaspar L, et al: Manifestation of the advantages and disadvantages of using the CO_2 laser in oral surgery. J Clin Laser Med Surg 1990;8:39.

ANGINA BULLOSA HAEMORRHAGICA

The sudden appearance of one or more blood blisters of the oral mucosa characterizes this entity. There is no associated skin or systemic disease. The blisters may be recurrent, occur most often in the soft palate, and usually present in middle-aged or elderly patients. No treatment is necessary.

Dominguez JD, et al: Recurrent oral blood blisters. Arch Dermatol 1999;135:593.
Giuliani M, et al: Angina bullosa haemorrhagica. Oral Dis 2002;8:54.
Yip HK: Angina bullosa haemorrhagica. Gen Dent 2004;52:162.

MUCOCELE

The term *mucocele* refers to a lesion that occurs as a result of trauma or obstruction of the minor salivary ducts. The most common type is the mucous extravasation phenomenon, which is usually seen inside the lower lip because it is caused by trauma from biting (Fig. 34-21). The inside of the upper lip and buccal mucosa are uncommonly involved. It presents as a soft, rounded, translucent projection; it commonly has a bluish tint. The lesion varies from 2 to 10 mm in diameter. It is painless, fluctuant, and tense. Incision of it, or sometimes merely compression, releases sticky, straw-colored fluid (or bluish fluid if hemorrhage has occurred into it).

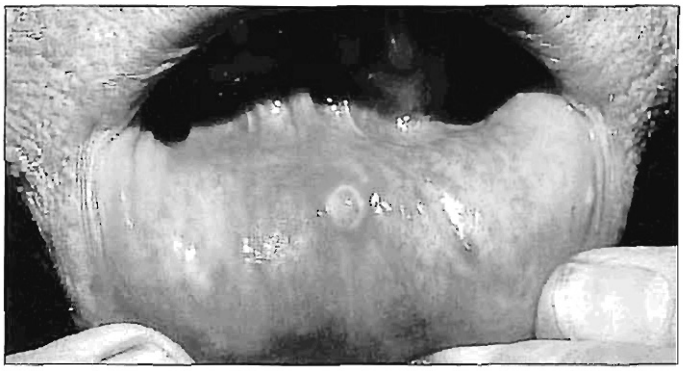

Fig. 34-21 Mucocele.

The cause is rupture of the mucous duct, with extravasation of sialomucin into the submucosa to produce cystic spaces with inflammation. Granulation tissue formation is followed by fibrosis. Excisional biopsy will document the diagnosis and eliminate the problem. Cryotherapy and argon laser ablation have also been reported to be successful.

There are true mucous retention cysts where there is true obstruction of the duct leading to an epithelial lined cavity. They are seen more in the posterior portions of the oral mucosa. A ranula (from *Rana*, the frog genus) is a mucocele of the floor of the mouth.

Two other cysts that may be present in the mouth are the parotid duct cyst, which occurs in musicians who use wind instruments (the cyst develops opposite the upper second molar on the buccal mucosa), and the dermoid cyst, which may occur on the floor of the mouth, especially in the sublingual area.

Bentley JM, et al: A review of common pediatric lip lesions. Clin Pediatr (Phila) 2003;42:475.

Gill D: Two simple treatments for lower lip mucoceles. Australas J Dermatol 1996;37:220.

Jensen JL: Superficial mucoceles of the oral mucosa. Am J Dermatopathol 1990;12:88.

Tran TA, et al: Removal of a large labial mucocele. J Am Acad Dermatol 1999;40:760.

ACUTE NECROTIZING ULCERATIVE GINGIVOSTOMATITIS (TRENCH MOUTH, VINCENT'S DISEASE)

Acute necrotizing ulcerative gingivitis (ANUG) is characterized by a rapid onset of characteristic punched-out ulcerations appearing on the interdental papillae and marginal gingivae. A dirty white pseudomembrane may cover the ulcerations. The lesions may spread rapidly and involve the buccal mucosa, lips, and tongue, as well as the tonsils, pharynx, and entire respiratory tract. The slightest pressure causes pain and bleeding. There is a characteristic foul, fetid odor that is always present. ANUG may lead to loss of clinical attachment of the gingiva and alveolar bone (necrotizing ulcerative periodontitis).

Trench mouth begins in a nidus of necrotic tissue, which provides an anaerobic environment for the infection by fusospirochetal organisms (*Bacteroides fusiformis*) in association with *Borrelia vincentii* and other organisms. Poor dental hygiene, smoking, poor nutrition, ingestion of methylenedioxymethamphetamine (ecstasy), and immunosuppression are predisposing factors. It may be seen as a component of the oral infections and inflammatory lesions that occur in immunocompromised HIV-infected patients.

Acute herpetic gingivostomatitis, primary HSV infection, may be confused with ANUG. Young children are susceptible to this severe febrile stomatitis with lymphadenitis. It is not primarily gingival in location and does not cause necrosis of the interdental papillae. Noma is a form of fusospirillary gangrenous stomatitis occurring in children with low resistance and poor nutrition. The onset is often triggered by measles. At the onset there is ulceration of the buccal mucosa; this rapidly assumes a gangrenous character and extends to involve the skin and bones, with resultant necrosis. It may end in the patient's death.

Treatment consists of thorough dental hygienic measures under the supervision of a dentist. Penicillin and debridement is the treatment of choice. Use of a 3% hydrogen peroxide mouthwash is also helpful.

Berthold P: Noma. Dent Clin North Am 2003;47:559.

Brazier WJ, et al: Ecstasy related periodontitis and mucosal ulceration. Br Dent J 2003;194:197.

Golayan MO: The epidemiology, etiology, and pathophysiology of acute necrotizing ulcerative gingivitis associated with malnutrition. J Contemp Dent Pract 2004;5:28.

Novak MJ: Necrotizing ulcerative periodontitis. Ann Periodontol 1999;4:74.

Salama C: Fusospirochetosis causing necrotic oral ulcers in patients with HIV infection. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;98:321.

ACATALASEMIA

Acatalasemia (Takahara's disease) is a rare disease in which the enzyme catalase is deficient in the liver, muscles, bone marrow, erythrocytes, and skin. There are several forms. The absence of catalase leads to progressive gangrene of the mouth, with recurrent ulcerations resulting from increased susceptibility to infection by anaerobic organisms.

Nearly 60% of affected individuals develop alveolar ulcerations, beginning in childhood. The mild type of the disease is characterized by rapidly recurring ulcers. In the moderate type, alveolar gangrene develops, with atrophy and recession of the alveolar bone, so that the teeth fall out spontaneously. In the severe type, widespread destruction of the jaw occurs. After puberty all lesions heal, even in individuals who have the severe type.

There is no gross difference in appearance between the blood of an acatalasic patient and that of a normal individual, but when hydrogen peroxide is added to a sample of blood, acatalasic blood immediately turns blackish-brown and the peroxide does not foam. Normal blood remains bright and causes the peroxide to foam exuberantly because of the presence of erythrocyte catalase.

Acatalasia is a rare peroxisomal disorder and is inherited as an autosomal-recessive trait. Treatment consists of extraction of the diseased teeth and the use of antibiotics to control the harmful effects of the offending bacteria.

Ogata M: Acatalasemia. Hum Genet 1991;86:331.

Perner H, et al: Acatalasemia—Takahara's disease. Hautazrt 1999;50:590.

CYCLIC NEUTROPENIA

Cyclic, or periodic, neutropenia is characterized by a decrease of circulating neutrophils and dermatologic manifestations. At regular intervals (21 days), neutropenia and mouth ulcerations develop, usually accompanied by fever, malaise, and arthralgia. Ulcerations of the lips, tongue, palate, gums, and buccal mucosa may be extensive. The ulcers are irregularly outlined and are covered by a grayish-white necrotic slough. The anterior teeth may show a grayish-brown discoloration. Premature alveolar bone loss and periodontitis occur. In addition, opportunistic cutaneous infections, such as abscesses, furuncles, noma, pyomyositis, and cellulitis, may develop during the neutropenic stage. Urticaria and erythema multiforme have been reported.

There is a cyclic depression of neutrophils occurring at intervals of 12 to 30 days (average, 21 days) and lasting 5 to 8 days. The neutrophils in the peripheral blood regularly fall to low levels or completely disappear. Some cases have been associated with agammaglobulinemia. The cause of cyclic neutropenia is a germline mutation of the gene encoding neutrophil elastase (ELA2). This is thought to produce apoptosis of bone marrow progenitor cells. Both the autosomal-dominant disease and sporadic cases have this abnormality. Severe congenital neutropenia is caused by a mutation in the same gene but at a different site. The latter condition predisposes to the development of myelodysplasia and acute myelogenous leukemia, while cyclic neutropenia does not.

In the differential diagnosis are other periodic fever syndromes, including periodic fever, aphthous stomatitis, pharyngitis and adenopathy (PFAPA) syndrome, Mediterranean fever, Hibernian fever and hyperimmunoglobulin D syndrome. PFAPA syndrome is defined clinically and is characterized by 4 days of high fevers (>40° C) that recur at regular intervals every 2 to 8 weeks separated by wellbeing between episodes. Associated with fevers are aphthous stomatitis (70%), pharyngitis (72%), and cervical adenitis (88%). It is not familial, begins before 5 years of age, and responds to small doses of prednisone for 1 to 2 days. Tonsillectomy has been reported to cure it.

Use of recombinant human granulocyte colony-stimulating factor (G-CSF) has been successful in the treatment of cyclic neutropenia patients. If the potential side effects limit use of this therapy, cyclosporin has been reported to be effective also. Administering antibiotics during infections seems to expedite recovery. Careful attention to oral hygiene, including plaque control, helps improve mouth lesions and reduces the risk of infections. Death may occur from pneumonia, sepsis, gangrenous pyoderma, or granulocytopenia.

Berlucchi M, et al: Update on treatment of Marshall's syndrome (PFAPA syndrome). Ann Otol Rhinol Laryngol 2003;112:365.

Dale DC, et al: Mutations in the gene encoding neutrophil elastase in congenital and cyclic neutropenia. Blood 2000; 96:2317.

Dale DC, et al: Cyclic neutropenia. Semin Hematol 2002;39:89.

Feder HM Jr: Periodic fever, aphthous stomatitis, pharyngitis, adenitis. Curr Opin Pediatr 2000;12:253.

Horwitz M, et al: Mutations in ELA2, encoding neutrophil elastase, define a 21-day biological clock in cyclic neutropenia. Nat Genet 1999;23:433.

Scholl PR: Periodic fever syndromes. Curr Opin Pediatr 2000; 12:563.

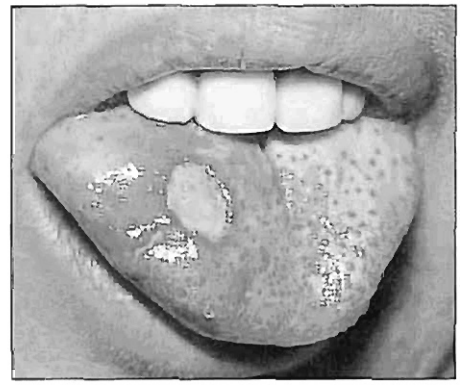

Fig. 34-22 Chronic herpes in a patient on cancer chemotherapy.

RECURRENT INTRAORAL HERPES SIMPLEX INFECTION

Recurrent intraoral infection with HSV is characterized by numerous small, discrete vesicles occurring in one or a few clusters. The site of involvement is a key feature in suspecting the diagnosis. The keratinized or masticatory mucosa (the palate, gingiva, and tongue) are affected. The grouped vesicles rupture rapidly to form punctate erosions with a red base. Smears from the base prepared with Wright stain will show giant multinucleated epithelial cells. Immunofluorescent tests and viral cultures are also confirmatory.

The differential diagnosis of this uncommon manifestation of HSV includes oral herpes zoster, herpangina, and oral aphthosis. The latter two involve nonattached mucosa, whereas recurrent HSV involves mucosa fixed to bone. Differentiation from zoster is made on clinical grounds or by culture and immunofluorescent testing.

Chronic progressive ulcerative and nodular intraoral herpes are seen occasionally in HIV-infected patients, or those with leukemia or neutropenia (Fig. 34-22).

Bruce AJ, et al: Acute oral ulcers. Dermatol Clin 2003;21:1.

Hirota TK, et al: a 64-year-old man with glossitis. Arch Dermatol 2001;137:85.

Glick M: Clinical aspects of recurrent oral herpes simplex virus infection. Compend Contin Educ Dent 2002;23(7 Suppl 2):4.

RECURRENT APHTHOUS STOMATITIS (CANKER SORES, APHTHOSIS)

Clinical Features

Aphthous stomatitis is a painful, recurrent disease of the oral mucous membrane. It begins as small, red, discrete or grouped papules, which in a few hours become necrotizing ulcerations. They are small, round, shallow, white ulcers (aphthae) generally surrounded by a ring of hyperemia (Fig. 34-23). As a rule, they are tender; they may become so painful that they interfere with speech and mastication. They are mostly about 5 mm in diameter but may vary in size from 3 to 10 mm. When larger, they are called *major aphthae*. Usually, one to five lesions occur per attack; however, they may occur in any number. They are located in decreasing frequency on the buccal and labial mucosa, edges of the tongue, buccal and lingual sulci, and soft palate. There is a marked predilection for the nonkeratinized mucosa (any not bound to underlying periosteum). This and the fact that they

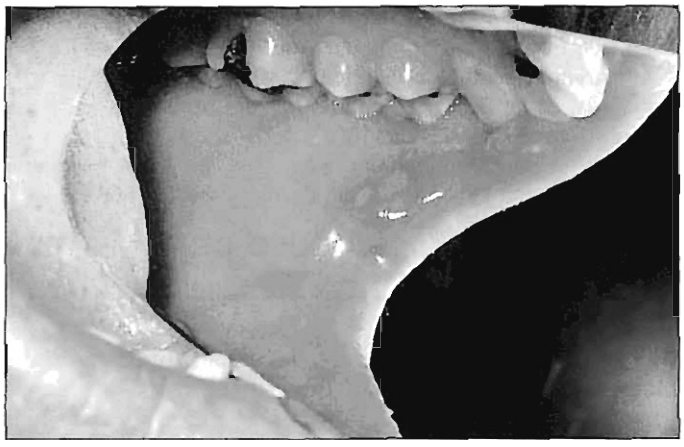

Fig. 34-23 Apthous stomatitis.

are rarely confluent, even when they occur as small crops of 1- or 2-mm lesions (herpetiform aphthae), help to distinguish them from the uncommon recurrent intraoral HSV infection. Aphthae may also occur on the vagina, vulva, penis, anus, and even the conjunctiva.

The lesions tend to involute in 1 to 2 weeks, but recurrences are common. These recurrences may be induced by trauma, such as self-biting, toothbrush injury, and dental procedures, spicy foods, citrus, fresh pineapple, walnuts, allergy, emotional stress, or hormonal changes in women, such as in menstruation, pregnancy, menarche, and menopause. A familial predisposition has also been described as familial epidemic aphthosis.

Recurrent aphthous stomatitis is the most common lesion of the oral mucosa, affecting from 10% to 20% of the population. It starts commonly in the second or third decade and patients may experience recurrent bouts of lesions several times yearly for many decades. A not uncommon presentation in children is a syndrome characterized by periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA). The high fevers and associated findings occur with striking periodicity every 4 weeks, last 4 to 6 days, and resolve only to recur the following month. The children are otherwise well. One or two dose of prednisone (2 mg/kg) aborts the attack and tonsillectomy may cure it.

Ulcerations such as these may also be the presenting sign in Beçhet syndrome. HIV infection, malabsorption, syndromes, gluten-sensitive enteropathy, pernicious anemia, cyclic neutropenia, neutropenia, ulcerative colitis, and Crohn's disease. History, physical examination, complete blood count, and long-term follow-up documenting the recurrent course in the absence of other symptoms will secure the diagnosis. Some patients have aphthosis associated with low folate or iron levels, so testing should include evaluation of these.

Etiologic Factors

Although individual patients often suspect one of the factors mentioned above is responsible for precipitating their recurrence, infectious or immunologic causation is favored by investigators. The true cause is unknown.

Histologically, the lesion consists of a lymphocytic inflammatory infiltration with occasional plasma cells and eosinophils, which suggests delayed hypersensitivity.

Diagnosis

Aphthous stomatitis must be differentiated from mucous patches of early syphilis, candidiasis, Vincent angina, the avitaminoses (particularly pellagra and scurvy), erythema multiforme, pemphigus, cicatricial pemphigoid, lichen planus, primary HSV infection of the mouth, recurrent labial herpes, and recurrent intraoral HSV infection.

Treatment

No permanent cure is available. Several topical agents will lessen the pain. A mixture of equal parts of elixir of Benadryl and Maalox held in the mouth for 5 min before meals is soothing. Kaolin may also be added to the mixture. Lidocaine (Xylocaine Viscous) 2% solution, keeping 1 teaspoonful in the mouth for several minutes, is helpful in allaying pain. Another useful topical anesthetic is dyclonine hydrochloride (Dyclone) 0.5% applied to the lesions. A large number of reasonably effective over-the-counter remedies are also available. Triggers, such as spicy foods, citrus, walnuts, pineapple, and other irritating substances should be avoided.

One may use other measures to shorten the course and induce healing of lesions. A mixture of equal parts of fluocinonide ointment and Orabase applied to the ulcers three or four times a day is effective in aiding the healing of existing ulcer; however, it does not prevent new ulcers. Some patients object to the thick sticky texture of Orabase and prefer fluocinonide gel. Clobetasol ointment can also be very effective. Intralesional steroids and short 3- or 4-day courses of oral steroids may help, particularly for indolent or large lesions. Nonsteroidal alternatives include 5 mL of an oral suspension of containing 250 mg of tetracycline; this is held in the mouth for 2 min and then swallowed. This is done four times daily for 1 week. Amlexanox 5% oral paste (Aphthasol) is a useful topical therapy to both induce healing and relieve pain. Sucralfate suspension, alone or compounded with a topical steroid, may be useful as has been described in peptic ulcer disease and the ulcerations of Behçet's disease.

To try to prevent new lesions known triggers for the individual patient should be avoided as much as possible. Dapsone in doses of 25 to 50 mg/day or colchicine 0.6 mg two or three times a day, may be tried. Thalidomide is another effective alternative, but caution regarding teratogenicity and neurotoxicity is necessary if this is to be considered. One method is thalidomide, 300 mg/day to start, 200 mg/day after 10 days, and 100 mg/day after 2 months. Relapses were treated with 100 mg/day for 12 days.

Several investigators have reported finding low folate, iron, or B_{12} levels in about 20% of aphthosis patients investigated, but others do not see this with such high frequency. Still, it is worth investigating as correction of the abnormality clears or improves the condition in most cases where an abnormality exists.

Akintoye SO, et al: Recurrent aphthous stomatitis. Dent Clin North Am 2005;49:31.

Berlucchi M, et al: Update on treatment of Marshall's syndrome (PFAPA syndrome). Ann Otol Rhinol Laryngol 2003;112:365.

Bruce AJ, et al: Acute oral ulcers. Dermatol Clin 2003;21:1.

Casiglia JM: Recurrent aphthous stomatitis. Gen Dent 2002; 50:157.

Flaitz CM, et al: Treatment approaches to common symptomatic oral lesions in children. Dent Clin North Am 2000;44:671.

Jacobson JM, et al: Thalidomide for the treatment of oral aphthous ulcers in patients with human immunodeficiency virus infection. N Engl J Med 1997;336:1487.
Katz J, et al: Prevention of recurrent aphthous stomatitis with colchicine. J Am Acad Dermatol 1994;31:459.
MacPhail L: Topical and systemic therapy for recurrent aphthous stomatitis. Semin Cutan Med Surg 1997;16:301.
Manders SM, et al: Thalidomide-resistant HIV-associated aphthae successfully treated with granulocyte colony-stimulating factor. J Am Acad Dermatol 1995;33:380.
Perri AJ 3rd, et al: A review of thalidomide's history and current dermatological applications. Dermatol Online J 2003;9:5.
Rogers RS III: Recurrent aphthous stomatitis. Semin Cutan Med Surg 1997;16:278.
Scully C, et al: The diagnosis and management of recurrent aphthous stomatitis. J Am Dent Assoc 2003;134:2000.
Shashy RG, et al: Aphthous ulcers. Am J Otolaryngol 2000;21:389.
Ship JA, et al: Recurrent aphthous stomatitis. Quintessence Int 2000;31:95.
Zunt SL: Recurrent aphthous stomatitis. Dermatol Clin 2003;21:33.

MAJOR APHTHOUS ULCER (PERIADENITIS MUCOSA NECROTICA RECURRENS)

In Sutton's disease, a major aphthous ulcer begins as a small shotlike nodule on the inner lip, buccal mucosa, or tongue, which breaks down into a painful sharply circumscribed ulcer with a deeply punched out and depressed crater.

It may at times begin in the faucial pillars or oropharynx (Fig. 34-24). It may persist for 2 to 12 weeks before healing with a soft, pliable scar. There are seldom more than one to three lesions present at one time. However, remissions tend to be short, and new lesions may appear before old ones have quite healed. The term *major aphthous ulcers* has supplanted the unwieldy Latin name for this disease.

The cause is unknown, but evidence favors an immunologic or infectious etiology. These painful lesions are frequently present in HIV-infected patients who may experience similar lesions in the esophagus, rectum, anus, and genitals.

Treatment is difficult, and the general measures discussed under recurrent aphthae should be employed. Intralesional or systemic steroids in short courses, which may be effective, are often given. If recurrences are such that systemic steroids are prescribed for more than two or three short courses per year, alternative oral medications such as colchicine, dapsone or thalidomide may be tried.

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BEHÇET SYNDROME (OCULO-ORAL-GENITAL SYNDROME)

Clinical Features

Behçet syndrome consists of recurrent oral aphthous ulcerations that recur at least three times in one 12-month period in the presence of any two of the following: recurrent genital ulceration, retinal vasculitis or anterior or posterior uveitis, cutaneous lesions (*erythema nodosum; pseudo*-folliculitis or papulopustular lesions; or acneiform nodules in postadolescent patients who are not receiving corticosteroid treatment), or a positive pathergy test.

Oral lesions occur on the lips, tongue, buccal mucosa, soft and hard palate, tonsils, and even in the pharynx and nasal cavity. The lesions are single or multiple, 2 to 10 mm or larger in diameter, and sharply circumscribed, with a dirty grayish base and a surrounding bright red halo. Other patients show deep ulcerations that leave scars resembling those caused by Sutton major aphthous ulcers. The lesions are so painful that eating may be difficult. A foul mouth odor is in most cases markedly noticeable.

Genital lesions occur in men on the scrotum (Fig. 34-25) and penis or in the urethra; in women, on the vulva, cervix, or vagina; they may be found in both sexes on the genitocrural fold, anus, perineum, or in the rectum. These ulcerations are similar to those seen in the mouth. In addition, macules, papules, and folliculitis may develop on the scrotum. Lesions in women may lead to deep destruction of the vulva. Swellings of the regional nodes and fever may accompany oral and genital attacks.

The ocular lesions start with intense periorbital pain and photophobia. Retinal vasculitis is the most classic eye sign and the chief cause of blindness. Conjunctivitis may be an early, and hypopyon a late, accompaniment of uveitis. Iridocyclitis is frequently seen. Both eyes are eventually involved. Untreated disease leads to blindness from optic atrophy, glaucoma or cataracts.

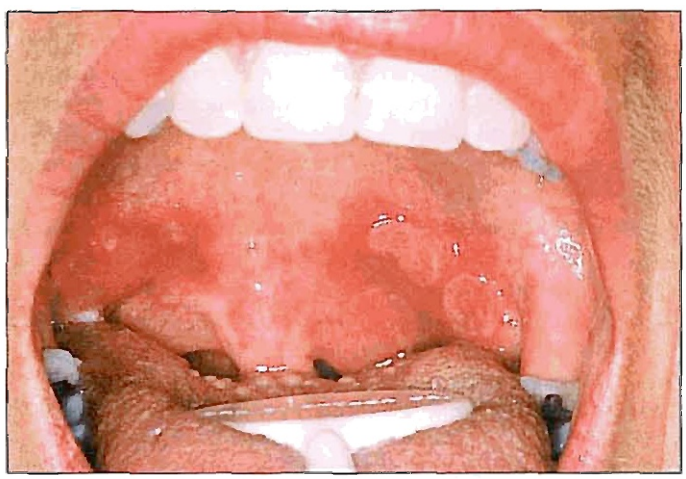

Fig. 34-24 Major apthae.

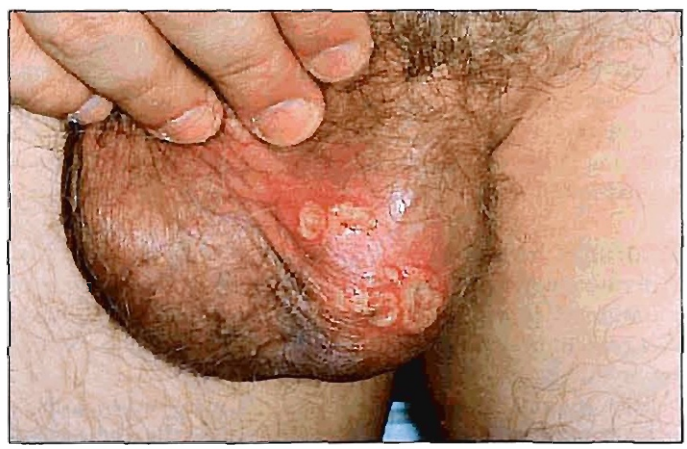

Fig. 34-25 Behçet disease.

Neurologic manifestations are mostly in the central nervous system and resemble most closely those of multiple sclerosis. Remissions and exacerbations are the rule. Thrombophlebitis occurs with some frequency. Thrombosis of the superior vena cava may also occur. Arthralgia is most often present in the form of polyarthritis.

Unfortunately, the international criteria include nonspecific common cutaneous lesions (pseudofolliculitis, papulopustular or acneiform lesions). Demonstration of either leukocytoclastic vasculitis or a neutrophilic vascular reaction on histologic examination of a lesion would make the cutaneous criteria more specific.

There is a relatively high prevalence of Behçet's disease in the Far East and Mediterranean countries, whereas in the US and Western Europe it is much less common. In large series of patients from areas of high prevalence, men with an age of onset in the 30s predominate. Mangelsdorf et al reported on 25 patients seen in a university dermatology referral practice in the US; 22 of their patients were young women with a high frequency of mucocutaneous lesions and a low prevalence of ocular involvement. This may reflect referral bias or could indicate the disease is less severe in the US.

On histologic examination, the early lesions show a leukocytoclastic vasculitis. There is perivascular infiltration, which is chiefly lymphocytic in older lesions, with endothelial proliferation that obliterates the lumen. The cause of Behçet's disease has been postulated to have an infectious, immunologic and/or genetic basis but the evidence is still inconclusive for any of these.

Diagnosis

Usually the disease starts with one oral ulceration, followed by others. It may take years before additional lesions develop. Therefore, the diagnosis requires two classic signs in addition to oral ulcerations. In women anal and genital lesions predominate, often with subsequent involvement of the eyes.

Behçet's disease must be differentiated from herpetic or aphthous stomatitis, pemphigus, oral cancer, and Stevens-Johnson syndrome (erythema multiforme). A skin puncture or pathergy test may be used to investigate patients further; however, it is not reliable in that it may be negative in otherwise well-documented cases. It is done by injecting 0.1 mL of normal saline solution into the skin or by simply pricking the skin with a sterile needle. A pustule appears at the site within 24 h. If results are negative, the test should be repeated at two to five points before results are accepted. Pathergy has been observed in patients with Behçet's disease, pyoderma gangrenosum, Sweet syndrome, and bowel-associated dermatosis–arthritis syndrome.

Treatment

Usually the ulcerations heal spontaneously. Mild mouthwashes and toothpastes and restricted use of the toothbrush should be prescribed when there are oral lesions. With regard to treating the symptoms and healing of the aphthae, local treatments as described for aphthae may be used. Sucralfate suspension has been studied in Behçet oral and genital ulcers and was found to decrease pain and healing time. On the whole, the therapeutic problem of aphthosis is not the healing of the individual lesions but the prevention of new attacks. For that purpose several options exist, none of which is optimal. Colchicine, 0.6 mg twice a day, may be started for 2 weeks. In the absence of response and gastrointestinal side effects, the dose may be increased to three times a day. Although this may not totally alleviate the mucocutaneous lesions, it may decrease their recurrence rate by 50% or more. Dapsone may be substituted or added to this for improvement of response. The usual therapeutic final dose is 100 mg/day. Thalidomide has been found to be effective in many patients. One dosing method is thalidomide 200 mg twice a day for 5 days and 100 mg twice a day for 15 to 60 days. It had no effect on iridocyclitis. Of course, long-term treatment will commonly be complicated by neurotoxicity and the teratogenicity of this medication is well known.

Methotrexate in a weekly oral dose of 7.5 to 20 mg should be reserved for severe refractory cases, as should more aggressive systemic treatments such as systemic corticosteroids, azathioprine, chlorambucil, cyclosporin, and cyclophosphamide.

The long-term outlook is for intermittent recurrent flares that may be life-long. Blindness, neurologic impairment and vascular thromboses are potential serious complications.

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CHAPTER

35 Cutaneous Vascular Diseases

RAYNAUD PHENOMENON AND RAYNAUD'S DISEASE

Raynaud phenomenon occurs in the presence of an associated disease, usually collagen vascular disease. Raynaud's disease occurs in the absence of such disease. In a series of 165 patients with Raynaud, 51 had primary disease (Raynaud's disease). A defined connective tissue disease was present in about a third of the remaining patients, but 54 had undefined connective tissue disease (35 with positive antinuclear antibody [ANA] titer). In another study of 142 patients with idiopathic Raynaud phenomenon followed for more than 10 years, 14% progressed to a definite connective tissue disease. The initial presence of ANAs, thickening of fingers, older age at onset, and female sex were predictors of connective tissue disease.

Raynaud Phenomenon

Raynaud phenomenon is produced by an intermittent constriction of the small digital arteries and arterioles. The digits have sequential pallor, cyanosis, and rubor (Fig. 35-1). The involved parts are affected in paroxysms by the attacks of ischemia, which cause them to become pale, cold to the touch, and numb. The phenomenon is more frequently observed in cold weather. When exposed to cold the digits become white (ischemic), then blue (cyanotic), and finally red (hyperemic). In time the parts may fail to regain their normal circulation between attacks and become persistently cyanotic and painful. If this phenomenon persists over a long period, punctate superficial necrosis of the fingertips develops; later, even gangrene may occur.

Raynaud phenomenon occurs most frequently in young to middle-aged women. It occurs with scleroderma, dermatomyositis, lupus erythematosus, mixed connective tissue disease (MCTD), Sjögren syndrome, rheumatoid arthritis, and paroxysmal hemoglobinuria. Scleroderma is the underlying diagnosis in more than half of patients in one series. Occlusive arterial diseases such as embolism, thromboangitis obliterans, and arteriosclerosis obliterans may be present. In addition, various diseases of the nervous system, cervical rib and the scalenus anticus syndrome, may produce the disorder. Physical trauma such as pneumatic hammer operation and that incurred by pianists and typists may also induce this phenomenon. Medications such as bleomycin or ergot may also be the cause. The clumping of red blood cells is believed to be responsible for the induction of Raynaud phenomenon with high titers of circulating cold agglutinins. It may occur in cryoglobulinemia and polycythemia vera.

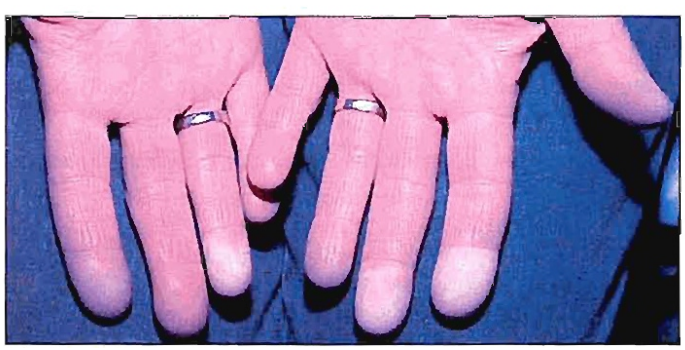

Fig. 35-1 Raynaud disease.

Simple tests and physical examination will generally distinguish between Raynaud's disease and Raynaud phenomenon. Sclerodactyly, digital pitted scars, puffy fingers with telangiectases, positive ANA, subcutaneous calcifications, basilar lung fibrosis, and changes on nailfold capillary microscopy (avascular "skip" areas with irregularly dilated capillary loops) are signs of connective tissue disease. Nailfold capillary changes are helpful prognostic indicators and periodic acid-Schiff (PAS)-positive globules in the proximal nailfold detected on biopsy correlate with connective tissue disease. An anticentromere antibody is an indicator of CREST syndrome.

Raynaud's Disease

Raynaud's disease is a primary disorder of cold sensitivity primarily seen in young women. The intermittent attacks of pallor, cyanosis, hyperemia, and numbness of the fingers are identical to those in Raynaud phenomenon. The disease is usually bilateral, and gangrene occurs in less than 1% of cases.

The diagnosis requires the absence of the diseases enumerated under Raynaud phenomenon. Although the current dictum is that Raynaud's disease should be present for 2 years before being classified as a primary process, it may take as long as 11 years for some systemic disorders to manifest. Overall, fewer than half of patients presenting with Raynaud symptoms will prove to have a connective tissue disease. The prognosis is good for idiopathic Raynaud's disease, although pulmonary hypertension has been reported.

Etiology

The cause of Raynaud phenomenon/disease is multifactorial. Increased α-2 sympathetic receptor activity on vessels, endothelial dysfunction, deficiency of calcitonin gene-related peptide protein-containing nerves and a central thermoregulatory defect have been implicated. Increased tyrosine phosphorylation by protein tyrosine kinase mediates cooling-induced contraction in Raynaud's disease. Elevated endothelin-1, a vasoconstrictor, has been found in Raynaud phenomenon/disease and systemic sclerosis. Women receiving unopposed estrogen replacement are twice as likely to

experience Raynaud phenomenon as women not receiving estrogen replacement or women receiving estrogen and progesterone. Infusion of calcitonin gene-related peptide in patients with Raynaud phenomenon demonstrates increased hand temperatures compared with saline controls, suggesting it opposes the vasoconstrictive mediators of the disease. Patients with ulcers healed with infusions, compared with none of the patients treated with saline controls.

Treatment

In both Raynaud phenomenon and Raynaud's disease, exposure to cold should be avoided. This includes avoidance of exposure to cold not only of the extremities but also of other parts of the body, since vasospasm may be induced by cooling of the body alone. Warm gloves should be worn whenever possible. Residence in a warm climate is helpful. Trauma to the fingertips should be avoided. Smoking is forbidden.

Vasodilating drugs may be helpful, including nifedipine, 10 to 20 mg three times a day, or prazosin, 1 mg three times a day increased to 3 mg three times a day. Nifedipine is considered to be the gold standard, and two-thirds of treated patients will respond favorably. The newer second-generation dihydropyridines, such as amlodipine, isradipine, nicardipine, and felodipine, have also been shown effective and are associated with few side effects. Silenafil and related drugs have been used. Pentoxifylline and stanozolol have shown variable success. An angiotensin II-receptor type I antagonist (losartan) or a selective serotonin-reuptake inhibitor (fluoxetine) may be useful in refractory cases. Tolazoline hydrochloride (Priscoline), 50 mg three times a day, can be helpful in mild cases. Preliminary data on low level laser irradiation appear promising in an open case series, suggesting that physical modalities could supplement or replace drug therapy in some patients.

The local application of 2% nitroglycerin in an ointment base (Nitro-Bid, Nitrostat) will give relief to some patients, but topical vasodilators may shift the blood supply to more vascularized areas and must be used cautiously. Sublingual administration of nitroglycerin was effective in only 2 of 10 patients in one study, while 8 of 10 were improved by biofeedback training, even 8 weeks after the sessions were over.

In severe, disabling cases of Raynaud with trophic changes, sympathectomy has been successful. Sympathetic ganglionectomy with resection of the sympathetic trunk for both the upper and lower extremities has produced good or excellent results in some series. Unfortunately, the effect is often temporary, lasting for only 6 months to 2 years.

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ERYTHROMELALGIA

Also called *erythermalgia* and *acromelalgia*, this rare form of paroxysmal vasodilation affects the feet with burning, localized pain, redness, and high skin temperature. Infrequently, the upper extremities may be involved. The burning paroxysms may last from a few minutes to several days, and are usually triggered by an increase in environmental temperature. Erythromelalgia is sometimes associated with Raynaud phenomenon, an interesting paradox as one manifests with vasodilatation and the other with constriction.

The disease may be primary or secondary to diseases such as polycythemia vera, thrombotic thrombocytopenic purpura, thrombocythemia, peripheral neuritis, myelitis, multiple sclerosis, systemic lupus erythematosus (SLE), hypertension, or diabetes mellitus. Acquired disease has been reported after topical exposure to isopropyl alcohol and after mushroom poisoning with *Clitocybe acromelalga and Clitocybe amoenolens*. Calcium-channel blockers and cyclosporin have been used to treat patients, but may exacerbate or even induce the condition. Childhood erythromelalgia often appears without an underlying disorder, may be familial, and tends to be resistant to aspirin. Autosomal-dominant inheritance has been linked to chromosome 2q, and mutations in SCN9A, a gene encoding a voltage-gated sodium channel α subunit expressed in sensory and sympathetic neurons. The pathophysiology is poorly understood. Many believe the disorder is related to peripheral small fiber neurotransmission and disturbed platelet function. Defective conduction in sympathetic peripheral fibers (C fibers) has been demonstrated in the majority of patients studied.

Erythromelalgia caused by thrombocytosis often responds to aspirin. Erythromelalgia caused by underlying disease processes tends to respond to treatment of the primary disorder. The symptoms may be relieved by measures, such as immersion in cold water, that cool the skin. Good results have been obtained with serotonin antagonists (methysergide, pizotifen, and sertraline) in some patients, which suggests that this may be a disease of peripheral serotonin activity. Misoprostol, 0.4–0.8 mg/day, was effective in a blinded trial. Iloprost, a synthetic prostacyclin analog, was effective in a small double-blinded trial. Other treatment modalities have been anecdotally successful, including propranolol, clonazepam, cyproheptadine, tricyclic antidepressants, anticonvulsants such as gabapentin, epinephrine, ephedrine, sublingual isoproterenol hydrochloride, nitroglycerin ointment, prednisone, phlebotomy, sodium nitroprusside, venlafaxine, oral magnesium, lumbar ganglionectomy, and peripheral nerve block or section.

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LIVEDO RETICULARIS

Livedo reticularis is a netlike mottled or reticulated pink or reddish-blue discoloration of the skin, mostly on the extremities, especially the legs. Exposure to cold usually accentuates the intensity of discoloration, although the lesions may be fixed and remain present on warming (sometimes referred to as *livedo racemosa*) (Fig. 35-2). The lesions are often asymptomatic; in other cases, coldness, numbness, paresthesia, or a dull ache may be present. Necrotizing livedo reticularis may be associated with cutaneous nodules and ulcerations.

Most cases are unassociated with any underlying cause, but livedo reticularis may be a manifestation of lupus erythematosus, dermatomyositis, scleroderma, rheumatic fever, or rheumatoid arthritis. It may be seen with hepatitis C, parvovirus B19, syphilis, meningococcemia, pneumococcal sepsis, tuberculosis, pancreatitis, decompression sickness, various forms of arteritis, Wegener granulomatosis, polycythemia vera, hypercalcemia, pheochromocytoma, mycosis fungoides, breast cancer, and thrombocytopenic purpura. It is a side effect of amantadine (Symmetrel), and has been reported as a photosensitivity phenomenon in patients taking quinidine. Some patients on long-term minocycline therapy have been shown to develop drug-induced arthritis, fever, livedo reticularis, and positive peripheral antineutrophil cytoplasmic autoantibodies (P-ANCA) titers. Livedo reticularis may be a complication of arteriography.

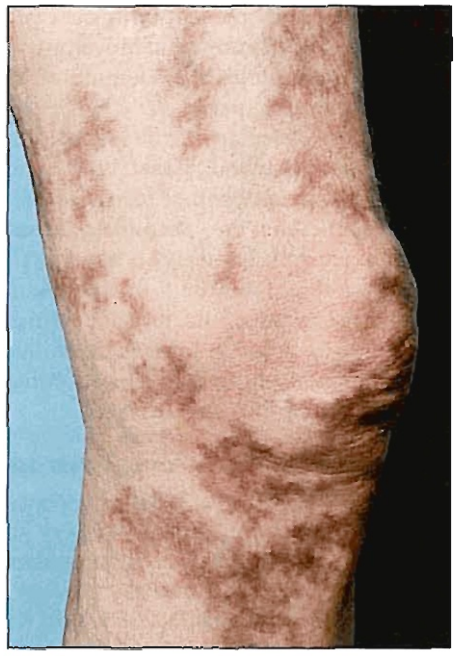

Fig. 35-2 Livedo racemosa.

Cholesterol emboli resulting from severe atherosclerotic disease may cause uni- or bi-lateral livedo reticularis. Patients frequently have concomitant cyanosis, purpura, nodules, ulceration, or gangrene. Peripheral eosinophilia is common. Older men with severe atherosclerotic disease are most affected. They are often on anticoagulant therapy, and many have recently undergone vascular surgery or instrumentation. The differential diagnosis includes vasculitis, septic staphylococcal emboli resulting from endocarditis or an infected aneurysm, and periarteritis nodosa. Mortality is 72%. Deep biopsy with serial sections may demonstrate the characteristic cholesterol clefts within thrombi. Frozen section evaluation with polarized microscopy is particularly sensitive. Livedo reticularis of recent onset in an elderly person warrants consideration of this diagnosis.

Necrotizing livedo reticularis has been reported with leukocytoclastic vasculitis, heparin-associated thrombosis, cryoglobulinemia, calciphylaxis, calcifying panniculitis, oxalosis, compressed air injury, bismuth or pentazocine injections, atrial myxomas, Wegener granulomatosis, Graves' disease, acute lymphocytic leukemia, renal cancer, SLE, and other connective tissue diseases.

Sneddon syndrome usually presents in young to middle-aged women. They present with livedo reticularis, then develop cerebrovascular infarcts. The prognosis is poor. Some patients have antiphospholipid antibodies and may have SLE. Up to 35% will be positive for antiendothelial cell antibodies (AECA). In some families, Sneddon syndrome may be inherited in an autosomal-dominant fashion.

Patients with SLE and livedo reticularis are apt to have more severe disease manifestations, such as renal disease, vasculitis, and anticardiolipin antibodies, even in the absence of Sneddon syndrome. Patients with antiphospholipid syndrome and livedo reticularis are more likely to develop epilepsy than those without livedo reticularis. Among patients with chronic headaches, the presence of livedo reticularis may be a marker for an increased risk of stroke.

Moyamoya's disease is a rare, chronic cerebrovascular occlusive disease characterized by progressive stenosis of the

arteries in the circle of Willis. Patients present with ischemic strokes or cerebral hemorrhages. Both idiopathic Moyamoya's disease and disease associated with factor V Leiden mutation have been associated with livedo reticularis.

Oxalosis may lead to livedo reticularis from deposition of oxalate crystals in and around blood vessel walls. The primary type comprises two rare autosomal-recessive disorders, each lacking one specific enzyme. Secondary forms also occur. The characteristic crystals are seen on biopsy.

Cutis marmorata is physiologic mottling of the skin. The skin resembles marble because of its mottled bluish discoloration. It is commonly seen on the lower extremities in young children and women exposed to cold. The mottling usually disappears when the extremities are warmed.

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LIVEDOID VASCULOPATHY

Synonyms for livedoid vasculopathy include *livedoid vasculitis*, *atrophie blanche*, and *PURPLE (painful purpuric ulcers with reticular pattern of the lower extremities)*. The histologic features of leukocytoclastic vasculitis are absent, so the term vasculopathy is preferred over vasculitis. The vasculopathy is characterized clinically by early, focal, painful purpuric lesions of the lower extremities that frequently ulcerate and heal slowly (Fig. 35-3). The ulcers heal with small, stellate and reticulated, white scars referred to as *atrophie blanche*. They may also show telangiectasis, hemosiderin-induced hyperpigmentation, and livedo racemosa. Atrophy blanche also occurs in patients with only stasis dermatitis and ulceration.

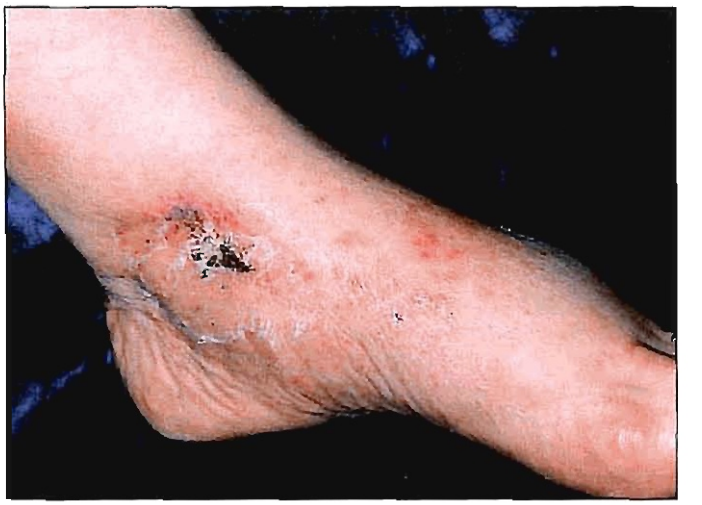

Fig. 35-3 Livedoid vasculopathy.

Livedoid vasculopathy may be associated with various systemic diseases, including primary or secondary hypercoagulable states, particularly those associated with anticardiolipin antibody syndrome, protein C deficiency, antithrombin III deficiency, other fibrinolytic anomalies (including prothrombin and factor V Leiden gene mutations), and hepatitis C. Clinical evaluation should exclude these disorders, as well as venous and arterial peripheral vascular diseases. Mononeuropathy multiplex has been reported in association with livedoid vasculopathy. In some patients, atrophie blanche and mononeuropathy multiplex may be associated with polyarteritis nodosa rather than hyalinizing vasculopathy; biopsy is recommended.

Histologically, livedoid vasculopathy is characterized by hyaline thickening of the walls of the small blood vessels. Fibrin, C3, and IgM are often found in the vessel walls. The vessels may demonstrate endothelial proliferation and thrombosis. Perivascular hemorrhage may be present. Endothelial thrombomodulin expression is elevated in many patients and platelet (P-selectin) and lymphocyte activation have been demonstrated.

Low-dose aspirin (325 or even 162 mg once or twice a day) and dipyridamole have been effective in some patients. The addition of a third antiplatelet drug may provide additional benefit. Beraprost sodium (120 μg/day) or minidose heparin, as little as 5000 U every 3 days, has been reported to be effective. Nifedipine, 10 mg three times a day, produced healing in a patient in whom dipyridamole and aspirin had failed. Pentoxifylline, 400 mg two or three times a day, with 400 mg/day for maintenance, is another treatment option. Treatment with metformin has shown mixed results. Intravenous iloprost has been effective in some patients with refractory disease. PUVA has been reported as useful in a few patients. Some patients with severe disease have responded to prednisolone, colchicine, azathioprine, or intravenous immunoglobulin (IVIG). The mode of action of these agents is unclear, as vasculitis is not present histologically. Low molecular weight dextran is used for hypofibrinolytic disease. Secondary infection of ulcers should be treated with systemic antibiotics.

Livedoid Dermatitis

Livedoid "dermatitis" is an embolic phenomenon (infarction) leading to temporary or prolonged local ischemia as a result of accidental arterial obliteration from the intragluteal injections of various drugs. (See Chapter 6 for a discussion of injection site reactions.)

Perinatal Gangrene of the Buttock

Perinatal gangrene of the buttock is similar to livedoid dermatitis. It usually is a complication of umbilical artery catheterization, exchange transfusion, or cord injections by means of a syringe. It may also be a spontaneous event.

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CALCIPHYLAXIS

Patients with end-stage renal disease with metastatic calcification are almost exclusively affected by this disease. Calciphylaxis appears as reticulated, violaceous, mottled patches, later progressing to ecchymosis, cordlike nodules (usually located on the abdomen and thighs), and livedo reticularis. Progression occurs with ecchymosis, central necrosis, and black eschars that may have a reticulated appearance (Fig. 35-4). Gangrene and self-amputation of digits or extremities has been reported. Necrosis may involve other sites, such as the penis, tongue, or breast. Ischemic myopathy may produce symptoms suggestive of dermatomyositis. Patients with diabetes and chronic renal failure have a much higher chance of developing acral gangrene, and central lesions are associated with a worse prognosis than peripheral lesions.

A serum calcium–phosphorus product of more than 60 mg/dL indicates great risk for calciphylaxis. Calcification occurs when an appropriate challenging factor is then introduced. Identified factors include vitamin D compounds, parathyroid hormone, phosphates, calcium salts, infections, high levels of matrix metalloproteinases, local trauma, intramuscular tobramycin, corticosteroids, intramuscular iron dextran complex, calcium heparinate, human immunodeficiency virus (HIV) infection, and cryofibrinogenemia. Crohn's disease in combination with short-bowel syndrome has been reported to cause calciphylaxis.

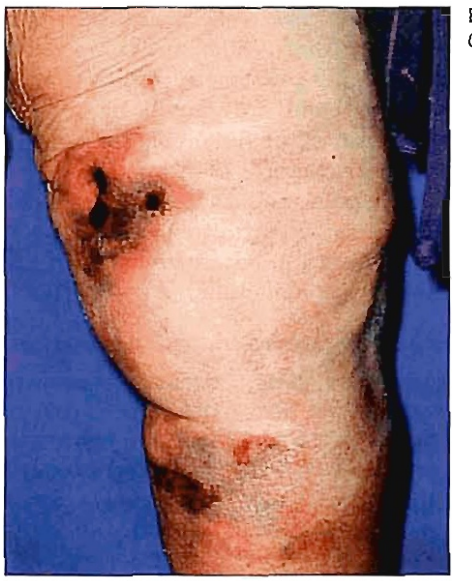

Fig. 35-4
Calciphylaxis.

The prognosis is guarded, and most patients experience significant morbidity and mortality. Death is usually caused by staphylococcal sepsis after infection of the chronic ulcerations. Patients with secondary hyperparathyroidism benefit from parathyroidectomy with autotransplantation of parathyroid tissue. Hyperbaric oxygen has been used with some success. Rapid improvement has been reported after intravenous pamidronate therapy in a patient with chronic renal failure. Intravenous sodium thiosulfate has also been used.

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MARSHALL-WHITE SYNDROME AND BIER SPOTS

The marbled mottling produced in the forearm and hand by occluding the brachial artery with a tight sphygmomanometer cuff is characterized initially, and chiefly, by pale

macules 1 or 2 cm in diameter. These were described by Bier in 1898 and are known as *Bier spots*. Wilkin re-examined this phenomenon with laser Doppler velocimetry and concluded that the red spots on the hand are caused by relative vasodilatation, with vasoconstriction in the pale areas.

Marshall-White syndrome consists of Bier spots associated with insomnia and tachycardia. This syndrome has been noted in white middle-aged men. The pale macules are cooler than the surrounding pink skin and become more apparent when the hands are lowered for some time.

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PURPURA

Purpura is multifocal extravasation of blood into the skin or a mucous membrane. It is manifested by distinctive brownish-red or purplish macules a few millimeters in diameter. Several types of purpura are recognized.

Petechiae are superficial, pinhead-sized (< 3 mm), round, hemorrhagic macules, bright red at first, then brownish or rust colored. They are most commonly seen in the dependent areas, are evanescent, occur in crops, regress over a period of days, and most often imply a disorder of platelets rather than a coagulation factor disorder. These disorders typically give rise to ecchymoses or hematomas rather than petechiae. *Petechiae may also be a sign of a blood vessel disease* such as scurvy or amyloidosis.

Ecchymoses are better known as bruises or "black and blue marks." These extravasations signify a deeper and more extensive interstitial hemorrhage, which forms a flat, irregularly shaped, bluish-purplish patch. Such patches gradually turn yellowish and finally fade away.

Vibices (singular, *vibex*) are linear purpuric lesions.

Hematoma designates a pool-like collection of extravasated blood in a dead space in tissue that, if of sufficient size, produces a swelling that fluctuates on palpation. *Hematomas are usually walled off by tissue planes.*

Pathogenesis

Purpura may result from hyper- and hypo-coagulable states, vascular dysfunction, and extravascular causes, including idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation (DIC), drug-induced thrombocytopenia, bone marrow failure, congenital or inherited platelet function defects, acquired platelet function defects (aspirin, renal or hepatic disease, or gammopathy), and thrombocytosis secondary to myeloproliferable diseases. Most of these disorders produce findings of nonpalpable purpura. Ecchymosis predominates in procoagulant defects, such as hemophilia, anticoagulants, DIC, vitamin K deficiency, and hepatic disease resulting in poor procoagulant synthesis. There is often a component of trauma. Increased frequency of ecchymotic skin can be the result of poor dermal support of blood vessels, most often localized to the area of trauma, and may result from actinic (senile) purpura, topical or systemic corticosteroid therapy, scurvy, systemic amyloidosis, Ehlers-Danlos syndrome, or pseudoxanthoma elasticum.

Occlusive disorders are those in which fibrin, cryoglobulin, or other material occludes vessels. Representative causes include monoclonal cryoglobulinemia, cryofibrinogenemia, DIC, purpura fulminans, protein C deficiency, warfarin-induced necrosis, heparin necrosis, cholesterol emboli, oxalate crystal occlusion, and antiphospholipid syndrome.

Evaluation

A history and physical examination is often all that is necessary. A family history of bleeding or thrombotic disorders, duration of symptoms, use of drugs and medications that might affect platelet function and coagulation, as well as a review of medical conditions that may result in altered coagulation, should be documented. Physical examination should stress the size, type, and distribution of purpura; a search for telangiectases; a joint examination; and an evaluation of skin elasticity, unusual scars, and unusual body habitus. Correlation of purpura morphology with pathogenesis allows for a more focused approach.

A complete blood cell count and differential can be used to assess for microangiopathic anemia, screen for myeloproliferative disorders, and assess the number and morphology of platelets. A bleeding time is the preferred method of assessing platelet function. The partial thromboplastin time (PTT) or the prothrombin time (PT) are tests to evaluate abnormal coagulation states.

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THROMBOCYTOPENIC PURPURA

Thrombocytopenic purpura may be classified into two large categories: states resulting from accelerated platelet destruction and states resulting from deficient platelet production. Accelerated platelet destruction may be immunologic or nonimmunologic. The former may be due to antibodies (autoimmune or drug-induced thrombocytopenia), isoantibodies (congenital or post-transfusion), immune complex disease, or other immunologic processes such as erythroblastosis fetalis, neonatal lupus, scleroderma, other connective tissue diseases, or acquired immunodeficiency syndrome (AIDS). The group of thrombocytopenias with accelerated platelet destruction caused by nonimmunologic processes includes thrombotic thrombocytopenic purpura and DIC. Deficient platelet production may be related to diseases such as aplastic anemia and leukemia.

"Idiopathic" Thrombocytopenic Purpura

"Idiopathic" thrombocytopenic purpura (ITP) is also known as *autoimmune thrombocytopenic purpura*, or *Werlhof's disease*. It is characterized by either an acute or gradual onset of petechiae or ecchymoses in the skin and mucous membranes, especially in the mouth. Epistaxis, conjunctival hemorrhages, hemorrhagic bullae in the mouth, and gingival bleeding may occur. Melena, hematemesis, and menorrhagia also occur, and the latter may be the first sign of this disease in young women. Chronic leg ulcers occasionally develop. The presence of splenomegaly usually excludes the diagnosis of immune thrombocytopenic purpura.

Bleeding occurs when the platelet count drops below 50,000/mm^3. Post-traumatic hemorrhage, spontaneous hemorrhage, and petechiae may appear. The risk of serious hemorrhage is greatly increased at levels below 10,000/mm^3, and the gravest complication, intracranial hemorrhage, most often occurs with counts below 2000/mm^3. Bleeding time is usually prolonged and coagulation time is normal, whereas the clot retraction is abnormal and capillary fragility is increased. Increased numbers of megakaryocytes are found in the bone marrow.

The acute variety most often occurs in children, and follows a viral illness in 50% of patients. Parvovirus B19 is frequently associated. The average lag between purpura and the preceding infection is usually 2 weeks. Most of these cases resolve spontaneously. A few patients will develop chronic thrombocytopenia, and deaths, usually from cerebral hemorrhage, have been reported. In a series of 332 children with ITP, 58 (17%) had episodes of major hemorrhage. One death resulted from sepsis. In another series of 427 cases, 323 (72%) had mild-to-benign disease. Roughly 85% of patients who undergo splenectomy experience remission. More than half of the remaining patients spontaneously remit within 15 years.

The chronic form occurs most often in adults, is persistent, and has a female-to-male ratio of between 2:1 and 4:1. In cases not responding to splenectomy, an evaluation for an accessory spleen should be performed using ^{99m}Tc radionuclide scan. Breast cancer has been associated with ITP, with a parallel course in one-third of cases. Other malignancies have also been associated with ITP. *Helicobacter pylori* infection and varicella have been reported in association with adult ITP.

ITP is the result of platelet injury by antibodies of the IgG class. Antiplatelet antibodies coat the platelets, triggering their removal by the spleen after a greatly reduced survival time, which may last from minutes to a few hours. Antiphospholipid antibodies are found in some patients.

Splenectomy is the most common form of therapy. Systemic corticosteroids are also used, but steroid treatment is associated with bone demineralization in both adults and children with the disease. Platelet transfusions may be lifesaving in acutely ill patients who are actively bleeding; however, they do not produce a sustained increase in the platelet count and thus are only indicated for emergencies. IVIG is used to treat and possibly postpone or eliminate the need for splenectomy in some patients. Patients responsive to IVIG are more likely to respond to splenectomy than those unresponsive to IVIG. In chronic ITP, laparoscopic splenectomy is an option. Anecdotal reports support the use of intravenous anti-D (anti-Rh_o), danazol, rituximab, vinca alkaloids, and other immunosuppressive agents (such as azathioprine, cyclophosphamide, and cyclosporine), interferon-α, plasma exchange, staphylococcal protein A immunoadsorption, dapsone, ascorbic acid, and colchicine.

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Drug-Induced Thrombocytopenia

Thrombocytopenic purpura resulting from drug-induced antiplatelet antibodies may be caused by drugs such as heparin, sulfonamides, digoxin, quinine, quinidine, chlorothiazides, penicillin, cephalosporins, minocycline, phenylbutazone, acetaminophen, allopurinol, methyldopa, furosemide, gold salts, rifampin, and lidocaine. Ticlopidine, an antiplatelet agent used to reduce the occurrence of atherothrombotic arterial events, has been associated with neutropenia, aplastic anemia, thrombocytopenia, and thrombotic thrombocytopenic purpura.

Heparin-induced thrombocytopenia (HIT) is associated with life-threatening arterial and venous thrombosis and, to a lesser extent, hemorrhagic complications. HIT is mediated by an antibody to the platelet factor 4 (PF4)-heparin complex. The antibody cross-links FcγRII receptors on the platelet surface, resulting in platelet activation, aggregation, and simultaneous activation of blood-coagulation pathways. Tests for HIT antibodies include immunoassays (such as ELISA) and functional tests (such as the ^{14}C-serotonin release assay).

Treatment for drug-induced thrombocytopenia consists of removal of the offending agent. Corticosteroids are helpful in moderately high dosage (60 mg/day prednisone) and are usually only necessary as a brief course. When a clinical diagnosis of HIT is made, heparin should be stopped immediately and treatment with an alternative anticoagulant (such as hirudin) should be started. Warfarin therapy can begin when the patient is clinically stable.

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Thrombotic Thrombocytopenic Purpura

Also known as *Moschcowitz syndrome*, thrombotic thrombocytopenic purpura (TTP) is a pentad of thrombocytopenia, hemolytic anemia, renal abnormalities, fever, and disturbances of the central nervous system (CNS). Focal neurologic symptoms may be the presenting feature. Multiple ecchymoses, jaundice, pallid mucous membranes, and an enlarged spleen may be found. Other associated findings include arthritis, pleuritis, Raynaud phenomenon, abdominal pain, and hepatomegaly. The presence of schistocytes on a blood smear is the morphologic hallmark of the disease, and a schistocyte count of greater than 1% in the absence of other known causes of thrombotic microangiopathy strongly suggests a diagnosis of TTP. Tests may show a decreased hematocrit and decreased platelets. A delay in diagnosis may lead to a mortality rate as high as 90%. TTP has been associated with several drugs, including cyclosporin, tacrolimus, sirolimus, mitomycin-C, ticlopidine, clopidogrel, statins, Plavix, and the Norplant contraceptive system. Cases have been reported in association with HIV infection.

Biopsies demonstrate hemorrhage and fibrin occlusion of vessels. Inflammation is absent. Studies of plasma samples from patients with active TTP have often shown the presence of unusually large von Willebrand factor multimers. In some cases, there has been an absence of the large forms during acute disease, secondary to binding of unusually large von Willebrand factor multimers to platelets with subsequent aggregation. The underlying pathogenesis is a deficiency of the von Willebrand factor cleaving protease ADAMTS13.

Until exchange plasmapheresis was instituted as the treatment of choice, 80% of these patients died; now, 80% survive. Cascade filtration is also highly effective and supplemental immunosuppressive therapy may be required. In recurrent or refractory disease, extracorporeal immunoadsorption, rituximab therapy or splenectomy may be needed. Cyclosporin, a drug associated with onset of TTP, has also been used to treat cases not associated with the drug.

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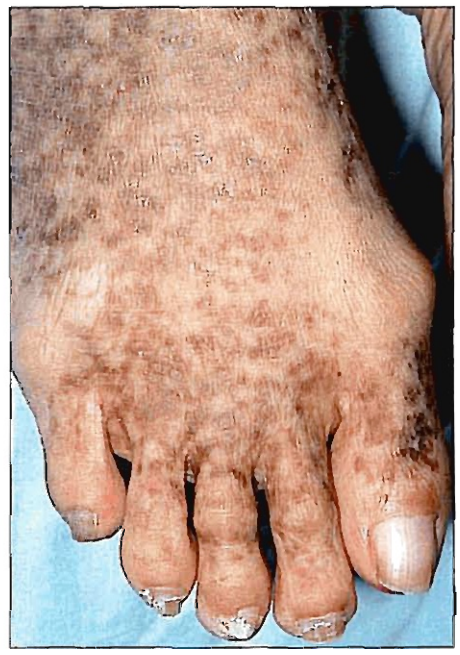

Fig. 35-5
Cryoglobulinemia.

NONTHROMBOCYTOPENIC PURPURA (DYSPROTEINEMIC PURPURA)

Cryoglobulinemia and Cryofibrinogenemia

The term cryoglobulinemia refers to the presence in the serum of proteins that precipitate at temperatures below 37° C and redissolve on rewarming. Abnormal serum proteins behaving as cryoglobulins and cryofibrinogens may be IgG, IgM, or both. Cryoglobulinemic purpura occurs most frequently in multiple myeloma and macroglobulinemia and is of a monoclonal IgM, IgG, or Bence Jones cryoglobulin form. Mixed cryoglobulinemia, in which the cryoglobulins are of various classes, may be seen in hepatitis C infection, hepatitis B infection, SLE, rheumatoid arthritis, and Sjögren syndrome. Mixed cryoglobulinemia is associated with hepatitis C virus infection in greater than 90% of cases, and the prevalence of thyroid disorders is increased in these patients.

Purpura is most apt to occur on exposed surfaces after cold exposure. Marked brown hyperpigmentation of the dorsal feet results (Fig. 35-5). In monoclonal disease, the biopsy reveals amorphous jelly-like eosinophilic material in the vessel lumen. In the mixed type, biopsy reveals classic leukocytoclastic vasculitis. In cryocrystalglobulin syndrome, vasculitic skin lesions occur and crystalline deposits are seen in the corneas and joint spaces. Follicular hyperkeratosis, purpura, acral blisters, and ulceration have also been reported.

Purpura secondary to these abnormal serum proteins tends to be chronic. Deaths have been related to nephropathy, cardiac failure, widespread vasculitis, B-cell lymphoma, and other associated malignancies. Chromosomal translocation (t 14, 18) and Bcl-2 activation have been demonstrated in B-lymphocytes of 80% of patients with hepatitis C virus (HCV)-related cryoglobulinemic vasculitis, and HCV infection is the main etiologic factor associated with hematologic malignancies in patients with cryoglobulinemia.

Treatment options include plasmapheresis, systemic steroids, immunosuppressors, and colchicine. Prolonged remission after treatment with high-dose gamma globulin

infusion has been reported. Interferon, alone or in combination with ribavirin, has been used for hepatitis B- and C-associated disease. Peginterferon produced an exacerbation of vasculitis in one reported patient. Mixed cryoglobulinemia with severe renal and cardiac disease refractory to corticosteroid therapy, plasmapheresis, chlorambucil and cyclophosphamide has responded to rituximab. Simple plasma exchange can be helpful, but cryofiltration apheresis is the best method to remove cryoproteins in the treatment of cryoprecipitate-induced diseases.

In contrast to cryoglobulinemia, cryofibrinogenemia is rarely symptomatic. The precipitating cryofibrinogen is a cold insoluble complex of fibrin, fibrinogen, and fibrin split products with albumin, cold insoluble globulin, factor VIII, and plasma proteins. Associated collagen–vascular disorders, infections, and malignancies are significantly more frequent in patients with combined cryofibrinogen and cryoglobulin than those with isolated cryofibrinogenemia. Cryofibrinogen has been associated with calciphylaxis in the setting of renal disease. The frequency of this association is unknown. Familial primary cryofibrinogenemia manifests as painful purpura with slow healing ulcerations and edema of both feet during the winter months.

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Waldenström Hyperglobulinemic Purpura (Purpura Hyperglobulinemica)

Waldenström hyperglobulinemic purpura presents with episodic showers of petechiae occurring on all parts of the body, most profusely on the lower extremities. The dorsum of the feet are intensely involved, and the petechiae diminish on the ascending parts of the feet (Fig. 35-6). A diffuse "peppery" distribution is commonly noted, resembling Schamberg's disease. The petechiae may be induced or aggravated by prolonged standing or walking, or by wearing constrictive garters or stockings.

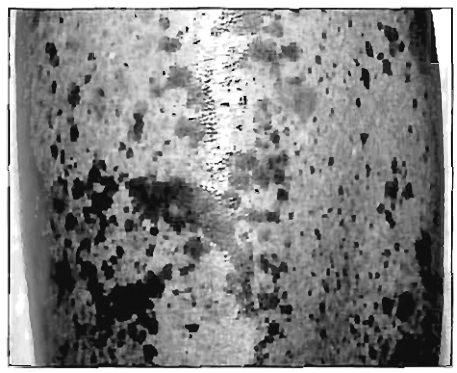

Fig. 35-6 Waldenström hyperglobulinemic purpura.

Serum protein electrophoresis demonstrates a broad-based peak (polyclonal hypergammaglobulinemia). The bulk of the protein increase is IgG, though occasionally increased amounts of IgA are also found. IgM is usually normal or decreased. Rheumatoid factor in varying amounts is present in almost all patients. Antithyroglobulins, increased erythrocyte sedimentation rate (ESR), leukopenia, antinuclear factors, and proteinuria may be found. Almost 80% of patients with hypergammaglobulinemic purpura of Waldenström have antibodies to Ro/SSA.

Hyperglobulinemic purpura occurs most commonly in women and is frequently seen with Sjögren syndrome, hepatitis C, keratoconjunctivitis sicca, rheumatoid arthritis, and multiple myeloma. It may also be a primary chronic benign illness. Hypergammaglobulinemic purpura associated with hepatitis C has a predilection for men, and has manifestations that usually last longer than those associated with Sjögren syndrome.

In about a third of patients, leukocytoclastic vasculitis is present. Patients with leukocytoclastic vasculitis have a higher prevalence of articular involvement, peripheral neuropathy, Raynaud phenomenon, renal involvement, antinuclear antibodies, rheumatoid factor, and anti-Ro/SS-A antibodies. Biopsy in patients without leukocytoclastic vasculitis demonstrates a perivascular infiltrate of mononuclear cells.

The course of the disease is essentially benign, but chronic. Rare deaths are related to associated cryoglobulin disease. Hyperglobulinemic purpura may be a manifestation or harbinger of connective tissue or hematopoietic diseases, and rarely, progression to myeloma has been reported.

Patients often improve with support stockings. Steroids should be reserved for severe disease. Indomethacin and hydroxychloroquine may be of value in the treatment of milder disease. Chlorambucil reduces the purpura but does not effect gross changes in the protein abnormality. Thioguanine, dipyridamole (Persantine), aspirin, and colchicine have been used with some success.

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Waldenström Macroglobulinemia

In 1944, Waldenström described an entity characterized by bleeding from the mucous membranes of the mouth and nose, lymphadenopathy, hepatosplenomegaly, hemorrhage of the retina, and cutaneous purpura. Gastrointestinal bleeding and anemia may occur. This disease occurs mostly in elderly white men who present with oronasal bleeding as a manifestation of plasma cell dyscrasia. Nonspecific cutaneous findings include Raynaud phenomenon, amyloidosis, pruritus, xanthomatosis, and urticaria. Some patients with Schnitzler syndrome (urticaria, bone pain, and paraproteinemia) satisfy the criteria for Waldenström macroglobulinemia. Waldenström macroglobulinemia may be associated with chronic liver disease and hepatocellular carcinoma. Hepatitis G, a new member of the *Flaviviridae* family, and hepatitis C infection have been implicated in some cases.

The histopathologic feature in most cases is a perivascular infiltrate containing lymphocytes and in some cases neutrophils and eosinophils. Two types of skin lesions may occur: violaceous to red indurated plaques, infiltrated with atypical lymphoid cells; or alternatively, translucent papules full of amorphous eosinophilic material that has proved on direct immunofluorescence (DIF) to be IgM. Basement membrane deposits of IgM have also been detected. Leukocytoclastic vasculitis associated with Waldenström macroglobulinemia has been rarely reported. Large amounts of monoclonal IgM are responsible for the variable clinical pattern. Fibrinogenopenia, fibrinolysis, circulating anticoagulants, coagulation factor deficiencies, intravascular or perivascular deposition of paraprotein, or associated cryoglobulinemia or cryofibrinogenemia may result in the bleeding tendencies. Age, hemoglobin, and serum albumin are among the most important prognostic factors.

Plasmapheresis is recommended until adequate doses of chlorambucil have been administered. Cyclophosphamide and corticosteroids or 2-chlorodeoxyadenosine (cladribine) have also been shown to be effective. PUVA has been used to alleviate symptoms of pruritus. Rituximab has shown a response rate of about 30%. Autologous and allogeneic stem cell transplantation may be considered for patients with refractory or relapsing disease.

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PURPURA SECONDARY TO CLOTTING DISORDERS

Hereditary disorders of blood coagulation usually result from a deficiency or qualitative abnormality of a single coagulation factor, as in hemophilia or von Willebrand's disease. Acquired disorders commonly result from multiple coagulation factor deficiencies, as in liver disease, biliary tract obstruction, malabsorption, or drug ingestion. Acquired clotting disorders may also involve platelet abnormalities, as in DIC. Hemorrhagic manifestations are common and may be severe, especially in hereditary forms. Ecchymoses and subcutaneous hematomas are common, especially on the legs. Severe hemorrhage may follow trauma, and hemarthrosis is frequent. Other hemorrhagic manifestations include respiratory obstruction resulting from hemorrhage into the tongue, throat, or neck; epistaxis; gastrointestinal and genitourinary tract bleeding; and, rarely, CNS hemorrhage.

Harley JR: Disorders of coagulation misdiagnosed as non-accidental bruising. Pediatr Emerg Care 1997;13:347.

Sham RL, et al: Evaluation of mild bleeding disorders and easy bruising. Blood Rev 1994;8:98.

DRUG- AND FOOD-INDUCED PURPURA

Drug-induced purpura may be related to platelet destruction, vessel fragility, interference with platelet function or vasculitis. Drug-induced thrombocytopenic purpura was discussed earlier in this chapter. Examples of purpurogenic drugs are: aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), allopurinol, thiazides, gold, sulfonamides, cephalosporins, hydralazine, phenytoin, quinidine, ticlopidine, and penicillin. Combinations of diphenhydramine and pyrithyldione can induce purpuric mottling and areas of necrosis. Cocaine-induced thrombosis with infarctive skin lesions is associated with skin popping. The Rumpel-Leede sign (a distal shower of petechiae that occurs immediately after the release of pressure from a tourniquet or sphygmomanometer) has been reported in association with drug-induced erythema multiforme.

Topical EMLA cream can induce purpura within 30 min of application, a result of a toxic effect on the capillary endothelium. Purpura has been associated with the use of acetaminophen in patients afflicted with infectious mononucleosis. Small-vessel vasculitis, including urticarial vasculitis, has been caused by the ingestion of tartrazine dye and benzoates. *Escherichia coli* O157:H7 in food has been associated with diarrhea, hemorrhagic colitis, hemolytic-uremic syndrome, and thrombotic thrombocytopenic purpura. Consumption of undercooked beef is the most common risk factor.

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penia presenting as Schamberg's disease. J Drugs Dermatol 2003;2:320.
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SOLAR PURPURA (SENILE PURPURA, ACTINIC PURPURA)

Solar purpura is characterized by large, sharply outlined, 1- to 5-cm, dark purplish-red ecchymoses appearing on the dorsa of the forearms and less often the hands. Usually the skin over the forearms is thin and inelastic. This is discussed in greater detail in Chapter 7.

PURPURA FULMINANS

Also known as *purpura gangrenosa*, this is a severe, rapidly fatal reaction occurring most commonly in children after an infectious illness. The sudden appearance of large ecchymotic areas, especially prominent over the extremities, progressing to acral hemorrhagic skin necrosis is characteristic (Fig. 35-7). Fever, shock, and DIC usually accompany the skin lesions, which on biopsy show noninflammatory necrosis, with platelet–fibrin thrombi occluding the blood vessels.

Purpura fulminans usually follows an acute infectious disease, such as scarlet fever and, rarely, streptococcal pharyngitis, meningococcal meningitis, pneumococcal sepsis, *Capnocytophaga canimorsus* (DF-2) infection, *Xanthomonas maltophilia* sepsis, or varicella. Purpura fulminans may also occur without any preceding illness. Asplenic patients, who are at risk for pneumococcal or meningococcal sepsis, are also predisposed to purpura fulminans. Neonates with homozygous protein C or protein S deficiencies may suffer purpura fulminans as a result of the lack of these natural anticoagulanta. Some patients develop transient deficiencies of proteins C and S in response to infection. IgG paraproteins may inhibit the functional anticoagulant activity of activated protein C. Autoimmune protein S deficiency has also been shown to be a mechanism in causing postinfectious idiopathic purpura fulminans. Other disease, such as the fibrinolysis syndrome, may have purpura fulminans as part of the symptom complex. An acquired form has been reported secondary to alcohol and acetaminophen ingestion. When purpura fulminans occurs in the setting of systemic lupus erythematosus, the catastrophic antiphospholipid antibody syndrome (CAPS) must be considered. Purpura fulminans has been reported as a presenting feature of the Churg-Strauss syndrome.

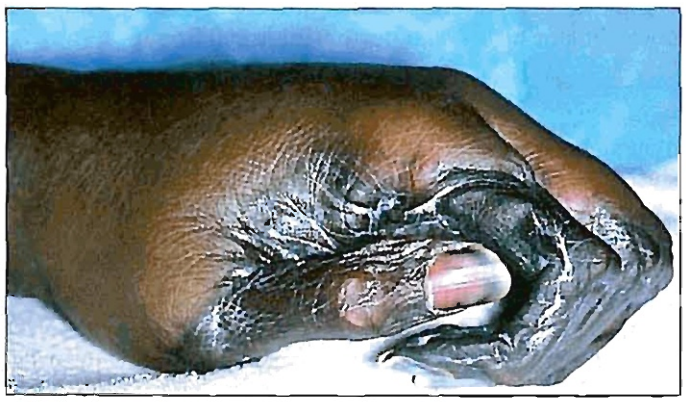

Fig. 35-7 Purpura fulminans.

Approximately 5% of white persons of European origin have a mutation in coagulation factor V. A number of cases of purpura fulminans associated with infections and this factor V Leiden mutation, with normal protein C and protein S levels, have been reported. Factor V Leiden deficiency may be a more frequent cause of purpura fulminans than previously appreciated.

Management is usually supportive, with treatment of the underlying disease process, such as antibiotics, and replacement therapy using fresh frozen plasma. Protein C and antithrombin replacement is useful in treating patients shown to have deficiencies. In fulminant meningococcemia, some data suggest that the doses of supplementation should be at least 150 IU/kg of antithrombin and 250 IU/kg of protein C as a loading dose, followed by 150 IU/kg and 200 IU/kg, respectively, as daily maintenance therapy. Despite these measures, amputations and deaths continue to occur in patients with severe disease. Fasciotomy during the initial management of these patients may reduce the depth of soft-tissue involvement and the extent of amputations. Tissue plasminogen activator has been used in meningococcal-associated disease, but is associated with a risk of intracerebral hemorrhage.

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DISSEMINATED INTRAVASCULAR COAGULATION

Up to two-thirds of patients with DIC have skin lesions, which may be the initial manifestation of the syndrome. Minute, widespread petechiae, ecchymoses, ischemic necrosis of the skin, and hemorrhagic bullae are the usual

findings. Purpura fulminans may supervene and progress to symmetrical peripheral gangrene. DIC may be initiated by a variety of disorders, including septicemic hypotension, hypoxemia, acidosis, malignancies, chemotherapy, obstetric crises, antiphospholipid antibody syndrome, SLE, arthropod envenomation, and leukemia. Long-term treatment with granulocyte colony-stimulating factor (G-CSF) has also been reported to precipitate DIC. Children with kaposiform hemangioendotheliomas are at risk for consumptive coagulopathy (Kasabach-Merritt syndrome).

DIC is the result of widespread intravascular coagulation in which certain coagulation factors are consumed faster than they can be replaced. Laboratory findings include decreased platelets, decreased fibrinogen, elevated PT, PTT, and fibrin degradation products. Control of the underlying disease is the paramount consideration, together with correction of hemostatic abnormalities, usually through the use of intravenous heparin. Vitamin K replacement will exclude vitamin K deficiency as a cause, and replace vitamin K stores, which are rapidly depleted in patients with DIC. Fresh frozen plasma, platelet transfusions, protein C, and, at times, select replacement of specific coagulant factors may be beneficial. The sepsis-related organ failure assessment (SOFA) score is useful for predicting outcome in DIC patients in the intensive care unit.

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Levi M, et al: Sepsis and disseminated intravascular coagulation. J Thromb Thrombolysis 2003;16:43.

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FIBRINOLYSIS SYNDROME (HYPOFIBRINOGENEMIA, DEFIBRINATING SYNDROME)

The fibrinolysis syndrome is characterized by an acute hemorrhagic state brought about by inability of the blood to clot. Massive hemorrhages into the skin produce blackish, purplish swellings and sloughing. There is an increased tendency to thrombosis and hemorrhage. It occurs as a complication of pregnancy in cases of placenta previa, eclampsia, and fetal death. It may be a complication in certain surgical operations, particularly in lobectomy and during extracorporeal circulation of blood. The syndrome has been repeatedly reported in amyloidosis, thrombotic thrombocytopenic purpura, liver disease, Waterhouse-Friderichsen syndrome, carcinoma of the prostate with metastases to bone marrow, and in other types of malignant disease. It may also follow snake bite. Treatment is by transfusions of fibrinogen concentrates.

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Funai EF, et al: Successful pregnancy outcome in a patient with both congenital hypofibrinogenemia and protein S deficiency. Obstet Gynecol 1997;89:858.

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BLUEBERRY MUFFIN BABY

Originally coined to describe the characteristic appearance of the purpuric lesions observed in newborns with congenital rubella, blueberry muffin baby is associated with many disorders that produce extramedullary erythropoiesis. The eruption consists of generalized dark blue to magenta, nonblanchable, indurated, round to oval, hemispheric papules ranging from 1 to 7 mm. Lesions favor the head, neck, and trunk.

Etiologic factors include congenital infections (rubella, cytomegalovirus, and parvovirus B19), hemolytic disease of the newborn (Rh incompatibility, blood group incompatibility), hereditary spherocytosis, twin transfusion syndrome, neuroblastoma, rhabdomyosarcoma, Langerhans cell histiocytosis, and congenital leukemia. Evaluation should include a peripheral blood cell count, hemoglobin level, TORCH serologies, viral cultures, and a Coomb test. A skin biopsy may also be helpful in determining the cause. Rhabdomyosarcoma may present with a blueberry muffin-like appearance.

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MISCELLANEOUS PURPURIC MANIFESTATIONS

Deep Venous Thrombosis

Immobilization is an important risk factor, and malignant neoplasms are the most common underlying condition, with bronchogenic carcinoma by far the most frequent. In 35% of cancer-associated cases, the thrombosis is the first sign of the cancer. Extensive venous thrombosis, almost always affecting at least the femoral vein, can cause reversible ischemia, or frank gangrene. Patients may develop severe pain, extensive edema, and cyanosis of the extremity. The left leg is more often affected than the right. Female patients slightly outnumber male, and the mean age is 52 years. Significant superficial vein thrombosis is considered a risk factor for deep vein thrombosis. The risk of pulmonary embolism from deep vein thrombosis is the major concern. Chronic complications include venous incompetence, with stasis dermatitis or ulcers, and postphlebitic syndrome.

Bates SM, et al: Clinical practice. Treatment of deep-vein thrombosis. N Engl J Med 2004;351:268.

Cushman M, et al: Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. Am J Med;117:19.

Superficial Thrombophlebitis

Samlaska and James have reviewed the vast number of primary and secondary hypercoagulable states that can present with superficial vein thrombosis. Painful induration with erythema, often in a linear or branching configuration

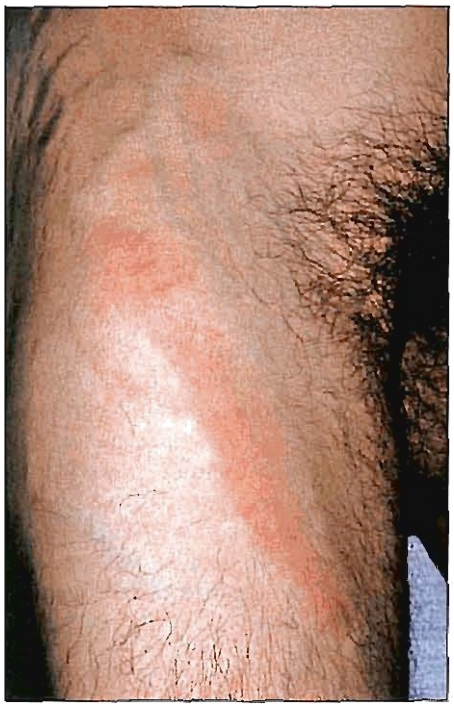

Fig. 35-8 Superficial migratory thrombophlebitis.

forming cords, is the classic presentation (Fig. 35-8). Patients may also exhibit indurated subcutaneous nodules and overlying purpura or brown discoloration indicative of post-inflammatory hyperpigmentation.

Primary hypercoagulable states that may be associated with superficial thrombophlebitis include deficiencies of antithrombin III, heparin cofactor II, protein C, protein S, and factor XII; disorders of tissue plasminogen activator; abnormal plasminogen; dysfibrinogenemia; and lupus anticoagulant. Secondary hypercoagulable states include varicosities, malignancy (Trousseau syndrome), pregnancy, oral contraceptive use, infusion of prothrombin complex concentrates, Behçet's disease, thromboangiitis obliterans, acute thrombophlebitis of superficial veins of the breast (Mondor's disease), septic thrombophlebitis, psittacosis, secondary syphilis, intravenous catheters, intravenous drugs (sugar solutions, protein hydrolysates, calcium, potassium, hypertonic concentrates, diazepam, nitrogen mustard, acridinylaniside, dacarbazine, and carmustine), and street drugs (cocaine, bulking agents such as paregoric, quinine, dextrose, sucrose, and lactose).

In the evaluation of superficial thrombophlebitis, one should consider the possibility of underlying deep venous disease. Superficial femoral vein involvement should alert the physician to underlying deep venous disease requiring anticoagulation. Lesser saphenous vein thrombophlebitis is also frequently associated with underlying deep vein thrombosis. Elliptic biopsies across the palpable cord may be required to exclude other considerations such as sarcoidal granulomas, cutaneous polyarteritis nodosa, Kaposi sarcoma, and vasculotropic metastasis.

Treatment is directed at the underlying cause. Leg elevation and local heat will help to promote the dissolution of clots, which may take up to 8 to 12 weeks to resolve. Heparin therapy may reduce the incidence of thromboembolic complications in high-risk individuals.

Mondor's Disease

Mondor's disease occurs three times as frequently in women as in men, and most patients are between 30 and 60 years of age. The sudden appearance of a cordlike thrombosed vein along the anterior–lateral chest wall is characteristic. It is at first red and tender and subsequently changes into a painless, tough, fibrous band. There are no systemic symptoms. Both sides of the chest have the same incidence of involvement. Mondor's disease may be associated with strenuous exercise, pregnancy, intravenous drug abuse, jellyfish stings, breast cancer, and breast surgery. The condition represents a localized thrombophlebitis of the veins of the thoracoepigastric area. The veins involved are the lateral thoracic, thoracoepigastric, and superior epigastric. In the end stage a thick-walled vein remains that has a hard, ropelike appearance and, on occasion, may result in a furrowing of the breast. Exceptionally, a vein coursing up the inside of the upper arm may be involved. Similar string-like phlebitis findings have been described in the penis, antecubital fossa, groin, abdomen, and axilla.

Treatment is symptomatic, with hot, moist dressings and analgesics or NSAIDs. The disease process runs its course in from 3 weeks to 6 months.

de Godoy JM, et al: The association of Mondor's disease with protein S deficiency: case report and review of literature. J Thromb Thrombolysis 2002;13:187.

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Samlaska CS, James WD: Superficial thrombophlebitis. II. Secondary hypercoagulable states. J Am Acad Dermatol 1990;23:1.

Postcardiotomy Syndrome

Two to 3 weeks after pericardiotomy, fever, pleuritis, pericarditis, or arthritis may appear together with petechiae on the skin and palate. This syndrome may be confused with infectious mononucleosis and bacterial endocarditis.

Orthostatic Purpura (Stasis Purpura)

Prolonged standing or even sitting with the legs lowered (as in a bus, airplane, or train) may produce edema and a purpuric eruption on the lower extremities. Elevation of the legs and the use of elastic stockings are helpful preventive strategies.

Obstructive or Traumatic Purpura

Purpura may also be evoked by mechanical obstruction to the circulation, with resulting stress on the small vessels. This may be encountered in cardiac decompensation, or after convulsions, vomiting episodes, the Valsalva maneuver, pertussis, or sexual climax. Nonpalpable purpura has been reported associated with the use of a mucus-clearing device, which requires the patient to exhale forcefully through a flutter valve (flutter valve purpura). Local obstruction of the blood flow with purpura may result from compression of the veins by tumors or a gravid uterus, by occlusions from thrombosis, or by a weakening of the elastic coat as in varicose veins.

Purpuric lesions in children brings into question the possibility of the battered child. Bruises and ecchymoses on the genital area, buttocks, or hands are suggestive of an abused child. Linear lesions on accessible areas raise the question of factitial disease. Ecchymoses of bizarre shapes may also correspond to trauma inflicted during religious rituals or cultural practices. Coin-rubbing and cupping performed as remedies for common diseases are examples. "Passion purpura" on the palate may result from fellatio, or on the neck or upper arms (a "hickey") from biting and sucking. Facial, cheek, and periorbital purpura can occur postictal and may be mistaken for spousal abuse. Bathtub suction-induced purpura occurs on the lower back location in a U-shaped distribution. It may be mistaken for abuse.

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Reis JJ, et al: Postictal hemifacial purpura. Seizure 1998;7:337.

Epidemic Dropsy

Epidemic dropsy manifests with eruptive angiomas, purpura, dyspnea, tachycardia, diarrhea, and fever. It has been reported in parts of India, Africa, and the Fiji Islands, and is the result of ingested mustard oil adulterated with sanguinarine (*Argemone mexicana* oil). A major outbreak of epidemic dropsy occurred in Delhi, India, in August–September 1998. The patients presented with pitting pedal oedema (100%), skin erythema (75%), limb tenderness (63%), diarrhea (51%) and hepatomegaly (34%). There were six deaths related to cardiac failure. Toxic alkaloids of *Argemone mexicana* oil induce capillary leakage with resulting renal hypoperfusion, restrictive ventilatory dysfunction, and right-sided failure.

Sharma BD, et al: Epidemic dropsy: observations on pathophysiology and clinical features during the Delhi epidemic of 1998. Trop Doct 2002;32:70.

Paroxysmal Nocturnal Hemoglobinuria

This acquired intravascular hemolytic anemia usually occurs in young adults. It is an acquired clonal disorder resulting from a somatic mutation in the hematopoietic stem cell that produces intravascular hemolysis, cytopenias, infections, bone marrow hypoplasia, and life-threatening venous thrombosis. Some cases evolve into acute leukemia. Initial erythematous cutaneous plaques may progress to hemorrhagic bullae. Vascular thrombi are found on biopsy. The physiologic drop in pH that occurs with sleep appears to be responsible for the hemolysis and is the basis for the specific Ham (acid hemolysis) test. Hematopoietic stem cell transplantation may be curative. Antilymphocyte globulin and cyclosporin have also been used.

Boschetti C, et al: Clinical and molecular aspects of 23 patients affected by paroxysmal nocturnal hemoglobinuria. Am J Hematol 2004;77:36.
Smith LJ: Paroxysmal nocturnal hemoglobinuria. Clin Lab Sci 2004;17:172.
White JM, et al: Haemorrhagic bullae in a case of paroxysmal nocturnal haemoglobinuria. Clin Exp Dermatol 2003;28:504.

Purpura-Associated Dermatoses

Purpura may be noted at times in erythema multiforme, dermatitis medicamentosa, serum sickness, pityriasis rosea, lichen nitidus, and herpes zoster. Petechiae or ecchymoses may be associated with measles, scarlet fever, and smallpox, and may appear extensively in cerebrospinal meningitis, typhus, parvovirus B19, and Rocky Mountain spotted fever. Disseminated strongyloidiasis can cause widespread thumbprint purpura by the passage of the larvae through vessel walls. Purpura may occur also in septicemia, Waterhouse-Friderichsen syndrome, bacterial endocarditis, malaria, miliary tuberculosis, and anthrax.

Drolet BA, et al: Painful, purpuric plaques in a child with fever. Arch Dermatol 1997;133:1500.
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Paroxysmal Hand Hematoma (Achenbach Syndrome)

Spontaneous focal hemorrhage into the palm or the volar surface of a finger may result in transitory localized pain, followed by rapid swelling and localized bluish discoloration. The lesion resolves spontaneously within a few days. Spontaneous hemorrhage from an arteriole appears to be responsible. The acute nature, purpuric findings, and rapid resolution are distinguishing features of Achenbach syndrome.

Eikenboom JC, et al: Paroxysmal finger haematoma: a neglected syndrome. Thromb Haemost 1991;66:266.
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Easy Bruising Syndromes

Young women who bruise easily despite normal coagulation profiles and normal platelet counts may have antiplatelet antibodies or increased megakaryocytes. They are divided into groups I (vasculitis) and II (qualitative platelet function abnormalities). A screen for bleeding time and blood eosinophilia should be performed on white children who develop easy bruising, particularly in Southeast Asia and East India. They should be screened periodically for as long as 12 months after arrival. An infectious etiology is suspected for the syndrome of acquired platelet dysfunction associated with eosinophilia. Bernard-Soulier syndrome is a rare inherited disorder characterized by giant platelets, thrombocytopenia, and a prolonged bleeding time. It is caused by genetic defects of the glycoprotein Ib-IX complex that consti-

tutes the von Willebrand factor receptor. Sebastian syndrome consists of giant platelets, leukocyte inclusions, and thrombocytopenia. Fechtner syndrome is a rare type of familial thrombocytopenia associated with large platelets, leukocyte inclusions, and features of Alport syndrome. The May-Hegglin anomaly consists of easy bruising with giant platelets and Dohle-like cytoplasmic inclusions in granulocytes. The inclusions appear as electron-dense long rods and needles oriented along the long axis of the spindle.

Balderramo DC, et al: Sebastian syndrome: report of the first case in a South American family. Haematologica 2003;88:ECR17.
Lackner H, et al: On the "easy bruising" syndrome with normal platelet count: a study of 75 patients. Ann Intern Med 1975; 83:190.
Matzdorff AC, et al: Perioperative management of a patient with Fechtner syndrome. Ann Hematol 2001;80:436.
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Sachs UJ, et al: Bernard-Soulier syndrome due to the homozygous Asn-45Ser mutation in GPIX: an unexpected, frequent finding in Germany. Br J Haematol 2003;123:127.
Tsoi WC, et al: A morphologic variant of May-Hegglin anomaly in a Chinese girl. Pathology 1994;26:53.

Painful Bruising Syndrome (Autoerythrocyte Sensitization, Gardner-Diamond Syndrome, Psychogenic Purpura)

Painful bruising syndrome is a distinctive localized purpuric reaction occurring primarily in young to middle-aged women who usually manifest personality disorders. There may be depression, anxiety, hysterical, or masochistic character traits, or inability to deal with hostile feelings. A recurrent type of eruption, it is characterized by extremely painful and tender, ill-defined ecchymoses about the extremities and sometimes on the face or trunk. The lesions evolve in a few hours and resolve within 5 to 8 days. New lesions may appear in crops. Emotional upsets are generally associated with the appearance of these painful sheets of purpura. It has been noted that some patients have a premonition as to when they will develop new lesions a few hours ahead of time by the tingling and burning sensation at the site of a future lesion. Extracutaneous somatic symptoms are common, such as headache, paresthesias, transient paresis, syncope, diplopia, abdominal distress, diarrhea, nausea and vomiting, and arthralgia.

Gardner and Diamond reported that intracutaneous injections of erythrocyte stroma evoked typical lesions. Since then, many have reported similar reactions to autologous whole blood, packed or washed red cells, or fractions of erythrocyte stroma. These are hard to assess, because similar reactions have been reported to substances as diverse as hemoglobin, phosphatidyl serine, histamine, histidine, trypsin, purified protein derivative (PPD), autologous serum, and platelets. Blinded, controlled testing, trying to avoid factitial trauma, has given mixed responses. Abnormalities in tissue plasminogen activator-dependent fibrinolysis, thrombocytosis, and anticardiolipin antibodies have also been implicated. Many believe this syndrome to be artifactual, whereas others believe the lesions are spontaneous.

Treatment has been mostly unavailing, though psychotherapy directed at emotional problems has helped in some cases. The disease follows an irregularly intermittent course, possibly exacerbated by emotional stress or physical injury.

A similar syndrome, reported as *DNA autosensitivity*, has been described in eight patients who were reactive to intracutaneous injections of purified calf thymus DNA or frozen and thawed buffy coat. Further case studies are needed to fully assess this syndrome. Documentation to date suffers from the same inconsistencies and lack of controlled, blinded studies as does the Gardner-Diamond syndrome.

Anderson JE, et al: Autoerythrocyte sensitization (psychogenic purpura): a case report and review of the literature. Pediatr Emerg Care 1999;15:47.
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PIGMENTARY PURPURIC ERUPTIONS (PROGRESSIVE PIGMENTARY DERMATOSIS, PROGRESSIVE PIGMENTING PURPURA, PURPURA PIGMENTOSA CHRONICA)

The pigmented purpuric eruptions of the lower extremities present with several clinical patterns. Clinical overlap between the various disorders may occur, and the histologies differ only by minor features.

The most common variant of progressive pigmentary dermatosis is Schamberg's disease. The typical lesions are thumbprint sized and composed of aggregates of pinhead-sized petechiae resembling grains of cayenne pepper along with golden-brown hemosiderin staining. The lesions commonly begin on the lower legs with slow proximal extension. These lesions seldom itch. The favored sites are around the lower shins and ankles, but lesions may be more widespread and occasionally affect the upper extremities or trunk.

Majocchi's disease is also known as *purpura annularis telangiectodes*. The early lesions are bluish-red 1- to 3-cm annular patches composed of dark red telangiectases with petechiae and hemosiderin staining (Fig. 35-9). Central involution and peripheral extension produce ringed, semicircular, target-like, or concentric rings such as are seen on the cross-cut section of a tree trunk. The eruption begins symmetrically on the lower extremities, spreads up the legs, and may extend onto the trunk and arms. Involution of individual patches is slow and because new lesions continue to form, it may continue indefinitely. The lesions are asymptomatic.

Gougerot-Blum syndrome (pigmented purpuric lichenoid dermatitis) is characterized by minute, rust-colored to violaceous, lichenoid papules that tend to fuse into plaques of various hues between red, violaceous, and brown (purpura with lichenoid dermatitis). Favorite locations are on the legs, thighs, and lower trunk. The chief difference between this and Schamberg's disease is the deeper color and presence of induration, both of which relate to the presence of a lichenoid band of lymphoid inflammation. Similar lesions have also occurred during interferon therapy for hepatitis C.

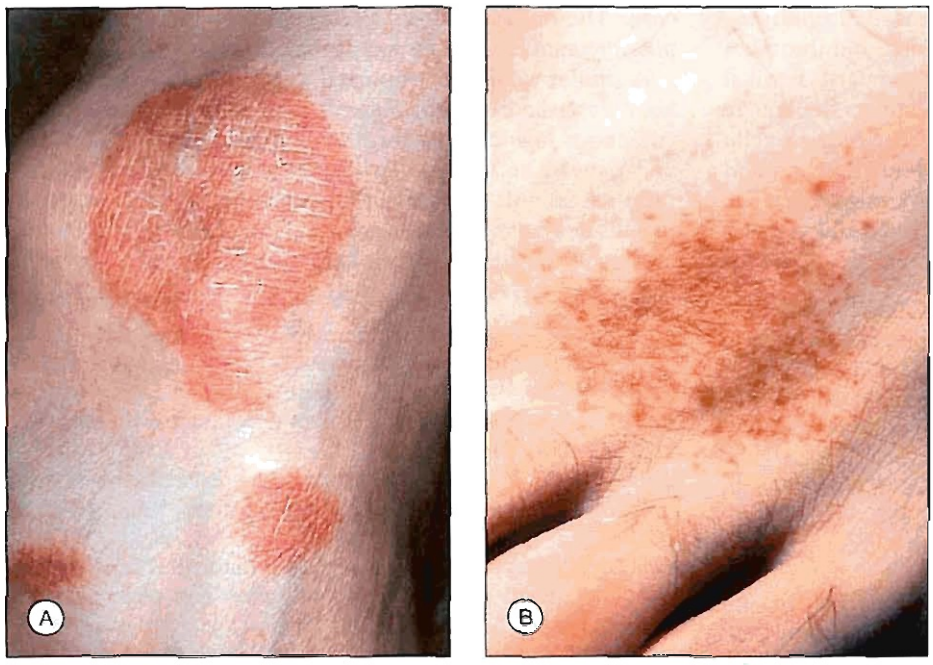

Fig. 35-9 Pigmented purpuric dermatosis.

Ducas and Kapetanakis pigmented purpura is scaly and eczematous. The eczematous patches also demonstrate petechiae and hemosiderin staining. It is distinguished histologically by the presence of spongiosis.

Lichen aureus is characterized by the sudden appearance of one or several golden or rust-colored, closely packed macules or lichenoid papules. The macules may be grouped into a patch and may occur on any part of the body. The patches are usually solitary and asymptomatic, but may occasionally be painful. Adults predominate, but children may also be affected. Many cases are related to an incompetent perforator valve causing a local increase in venous and capillary pressure. Linear segmental lesions may occasionally occur, and a single case of evolution to linear morphea has been reported.

Histologically, all forms of pigmenting purpura demonstrate lymphoid capillarities with erythrocyte extravasation. As lesions evolve, hemosiderin deposition becomes prominent. There may be a lichenoid band of lymphoid inflammatory cells (Gougerot-Blum type) or spongiosis (Ducas and Kapetanakis type). An iron stain (Perl, Prussian blue, ferricyanide) is sometimes used to demonstrate the hemosiderin deposition. Lichenoid purpura must be distinguished from mycosis fungoides, which it can closely resemble both clinically and histologically. The absence of epidermotropism or the presence of only a few lymphocytes with spongiosis favors the diagnosis of pigmented purpura. Purpuric pityriasis rosea my resemble Ducas and Kapetanakis pigmenting purpura.

Anecdotal reports of benefit from topical steroids make a therapeutic trial for 4 to 6 weeks reasonable. Pentoxifylline, 400 mg three times a day, has also been reported to provide significant improvement within 2 to 3 weeks. Oral rutoside, 50 mg twice a day, and ascorbic acid, 500 mg twice a day, have cleared a few patients. Pigmenting purpura frequently occurs in the setting of venous stasis, and support stockings may be of benefit. Paradoxically, some cases represent an allergic response to textile dyes in stockings, especially the azo dyes Disperse Blue 124, 106, and 85. Positive patch reactions have also been noted to Disperse Red 17, and Basic Red. Fabric resins, including ethyleneurea melamine formaldehyde, dimethylol dihydroxyethyleneurea, dimethylol propyleneurea, tetramethylol acetylenediurea, and urea formaldehyde have also been implicated. The finding of a purpuric reaction of patch testing is diagnostic in such cases. Sometimes, the positive patch site does not develop clinical purpura, but the dermatosis fades with elimination of the allergen.

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PURPURIC AGAVE DERMATITIS

Agave americana is a large, thick, long-leaved, subtropical plant with a striking blue-gray color. It is commonly used in ornamental beddings in the southwestern US. The plant grows up to 8 feet in diameter and may overgrow the surrounding landscape. As they are very deep-rooted and difficult to remove, some individuals have attempted

removal with the help of a chain saw. A striking purpuric dermatosis occurs in a pattern corresponding to the splatter of the plant's sap. Histologically, there is vascular damage at the level of the capillary and postcapillary venule with a sparse infiltrate of neutrophils and karyorrhectic debris, suggesting low-grade leukocytoclastic vasculitis. Papulovesicular lesions have also been described. The plant's sap contains calcium oxalate crystals as well as various acrid oils and saponins. The causative component is unknown.

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VASCULITIS

Vasculitis is a clinicopathologic process characterized by inflammation and necrosis of blood vessels. Since the clinical morphology correlates with the size of the affected blood vessel(s), these disorders are classified by the blood vessel(s) affected. Diseases may involve vessels of overlapping size. In general, small-vessel disease (affecting postcapillary venules) causes urticarial lesions and palpable purpura; small-artery disease manifests as subcutaneous nodules; medium-sized arteries with necrosis of major organs, livedo reticularis, purpura, and mononeuritis multiplex; and large-vessel disease with symptoms of claudication and necrosis.

Classification

Numerous classification schemes have been proposed, all of which have limitations. It is important to remember that infectious and thrombotic conditions, which histologically "classically" show thrombosis of vessels, may also at times show true leukocytoclastic vasculitis. Hence, infectious, embolic, and thrombotic causes of vessel damage must always be considered before unequivocally diagnosing a case as an "inflammatory" vasculitis. Leukocystoclastic vasculitis is also commonly seen adjacent to suppurative folliculitis and at the base of chronic ulcers. The discovery of the association of some forms of small- and medium-vessel vasculitides with positive ANCAs has made their diagnosis and classification much easier (Box 35-1).

Box 35-1 Classification of vasculitis

I. Cutaneous small-vessel (postcapillary venule)
   - A. Idiopathic cutaneous small-vessel vasculitis
   - B. Henoch-Schönlein purpura
   - C. Acute hemorrhagic edema of infancy
   - D. Urticarial vasculitis
   - E. Cryoglobulinemic vasculitis
   - F. Erythema elevatum diutinum
   - G. Granuloma faciale
   - H. Other diseases with leukocystoclastic vasculitis: drug-induced vasculitis, malignancy (lymphoreticular more common than solid tumor), connective tissue diseases, hyperglobulinemic purpura, inflammatory bowel disease, bowel-associated dermatitis–arthritis syndrome (bowel bypass), HIV infection, and neutrophilic dermatoses (Behçet; Sweet; erythema nodosum leprosum; septic vasculitis; autoinflammatory conditions-familial Mediterranean fever, and serum sickness)

II. Medium-vessel
   - A. Polyarteritis nodosa
     1. Benign cutaneous forms
     2. Systemic form

III. Mixed Size (medium and small) vessel disease
   - A. Connective tissue disease associated (usually rheumatoid vasculitis)
   - B. Septic vasculitis
   - C. ANCA-associated
     1. Microscopic polyangiitis
     2. Wegener granulomatosis
     3. Allergic granulomatosis (Churg-Strauss)
     4. Occasional drug-induced (most are post-capillary venule only)

IV. Large-vessel vasculitis
   - A. Giant-cell arteritis
   - B. Takayasu arteritis

Fiorentino DF: Cutaneous vasculitis. J Am Acad Dermatol 2003;48:311.

SMALL-VESSEL VASCULITIS

Cutaneous Small-Vessel Vasculitis (Cutaneous Leukocytoclastic Angiitis)

The vast majority of cases of cutaneous leukocytoclastic vasculitis follow an acute infection or exposure to a new medication. Palpable purpura is the hallmark of this disease, with lesions ranging from pinpoint to several centimeters in diameter (Figs 35-10 and 35-11). Annular, vesicular, bullous,

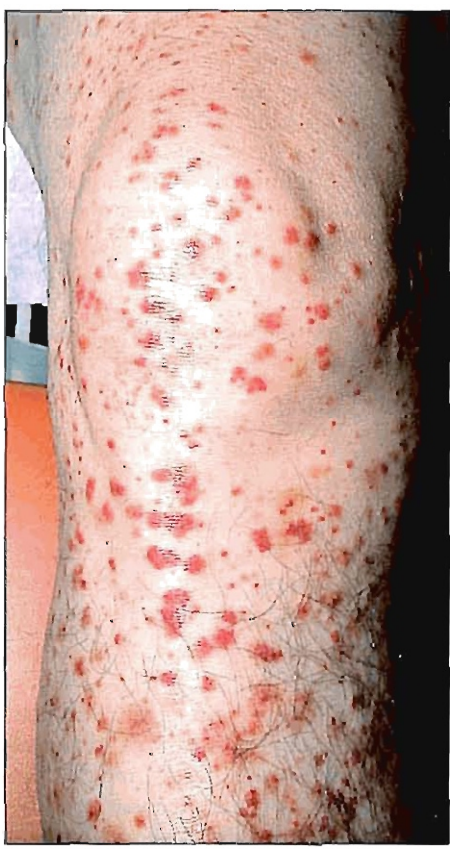

Fig. 35-10 Leukocytoclastic vasculitis, palpable purpura.

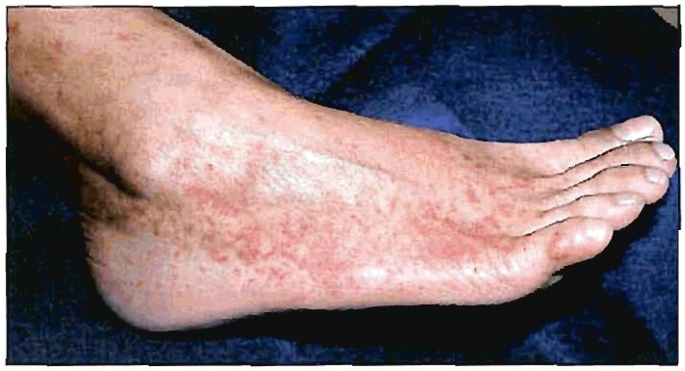

Fig. 35-11 Leukocytoclastic vasculitis, concentration of lesions along the dividing line between the dorsal foot and sole (Wallace line).

pustular, or ulcerated lesions may develop. They predominate on the ankles and lower legs, affecting mainly dependent areas or areas under local pressure. Edema, especially of the ankles, is usually noted. Mild pruritus, fever, and malaise may occur. Arthralgias or, less commonly, frank arthritis may be seen. Other systemic involvement is rare and should raise the consideration of another diagnosis.

The lesions usually resolve within 3 to 4 weeks with residual postinflammatory hyperpigmentation. Because the inciting event is time limited, usually the disease is self-limited. Ten percent of cases of cutaneous leukocytoclastic vasculitis may have recurrences. A persistent underlying cause must be sought in cases which are chronic.

Histology

There is angiocentric segmental inflammation of the post-capillary venule with expansion of the vessel wall, fibrin deposition, and infiltration by neutrophils that show fragmentation of their nuclei (karyorrhexis or leukocytoclasia). Endothelial cell swelling is common, but endothelial necrosis suggests more serious illness (including septic vasculitis, ANCA-associated vasculitis). Vascular thrombosis may be present. Immunofluorescence and ultrastructural studies have shown the presence of immunoglobulins, complement components, and fibrin deposits within postcapillary venule walls if the biopsy is taken within the first 24 h. Later, fibrin is prominent, but immunoglobulin deposits may have been destroyed. An important exception is Henoch-Schönlein purpura, which usually demonstrates prominent IgA deposits even in more advanced lesions.

Pathogenesis

Cutaneous small-vessel vasculitis is felt to be caused by circulating immune complexes. These complexes lodge in vessel walls and activate complement. Various inflammatory mediators are produced, contributing to endothelial injury. Cocaine use may cause or exacerbate small-vessel vasculitis.

Etiology

The types of antigens inducing immune complexes vary, but infections and drugs are most common. A host of infectious agents, such as beta-hemolytic *Streptococcus* group A and rarely *Mycobacterium tuberculosis* may cause palpable purpura. Patients with lymphoproliferative neoplasms (Hodgkin's disease, mycosis fungoides, adult T-cell leukemia, and multiple myeloma), as well as solid tumors (lung, colon, ovarian, renal, prostate, head and neck, and breast cancer) may experience cutaneous small-vessel vasculitis at some time during the course of their disease.

Clinical Evaluation

Given the vast number of conditions that may result in small-vessel vasculitis a detailed history and physical examination are essential. The history should focus on possible infectious disorders, prior associated diseases, drugs ingested, and a thorough review of systems. Screening laboratory tests may help to elucidate the underlying cause or extent of organ involvement. When the history suggests a recent drug and the patient is clinically well, nothing more than a urinalysis may be required. A complete blood count, urinalysis, strep throat culture or ASO titer, hepatitis B and C serologies, and antinuclear antibodies are a reasonable initial screen for patients with no obvious cause for their vasculitis. Serum protein electrophoresis, serum complements, ANCAs, and cryoglobulins may be required in some cases. A skin biopsy should be performed to confirm the diagnosis of leukocytoclastic vasculitis.

Treatment

The initial treatment of most cases of leukocytoclastic vasculitis in patients who are clinically well and have a normal urinalysis should be nonaggressive, since the majority of cases are acute and self-limited, affect only the skin, and do not threaten progressive deterioration of internal organs. Rest and elevation of the legs is likely to be helpful. Analgesics and avoidance of trauma and cold are prudent general measures. An identified antigen or drug should, of course, be eliminated and any identified infectious, connective tissue or neoplastic disease treated.

A variety of systemic treatments may be required for severe, intractable, or recurrent disease, especially if significant organ involvement is present. For disease limited to the skin, NSAIDs can be considered for the arthralgias. Colchicine, 0.6 mg two to three times a day, or dapsone, 50 to 200 mg/day, as trials of 2 to 3 weeks each, may be useful for chronic vasculitis. Low doses of colchicine and dapsone may be combined, if either medication alone is unsuccessful or effective doses of either drug cannot be reached. Although one controlled trial suggested that colchicine was ineffective in leukocytoclastic vasculitis, even in that trial a portion of the patients did respond and flared when the drug was stopped. Systemic corticosteroids in doses ranging from 60 to 80 mg/day are recommended for patients with serious systemic manifestations or necrotic lesions. Usually a brief course leads to resolution, and chronic treatment is rarely required. In refractory patients immunosuppressive agents, such as mycophenolate mofetil, 2 to 3 g/day; methotrexate, 5 to 25 mg/week; or azathioprine, 50 to 200 mg/day (2–3.5 mg/kg/day) may be considered. Azathioprine dosing is based on thiopurine methyltransferase levels. In more difficult cases cyclophosphamide, monthly intravenous pulses of steroids or cyclophosphamide, or cyclosporin, 3 to 5 mg/kg/day, may be effective. The tumor necrosis factor (TNF)-blockers, especially infliximab and to a lesser degree etanercept, may be effective in cutaneous small-vessel vasculitis. These agents may also cause vasculitis.

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Subtypes of Small-Vessel Vasculitis

Henoch-Schönlein Purpura Henoch-Schönlein purpura (HSP) is characterized by purpura, arthralgias (74–84%), abdominal pain (61–76%), and renal disease (44–47%). Typically, mottled purpura appears on the extensor aspects of the extremities, which become hemorrhagic within a day and start to fade in about 5 days (Fig. 35-12). New crops may appear over a period of a few weeks. Urticarial lesions, vesicles, necrotic purpura, and hemangioma-like lesions may also be present at some stages. It occurs primarily in male children, with a peak age between 4 and 8 years; however, adults may also be affected. A viral infection or streptococcal pharyngitis is the usual triggering event. Other possibilities include other bacterial infections, foods, drugs, and lymphoma.

In about 40% of cases the cutaneous manifestations are preceded by mild fever, headache, joint symptoms, and abdominal pain for up to 2 weeks. Arthralgia progressing to arthritis produces periarticular swelling around the knees and ankles. There may be pulmonary hemorrhage, which can be fatal. Abdominal pain and gastrointestinal bleeding may occur at any time during the disease; severe abdominal pain may even suggest—or portend—an acute surgical abdomen. Paralytic ileus may occur. Vomiting, rebound tenderness, and distension are other manifestations. Gastrointestinal radiographs may show "spiking" or a marbled "cobble-stone" appearance. Renal involvement manifests as microscopic or even gross hematuria and may occur in 25% or more of patients. The long-term prognosis in children with gross hematuria is very good; however, progressive glomerular disease and renal failure may develop in a small percentage, so that careful follow-up is necessary for those with hematuria.

IgA, C3, and fibrin depositions have been demonstrated in biopsies of both involved and uninvolved skin by immunofluorescence techniques. Uninvolved skin is a preferable site for biopsy because tissue morphology is better. There may be raised levels of IgA immune complexes even in the absence of nephritis or purpura.

Treatment is supportive. The usual duration of illness is 6 to 16 weeks. Between 5% and 10% of patients will have persistent or recurrent disease. Dapsone 50 to 200 mg/day or colchicine 0.6 mg/day to 1.2 mg twice a day can be used initially if treatment is required and skin lesions are the primary concern. For abdominal pain an H_2 blocker and/or corticosteroids (prednisone at 1 mg/kg/day) can be effective. Corticosteroids are more effective for abdominal pain than is analgesia. The value of systemic corticosteroids in the treatment of renal disease is controversial, but it may be used preventively or to treat active nephritis. IVIG can be used in refractory skin disease and persistent abdominal pain, and to arrest rapidly progressive glomerulonephritis. NSAIDs are best avoided as they may cause renal or gastrointestinal complications.

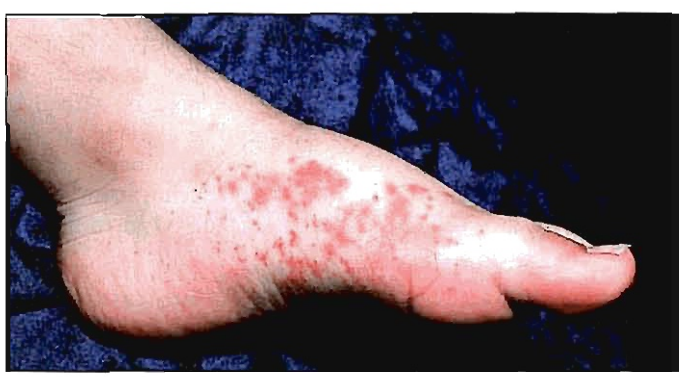

Fig. 35-12 Henoch-Schönlein purpura.

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Acute Hemorrhagic Edema of Infancy Also known as Finkelstein's disease, Seidlmayer syndrome, medallion-like purpura, infantile postinfectious iris-like purpura and edema, and purpura en cocarde avec oedema, acute hemorrhagic edema (AHE) of infancy affects children under the age of 2 with a recent history of an upper respiratory illness (75%), a course of antibiotics, or both. The children are often nontoxic in appearance. There is abrupt onset of large cockade, annular, or targetoid purpuric lesions involving the face, ears, and extremities (Fig. 35-13). Scrotal purpura may also occur. Early in the course there may first be acral edema, with subsequent proximal spread. The edema is nontender and may be asymmetrical. A low-grade fever is common, and involvement of internal organ systems (joint pains, gastro-

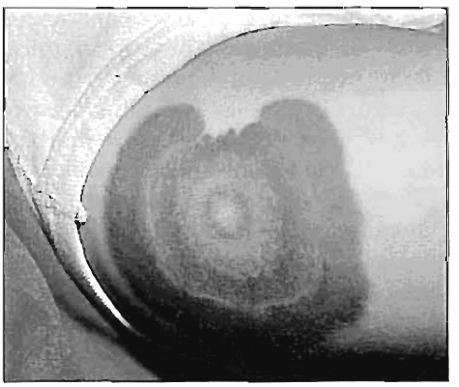

Fig. 35-13 Acute hemorrhagic edema, typical large annular hemorrhagic plaques.

intestinal symptoms, and renal involvement) is rare. Routine laboratory tests are unremarkable. Spontaneous recovery without sequelae occurs within 12 to 20 days. The differential diagnosis includes HSP, meningococcemia, erythema multiforme, urticaria, and Kawasaki's disease. There are some similarities between HSP and AHE (postinfectious, seasonal, favors males), but it is different in that it favors younger children (<2 years), resolves more quickly, lacks IgA on DIF in most cases, and is rarely associated with systemic symptoms. From a clinical point of view the most urgent need is to exclude the possibility of septicemia, especially meningococcemia.

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Urticarial Vasculitis A significant percentage of patients (reported as high as 5–10%, but probably less) with fixed urticarial lesions will have vasculitis histologically. This is termed "urticarial" vasculitis (Fig. 35-14). This urticarial morphology is maintained throughout the course of the illness. Microscopic hemorrhage into the urticarial plaques may occur, resulting in a bruise-like appearance as the lesions fade. Determination of the serum complement levels (CH50, C3, C4, and anti-C1q precipitins) is critical in the evaluation of urticarial vasculitis. Patients with normal complement levels usually have a leukocytoclastic vasculitis, which is idiopathic, limited to the skin, self-resolving, and is best considered a subset of cutaneous small-vessel vasculitis. Hypocomplementemic urticarial vasculitis is a distinctive syndrome seen virtually always in women. Clinical features include arthritis (50%), arthralgias, angioedema, eye symptoms, asthma, and obstructive pulmonary disease (20%), and gastrointestinal symptoms (20%). Glomerulonephritis may be present.

Underlying diseases associated with all forms of urticarial vasculitis include gammopathies (IgG and IgM gammopathy), SLE, Sjögren syndrome, serum sickness, and viral infections, especially hepatitis C. All patients with hypocomplementemic urticarial vasculitis have anti-C1q antibodies

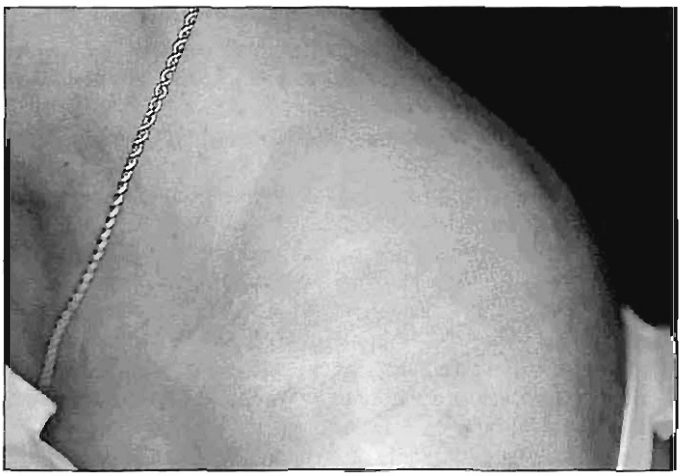

Fig. 35-14 Urticarial vasculitis.

directed against the collagen-like region of that molecule, a feature used to define this disease. Patients with SLE may also have these autoantibodies. Many patients with hypocomplementemic urticarial vasculitis will have positive ANAs and up to a quarter will have positive anti-dsDNA antibodies. The vast majority (96%) will have a positive "lupus band test." Over time more than 50% will meet the criteria for the diagnosis of SLE. For this reason some consider hypocomplementemic urticarial vasculitis a form of SLE.

Three clinical features distinguish the skin lesions of urticarial vasculitis from true urticaria: 1) the lesions are often painful, rather than pruritic; 2) the lesions last longer than 24 h and are fixed, rather than migrating; and 3) on resolving there is postinflammatory purpura or hyperpigmentation. More difficult is the distinction of urticarial vasculitis from neutrophilic urticaria, as patients with the latter condition can have painful, more persistent lesions. Histologic evaluation is critical.

Histologically, patients with hypocomplementemic urticarial vasculitis will show both leukocytoclastic vasculitis and diffuse interstitial neutrophils. Eosinophils are more likely to be seen in patients with neutrophilic urticaria or normocomplementemic urticarial vasculitis. Sweet syndrome shows a more intense dermal infiltrate with marked upper dermal edema. Sweet syndrome and vasculitis share the presence of karyorrhexis. While virtually all biopsies of idiopathic urticaria demonstrate neutrophils, karyorrhexis is usually distinctly absent.

The treatment of hypocomplementemic urticarial vasculitis is directed at the symptomatology and severity of the disease. Indomethacin has been particularly effective. Antihistamines, dapsone, and colchicine may be tried. The addition of pentoxyphylline to dapsone may be effective. Antimalarials can be beneficial, as would be expected in this autoimmune connective tissue disease. Immunosuppressive therapy with prednisone and the steroid-sparing agent mycophenolate mofetil (2 g/day) can be considered in refractory and severe cases.

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Cryoglobulinemic Vasculitis About 15% of patients with a circulating cryoprecipitable protein are symptomatic and have cryoglobulinemic vasculitis. They typically have mixed cryoglobulinemia. Mixed cryoglobulinemia follows a benign course in half of cases, but in about one-third liver or renal failure occur. Fifteen percent of cases develop malignancy, usually B-cell lymphoma, and less frequently hepatocellular or thyroid cancer. By far the most common cause of cryoglobulinemic vasculitis is HCV infection, but autoimmune diseases and lymphoproliferative disorders can also be associated with cryoglobulinemic vasculitis. Cryoglobulinemic vasculitis usually presents with macular or palpable purpura, typically confined to the lower extremities. Lesions may be limited or severe. Two-thirds of patients show confluent areas of hemosiderosis of the feet and lower legs, characteristic of prior episodes of purpura. While only 30% of patients report an exacerbation with cold exposure, up to 50% will have Raynaud phenomenon and cold-induced acrocyanosis of the ears. Other morphologies include ecchymoses, livedo reticularis, urticaria, and ulcerations. Widespread systemic vasculitis occurs in about 10% of patients. Neuropathy, and other neurologic complications occur in 40% of patients. Arthralgias, xerostomia, and xerophthalmia are frequent complaints. Laboratory evaluation will reveal a cryoglobulin, hypocomplementemia (90%), and a positive rheumatoid factor (70%). ANCAs are rarely positive. A skin biopsy will show leukocytoclastic vasculitis.

The treatment of cryoglobulinemic vasculitis is the treatment of the underlying disease if possible. In the case of HCV infection this usually is interferon-α plus ribavirin. Cryoglobulinemic vasculitis associated with HCV may also be flared by interferon treatment. Colchicine, dapsone, cyclosporin, IVIG, infliximab, and rituximab (anti-CD20 monoclonal antibody) can be attempted.

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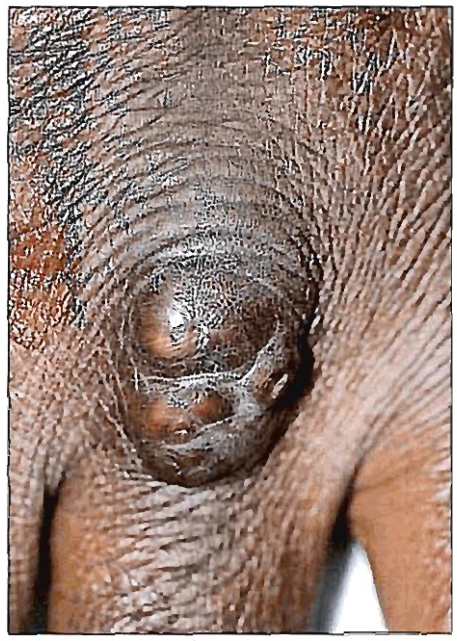

Fig. 35-15 Erythema elevatum diutinum.

Erythema Elevatum Diutinum A rare condition, erythema elevatum diutinum (EED) is considered to be a chronic fibrosing leukocytoclastic vasculitis. Classically, multiple orange-to-yellow papules and plaques develop over the joints (Fig. 35-15), particularly the elbows, knees, hands, and feet. Lesions may also involve the buttocks and areas over the Achilles tendon. Petechiae and purpura can be associated with early lesions. More rarely, large plaques, with nodules at the periphery may affect the trunk and extremities. With time the papules take on a doughy to firm consistency and develop a red or purple color. In HIV infection, skin-colored or red nodules affect the soles, producing lesions resembling keloids, Kaposi sarcoma, or bacillary angiomatosis. Pruritus, arthralgias, and pain have been reported; however, most patients are asymptomatic. Systemic complications are rare, but an unusual and potentially rapidly destructive keratitis can lead to blindness. EED has been associated with HIV infection, SLE, hematologic disease (IgA monoclonal gammopathy and lymphoma), and celiac disease. Chronic and recurrent streptococcal infections cause exacerbations of the disease in some patients. These may all represent conditions with persistent circulating immune complexes which might trigger a chronic vasculitis. Pathogenically, ANCAs (60% IgA and 33% IgG) are found in EED and not in Sweet or pyoderma gangrenosum. ANCA-positive vasculitides such as Wegener have rarely been reported to have EED-like lesions.

Histologically, early lesions are a leukocytoclastic vasculitis, but with prominent interstitial neutrophils. Well-formed lesions are composed of nodular and diffuse mixed infiltrates of neutrophils and nuclear dust, eosinophils, histiocytes, and plasma cells that often extend into the subcutaneous fat. The prominence of eosinophils; the chronicity of the process, which results in an onion skin-like perivascular fibrosis; and the admixture of plasma cells and many lymphocytes are the hallmarks of EED. Erythrocyte extravasation may lead to extracellular cholesterol crystals in long-standing cases.

Dapsone is the treatment of choice. Patients with celiac disease may respond to a gluten-free diet. Intermittent plasma

exchange has been used successfully in patients with IgA paraproteinemia. The interstitial keratitis also responds to dapsone. Unfortunately, the late nodular lesions may not resolve with dapsone treatment.

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Granuloma Faciale Characterized by brownish-red, infiltrated papules, plaques, and nodules, granuloma faciale involves the facial areas, particularly the nose. Healthy, middle-aged (mean 53 years) white men (male-to-female ratio, 5:1) are most typically affected. Childhood cases have been reported. Extrafacial disease occurs in up to 20% of cases, usually affecting the upper trunk and extremities.

The pathology of granuloma faciale is similar to that of EED, with focal leukocytoclastic vasculitis, diffuse dermal neutrophilia with leukocytoclasia, tissue eosinophilia, and perivascular fibrosis.

A variety of treatment options are available. Intralesional corticosteroids are the recommended first approach. Cryotherapy in combination with intralesional corticosteroids has been shown to be very effective. Topical corticosteroids may also be useful. Although controlled clinical trials are lacking, if the patient remains unresponsive, dapsone, colchicine, or antimalarials could be considered. Laser treatment with pulsed dye and argon lasers has been effective in multiple cases, making it a reasonable consideration as first-line treatment.

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POLYARTERITIS NODOSA

Polyarteritis nodosa (PAN) is characterized by necrotizing vasculitis affecting primarily the medium-sized arteries, but PAN may affect small vessels as well. Muscular arteries of such caliber as the renal, hepatic, and coronary vessels, and the arteries in the subcutaneous tissue and sometimes adjacent veins can be affected. There are two major forms: the benign cutaneous and the systemic, although even long-standing benign cutaneous disease can evolve into systemic disease.

PAN is four times more common in men than in women and the mean age of presentation is 45 years. It has been seen in intravenous drug abusers and in association with SLE, inflammatory bowel disease, hairy cell leukemia, familial Mediterranean fever, and Cogan syndrome (nonsyphilitic interstitial keratitis and vestibulo-auditory symptoms). Infectious associations include hepatitis B, hepatitis C, and antecedent streptococcal infections. HBV is present in 5% to 7% of cases overall, but in up to 50% of cases in some series, but this percentage is falling with HBV immunization. The identification of associated hepatitis virus infection has therapeutic implications.

The skin is involved in up to 50% of patients with the systemic form of PAN with wide-ranging findings. The most striking and diagnostic lesions (15% of patients) are 5- to 10-mm subcutaneous nodules occurring singly or in groups distributed along the course of the blood vessels, above which the skin is normal or slightly erythematous (macular arteritis). These nodules are often painful and may pulsate and, in time, ulcerate (Fig. 35-16). Common sites are the

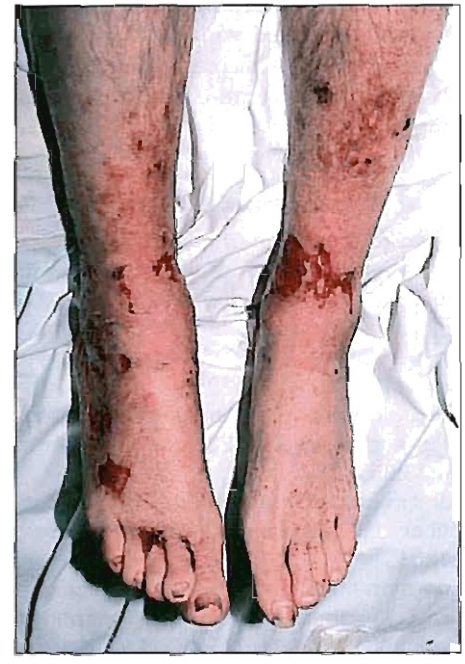

Fig. 35-16 Polyarteritis nodosa with multiple leg ulcerations.

lower extremities, especially below the knee. Ecchymoses and peripheral gangrene of the fingers and toes may also be present. Livedo reticularis in combination with subcutaneous nodules strongly suggests the diagnosis of PAN. Palpable purpura with histologic features of cutaneous leukocytoclastic vasculitis with endothelial necrosis may be seen in PAN.

Classic systemic PAN may involve the vessels throughout the entire body. It has a particular predilection to affect the skin, peripheral nerves, gastrointestinal tract, and kidneys. Hypertension, tachycardia, fever, edema, and weight loss are cardinal signs of the disease. Hepatomegaly, icterus, lymphadenopathy, hematuria, and leukocytosis are also frequently found. Arthralgia, myocardial and intestinal infarctions, glomerulosclerosis, and peripheral neuritis are also seen. Mononeuritis multiplex, most often manifested as foot drop, is a hallmark of PAN. Involvement of the meningeal, vertebral, and carotid arteries may lead to hemiplegia and convulsions. The lungs and spleen are rarely involved. Aneurysms develop, which may result in multiorgan infarcts.

A leukocytosis of as high as 40,000/mm^3 may occur, with neutrophilia to 80%; thrombocytosis, progressive normocytic anemia, and an elevated sedimentation rate may also be found. Hypergammaglobulinemia with macroglobulins and cryoglobulins may be present. Hepatitis B and C studies should be performed. Urinary abnormalities such as proteinuria, hematuria, and casts are present in 70% of patients.

The histology is that of an inflammatory necrotizing and obliterative panarteritis that attacks the small and medium-sized arteries. Focal vasculitis forms nodose swellings that become necrotic, producing aneurysms and rupture of the vessels. Hemorrhage, hematoma, and ecchymosis may result. Obliteration of the lumen may occur, with ischemic necrosis of surrounding tissue. Characteristically, the arteries are affected at their branching points.

The mainstay of diagnosis is the presence of these histologic features. The preferable site for biopsy is an accessible site such as skin, muscle, or testis. If these are not involved, angiography may detect aneurysmal dilations as small as 1-cm wide in the renal, hepatic, or other visceral vessels.

Treatment

Untreated classic PAN can be fatal; death usually occurring from renal failure or cardiovascular or gastrointestinal complications. Death usually occurs early in the course of the disease and there is only a 5% to 10% chance of serious sequelae or death occurring beyond the first few years of diagnosis. Treatment with corticosteroids and cytotoxic agents has increased the survival rate to more than 90%. Corticosteroids in the range of 1 mg/kg/day are given initially. Once the disease remits the dose should be reduced. After an average of 3 to 6 months, with the patient in remission, the steroids are slowly tapered to discontinuation.

Cyclophosphamide is given with steroids or sometimes as a single agent. An initial dose of 2 mg/kg/day as a single dose is recommended. Twice this dosing may be required for severely ill patients. The oral dose is then adjusted to maintain the white blood cell count between 3000 and 3500/mm^3 and the neutrophil count above 1500 cells/mm^3. When the disease has been quiescent for at least a year, the cyclophosphamide may be tapered and stopped. On average, 18 to 24 months of therapy is required. Pulsed intravenous cyclophosphamide is associated with a lower incidence of hemorrhagic cystitis. In cases of HBV-associated PAN, lamivudine may be given in combination with immunosuppressive treatment, improving outcome.

Ulcerations in PAN can be very painful due to the associated neuropathy. They should be managed like nonhealing leg ulcers. The use of bioengineered skin equivalents and cultured keratinocytes may lead to healing of the ulcers and improvement of the pain.

Cutaneous Polyarteritis Nodosa About 10% of patients present with PAN localized to the skin and with limited systemic involvement, usually neuropathy. Over time they may have few complications and a good prognosis, and may require less aggressive treatment to control their disease. This form of PAN is the most common childhood pattern of PAN. It is controversial as to whether there are two clear subsets of patients, cutaneous or systemic PAN, or rather a spectrum of disease. Patients with "cutaneous" PAN must be followed carefully and regularly evaluated to exclude the development of systemic involvement.

Patients usually have recurrent skin, joint, muscle and nerve involvement. The cutaneous findings are almost always subcutaneous nodules associated with livedo reticularis. Atrophie blanche-like lesions around the ankles may be the sole cutaneous manifestation of cutaneous PAN. On superficial biopsies the diagnosis of livedoid vasculopathy may be made, but on deeper biopsies, the features of a medium-sized vessel vasculitis are seen. Some of these patients have neurologic involvement with neuropathic and lesional pain and dysesthesia, allowing the clinician to separate these cases from other conditions causing atrophie blanche-like scars (venous insufficiency, cryoglobulinemia, antiphospholipid syndrome).

Cutaneous PAN has been associated with HBV surface antigenemia, HCV infection, Crohn's disease, Takayasu arteritis, relapsing polychondritis, streptococcal infections, tuberculosis, and medications (minocycline). Typically the only laboratory abnormality is an elevated ESR. In some cases a P-ANCA may be present. Most patients respond well to aspirin, NSAIDs, prednisone, pentoxyphylline, sulfapyridine, or methotrexate, alone or in combination, usually resulting in clinical responses within a few days. In childhood cutaneous PAN, since streptococcal infection is common, penicillin treatment may be used. In refractory cases IVIG may be used.

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ANCA-POSITIVE SMALL-VESSEL VASCULITIDES

ANCAs have become an important laboratory finding used in the diagnosis and in some cases the prognosis of systemic vasculitis. ANCAs occur in three patterns: cytoplasmic (C-ANCA); perinuclear (P-ANCA); and atypical ANCA. C-ANCA is associated with antibodies directed against proteinase 3 (PR3). Antibodies against myeloperoxidase result in the P-ANCA pattern, but antibodies against other antigens may also give this pattern. Atypical ANCAs are not directed against myeloperoxidase or PR3. Most laboratories now perform specific tests to determine whether positive ANCAs are reactive against myeloperoxidase or PR3. Anti-PR3 antibodies are relatively specific for Wegener granulomatosis and microscopic polyarteritis. Antibodies against myeloperoxidase are less specific and can be found in microscopic polyarteritis, Churg-Strauss syndrome, and drug-induced vasculitis. Usually either antimyeloperoxidase or anti-PR3 antibodies are found, but not both. If both patterns are found, drug-induced vasculitis should be suspected. ANCAs have been used to delineate a group of small-vessel vasculitides called "ANCA small-vessel vasculitides" or ANCA-SVV. These include microscopic polyangiitis, Wegner granulomatosis, and Churg-Strauss Syndrome. These diseases have overlapping features, but characteristically pulmonary hemorrhage and necrotizing glomerulonephritis (pulmonary–renal syndrome) and 60% of patients with the pulmonary–renal syndrome will have ANCA-SVV. With ANCA testing, ANCA-SVV can be diagnosed with 85% sensitivity and 98% specificity. While ANCAs are usually negative in Takayasu arteritis, giant-cell arteritis, Kawasaki's disease, and Behçet; positive ANCAs can be found in cryoglobulinemia and other forms of skin-limited vasculitis, in 20% of patients with SLE, and in a higher percentage of patients with rheumatoid arthritis. ANCAs are used in the setting of vasculitis with systemic features or in situations where the clinical findings suggest ANCA-SVV. ANCA testing does not replace other tests or more importantly histologic confirmation of the presence of vasculitis. While the ANCA-SVV are of unknown etiology, in multiple cases a solid tumor has been identified at the time of the diagnosis of the vasculitis.

Microscopic Polyangiitis

Most patients with microscopic polyangiitis have systemic symptoms, such as fever, weight loss, myalgias, and arthralgias for months to years before an explosive phase of their disease. Most patients with microscopic polyangiitis will have segmental necrotizing and crescentic glomerulonephritis with pulmonary involvement in 25% to 50% of cases. Pulmonary hemorrhage occurs in 12% to 29%. The skin is involved in 62%. Palpable purpura is present in 46% of cases and cutaneous ulceration may result. Urticarial lesions, purpura and petechiae, livedo and erythema of the hands and/or fingers have been described. Skin biopsies may not be specific, except in cases with typical palpable purpura. Vasculitic neuropathy is common (58%) and eye disease may occur. Eosinophilia and asthma are not seen. ANCAs are positive in 70% of cases, P-ANCA more frequently than C-ANCA. Microscopic polyangiitis is separated from PAN by the presence of glomerulonephritis, pulmonary symptoms, and the absence of hypertension and microaneurysms. ANCAs are usually negative in PAN. Microscopic polyangiitis is managed like other forms of ANCA-SVV with systemic corticosteroids and often cytotoxic agents from the disease onset. In cases with limited involvement, less aggressive treatment may be considered. Cyclophosphamide is usually used in the early induction phase of treatment (6–12 months) as monthly pulses (as opposed to daily treatment). Lower toxicity immunosuppressives (methotrexate, azathioprine, mycophnolate mofetil) may be used as maintenance or in milder cases. IVIG and anti-TNF agents (infliximab/etanercept) may be considered in refractory cases. Relapses are frequent, the 5-year survival is about 75%, and 7-year survival is 62%.

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Wegener Granulomatosis

Wegener granulomatosis is a syndrome consisting of necrotizing granulomas of the upper and lower respiratory tract, generalized necrotizing angiitis affecting the medium-sized blood vessels, and focal necrotizing glomerulitis. By far the most common initial manifestation, present in 90% of patients, is the occurrence of rhinorrhea, severe sinusitis, and nasal mucosal ulcerations, with one or several nodules in the nose, larynx, trachea, or bronchi. Fever, weight loss, and

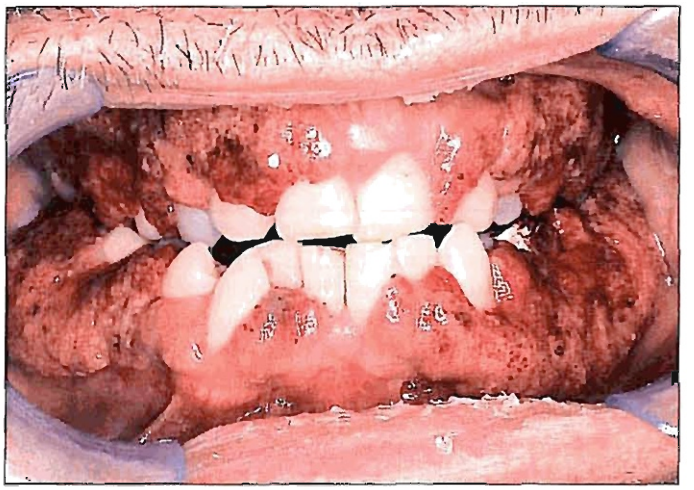

Fig. 35-17 Wegener granulomatosis, strawberry gingival.

malaise occur in these patients, who are usually 40 to 50 years of age and more often male than female (1.3:1). Obstruction in the nose may also block the sinuses. The nodules in the nose frequently ulcerate and bleed. The parenchymal involvement of the lungs produces cough, dyspnea, and chest pain. Granulomas may occur in the ear and mouth, where the alveolar ridge becomes necrotic and ulceration of the tongue and perforated ulcers of the palate develop. The combination of nasal and palatal involvement may lead to saddle-nose deformity. The "strawberry gums" appearance of hypertrophic gingivitis is characteristic and biopsy from these lesions may be diagnostic (Fig. 35-17).

Cutaneous findings occur in 45% of patients. Nodules may appear in crops, especially along the extensor surfaces of the extremities. The firm, slightly tender, flesh-colored or violaceous nodules may later ulcerate. These may be mistaken for ulcerating rheumatoid nodules. The necrotizing angiitis of the skin may present as a petechial or hemorrhagic pustular eruption, subcutaneous nodules, or ulcers. Livedo reticularis is rare in Wegener granulomatosis. Patients may present with pyoderma gangrenosum-like lesions and several patients have been reported presenting with features of temporal arteritis. The condition previously described as "malignant pyoderma" is now felt to represent Wegener granulomatosis.

Limited forms involving the upper respiratory tract without renal involvement may also occur and have a better prognosis. Cutaneous findings can be associated with limited disease. Focal necrotizing glomerulitis occurs in 85% of patients. It may be fulminant from the outset or may become more severe as the disease progresses. Renal failure was the most frequent cause of death before cyclophosphamide treatment. Other organs frequently involved include the joints (arthralgia in two-thirds); eyes (conjunctivitis, episcleritis, and proptosis) in 58%; and CNS and cardiac involvement in 22% and 12% of patients, respectively.

Histologically, the cutaneous lesions may demonstrate a leukocytoclastic vasculitis with or without granulomatous inflammation. Granulomatous vasculitis may be seen. Palisaded granulomas with multinucleated giant cells and a central core of neutrophils and debris are a characteristic finding. Often, if the lesions are ulcerated they are nonspecific histologically. Biopsy of another affected organ may be required to confirm the diagnosis. The early detection of Wegener granulomatosis has improved with the availability of ANCA testing, as 75% to 80% of patients are C-ANCA (anti-PR3) positive.

Untreated Wegener granulomatosis has a mean survival time of 5 months and a 90% mortality over 2 years. Cyclophosphamide therapy has dramatically changed the prognosis. Treatment recommendations are cyclophosphamide, 2 mg/kg/day, and prednisone, 1 mg/kg/day, followed by tapering of the prednisone to an alternate-day regimen. Complete remission is achieved in up to 93% of patients and lasts an average of 4 years for still living patients. In more limited disease, patients may respond to methotrexate alone or methotrexate in combination with prednisone. After initial induction therapy and a remission, methotrexate, azathioprine, leflunomide, or mycophenolate mofetil may be used instead of cyclophosphamide. Treatment should be continued for at least 1 year. Trimethoprim–sulfamethoxazole may decrease the relapse rate and can be considered for long-term treatment of patients with limited upper respiratory tract involvement in remission in combination with conventional immunosuppressive protocols. In refractory cases, IVIG and anti-TNF therapy (infliximab) may be used. Tacrolimus, 0.1 mg/kg/day, was successful in treating a pyoderma gangrenosum-like ulceration in a patient with Wegener.

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Churg-Strauss Syndrome

Churg-Strauss syndrome occurs in three phases. The initial phase, often lasting many years, consists of allergic rhinitis, nasal polyps, and asthma. The average age of onset of the asthma is 35 years in Churg-Strauss syndrome (as opposed to allergic asthma which often presents in childhood). A debilitated asthmatic begins after 2 to 12 years to experience attacks of fever and eosinophilia (20–90%) with pneumonia and gastroenteritis (second phase). After a few more months or years, but on average 3 years after the initial symptoms,

a diffuse angiitis involves the lungs, heart, liver, spleen, kidneys, intestines, and pancreas. Mononeuritis multiplex is common. Triggers of this third phase have included vaccination, desensitization, leukotriene inhibitors, cocaine use, azithromycin, or rapid discontinuation of corticosteroids. Renal involvement is less common than in Wegener granulomatosis or microscopic polyangiitis. A fatal outcome is likely in most untreated patients, with congestive heart failure resulting from granulomatious inflammation of the myocardium the most frequent cause of death.

Cutaneous lesions are present in two-thirds of patients. Palpable purpura is seen in nearly 50% of patients. Subcutaneous nodules on the extensor surfaces of the extremities and on the scalp are seen in 30%. Firm, nontender papules may be present on the fingertips. Urticaria and livedo reticularis can occur in Churg-Strauss syndrome. Plaques with the histologic features of eosinophilic cellulitis (Well syndrome) can be seen.

Laboratory studies are significant for a peripheral eosinophilia, which correlates with disease severity. ANCAs are frequently positive (55–70%), most commonly for anti-myeloperoxidase (P-ANCA) and less frequently for anti-PR3 (C-ANCA), and tend to correlate with disease severity.

Histologically, a small-vessel vasculitis is present that involves not only superficial venules, but also larger and deeper vessels. The tissue is often diffusely infiltrated with eosinophils and granulomas may be present. Palisaded granulomas differ from those in Wegener granulomatosis in that they generally lack multinucleated giant cells and the core contains eosinophils. In some patients, flame figures, similar to those in Well syndrome, are noted in the dermis.

Corticosteroids alone may be used in patients with CSS. Cyclophosphamide alone or in combination with corticosteroids should be used in cases of neuropathy, refractory glomerulonephritis, myocardial disease, severe gastrointestinal disease, and CNS involvement. Methotrexate can be used as a steroid sparing agent, especially for maintenance. Interferon alfa, mycophenolate mofetil, and the anti-TNF agents (infliximab and etanercept) have also been used successfully in CSS.

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GIANT-CELL ARTERITIS/TEMPORAL ARTERITIS

Giant-cell arteritis is a systemic disease of people over the age of 50, favoring women (2:1). It is uncommon in African Americans and favors whites. Its best known location is in the temporal artery, where it is known as *temporal arteritis*, *cranial arteritis*, and *Horton's disease*. It is characterized by a necrotizing panarteritis with granulomas and giant cells, which produce unilateral headache and exquisite tenderness in the scalp over the temporal or occipital arteries in 50% to 75% of patients. Temporal headaches are characteristically constant, severe, and boring. Ear and parotid pain and mastication-induced jaw claudication may occur. Fever, anemia, and a high sedimentation rate are usually present. Proximal, symmetrical, and severe morning and even day-long stiffness, soreness, and pain occur in 50% of patients. It is rarely fatal. The disease has also been shown to involve the vessels of the coronary arteries, breast, uterus, legs, abdomen, retina, and hand. Blindness may develop and is the most feared complication of the disease. Many patients who develop visual loss have premonitory symptoms allowing for the diagnosis and intervention, which may prevent permanent visual loss. Aortic aneurysms resulting in aortic rupture have been reported.

The cutaneous manifestations may be only inflammatory. The affected artery becomes evident as a hard, pulsating, tender, tortuous bulge under red or cyanotic skin. Another manifestation is gangrene of the scalp. The lesions may first appear as ecchymoses with a zonal distribution over the affected area. Later they may become vesicular or bullous and are followed by gangrene. Urticaria, purpura, alopecia, tender nodules, prurigo-like nodules, and livedo reticularis may be seen. Lingual artery involvement may cause an accompanying red, sore or gangrenous tongue.

Polymyalgia rheumatica (PMR) has a significant clinical association with giant-cell arteritis. Prompt treatment may forestall serious disease. About 10% of central retinal artery occlusions are due to giant-cell arteritis. ESRs are elevated in more than 90% of patients with giant-cell arteritis. Temporal artery biopsy is generally diagnostic provided that at least a 2-cm segment is provided. Even arteries which are normal to palpation may show diagnostic findings. Magnetic resonance angiography is a noninvasive diagnostic method that may aid in confirming the clinical suspicion and identify the best site to biopsy. Not all patients with arteritis of the temporal artery have giant cell arteritis, as temporal arteritis may be a manifestation or part of the systemic vasculitides such as PAN, Wegener granulomatosis, or microscopic polyarteritis. Pathogenically, the presence of TNF polymorphisms in patients with PMR and temporal arteritis suggests a genetic predisposition.

Treatment is usually begun with prednisone, 60 mg/day, continued for 1 month or until all reversible clinical and laboratory parameters (such as the ESR) have returned to normal. The disease is quite steroid responsive and tapering to a dose of 7.5 to 10 mg/day is usually possible. Daily therapy seems to be important and is usually necessary for a

minimum of 1 to 2 years. Most patients achieve complete remission that is often maintained after therapy is withdrawn. Anti-TNF agents may be used in refractory cases, but relapses occur when infusions are stopped, and corticosteroid therapy is usually required.

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Takayasu Arteritis

Known also as *aortic arch syndrome* and *pulseless disease*, Takayasu arteritis is a thrombo-obliterative process of the great vessels stemming from the aortic arch, occurring generally in young women (female-to-male ratio, 9:1) in the second or third decade of life. It is more common in Japan, Southeast Asia, India, and South America. Radial and carotid pulses are typically obliterated. Skin changes are due to the disturbed circulation. There may be loss of hair and atrophy of the skin and its appendages, with underlying muscle atrophy. Occasional patients with cutaneous necrotizing or granulomatous vasculitis of small vessels have been reported. Erythema nodosum may rarely occur. Pyoderma gangrenosum-like ulcerations are well-described in Japan with more than 35 cases reported. Pyoderma gangrenosum lesions precede the diagnosis of the arteritis by an average of 3 years. These lesions are more commonly generalized and in three-quarters of cases occur on the upper extremities.

Treatment of Takayasu arteritis with prednisone 1 mg/kg/day tapered in 8 to 12 weeks to 20 mg/day or less is recommended. Methotrexate may be used for its steroid-sparing effects. With active medical and surgical intervention the aggressive course of this disease can be modified. The pyoderma gangrenosum-like lesions are also treated with systemic steroids, but azathioprine, cyclophosphamide, mycophenolate mofetil, cyclosporin, and tacrolimus have also been effective.

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MALIGNANT ATROPHIC PAPULOSIS

Papulosis atrophicans maligna, also known as *Degos' disease*, is a potentially fatal obliterative arteritis syndrome. Some affected patients have a long benign course, while in others, death occurs within a few years. Degos' disease occurs three times more frequently in men than in women, often presenting between the ages of 20 and 40. Familial kindreds are well-reported. In patients with the more aggressive variant, survival averages 2 to 3 years after the disease has developed.

Skin lesions are usually the first sign of the disease. Clinically, Degos' disease is characterized by the presence of pale rose, rounded, edematous papules occurring mostly on the trunk. Similar lesions may occur on the bulbar conjunctiva and oral mucosa. Later, the lesions become umbilicated, with a central depression, which enlarges. The center becomes distinctively porcelain-white, while the periphery becomes livid red and telangiectatic. Atrophy occurs eventually. The eruption proceeds by crops in which only a few new lesions appear at any one time. One patient was reported to develop panniculitis. Lesions characteristic of Degos' disease may be seen in patients with lupus erythematosus or dermatomyositis.

Systemically, anemic infarcts involve the intestines producing acute abdominal symptoms, including epigastric pain, fever, and hematemesis. Death is usually due to fulminating peritonitis caused by multiple perforations of the intestine. Less commonly, death occurs from cerebral infarctions.

Wedge-shaped necroses brought on by the occlusion of arterioles and small arteries account for the clinical lesions. Proliferation of the intima and thrombosis is the typical histologic picture. The thrombosing process is usually pauci-inflammatory, although neutrophils or lymphocytes may be found associated with the thrombosis. The overlying dermis, which is infarcted, contains abundant mucin, especially early in the lesion's evolution. Adnexae are typically necrotic and the depressed central portion may be noted histologically.

The etiology of this disease is unknown, but based on the infarctive nature of the lesions and the universal presence of arteriolar thrombosis, a hyperthrombotic state or endothelial abnormality is suggested. While most patients have not had abnormalities identified, abnormal platelet aggregation, and abnormal coagulation have been identified in some patients. The response of this condition to anticoagulant regimens in some patients supports this hypothesis. In some patients with lupus erythematosus and Degos-like lesions, anti-phospholipid antibodies have been found.

Administration of immunosuppresssives has not been beneficial. Ingestion of low-dose acetylsalicylic acid alone or in combination with dipyridamole (Persantine) has been effective in some patients. Heparin, as described by Degos, has been helpful, and should be considered if antiplatelet therapy is ineffective. Nicotine patches (5 mg/day) were effective in one case. In severe crises, fibrinolytic therapy should be considered.

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THROMBOANGIITIS OBLITERANS (BUERGER'S DISEASE)

Thromboangiitis obliterans is a nonatherosclerotic segmental inflammatory disease affecting the arteries, veins and nerves of multiple extremities. As opposed to classic atherosclerotic disease, the upper extremities are commonly affected. It is most often seen in men between the ages of 20 and 40 who smoke heavily. Smoking and, rarely, the use of smokeless tobacco is intimately tied to Buerger's disease. Various diagnostic criteria have been proposed; they usually include: age younger than 45 (or 50); history of tobacco use; distal extremity (infrapopliteal segmental arterial occlusion with sparing of the proximal vasculature); frequent distal upper extremity involvement (Raynaud or digital ulcers); consistent angiographic findings; superficial thrombophlebitis; exclusion of autoimmune disease, diabetes mellitus, and hypercoagulable or embolic states.

The vasomotor changes in early cases may be transitory or persistent; they produce blanching, cyanosis, burning, and tingling. Superficial thrombophlebitis in the leg and foot occurs in 38% of cases and 44% of patients may have Raynaud phenomenon. The color of the part may change when it is elevated or lowered below heart level, being red when dependent and white when elevated. An Allen test will be positive, confirming distal artery occlusion.

Pain is a constant symptom, coming only at first after exercise and subsiding on resting. Instep claudication is the classic complaint. Ultimately, the dorsalis pedis and posterior tibial pulses disappear, followed by others. In thromboangiitis obliterans, skin supplied by affected arterioles tends to break down, with central necrosis and ulceration, and eventual gangrene. Gastrointestinal involvement has been reported. Exposure to cold may cause exacerbations.

Arteriography should be done to investigate for central atherosclerotic disease, which may be operable, rather than the inoperable distal damage of Buerger's disease. A characteristic tapering and occlusion of the major arteries with "corkscrew" collateral arteries is found in Buerger's disease on angiography. Biopsy demonstrates a thrombosed vessel that characteristically contains prominent neutrophilic inflammation within the thrombus. A vasculo-occlusive syndrome similar to Buerger's disease has been reported in cannabis smokers, but venous occlusion (thrombophlebitis) does not occur.

The most important therapeutic aspect is the cessation of smoking. Even one to two cigarettes/day, smokeless tobacco, or nicotine replacement may keep the disease active. Intravenous Iloprost (a prostaglandin analog) may help the patient with critical limb ischemia get through an acute episode. In patients who stop smoking and do not have gangrene, major amputations are rare. In continued smokers at least 43% will require amputations. Sympathectomy or implantation of a spinal cord stimulator may be tried. Ultimately, serial amputations are often necessary if the patient continues to use tobacco.

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ARTERIOSCLEROSIS OBLITERANS

Arteriosclerosis obliterans is an occlusive arterial disease most prominently affecting the abdominal aorta and the small- and medium-sized arteries of the lower extremities. The symptoms are due to ischemia of the tissues. There is intermittent claudication manifested by pain, cramping, numbness, and fatigue in the muscles on exercise; these are relieved by rest. There may be "rest pain" at night when in bed. Also, sensitivity to cold, muscular weakness, stiffness of the joints, and paresthesia may be present. Sexual impotence is common and there is an increased frequency of coronary artery disease.

Impaired to absent pulses (dorsalis pedis, posterior tibial, or popliteal arteries) may be found on physical examination, confirming the diagnosis. The feet, especially the toes, may be red and cold. Striking pallor of the feet on elevation and redness when dependent are compatible findings. Decreased to absent hair growth may be observed on the legs. Ulceration and gangrene may supervene. If present, they usually begin in the toes and are quite painful. Arteriography may be indicated as a preliminary to corrective surgery (arterial grafts). Occasionally, subclavian atherosclerosis may give rise to these signs in the distal upper extremity, producing painful nails and loss of digital skin. Diabetes mellitus, smoking, and hyperlipidemia are risk factors for the development of atherosclerosis.

Claudication and diminished blood pressure in the affected extremity are findings that may lead to earlier diagnosis and thus to curative surgical intervention. Usually, bypass of the affected artery or sympathectomy, or both, are the preferred treatment. Balloon angioplasty or stent placement may also be effective.

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MUCOCUTANEOUS LYMPH NODE SYNDROME (KAWASAKI'S DISEASE)

The typical presentation is an irritable, ill-appearing, febrile infant or child younger than 5 years old. Clinical findings (four of which plus fever for 5 days are diagnostic of Kawasaki syndrome) include a skin eruption; stomatitis (injected pharynx, strawberry tongue) and fissuring cheilitis; edema of the hands and feet; conjunctival injection; and cervical lymphadenitis. The skin eruption is polymorphous and may be macular, morbilliform, urticarial, scarlatiniform, erythema multiforme-like, pustular, or resemble erythema marginatum. An early finding (within the first week) is the appearance of an erythematous, desquamating perianal eruption in about two-thirds of patients. Periorbital edema has been reported. Pincer nail deformities may appear and resolve spontaneously. Intestinal pseudo-obstruction may occur. The acute illness evolves over 10 to 20 days. A week or two following the acute illness, the fingers and toes desquamate, starting around the nails. Coronary artery aneurysms occur in 20% to 25% of untreated children. This may lead to immediate cardiac complications, the major cause of morbidity and mortality. In addition, over time, those with aneurysms can develop coronary artery stenosis and as a result acute cardiac events can occur in young adulthood.

Pathogenesis

Recently, a corona virus has been identified as the cause in a cohort of patients. A viral pathogenesis is attractive for the following reasons: 1) cases were rare before 1950; 2) it affects children older than 3 months but younger than 8 years; 3) seasonal peaks occur in the winter and spring; 4) focal epidemics have been reported; and 5) oligoclonal IgA immune responses are found, suggesting a respiratory portal of entry of an infectious agent.

Coronary arterial disease occurs, in combination with thrombocythemia (up to 1 million). This combination of an altered endovascular surface and too many platelets leads to occlusion of the vessels and the subsequent cardiac events, which occur as the child is recovering from the acute illness.

Treatment

IVIG is the cornerstone of therapy, given in a single dose of 2 g/kg infused over 10 to 12 h. Response to treatment is best if given during the first 5 to 6 days of the illness; however, children with persistent fever beyond this period may benefit from later treatment. Aspirin is used to reduce inflammation and platelet aggregation. The dose is 80 to 100 mg/kg/day in four divided doses. Once the child has been afebrile for 3 to 7 days, the aspirin dose is decreased to a single daily dose of 3 to 5 mg/kg. If the child remains febrile, a second 2 g/kg dose of IVIG should be given. A single dose of infliximab 5 mg/kg has been reported to be effective in refractory cases, but response, as with other treatments, is not universal. Angioplasty, thrombolytic therapy, or coronary artery bypass surgery may be required for patients with severe disease.

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TELANGIECTASIA

Telangiectasia are fine linear vessels coursing on the surface of the skin: the name given to them collectively is *telangiectasia*. Telangiectasia may occur in normal skin at any age, in both sexes, and anywhere on the skin and mucous membranes. Fine telangiectases may be seen on the alae nasi of most adults. They are prominent in areas of chronic actinic damage. In addition, persons long-exposed to wind, cold, or heat are subject to telangiectasia. Calcium-channel blockers may lead to telangiectatic lesions in a generalized or photodistribution and contribute to the appearance of photoaging. Telangiectasias may also be found on the legs as a result of heredity, varicosities, pregnancy, and birth control pill use.

Telangiectases can be found in conditions such as radiodermatitis, xeroderma pigmentosum, lupus erythematosus, scleroderma and the CREST syndrome, rosacea, pregnancy, cirrhosis of the liver, AIDS, poikiloderma, basal cell carcinoma, necrobiosis lipoidica diabeticorum, lichen sclerosis et atrophicus, sarcoid, lupus vulgaris, keloid, and adenoma sebaceum. Kaposiform hemangioendothelioma, angioma serpiginosum, angiokeratoma corporis diffusum, hereditary benign telangiectasia, Cockayne syndrome, ataxia-telangiectasia, and Bloom syndrome.

Altered capillary patterns on the finger nailfolds (cuticular telangiectases) are indicative of collagen vascular disease, such as lupus erythematosus, scleroderma, or dermatomyositis. They may infrequently be present in rheumatoid arthritis. These disorders are reviewed in Chapter 8.

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Generalized Essential Telangiectasia

Generalized essential telangiectasia is characterized by the dilation of veins and capillaries over a large segment of the body without preceding or coexisting skin lesions. Characteristic features include: 1) widespread cutaneous distribution; 2) progression or permanence of the lesions; 3) accentuation in dependent areas and by dependent positioning; and 4) absence of coexisting epidermal or dermal changes such as atrophy, purpura, depigmentation, or follicular involvement. The telangiectases may be distributed over the entire body or localized to some large area such as the legs, arms, and trunk. They may be discrete or confluent. Distribution along the course of the cutaneous nerves may occur. Systemic symptoms are absent, although conjunctival telangiectasias can also be seen. Generalized essential telangiectasia is usually not believed to be associated with an increased risk of bleeding.

Generalized essential telangiectasia develops most frequently in women in their 40s and 50s. The initial onset is on the lower legs and then spreads to the upper legs, abdomen, and arms. The dilations persist indefinitely. Families with this disorder have been reported, inherited as an autosomal-dominant trait. The cause of essential telangiectasia is unknown. Treatment is with vascular lasers, if required.

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Unilateral Nevoid Telangiectasia

In this disorder, fine, thread-like telangiectases develop in a unilateral, sometimes dermatomal (or following the lines of Blaschko) distribution. The condition is rare in men and tends to be associated with conditions with increased levels of estrogen: puberty, pregnancy, and cirrhosis. Hepatitis C-associated unilateral nevoid telangiectasia has been reported.

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HEREDITARY HEMORRHAGIC TELANGIECTASIA (OSLER'S DISEASE)

Also known as *Osler-Weber-Rendu disease*, hereditary hemorrhagic telangiectasia (HHT) is characterized by small tufts of dilated capillaries scattered over the mucous membranes and the skin. These slightly elevated lesions develop mostly on the lips, tongue, palate, nasal mucosa, ears, palms, fingertips, nailbeds, and soles. They may closely simulate the telangiectases of the CREST variant of scleroderma, which may be distinguished by the lack of other features of CREST syndrome and by anticentromere antibodies, which are not found in HHT. Diagnostic criteria have been proposed and include: 1) epistaxis—spontaneous, recurrent nosebleeds; 2) telangiectases—multiple at characteristic sites (lips, oral cavity, fingers, nose) (Figs 35-18 to 35-20); 3) visceral lesions—gastrointestinal telangiectasia, pulmonary, hepatic, cerebral or spinal arteriovenous malformation (AVM); and 4) family history—one affected first-degree relative. The presence of three of the four criteria indicates a definite diagnosis and two of four, a possible diagnosis. There are at least two variants, HHT1 and HHT2. A third variant may be associated with juvenile polyposis.

Frequent nosebleeds and melena are experienced because of the telangiectasia in the nose and gastrointestinal tract. Epistaxis is the most frequent and persistent sign. Gastrointestinal bleeding is the presenting sign in up to 25% of

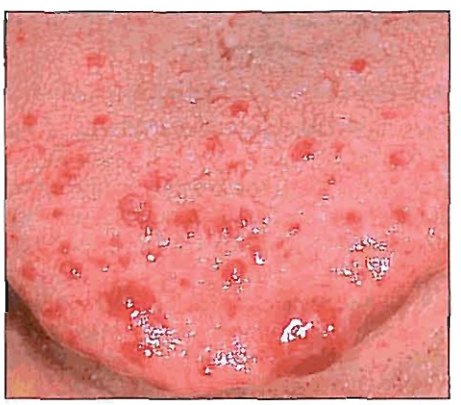

Fig. 35-18 Hereditary hemorrhagic telangiectasia.

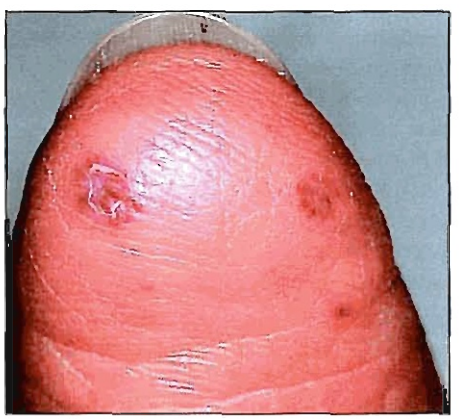

Fig. 35-19 Hereditary hemorrhagic telangiectasia.

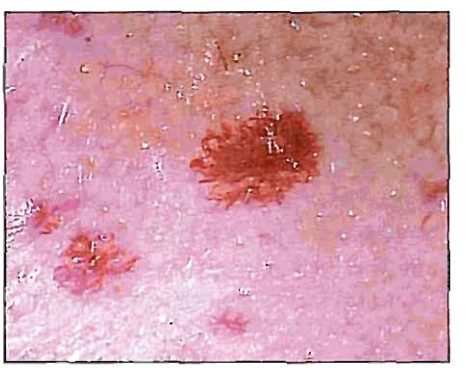

Fig. 35-20 Hereditary hemorrhagic telangiectasia.

cases; however, 40% to 50% develop gastrointestinal bleeding sometime during the course of their disease. The spleen may be enlarged. Pulmonary and CNS AVMs may appear later in life. Liver failure can result from diffuse intrahepatic shunting. Pulmonary hypertension can occur, especially in HHT2. Retinal arteriovenous aneurysms occur only rarely. Other sites of bleeding may be the kidney, spleen, bladder, liver, meninges, and brain. The risk of cerebral hemorrhage from cerebral AVMs, cerebral abscesses, and pulmonary hemorrhage from pulmonary AVMs is probably high enough that asymptomatic patients should be screened for the presence of cerebral and pulmonary AVMs. Because of the risk of cerebral abscess, some have advocated antibiotic prophylaxis for dental and contaminated skin procedures.

The telangiectases tend to increase in number in middle age; however, the first appearance on the undersurface of the tongue and floor of the mouth is at puberty. Pulmonary or intracranial arteriovenous fistulas and bleeding in these areas may be a cause of death.

HHT is inherited as an autosomal-dominant trait. The vascular abnormalities found in HHT consist of direct arteriovenous connections without an intervening capillary bed. Affected patients have mutations in one of two different genes, endoglin (ENG) or ALK-1 (activin A receptor type II, ACVRL1). They encode a homodimeric integral membrane glycoprotein which is a TGF-β receptor. TGF-β mediates vascular remodeling. HHT1 is associated with ENG mutations, and HHT2 associated with ALK-1 mutations. HHT1 patients have a higher prevalence of pulmonary AVMs and HHT2 patients tend to have a milder phenotype and later age of onset. Patients with HHT and juvenile polyposis have mutations in the MADH4 gene, a downstream effector of TGF-β signaling.

Treatment is directed at controlling the specific complication, and identifying and treating AVMs before they become symptomatic. The tendency to epistaxis has been reduced by estrogen therapy and some recommend oral contraceptives for affected postpubertal females. Dermoplasty of the bleeding nasal septum may be performed by replacing the mucous membrane with skin from the thigh or buttock. Repeated laser treatments of the nasal and gastrointestinal mucosa are often required. Topical tranexamic acid has been used to control epistaxis. Bleeding episodes are treated supportively. Interventional radiology with selective embolization can treat AVMs and episodes of bleeding, avoiding invasive surgeries.

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LEG ULCERS

Leg ulcers are a common medical condition, affecting 3% to 5% of the population over the age of 65. The cause of chronic leg ulceration is venous insufficiency alone in 45% to 60% of cases, arterial insufficiency in 10% to 20%, diabetes mellitus in 15% to 25%, or combinations in 10% to 15%. Smoking and obesity increase the risk for ulcer development and persistence, independent of the underlying cause. Defining the cause of the leg ulceration is important in healing the ulceration. However, except in the case of significant arterial insufficiency, most leg ulcers can be healed without treating the anatomic underlying cause.

The wound healing response is complex, involving intricate interactions between different cell types, structural proteins, growth factors, and proteinases. Normal wound repair consists of three phases—inflammation, proliferation, and remodeling—that occur in a predictable sequence and comprise a series of cellular and biochemical events. Abnormalities in any one of these components can produce delayed or ineffectual wound healing.

VENOUS DISEASES OF THE EXTREMITIES

Stasis Dermatitis

Stasis dermatitis presents as erythema and a yellowish or light-brown pigmentation of the lower third of the lower legs, especially in the area just superior to the medial

malleolus. An associated eczematous dermatitis may occur. The dermatitis may be weepy or dry, scaling or lichenified; it is almost invariably hyperpigmented by melanin and hemosiderin. Varicose veins are usually present, though they need not be numerous or conspicuous. Stasis dermatitis is a cutaneous marker for venous insufficiency. The approach to management should be two-fold: relief of symptoms and treatment of the underlying venous insufficiency. Patients with pruritus and an eczematous component should be treated with emollients and class IV or V topical corticosteroids. The daily use of support stockings is strongly recommended.

Venous Insufficiency Ulceration

Stasis dermatitis and venous ulceration result from increased pressure in the venous system of the lower leg. The most common cause is insufficiency of the valves in the deep venous system and lower perforating veins of the lower leg. With each contraction of the calf, blood should be pumped to the heart (muscle pump). Intact valves in the lower leg are required to prevent this "pumped" blood from refluxing out through the perforators into the superficial system. The hypertrophy of these superficial veins is marked by the development of "varicose veins." Increased pressure on the iliac veins from pregnancy or obesity, or simple inactivity may also result in the appearance of "venous insufficiency" as well. The valvular insufficiency results in disorder in the venous and capillary circulation in the leg. Valve insufficiency may occur from prior thrombophlebitis or congenital "weakness." Prolonged standing in one position, sitting for long periods, anemia, zinc deficiency, and a defective fibrinolytic system may accelerate the process. If a history of thrombophlebitis is present, an evaluation for a hypercoagulable state, such as a deficiency of Leiden Factor V, should be considered

Edema and fibrosis develop in the skin over the medial aspect of the ankle and lower third of the shin (Fig. 35-21). Following minor trauma, a macular hemorrhage appears. This is the premonitory sign of an impending ulceration. Venous ulcers usually occur on the lower medial aspect of the leg. They may appear on the background of stasis dermatitis with lipodermatosclerosis.

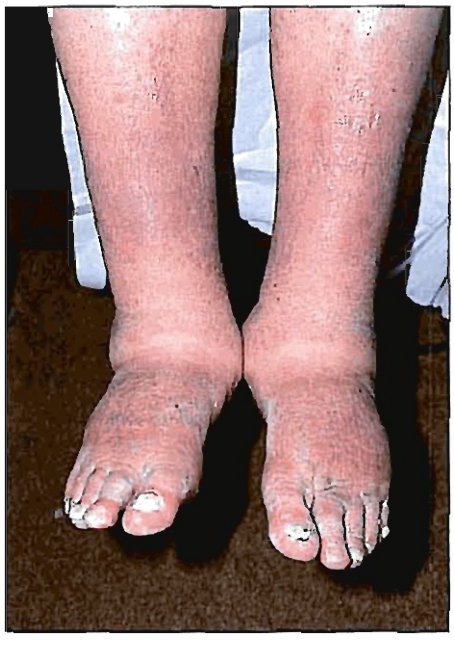

Fig. 35-21 Stasis dermatitis, venous insufficiency.

In most cases the diagnosis of a venous ulceration can be made on clinical grounds. If there is no clear history or physical findings of venous insufficiency, venous rheography can be performed. An ABI (ratio of blood pressure in the leg to the arm) should be considered in cases where peripheral pulses are diminished, and hair on the lower legs is lost. This will identify coexistent arterial disease. In most leg ulcers of the lower medial leg, even if cutaneous findings of venous insufficiency are absent, venous insufficiency will still be the most common cause of the ulcer. Lesions in atypical locations, those that do not respond appropriately to therapy, and those in which venous rheography is normal, may require a biopsy to exclude other causes, including a cutaneous neoplasm. Additional work-up may also be required to identify other, less common causes of leg ulcers, such as cholesterol emboli, atherosclerotic disease, diabetes mellitus, sickle cell disease, vasculitis, infection, and pyoderma gangrenosum.

Treatment is primarily to improve venous return and reduce edema. Compression therapy is the mainstay of treatment. This involves the use of pressure wraps, such as Unna boots covered with coban or elastic wraps. Elevation of the leg above the heart as much of the time as possible (a minimum of 2 h twice a day) is also beneficial. Elastic support of the legs must be continued after the ulcer heals. Other causes of edema, such as cardiac failure, must be addressed, especially if there is associated bullous lymphedema. The avoidance of long, cramped sitting (in airplanes or vehicles) or prolonged standing is advisable. Diuretics are overused and not proven to be of benefit. If there is a central cause of fluid retention (cirrhosis, heart failure, renal failure), diuretics may be beneficial, but otherwise they are best avoided. Avoidance of trauma is important. Pentoxyphylline 400 to 800 mg three times a day, in addition to compression, is beneficial in healing refractory venous ulcerations. A cooperative patient and a patient physician are necessary in the long-term management of venous disease. Topical antiinfectives are usually not necessary (except metronidazole gel to prevent anaerobic overgrowth). There is a high risk of allergic contact dermatitis from other topical antibiotics. Oral antibiotics should only be used to treat associate invasive infection. A rim of erythema commonly surrounds an ulcer. Expanding erythema, an enlarging ulcer, or increasing pain or tenderness may be signs of infection. Surface cultures and gram stains may demonstrate colonizing, but not pathogenic, bacteria. Biopsy for histology and tissue homogenate culture is the most effective way to demonstrate a true invasive pathogen.

Many treatment options have been developed for chronic ulcers. Unfortunately, conclusive comparative studies between the various treatment alternatives are lacking. All are to be used in combination with compression treatment. Occlusive and semipermeable biosynthetic wound dressings can be very effective when combined with compression. They can speed healing, reduce pain, make dressing changes infrequent, and help debridement. If a hard eschar is present over the ulcer when first seen, a dressing will assist in its removal. Enzymatic debridement with or without the addition of chlorophyll may be helpful. Dressings containing dilute acetic acid or silver may help reduce bacterial overgrowth in the wound, as will the application of topical metronidazole gel 0.075%. Becaplermin (Regranex) is expensive, but promotes wound healing. Granulation tissue formation is enhanced. It may be

useful in wounds which have stopped healing. Injection of granulocyte–macrophage colony-stimulating factor (GM-CSF) into the ulcer base may also stimulate refractory ulcers to heal. It is very expensive. Grafts and skin substitutes should be reserved for refractory ulcers which have failed conservative therapy.

Risk factors that predict failure to heal within 24 weeks of limb-compression therapy include a large wound area, history of venous ligation or stripping, history of hip or knee replacement, ankle brachial index (ABI) of less that 0.80, fibrin on 50% or more of the wound surface, and the presence of the ulcer for an extended time. For every 6 months of duration, the ulcer healing time doubles.

ARTERIAL INSUFFICIENCY (ISCHEMIC) ULCER

Ischemic ulcers are mostly located on the lateral surface of the ankle or the distal digits. The initial red, painful plaque breaks down into a painful superficial ulcer with a surrounding zone of purpuric erythema. Granulation tissue is minimal, little or no infection is present, and a membranous inactive eschar forms over the ulcer. Patients at risk are those with long-standing hypertension, smokers, diabetics, and those with hyperlipidemia. The presence of an arterial ulceration identifies patients at increased risk for limb loss.

Signs and symptoms indicative that arterial disease is the cause of the ulceration include thinning of the skin, absence of hair, decreased or absent pulses, pallor on elevation, coolness of the extremity, dependent rubor, claudication on exercise, and pain on elevation (especially at night) relieved on dependency. In progressive disease the diagnosis of thromboangiitis obliterans, or Buerger's disease, should be considered.

The diagnosis of arterial insufficiency can usually be confirmed by physical examination and careful palpation of the pulses in the legs. For more accurate evaluation, take the blood pressure in the arm and leg. They should be nearly identical. The ratio of the popliteal-to-brachial pressure is called the ABI. If it is less than 0.75, arterial insufficiency exists, and if less than 0.5, the insufficiency is substantial.

Surgical intervention may be required to heal the ulceration. If the blood supply cannot be improved, little can be done except to prevent infection by the measures described under venous ulcers. The area should be protected from injury and cold, and smoking and tight socks should be avoided. Hyperbaric oxygen may be of some use, but it is limited by availability and cost.

NEUROPATHIC ULCERS

Foot ulcers in diabetics are usually related to sensory neuropathy. Offloading the ulcer is the primary principal of management. Necrotic tissue should be debrided back to bleeding viable tissue. As the foot is typically insensate, this can be done in the office without the need for anesthetic. Associated osteomyelitis is best treated by removal of the infected bone. Consultation with or referral to a podiatrist or orthopedic surgeon may be indicated. Various shoes and padded boots can be used to offload different areas of the foot. An orthotics consultation is usually indicated. Clinical infection should be treated, but simple colonization typically does not require treatment. After the ulcer heals, a shoe of appropriate depth and width will help to prevent recurrence. Frequent foot inspections for the presence of "hot spots" as well as debridement of dystrophic nails are important facets of prevention.

LEG ULCERS OF OTHER CAUSES

Hematopoietic ulcers are those occurring with sickle cell anemia, Cooley anemia (thalassemia), congenital hemolytic anemia, polycythemia vera, thrombocytopenic purpura, macroglobulinemia, and cryoglobulinemia. In addition, cryofibrinogenemia may also be manifested by ulcerations on the lower extremities.

The diagnosis is usually established by the accompanying signs and symptoms of the original disease. Treatment of the underlying disease should be maximal and then general measures used for leg ulcers should be followed.

Leg ulcers resulting from collagen vascular disease are most common in rheumatoid vasculitis, although ulcers may sometimes be seen with SLE, Felty syndrome, scleroderma, dermatomyositis, and mixed connective tissue disease. The ulcers are deep, indolent, and dry. Basal cell and squamous cell carcinoma, malignant melanoma, Kaposi sarcoma, and malignant lymphomas may be the cause of leg ulcers. Diagnosis of neoplastic causes of leg ulcers requires biopsy of the ulcer margin. Burns, radiodermatitis, decubitus ulcers, neurotic excoriations, factitial ulcers, and trophic ulcers are in this category.

Necrobiosis lipoidica, gout, diabetes, pellagra, prolidase deficiency, Gaucher's disease, Klinefelter syndrome, ulcerative colitis, and primary amyloidosis form another group in which leg ulcers may be found. The ulcers of lupus vulgaris, mycobacterial ulcers, sporotrichosis, blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, and schistosomiasis are some of the more important infectious leg ulcers. The gummatous ulcers of late syphilis should not be forgotten.

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LYMPHEDEMA

Lymphedema is the swelling of soft tissues in which an excess amount of lymph has accumulated. Chronic lymphedema is characterized by long-standing, nonpitting edema. A working classification of lymphedema is shown in Box 35-2.

The most prevalent worldwide cause of lymphedema is filariasis. In the US the most common cause is postsurgical. If lymphedema is long-standing, a verrucous appearance to the affected extremity develops (elephantiasis verrucosa nostra).

Types

Lymphedema is classified by clinical type (Box 35-2). Primary types include congenital, early and late onset types. Other primary types of lymphedema are asssociated with characteristic features or syndromes. Some cutaneous disorders are associated with or are a complication of primary lymphedema. Secondary lymphedema can occur from numerous causes, including neoplasia and its treatment, infections, and physical factors.

Lymphedema Praecox Lymphedema praecox develops in females between the ages of 9 and 25. Swelling appears around the ankle and then extends upward to involve the entire leg. With the passage of time the leg becomes painful, with a dull, heavy sensation. Once this stage has been reached, the swollen limb remains swollen. Primary lymphedema is caused by a defect in the lymphatic system. Lymphangiography demonstrates hypoplastic lymphatics in

Box 35-2 Classification of lymphedema

Primary lymphedema
- Congenital lymphedema (Milroy's disease)
- Lymphedema praecox
- Lymphedema tarda

Syndromes associated with primary lymphedema
- Yellow nail syndrome
- Turner syndrome
- Noonan syndrome
- Pes cavus
- Phakomatosis pigmentovascularis
- Distichiasis-lymphedema

Cutaneous disorders sometimes associated with primary lymphedema
- Yellow nails
- Hemangiomas
- Xanthomatosis and chylous lymphedema
- Congenital absence of nails

Secondary lymphedema
- Postmastectomy lymphedema
- Melphalan isolated limb perfusion
- Malignant occlusion with obstruction
- Extrinsic pressure
- Factitial lymphedema
- Postradiation therapy
- Following recurrent lymphangitis/cellulitis
- Lymphedema of upper limb in recurrent eczema
- Granulomatous disease
- Rosaceous lymphedema
- Primary amyloidosis

Complications of lymphedema
- Cellulitis of lymphedema
- Elephantiasis nostras verrucosa (Fig. 35-22)
- Ulceration
- Lymphangiosarcoma

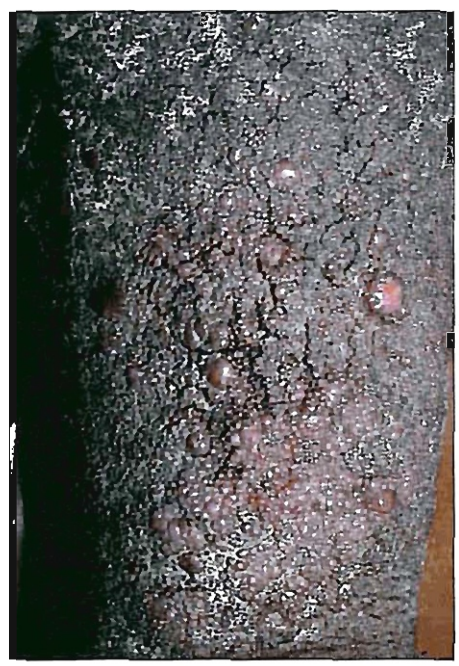

Fig. 35-22 Elephantiasis verrucosa nostra.

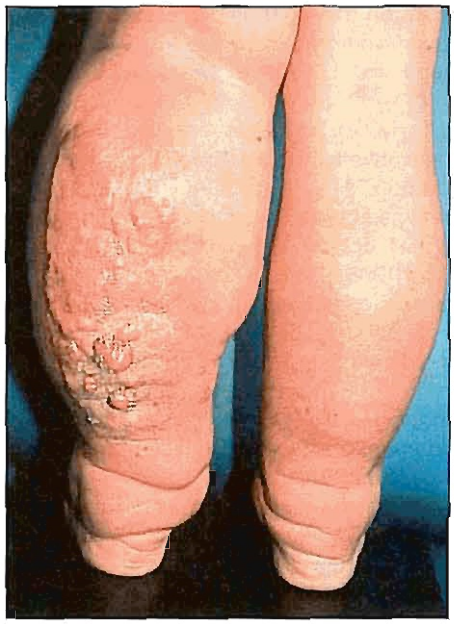

Fig. 35-23 Milroy's disease. (Courtesy Lawrence Lieblich MD).

87%, aplasia in approximately 5%, and hyperplasia with varicose dilation of the lymphatic vessels in 8%.

Nonne-Milroy-Meige Syndrome (Hereditary Lymphedema) Milroy hereditary edema of the lower legs is characterized by a uni- or bi-lateral lymphedema present at birth and inherited as an autosomal-dominant trait. The edema is painless, pits on pressure, is not associated with any other disorder, and persists throughout life (Fig. 35-23). It may involve the genitalia and produce lymphangiectasias superficially. Chylous discharge can occur. Most frequently the affection is unilateral, and females are predominantly affected.

Treatment of this particular type of edema is extremely difficult since the disease is an anomaly of the lymph-draining vessels. Decongestive physiotherapy can be considered. In some cases, surgical procedures to remove affected tissue can be performed. This condition may be linked to a mutation that inactivates VEGFR3.

Lymphedema-Distichiasis Syndrome The association of distichiasis (double row of eyelashes) and late-onset lymphedema is a form of hereditary lymphedema called *lymphedema-distichiasis syndrome* (Fig. 35-24). It is an autosomal-dominant syndrome with the appearance of bilateral lymphedema beginning between the ages of 8 and 10 in affected boys, and 13 and 30 in affected girls. Lymphatic vessels are increased (not hypoplastic or absent as in other forms of congenital lymphedema) in the affected legs. Associated findings are varicose veins in 50% by age 64; congenital ptosis (31%); and congenital heart disease (6.8%), cleft palate (4%), scoliosis, and renal abnormalities. There may be phenotypic heterogeneity in this syndrome, as different types of mutations may lead to slightly different phenotypes, especially with regards to the ancillary features associated with the syndrome. This syndrome is due to a mutation in the FOXC2 transcription factor. This factor is expressed in both developing eyelids and lymphatics and other tissues with abnormalities in this syndrome.

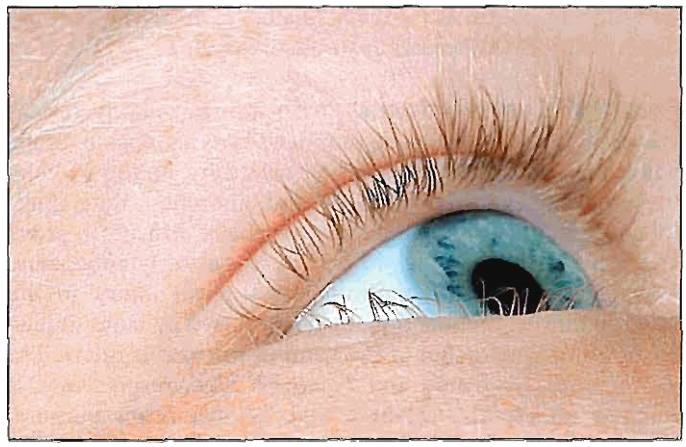

Fig. 35-24 Distichiasis. (Courtesy of Curt Samlaska, MD)

Primary Lymphedema Associated with Yellow Nails and Pleural Effusion (Yellow Nail Syndrome) Primary lymphedema is confined mostly to the ankles, although other areas may be involved. The nails show a distinct yellowish discoloration and thickening. Recurrent pleural effusion or bronchiectasis may be a feature.

Secondary Lymphedema In some malignant diseases, involvement of the lymph nodes will produce blockage and lymphedema. Malignant disease of the breast, uterus, prostate, skin, bones, or other tissues may cause such changes. Hodgkin's disease and, especially, Kaposi sarcoma may be accompanied by chronic lymphedema. Chronic lymphedema is frequently seen after mastectomy and the removal of the axillary nodes; it may occur after varying lengths of time.

Postmastectomy Lymphangiosarcoma (Stewart-Treves Syndrome) This type of vascular malignancy usually arises in chronic postmastectomy lymphedema. The lesions are bluish or reddish nodules arising on the arm. Similarly, primary or secondary lymphedema of the lower extremity may be complicated by angiosarcoma. Angiosarcoma arising in a lymphedematous extremity often presents with multiple lesions. Metastasis and death commonly result. Early aggressive surgical treatment with amputation may be life-saving. The treatment of breast cancer with lumpectomy and local radiation therapy may be complicated by angiosarcoma of the breast with minimal or no associated lymphedema. This is called cutaneous postradiation angiosarcoma of the breast. This form of angiosarcoma also frequently results in metastasis and death.

Postinflammatory Lymphedema The lymphedematous extremity may be caused by and worsened by repeated bacterial infections. It is these recurrent attacks, when they complicate filariasis, which cause the elephantiasis. Streptococcal cellulitis following venectomy in patients who had undergone coronary bypass surgery is a well-documented cause. However, almost any chronic or recurrent infection can cause this. Chronic antibiotic therapy can halt the progression by preventing the attacks of bacterial cellulitis.

Bullous Lymphedema Commonly misdiagnosed as an immunobullous disease, bullous lymphedema usually occurs

with poorly controlled edema related to heart failure and fluid overload. Compression results in healing.

Factitial Lymphedema Also known as *hysterical edema*, lymphedema can be produced by wrapping an elastic bandage, cord, or shirt around an extremity, and/or holding the extremity in a dependent and immobile state. Self-inflicted causes of lymphedema are usually difficult to prove and may occur in settings of known causes of lymphedema, such as postphlebitic syndrome or surgical injury to the brachial plexus. Factitial lymphedema caused by blunt trauma localized to the dorsum of the hand or forearm is referred to as *Secretan syndrome* and *l'oedeme blue*, respectively. It often is unilateral and there may be significant purpura. Effective care of such patients requires psychiatric intervention. Occupational causes must be excluded.

Other Causes Occupational persistent hand edema in divers, related to the constrictive action of the divers' suits and pricks from sea urchin spines, can occur.

Evaluation

The diagnosis is usually based on a classic presentation; however, in the early stages the disease may require further investigation. Considerations include isotopic lymphoscintigraphy, indirect and direct lymphography, magnetic resonance imaging, computed tomography, and ultrasonography.

Treatment

Most cases are treated conservatively by means of various forms of compression therapy, complex physical therapy, pneumatic pumps, and compressive garments. Chronic antibiotic treatment may be beneficial in patients suffering repeated episodes of erysipelas or cellulitis. In diabetics with insensate feet, the frequency of infection can be reduced by wearing properly fitting shoes. Volume-reducing surgery and lymphatic microsurgery are rarely performed, although a few centers consistently report favorable results. It is best to refer these patients to a center versed in the treatment of these complicated conditions, to optimize patient compliance and customize therapy to the patient's lifestyle.

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CHAPTER

36 Disturbances of Pigmentation

The visible pigmentation of the skin or hair is a combination of the amount of melanin, type of melanin (eumelanin versus pheomelanin), degree of vascularity, presence of carotene, and thickness of the stratum corneum. Other materials can be deposited abnormally in the skin leading to pigmentation. Eumelanin is the primary pigment producing brown coloration of the skin. Pheomelanin is yellow or red and is also produced solely in melanocytes. Melanin is formed from tyrosine, via the action of tyrosinase, in the melanosomes of melanocytes. Melanosomes are lysosome-related organelles. Melanosome formation and the end result, pigmentation, require both the adequate manufacture of melanin and the appropriate transport of melanosomes within the melanocyte. The melanosomes are transferred from a melanocyte to a group of 36 keratinocytes called the epidermal melanin unit, to which they provide melanin. The variations in skin color between persons and races are related to the degree of melanization of melanosomes, their number, and their distribution in the epidermal melanin unit. Disorders of loss or reduction of pigmentation may be related to loss of melanocytes or the inability of melanocytes to produce melanin or transport melanosomes correctly. Wood's light examination is often performed to evaluate lesions of hyper- or hypo-pigmentation. Hyperpigmented lesions which enhance with Wood's light usually have increased epidermal melanocyte number or activity. If the lesions do not enhance, the melanin is located in the dermis. Wood's light will markedly enhance depigmented lesions (complete loss of pigment), but not enhance lesions with partial pigment loss (hypopigmentaton).

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PIGMENTARY DEMARCATION LINES

Pigmentary demarcation boundaries of the skin can be classified into six groups, as follows:

1. Group A: Lines along the outer upper arms with variable extension across the chest
2. Group B: Lines along the posteromedial aspect of the lower limb (Fig. 36-1)
3. Group C: Paired median or paramedian lines on the chest, with midline abdominal extension
4. Group D: Medial, over the spine
5. Group E: Bilaterally symmetrical, obliquely oriented, hypopigmented macules on the chest
6. Group F: Facial pigmentary demarcation lines.

More than 70% of black patients have one or more lines; they are much less common in white patients. Type B lines often appear for the first time during pregnancy.

Pigmentary demarcation lines must be distinguished from the much rarer condition acquired dermal melanocytosis. This rare condition affects primarily Asians and Hispanic women (male-to-female ratio, 1:17). It often first appears during pregnancy or the therapeutic use of estrogen/progesterone. Lesions present as blue–gray patches with superimposed brown macules affecting the face trunk or extremities. Lesions do not enhance with Wood's light. They may be localized (following trauma) or more diffuse. Biopsy shows melanocytes in the dermis, similar to the findings in Mongolian spot, Nevus of Ota, and Nevus of Ito.

Bonci A, Patrizi A: Pigmentary demarcation lines in pregnancy. Arch Dermatol 2002;138:127.

Rubin AI, et al: Acquired dermal melanocytosis: Appearance during pregnancy. J Am Acad Dermatol 2001;45:609.

Ruiz-Villaverde R, et al: Pigmentary demarcation lines in a pregnant Caucasian woman. Int J Dermatol 2004;43:911.

ABNORMAL PIGMENTATION

Hemosiderin Hyperpigmentation

Pigmentation due to deposits of hemosiderin occurs in purpura, hemochromatosis, hemorrhagic diseases, and stasis dermatitis. Clinically, hemosiderin hyperpigmentation is distinguished from postinflammatory dermal melanosis by a golden brown hue versus the brown or gray–blue pigmentation of epidermal and dermal melanin, respectively.

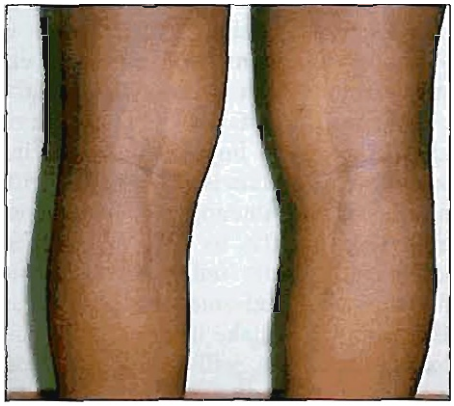

Fig. 36-1
Pigmentary demarcation lines.

Postinflammatory Hyperpigmentation

Any natural or iatrogenic inflammatory condition can result in hyper- or hypo-pigmentation. Postinflammatory dyspigmentation is more frequent in persons with Fitzpatrick skin types IV, V, and VI, especially those of skin types IV and V. It is equally common in males and females. Hyperpigmentation may result from two mechanisms: 1) increased epidermal pigmentation via increased melanocyte activity; or 2) dermal melanosis from melanocyte damage and melanin drop out from the epidermis into the dermis. Wood's light examination will distinguish these two patterns of postinflammatory hyperpigmentation. Lesions of hyperpigmentation tend to be tan to brown and may have a gray hue (due to dermal melanin). Hypopigmented lesions are prominently lighter than the surrounding skin. If the prior inflammatory process is treated, the dyspigmentation may improve. Histologically, there is melanin in the upper dermis and around upper dermal vessels, located primarily in macrophages (melanophages). The pattern of the dermal melanosis does not predict whether the lesion will be lighter or darker as a result of the prior inflammatory process—hence the tendency of pathologists to provide a diagnosis of "postinflammatory pigmentary alteration" in such cases. Postinflammatory dyspigmentation is treated initially by treating the underlying skin disease, if possible. Hydroquinone may be used in hyperpigmented cases which enhance with Wood's light. Tretinoin application may enhance the effect of hydroquinone. Laser treatments and chemical peels may also be beneficial, but in most cases, the best course is observation and support.

Lacz NL, et al: Postinflammatory hyperpigmentation: a common but troubling condition. Int J Dermatol 2004;43:362.

HEMOCHROMATOSIS (BRONZE DIABETES)

Hemochromatosis is a disorder caused by mutations in at least five different genes involved in iron absorption. It is very common in the white European population. At least four different phenotypes are described. Many of the patients with the most common genetic defects do not develop any disease (perhaps 25% of men and 6% of women). Men are affected more frequently and at an earlier age (usually between 30 and 50 years). The characteristic cutaneous manifestation is gray to brown mucocutaneous hyperpigmentation. It is enhanced in sun-exposed areas of the forearms, dorsal hands, and face, as well as in the inguinal area. The mucous membranes are pigmented in up to 20% of patients, koilonychia occurs in 50%, and localized ichthyosis in 40%. Alopecia is common and pruritus can occur. Porphyria cutanea tarda may be present. Biopsy of affected skin shows dermal iron deposition, but the visible pigmentation is actually increased epidermal melanin in the basal cell layer.

The most commonly affected organ is the liver. Hepatomegaly and elevated liver function tests are the first signs of hepatic iron overload. Cirrhosis and hepatocellular carcinoma may develop. The endocrine system is also affected with diabetes mellitus, impotence, and amenorrhea being most common. Arthropathy is seen in 20% to 70% of patients. Cardiac abnormalities include heart failure and cardiac arrhythmias. Consuming alcohol and smoking, as well as coexistent hepatitis C infection, all make it more likely that persons with genetic predisposition will develop clinical disease.

Laboratory evaluation should be pursued in persons with appropriate clinical findings, suggesting the diagnosis of hemochromatosis. Levels of plasma iron and the serum iron-binding protein are elevated. The transferrin saturation (TS) is a useful screening measure calculated as 100 × (serum iron/total iron-binding capacity). Forty-five or less is normal, except in premenopausal women where greater than 35 may be considered abnormal. High serum ferritin levels are also present. Genotyping is now performed in persons with a TS greater than 45 and an elevated ferritin, and confirms the diagnosis. Liver biopsy is reserved for persons with elevated liver function tests, a ferritin greater than 1000, or age older than 40.

Four different genes cause autosomal-recessive hemochromatosis and one causes autosomal-dominant disease. The most common autosomal-recessive form is due to a mutation in the HFE gene, most frequently C282Y, and less commonly H63D. The incidence of homozygosity for C282Y is 5 in 1000 persons of northern European descent, making it 10 times more common than cystic fibrosis. Compound heterozygotes (C282Y/H63D) also develop disease. Two autosomal-recessive forms of juvenile hereditary hemochromotosis are described, due to mutations in the Hemojuvelin and Hepcidin genes, respectively. Mutations in the transferrin receptor 2 gene lead to a form of autosomal-recessive adult onset hemochromatosis. Ferroportin mutation leads to an adult-onset form of autosomal-dominant hemochromatosis.

All forms of hemochromatosis are treated with phlebotomy until satisfactory iron levels are attained. Vitamin C supplementation must be avoided as it can worsen the disease. Raw seafood should be avoided as *Vibrio vulnificus* infection may occur. Phlebotomy can prevent cirrhosis. Once cirrhosis is present, phlebotomy does not prevent the development of hepatocellular carcinoma which occurs in 30% of patients.

Held JL, et al: Hyperpigmentation and secondary hemochromatosis: a novel treatment with extracorporeal chelation. J Am Acad Dermatol 1993;28:253.

Limdi JK, Crampton JR: Hereditary haemochromatosis. Q J Med 2004;97:315.

Pietrangelo A: Hereditary hemochromatosis – A new look at an old disease. N Engl J Med 2004;350:2383.

MELASMA (CHLOASMA FACIEI)

Melasma is characterized by brown patches, typically on the malar prominences and forehead. There are three clinical patterns: 1) centrofacial, 2) malar, and 3) mandibular. The centrofacial and malar patterns comprise the majority of patients (Fig. 36-2). The pigmented patches are usually quite sharply demarcated. It tends to affect darker-complexioned individuals, especially Asians and Hispanics with Fitzpatrick skin types IV and V. It may at times be found on the forearms. Subtle melasma, as identified by ultraviolet (UV) light examination, may be seen in up to 30% of middle-aged Asian females.

Melasma occurs frequently during pregnancy and with the ingestion of estrogen, as may occur in oral contraceptives or with hormone replacement therapy (HRT) at menopause. It may also be seen in other endocrinologic disorders. It is seen most frequently in young women, but men make up 10% of

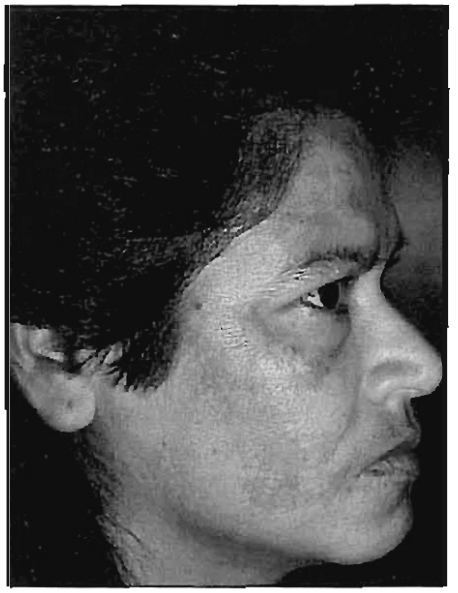

Fig. 36-2 Melasma of the cheek.

reported cases. Use of dilantin may induce melasma. Discontinuing the use of contraceptives rarely clears the pigmentation and it may last for many years after discontinuing them. In contrast, melasma of pregnancy usually clears within a few months of delivery. While melasma has classically been classified as epidermal- or dermal-based on the presence or absence of Wood's light enhancement, respectively, most cases show both epidermal and dermal melanin. Dermal melanophages are a normal finding in Asian sun-exposed skin. Independent of Wood's light findings, a therapeutic trial of some form of hypopigmenting agent should be recommended if the patient requests it.

A number of topical therapies are available. Exposure to sunlight should be avoided and a complete sunblock with broad-spectrum UVA coverage should be used daily. Bleaching creams with hydroquinone are the gold standard and are moderately efficacious; they contain from 2% (available over the counter) to 4% hydroquinone. Tretinoin cream may be added to increase efficacy. While tretinoin alone may reduce melasma, it may also increase pigmentation via its irritant effect. The combination of hydroquinone and tretinoin, administered in conjunction with a topical steroid, has been called "Kligman's formula" and is excellent. This is now available as a commercial product, Triluma, used once a day. The efficacy of this product has been reported to be superior to any combination of two of its ingredients, with a more rapid and complete response with the triple combination. Glycolic acid is at times added to hydroquinone to enhance its efficacy. In some patients with melasma 4% hydroquinone is insufficient and higher doses of hydroquinone must be compounded. Satellite pigmentation and local ochronosis are potential complications from use of these higher-concentration preparations. Azelaic acid, kojic acid, *N*-acetyl-4-cysteaminyphenol, licorice extract, and Arbutin are other therapies with efficacy, although generally not as effective as hydroquinone. Various surgical procedures such as peels and laser treatment have variable results, with some authors strongly supporting their use and others documenting lack of efficacy. These variable results may be in part technique dependent. The use of surgical modalities for the treatment of melasma should be approached with caution. Pretreatment with hydroquinone seems to enhance the long-term result of some surgical treatments.

Balkrishnan R, et al: Improved quality of life with effective treatment of facial melasma: the pigment trial. J Drugs Dermatol 2004;3:377.

Guevara IL, Pandya AG: Safety and efficacy of 4% hydroquinone combined with 10% glycolic acid, antioxidants, and sunscreen in the treatment of melasma. Int J Dermatol 2003; 42:966.

Halder RM, Richards GM: Topical agents used in the management of hyperpigmentation. Skin Therapy Lett 2004;9:1.

Hassan I, et al: Hormonal milieu in the maintenance of melasma in fertile women. J Dermatol 1998;25:510.

Hurley ME, et al: Efficacy of glycolic acid peels in the treatment of melasma. Arch Dermatol 2002;138:1578.

Kang WH, et al: Intermittent therapy for melasma in Asian patients with combined topical agents (retinoic acid, hydroquinone and hydrocortisone). J Dermatol 1998;25:587.

Kang WH, et al: Melasma: histopathological characteristics in 56 Korean patients. Br J Dermatol 2002;146:228.

Lim JT, et al: Glycolic acid peels in the treatment of melasma among Asian women. Dermatol Surg 1997;23:177.

Nanda S, et al: Efficacy of hydroquinone (2%) versus tretinoin (0.025%) as adjunct topical agents for chemical peeling in patients of melasma. Dermatol Surg 2004;30:385.

Naser A, et al: Psoralen plus ultraviolet A irradiation-induced lentigines arising in vitiligo: involvement of vitiliginous and normal appearing skin. Clin Exp Dermatol 2004;29:380.

Rendon MI: Utilizing combination therapy to optimize melasma outcomes. J Drugs Dermatol 2004;3:S27.

Varma S, Roberts DL: Melasma of the arms associated with hormone replacement therapy. Br J Dermatol 1999;141:592.

Wang CC, et al: Intense pulsed light for the treatment of refractory melasma in Asian persons. Dermatol Surg 2004;30:1196.

PIGMENTED ANOMALIES OF THE EXTREMITIES

Dyschromatosis Symmetrica Hereditaria (Reticulate Acropigmentation of Dohi)

Originally described in and still reported primarily in the Japanese, acropigmentation of Dohi has been found to affect individuals from Europe, India, and the Caribbean. It is also referred to as *dyschromatosis symmetrica hereditaria (DSH)* or *symmetrical dyschromatosis of the extremities.* It is inherited most commonly as an autosomal-dominant trait, although autosomal-recessive kindreds have been reported. Patients develop progressive pigmented and depigmented macules, often mixed in a reticulate pattern, concentrated on the dorsal extremities. Freckle-like macules are present on the face. Lesions appear in infancy or early childhood and commonly stop spreading before adolescence. The pigmentary lesions last for life. The autosomal-dominant form of DSH is due to a mutation in the DSRAD gene which encodes a double-stranded RNA-specific adenosine deaminase, an RNA editing enzyme.

Alfadley A, et al: Reticulate acropigmentation of Dohi: A case report of autosomal recessive inheritance. J Am Acad Dermatol 2000;43:113.

Li M, et al: A novel mutation of the DSRAD gene in a Chinese family with dyschromatosis symmetrica hereditaria. Clin Exp Dermatol 2004;29:533.

Oyama M, et al: Dyschromatosis symmetrica hereditaria (reticulate acropigmentation of Dohi): report of a Japanese family with the condition and a literature review of 185 cases. Br J Dermatol 1999;140:491.

Dyschromatosis Universalis Hereditaria

Dyschromatosis universalis hereditaria is a rare genodermatosis characterized by reticulate hyper- and hypo-pigmented macules in a generalized distribution. Lesions appear in childhood, often in the first few months of life. The palms, soles, and mucous membranes of the mouth and tongue may be diffusely pigmented, with hypopigmented macules interspersed. Nail, teeth, and hair abnormalities may be associated. The patients are otherwise well.

Al Hawasai K, et al: Dyschromatosis universalis hereditaria: report of a case and review of the literature. Pediatr Dermatol 2002;19:523.

Nuber UA, et al: Dyschromatosis universalis hereditaria: familial case and ultrastructural skin investigation. Am J Med Genet A 2004;125:261.

Sethuraman G, et al: Dyschromatosis universalis hereditaria. Clin Exp Dermatol 2002;27:477.

Reticular Pigmented Anomaly of the Flexures (Dowling-Degos' Disease)

Reticular pigmented anomaly of the flexures is a rare autosomal-dominant pigmentary disorder; it is sometimes called *Dowling-Degos' disease* or *dark dot disease*. Pigmentation appears in adolescence or adulthood, affecting the axillae, neck, and inframammary/sternal areas. In some cases the dorsal hands are involved. The pigmentation is reticular; at the periphery, discrete, brownish-black macules surround the partly confluent central pigmented area. In more mildly affected patients the pigmentation is dappled. The pigmentation progresses very gradually. There are frequently acneiform pitted scars, sometimes pigmented, about the mouth. Comedonal and cystic lesions have been described on the flexures and axilla. Hidradenitis suppurativa-like lesions in the groin and axilla may occur. Patients may complain that it is worse during hot weather. Squamous cell carcinoma of the buttocks or perianal area have been described.

Histologically, the appearance is distinctive—elongation, tufting, and deep hyperpigmentation of the rete ridges, with protrusion of similar tufts even from the sides of the follicles. Small horn cysts may be present, so that the pattern resembles that of a reticulated seborrheic keratosis. Comedones may be present. Erbrium:YAG laser has treated the pigmented lesions of the chest.

Kossard S, Krivanek J: Dowling-Degos' disease — A heat aggravated variant. Australas J Dermatol 2001;42:214.

Loo WJ, et al: Hydradenitis suppurativa, Dowling-Degos and multiple epidermal cysts: a new follicular occlusion triad. Clin Exp Dermatol 2004;29:622.

Galli-Galli Disease

This rare condition has close resemblance clinically to Dowling-Degos' disease, but is histologically distinct. The condition appears in adult life and favors males. The skin lesions are 1- to 2-mm slightly keratotic red to dark brown papules which are focally confluent in a reticulate pattern. The skin lesions favor skinfolds but also other skin sites. The neck, axillae, upper extremities, dorsal hands, trunk, groin, and even the scrotum and lower extremities may be affected. Histologically there is prominent digitate downgrowth of the rete ridges, identical to that seen in Dowling-Degos. The characteristic histologic feature is a suprabasilar cleft and suprapapillary thinning of the epidermis. There is no dyskeratosis as is seen in Grover's disease. Treatment is unsuccessful. Since two brothers were initially reported, the syndrome may have a genetic component.

Braun-Falco M, et al: Galli-Galli disease: an unrecognized entity or an acantholytic variant of Dowling-Degos' disease? J Am Acad Dermatol 2001;45:760.

Reticulate Acropigmentation of Kitamura

Reticulate acropigmentation of Kitamura consists of linear palmar pits and pigmented macules 1 to 4 mm in diameter on the volar and dorsal aspects of the hands and feet. It is usually an autosomal-dominantly inherited disorder. Acropigmentation of Dohi, Dowling-Degos' disease, and reticulate acropigmentation of Kitamura in most cases can be distinguished, but cases with overlapping features have been reported.

Al Hawsawi K, et al: Reticulate acropigmentation of Kitamura-Dowling Degos' disease overlap: a case report. Int J Dermatol 2002;41:518.

Cox NH, et al: Dowling-Degos' disease and Kitamura's reticulate acropigmentation: support for the concept of a single disease. Br J Dermatol 1991;125:169.

Ostlere L, et al: Dowling-Degos' disease associated with Kitamura's reticulate acropigmentation. Clin Exp Dermatol 1994;19:492.

Singal A, et al: Is the heredity of reticulate acropigmentation of Kitamura always autosomal dominant? J Dermatol 1998; 25:57.

DERMATOPATHIA PIGMENTOSA RETICULARIS

Dermatopathia pigmentosa reticularis is composed of the triad of generalized reticulate hyperpigmentation, noncicatricial alopecia, and onychodystrophy. Additional associations include adermatoglyphia, hypo- or hyper-hidrosis, palmoplantar hyperkeratosis, and nonscarring blisters on the dorsa of the hands and feet. An autosomal-dominant inheritance pattern has been reported.

Bu TS, et al: A case of dermatopathia pigmentosa reticularis. J Dermatol 1997;24:266.

Heimer WL II, et al: Dermatopathia pigmentosa reticularis. J Am Acad Dermatol 1992;26:298.

Maso MJ, et al: Dermatopathis pigmentosa reticularis. Arch Dermatol 1990;126:935.

TRANSIENT NEONATAL PUSTULAR MELANOSIS

Also called *transient neonatal pustulosis*, this disorder is present at birth. Newborns present with 1- to 3-mm flaccid,

superficial fragile pustules. Some of the pustules may have already resolved in utero, leaving pigmented macules. Lesions affect the chin, neck, forehead, back and buttocks, but can occur anywhere. In dark-skinned infants, pigmented macules may persist for weeks or months after the pustules have healed, whereas in affected lighter-skinned neonates, dyspigmentation less commonly occurs. The condition is observed in 4.4% of black and 0.6% of white newborns.

Histologically, there are intracorneal or subcorneal aggregates of predominantly neutrophils, but eosinophils may also be found. Dermal inflammation is composed of a mixture of neutrophils and eosinophils. The differential diagnosis includes erythema toxicum neonatorum, neonatal acne, and acropustulosis of infancy.

Van Praag MC, et al: Diagnosis and treatment of pustular disorders in the neonate. Pediatr Dermatol 1997;14:131.

Wagner A: Distinguishing vesicular and pustular disorders in the neonate. Curr Opin Pediatr 1997;9:396.

PEUTZ-JEGHERS SYNDROME

Peutz-Jeghers syndrome (PJS) is characterized by hyperpigmented macules on the lips and oral mucosa and polyposis of the small intestine. The dark brown or black macules appear typically on the lips, especially the lower lip, in infancy or early childhood (Fig. 36-3). Similar lesions may appear on the buccal mucosa, tongue, gingiva, and genital mucosa; macules may also occur around the mouth, on the central face, and on the backs of the hands, especially the fingers, toes, and tops of the feet. Once suspected, conventional imaging work-up should be performed. Capsule endoscopy may aid in establishing the diagnosis, since the polyps may be in regions of the intestine not directly accessible to routine endoscopy.

The associated polyposis involves the small intestine by preference (64–78%), but hamartomatous polyps may also occur in the stomach (38–49%), colon (42–53%), and rectum (28–32%). The polyposis of the small intestine may cause repeated bouts of abdominal pain and vomiting; bleeding is common; intussusception is frequent.

Patients with PJS have a 10- to 18-fold greater lifetime cancer risk than the general population. Half of patients with PJS will develop cancer at a mean age of 40 years. The greatest risk is for gastrointestinal malignancy of the colon and duodenum, but cancers both in the gastrointestinal tract and extraintestinal sites occur. Pancreas, breast (bilateral), lung, cervix, uterus, and thyroid carcinomas may develop. The lifetime risk for pancreatic cancer is 10%. Mucinous ovarian cystadenofibromas, Sertoli-Leydig cell stromal tumors, and sex cord tumors with annular tubules can occur.

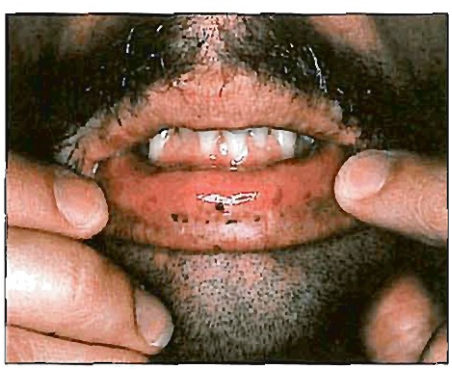

Fig. 36-3 Peutz-Jeghers, macular pigmentation of the lower lip.

The syndrome is transmitted as a simple mendelian dominant trait. At least 50% to 75% of patients with PJS have a germline mutation of the STK11/LKB1 tumor suppressor gene on chromosome 19p13. The gene product is a serine–threonine kinase involved in signal transduction. Patients have one inactive copy of this gene. About 5% of pancreatic cancers unassociated with PJS also have inactivation of both alleles of this gene, supporting its role as a tumor suppressor.

Patients with PJS should have routine colonoscopy from the time of diagnosis. Upper gastrointestinal endoscopy and upper gastrointestinal studies with small bowel follow-through should be performed every 2 years. Screening for pancreatic cancer should also be considered.

Laugier-Hunziker syndrome and Cronkhite-Canada syndrome should be considered in the differential diagnosis. Laugier-Hunziker syndrome presents with mucosal pigmentation and pigmented nail streaks. Cronkite-Canada syndrome consists of melanotic macules on the fingers and gastrointestinal polyposis. Also there is generalized, uniform darkening of the skin, extensive alopecia, and onychodystrophy. The polyps that occur are usually benign adenomas and may involve the entire gastrointestinal tract. A protein-losing enteropathy may develop and is associated with the degree of intestinal polyposis. Onset is typically after age 30 in this sporadically occurring, generally benign condition. Hypogeusia is the dominant initial symptom, followed by diarrhea and ectodermal changes. Seventy-five percent of all cases have been reported from Japan. Zinc therapy may improve the hypogeusia and other symptoms.

Allbritton J, et al: Cronkhite-Canada syndrome. Cutis 1998; 61:229.

Boardman LA, et al: Increased risk for cancer in patients with the Peutz-Jeghers syndrome. Ann Intern Med 1998;128:896.

Boyanton BL, Shinault SS: Pathologic quiz case: A 27-year-old man with abdominal pain. Arch Pathol Lab Med 2004;128:483.

Brinster DR, Raper SE: Synchronous colon and pancreatic cancers in a patient with Peutz-Jeghers syndrome: Report of a case and review of the literature. Surgery 2004;135:352.

De Palma GD, et al: Image of the month: Minimally invasive diagnosis of Peutz-Jeghers syndrome. Clin Gastroenterol Hepatol 2004;2(10):xxiv.

Gruber SB, et al: Pathogenesis of adenocarcinoma in Peutz-Jeghers syndrome. Cancer Res 1998;58:5267.

Hanzawa M, et al: Surgical treatment of Cronkhite-Canada syndrome associated with protein-losing enteropathy. Dis Colon Rectum 1998;41:932.

Resta N, et al: STK11 mutations in Peutz-Jeghers syndrome and sporadic colon cancer. Cancer Res 1998;58:4799.

Wong SS, et al: Peutz-Jeghers syndrome associated with primary malignant melanoma of the rectum. Br J Dermatol 1996; 135:439.

RIEHL MELANOSIS

This pigmentary disease, first described by Riehl, is a form of contact dermatitis. It begins with pruritus, erythema, and pigmentation gradually spreads and, after reaching a certain extent, becomes stationary. The melanosis occurs mostly in women and develops slowly over the course of several months. Most reported cases occur in Japan.

The characteristic feature is spotty light to dark brown pigmentation. This is most intense on the forehead, on the malar regions, behind the ears, on the sides of the neck, and on other sun-exposed areas. The pathogenesis of Riehl melanosis is believed to be sun exposure following the use of some perfumes or creams (a photocontact dermatitis). Serrano et al reported a positive patch test to lemon oil, geraniol, and hydroxycitronellal. Treatment is removal of the contactant.

Hanada K, et al: Melanosis Riehl-like facial pigmentation in a Japanese case of AIDS. J Dermatol 1994;21:363.
Miyoshi K, et al: Riehl's melanosis-like eruption associated with Sjögren's syndrome. J Dermatol 1997;24:784.
Seike M, et al: Coexistence of Riehl's melanosis and lichen planus. J Dermatol 2003;30:132.
Serrano G, et al: Riehl's melanosis. J Am Acad Dermatol 1989; 21:1057.

TAR MELANOSIS (MELANODERMATITIS TOXICA LICHENOIDES)

Tar melanosis is an occupational dermatosis that occurs among tar handlers after several years' exposure. Severe widespread itching develops and is soon followed by the appearance of reticular pigmentation, telangiectases, and a shiny appearance of the skin. In addition, there is a hyperhidrotic tendency. Small, dark, lichenoid, follicular papules become profuse on the extremities, particularly the forearms. Bullae are sometimes observed. This represents a photosensitivity or phototoxicity induced by tar.

Lehowhl M, et al: Tar melanosis. Mt Sinai J Med 1995;62:412.

FAMILIAL PROGRESSIVE HYPERPIGMENTATION

Familial progressive hyperpigmentation (FPH) is characterized by patches of hyperpigmentation, present at birth, which increase in size and number with age. Later, hyperpigmentation appears in the conjunctivae and the buccal mucosa. Eventually, a large portion of the skin and mucous membranes becomes involved. Inheritance is in an autosomal-dominant pattern with variable penetrance. A focus in a small village in Germany has recently been reported. FPH is differentiated from other hyperpigmentations mainly by the presence of bizarre, sharply marginated patterns of hyperpigmented skin.

Betts CM, et al: Progressive hyperpigmentation: case report with a clinical, histological, and ultrastructural investigation. Dermatology 1994;189:384.
Ling DB, et al: Familial progressive hyperpigmentation. Br J Dermatol 1991;125:607.
Zanardo L, et al: Progressive hyperpigmentation and generalized lentigiosis without associated systemic symptoms: a rare hereditary pigmentation disorder in south-east Germany. Acta Derm Venereol 2004;84:57.

PERIORBITAL HYPERPIGMENTATION

Dark circles around the eyes are not uncommon, often familial, and are frequently found in individuals with dark pigmentation or Mediterranean ancestry. Atopic patients may also exhibit periorbital pigmentation (allergic shiners). Treatment is ineffective.

METALLIC DISCOLORATIONS

Pigmentation may develop from the deposit of fine metallic particles in the skin. The metal may be carried to the skin by the blood stream or may permeate into it from surface applications.

Argyria

Argyria is a localized or widespread slate-colored pigmentation resulting from the presence of silver in the skin. The pigmentation is most noticeable in parts exposed to sunlight (the face and hands) and spares the skinfolds; however, it also occurs in the conjunctivae, sclerae, mucous membranes, and nails. The binding of silver to protein is enhanced by light and the tissue silver is felt to stimulate melanocytes, explaining the photoaccentuation. At first the discoloration is hardly perceptible, it has a faint bluish-gray tone, but as it becomes more pronounced, a slate-gray color develops. The oral mucous membranes and the sclerae are usually pigmented in a distinctive diffuse manner. Most cases of systemic argyria are due to nose or eye drops containing silver or to the ingestion of silver in "tonics." These "tonics" are no longer regulated by the US Food and Drug Administration and can be sold as "food supplements" over the internet. Local treatment with a silver-containing product may produce argyria localized to the region of use: for example, the conjunctivae, from eye drops; a wound, from silver sulfadiazine cream; the earlobes, from silver earrings; and from silver acupuncture needles. It can also occur from occupational exposure, usually in jewelers. In these localized exposures, the appearance may be separated by many years from the exposure.

Histologically, systemic argyria and localized argyria have the same features. The skin appears relatively normal at lower magnifications. Fine black granules are found in the lamina propria surrounding the sweat glands, as well as surrounding blood vessel walls, the dermoepidermal junction, and along the arrector pili muscles. Examination of an unstained biopsy section by darkfield illumination demonstrates silver granules outlining the basement membrane of the epidermis and the eccrine sweat glands. Electron probe microanalysis can be used to confirm the diagnosis. There is no effective treatment and the pigmentation may last for many years.

Arsenic

Acute arsenic poisoning is associated with flushing on day one of exposure, and facial edema on days 2 through 5. A morbilliform eruption appears on days 4 through 6. Hepatic dysfunction occurs simultaneously with the appearance of an eruption of discrete red–brown, erythematous papules in the intertrigionous areas (areas of friction) of the lower abdomen, buttocks, and lateral upper chest. It regresses after 2 to 3 weeks, at times accompanied by acral desquamation. Three months after exposure Mee's lines, total leukonychia, Beau's lines, and onychodystrophy may be seen. Periungual pigmentation occurs in up to half of acutely poisoned patients at 3 months.

Arsenic is an elemental metal that is ubiquitous, existing in nature as metalloids, alloys, and a variety of chemical compounds. These various forms of arsenic may be deposited into water, soil, and vegetation, producing serious health risks. In West Bengal, India, an estimated 200,000 people have arsenic-induced skin disorders and more than 1 million Indians are drinking arsenic-laced water from contaminated wells. Arsenic-contaminated water sources are a worldwide health concern also affecting countries such as Japan, Chile, Taiwan, and Mongolia. It is not known what are safe levels of arsenic in drinking water. The World Health Organization (WHO) current permissible levels are under 0.01 mg/L.

Industries using arsenical compounds place their workers at risk of exposure. Use of arsenic pesticides and exposure to sodium arsenite, used as a veterinary pesticide exposing sheep-dip workers, has resulted in chronic arsenism. In the US arsenic is used for pesticides, rodenticides, herbicides, insecticides, desiccants, feed additives, and wood preservatives. Pressure-treated lumber, particularly the marine-treated plywood, exposes carpenters and shipbuilders. The largest risk from wood products, however, occurs when pretreated wood is burned and the arsenic fumes are inhaled. Electroplating silver may also require arsenic. Another potential source of exposure during the 1960s was American tobacco, resulting mostly from the use of arsenic-containing insecticides.

Chronic exposure to inorganic arsenic may lead to cutaneous hyperpigmentation. It is often accentuated in the inguinal folds and the areolae. Areas of hypopigmentation may be scattered in the hyperpigmented areas, giving a "raindrop" appearance. The pigmentation may resolve or persist indefinitely. Punctate keratoses on the palms and soles are characteristic. Diffuse palmoplantar keratoderma may rarely occur. The most common source of current exposure is from drinking water contaminated with arsenic (hydroarsenicism). In the past, elixirs to treat asthma (Fowler's solution, Bell's Special Asthma Mixture) were a source of exposure. Histologically, the arsenical keratosis on the palms and soles show hyperkeratosis, acanthosis, and minimal-to-moderate basilar atypia. Arsenic exposure leads to the development of nonmelanoma skin cancers 2 to 20 years after exposure. In most reports Bowen's disease represents the majority of arsenic-induced skin cancers and may appear on sun-exposed or -protected skin. Basal cell carcinomas are frequent, usually multiple, most common on the trunk, and can be in sun-protected sites. Squamous cell carcinoma may also occur. Acetretin may improve "arsenical" keratoses. Increased risk for lung, bladder, and renal carcinoma may also occur.

Lead

Chronic lead poisoning can produce a "lead hue," with lividity and pallor, and a deposit of lead in the gums may occur: the "lead line."

Iron

In the past, soluble iron compounds were used in the treatment of allergic contact and other dermatitides. In eroded areas iron was sometimes deposited in the skin, like a tattoo. The use of Monsel solution can produce similar tattooing, so aluminum chloride is now preferred. If Monsel is used, to minimize tattooing, it is best applied with a cotton-tipped applicator barely moistened with the solution, then rolled across a wound that has just been blotted dry.

Titanium

A titanium-containing ointment caused yellowish papules on the penis in a patient. Titanium screws used for orthopedic procedures, if they come in close proximity to the skin, can cause cutaneous blue–black hyperpigmentation.

Gold

Chrysiasis may be induced by the parenteral administration of gold salts, usually for the treatment of rheumatoid arthritis. It appears to be more commonly recognized in white patients. A mauve, blue, or slate-gray pigmentation develops initially on the eyelids, spreading to the face, dorsal hands, and other areas. The severity of chrysiasis is related to the total dose received and it is rare below a total dose of 20 mg/kg of elemental gold. The pigmentation is accentuated in light-exposed areas, and sun-protected areas do not histologically demonstrate gold, even when the patient has documented chrysiasis at other sites. Localized chrysiasis has been induced by Q-switched ruby laser treatment in a patient who had received parenteral gold therapy. Melanin is not increased in the areas of hyperpigmentation. Therefore, it appears the gold itself contributes to the visible hyperpigmentation. Mucous membrane and scleral pigmentation is very uncommon.

Histologically, there is no inflammation in the skin and gold is deposited in the dermis predominantly in a perivascular pattern. The epidermis and dermoepidermal junction are spared, but the granules are accentuated in the basement membrane zone of sweat glands. Darkfield examination will demonstrate the granules and electron probe microanalysis can be used to confirm the presence of gold. Patients with chrysiasis are not at increased risk of developing other gold-related cutaneous complications, namely lichenoid and psoriasiform drug eruptions.

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CANTHAXANTHIN

The orange-red pigment canthaxanthin is present in many plants (notably algae and mushrooms) and in bacteria, crustaceans, sea trout, and feathers. When ingested for the purpose of simulating a tan, its deposition in the panniculus imparts a golden orange hue to the skin. Stools become brick red and the plasma orange, and golden deposits appear in the retina. Its use is not recommended since it may be associated with liver and retinal damage.

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IDIOPATHIC GUTTATE HYPOMELANOSIS (LEUKOPATHIA SYMMETRICA PROGRESSIVA)

Idiopathic guttate hypomelanosis is a very common acquired disorder that affects women more frequently than men. It usually occurs after age 40 and its prevalence increases with age. The lesions occur chiefly on the shins and forearms, suggesting sun exposure may play a role. Individual lesions are small (2–5 mm on average) hypopigmented macules. They usually number between 10 and 30, but numerous lesions may occur. Lesions spare the trunk and face. The lesions are irregularly shaped and very sharply defined, like depigmented ephelides, and are of only minor cosmetic significance. Cryotherapy can improve the appearance of the lesions.

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VITILIGO

Vitiligo usually begins in childhood or young adulthood, with about half of cases beginning before the age of 20. The prevalence ranges from 0.5% to 1%. Although females are disproportionately represented among patients seeking care, it is not known whether they are actually more commonly affected or simply are more likely to seek medical care. Vitiligo has developed in recipients of bone marrow transplant or lymphocyte infusions from patients with vitiligo.

Clinical Features Vitiligo is an acquired pigmentary anomaly of the skin manifested by depigmented white patches surrounded by a normal or a hyperpigmented border. There may be intermediate tan zones or lesions halfway between the normal skin color and depigmentation—so-called trichrome vitiligo. The hairs in the vitiliginous areas usually become white also. Very rarely, the patches may have a red, inflammatory border. The patches are of various sizes and configurations.

Four types have been described according to the extent and distribution of the involved areas: localized or focal (including segmental), generalized (common symmetric), universal (Fig. 36-4), and acrofacial (Fig. 36-5). The generalized pattern is most common. Involvement is symmetrical. The most commonly affected sites are the face, upper part of the chest, dorsal aspects of the hands, axillae, and groin. There is a tendency for the skin around orifices to be affected, namely the eyes, nose, mouth, ears, nipples, umbilicus, penis, vulva, and anus. Lesions appear at areas of trauma, so vitiligo favors the elbows and knees. Universal

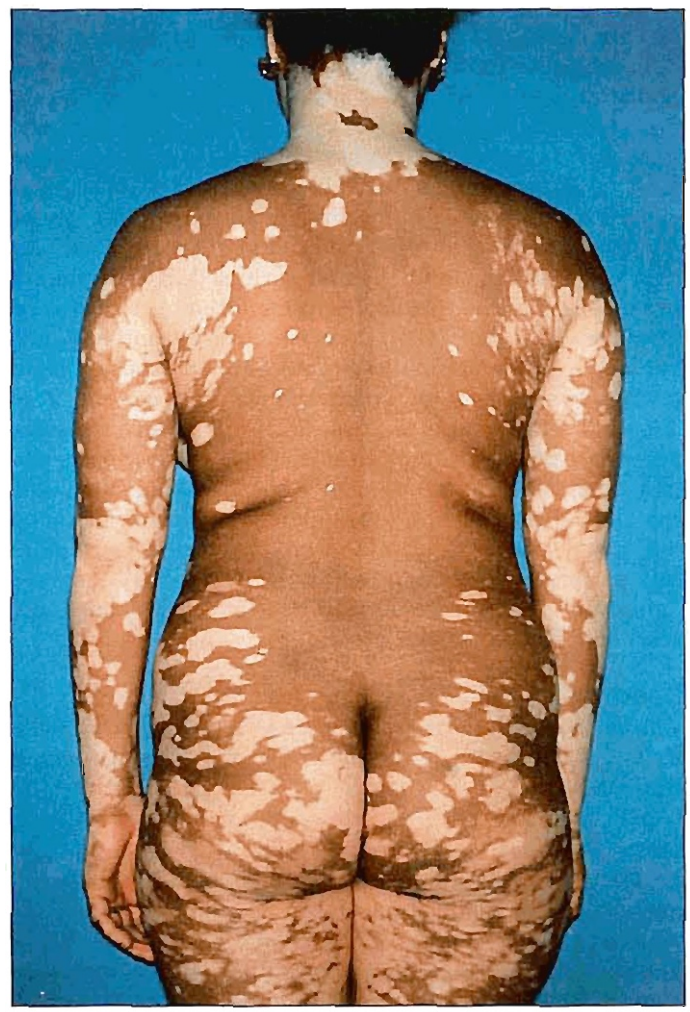

Fig. 36-4 Vitiligo, generalized.

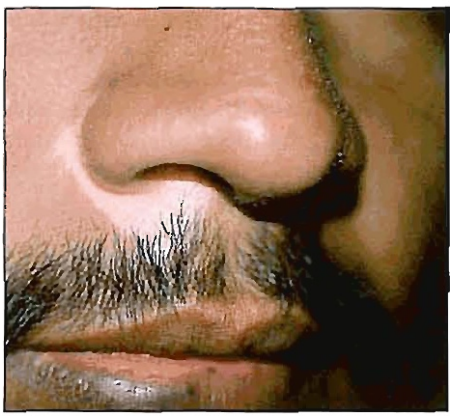

Fig. 36-5 Vitiligo, characteristic periorificial location.

vitiligo applies to cases where the entire body surface is depigmented. The acrofacial type affects the distal fingers and facial orifices (lips and tips). Focal vitiligo may affect one nondermatomal site (such as the glans penis) or asymmetrically affect a single dermatome or band. This segmental form of vitiligo is treatment resistant, has an earlier onset, and is less frequently associated with other autoimmune phenomena. It represents 5% of adult vitiligo and 20% of childhood vitiligo.

Local loss of pigment may occur around nevi and melanomas, the so-called halo phenomenon. Vitiligo-like leukoderma occurs in about 1% of melanoma patients. In those with previously diagnosed melanoma, it suggests metastatic disease. Paradoxically, however, as the reaction indicates an autoimmune response against melanocytes, patients who develop it have a better prognosis than patients without leukoderma. Halo nevi are also common in patients with vitiligo. Lesions of vitiligo are hypersensitive to UV light and burn readily when exposed to the sun. It is not unusual to note the onset of vitiligo after a severe sunburn.

Ocular abnormalities are increased in patients with vitiligo, including iritis and retinal pigmentary abnormalities. Patients have no visual complaints. Eight percent of patients with idiopathic uveitis have vitiligo or poliosis. The conditions most frequently associated with vitiligo are other "autoimmune" diseases. These include insulin-dependent diabetes mellitus, pernicious anemia, Hashimoto thyroiditis, Graves' disease, Addison's disease, and alopecia areata. Screening should be directed by signs and symptoms. Vitiligo occurs in 13% of patients with the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome.

Although familial aggregation of vitiligo is seen—up to 30% of vitiligo patients have an affected relative—it is not inherited as an autosomal-dominant or -recessive trait, but rather seems to have a multifactorial genetic basis.

The psychologic effect of vitiligo should not be underestimated. Patients are frequently anxious or depressed because of the appearance of their skin and the way it affects their social interactions. Referring the patient to a mental health professional or the National Vitiligo Foundation (www.nvfi.org) may be helpful in this situation.

Occupational Vitiligo

Thiols, phenolic compounds, catechols, mercaptoamines, and several quinines (including chloroquine) can produce depigmentation. These compounds have a structure similar to tyrosine and may be converted by tyrosine-related protein-1 to compounds toxic to the melanocyte. The clinical pattern may be very similar to idiopathic vitiligo, but lesions tend to be concentrated in areas of contact with the incriminated substance. Occupational vitiligo may occur in individuals who work in rubber garments or wear gloves that contain an antioxidant, monobenzyl ether of hydroquinone. Many phenolic compounds can produce leukoderma, with or without antecedent dermatitis. Examples are paratertiary butylphenol, amylphenol, and butylcatechol; alkyl phenols; sulfhydryls; and monobenzyl ether of hydroquinone. One source of these is phenolic antiseptic detergents used in hospitals. Adhesives and glues containing them may be found in shoes, wristbands, adhesive tape, and rubber products used in brassieres, girdles, panties, or condoms may also be at fault. Self-sticking bindis (the cosmetic used by many Indian women on the forehead) has been reported to induce leukoderma from the adhesive material. Also, electrocardiograph electrodes may cause similar round hypopigmented spots at the site of contact. A similar pattern of postinflammatory hypopigmentation simulating vitiligo is observed around the mouth, in persons with no prior history of allergic dermatitis but with a positive patch test to cinnamates.

Pathogenesis Four possible mechanisms have been proposed as inducing vitiligo: autoimmunity (currently favored), neurohumoral factors, autocytotoxicity (increased susceptibility to oxidative stress), and melanocytorrhagy. This later theory proposes that vitiligo results from defective adhesion (with altered response [detachment] to friction). None of these mechanisms has been conclusively proven and several may be operative in various forms of vitiligo.

Histopathology There is a complete absence of melanocytes. Usually there is no inflammatory infiltrate.

Differential Diagnosis Vitiligo must be differentiated from morphea and lichen sclerosis, both of which are hypopigmented, but associated with a change in the skin texture. Pityriasis alba has a fine scale, is slightly papular, and poorly defined. Tinea versicolor favors the center back and chest, has a fine scale, and yeast and hyphal forms are demonstrable with potassium hydroxide (KOH) examination. The tertiary stage of pinta might easily lead to diagnostic confusion, but a travel history and serologic testing will help elucidate the diagnosis.

Treatment Vitiligo is a frustrating condition to treat. Spontaneous repigmentation occurs in no more than 15% to 25% of cases. Response is slow, and response rates are low. In addition, some forms of treatment, such as phototherapy, actually worsen the appearance of the vitiligo initially by pigmenting surrounding skin, accentuating the depigmented areas.

Because the major concern is cosmetic, various cover-up strategies have been developed. There are various brands of make-up available to temporarily conceal the lesions. Topical dyes are more resistant to washing off and are very acceptable to some patients. The newer self-tanning creams containing dihydroxyacetone are useful for light-skinned and olive complexioned patients with acral lesions.

Fair-skinned patients (skin types I and II) with vitiligo may sometimes effectively manage their disease with sunblock. If the patient can prevent tanning of the skin around the vitiligo lesions, the lesions will appear similar to the untanned skin and require no additional treatment. Sun protection is mandatory in all patients with vitiligo because of the increased risk for skin cancer in depigmented areas.

Topical steroids may be useful on focal or limited lesions. The thinner skinned areas of the face seem to respond best. Trunk and acral lesions are often resistant to this treatment. Mid to super high-potency steroids are often required, with the strength tapered as the lesions respond. A 2-month trial should be attempted. Topical calcipotreinene once a day may increase the efficacy of topical steroid treatment. Although systemic steroids lead to temporary repigmentation, this is usually lost as the steroidal agents are tapered, so this is usually not a viable long-term strategy.

Tacrolimus ointment 0.1% has been particularly efficacious in treating facial vitiligo. It is as effective as topical steroids and avoids the complications of atrophy and acne induced by topical steroids. Head and neck lesions improve by 75% or more in half of children treated, whereas only 25% of trunk and extremity lesions resolve by 75% or more. Patients who initiate treatment in the summer have a higher rate of response. Continual application may be required to maintain the response. New areas of vitiligo appear in untreated areas, suggesting there is no systemic effect.

Narrow-band UVB twice weekly has become the preferred form of phototherapy to treat vitiligo. It avoids the need for prolonged eye protection and the occasional psoralen-induced nausea. About half of patients will achieve more than 50% repigmentation of the face, trunk, arms and legs. Hand and foot lesions repigment in less than 25% of patients. Children may have slightly higher response rates than adults. Long courses of treatment may be required. PUVA therapy can also be used to treat vitiligo. The addition of calcipotriene 0.005% once a day adds significantly to the rate and extent of response to narrow-band UVB and PUVA phototherapy, and should be used if there is no contraindication. Repigmentation from phototherapy may begin after 15 to 25 treatments; however, significant improvement may take as many as 100 to 200 treatments (6–24 months). If follicular repigmentation has not appeared after 3 to 6 months or approximately 50 treatments, phototherapy treatments should be discontinued. Known photosensitivity, porphyria, and systemic lupus erythematosus are contraindications to phototherapy.

Topical application of 8-methoxypsoralen at a concentration of 0.05% to 0.1%, followed by UVA exposure, may lead to repigmentation. Topical PUVA is used for focal or limited lesions. Inadvertent burns with blistering are frequent during treatment, even when the patient is treated by professionals. For this reason, topical PUVA is very difficult for the patient to do at home. The combination of topical tacrolimus plus the 308-nm xenon chloride eximer laser appears effective for local lesions and avoids the toxicity of topical PUVA. This combination is more effective than the laser alone and can even be effective in lesions which tend to be UV resistant.

Surgical treatments can be applied to limited lesions if the above methods do not prove beneficial, but these are time consuming. They are recommended primarily in patients with segmental vitiligo (which is relatively treatment resistant) and in patients who have failed other forms of treatment *and* have stable disease (no new lesions or expansion of lesions for 1 year). Surgical procedures are not effective in patients who exhibit Koebner phenomenon at the donor site or have active vitiligo. Epidermal grafting, autologous minigrafts, and transplantation of cultured melanocytes and noncultured melanocytes/keratinocytes have all been reported.

Total Depigmentation

If more than 50% to 80% of the body surface area is affected by vitiligo, the patient can consider depigmentation. This form of treatment should be considered permanent and the goal of treatment is total depigmentation. Limited areas (such as those exposed daily) may be treated, but satellite and distant depigmentation may occur, so the action of the medication cannot be limited to the applied area. Monobenzone (monobenzyl ether of hydroquinone) 20% is applied twice a day for 3 to 6 months to residual pigmented areas. Up to 10 months may be required to complete the treatment. About one in six patients treated experiences acute dermatitis, usually confined to the still-pigmented areas, but this rarely limits treatment. Topical 20% 4-methoxyphenol cream (mequinol, monomethylether of hydroquinone) can also be used for depigmentation. The Q-switched laser selectively destroys melanocytes and can also achieve depigmentation. It can be combined with a topical depigmenting agent for added efficacy.

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VOGT-KOYANAGI-HARADA SYNDROME

Vogt-Koyanagi-Harada (VKHS) syndrome is a disease complex affecting the eyes, skin, auditory system, and central nervous system (CNS). It affects primarily pigmented races and is rare in white persons. It is more common in females, and affects all ages. The disease occurs in four phases. The prodromal phase or meningoencephalitic phase occurs with fever, malaise, headache, nausea, and vomiting. The CNS involvement can include meningismus, headaches, mental status changes, cerebrospinal fluid pleocytosis, tinnitus, and dysacusis. Recovery is usually complete. The second phase, the uveitic phase is characterized by anterior and/or posterior uveitis and inflammation of many other parts of the eye. The third or convalescent phase begins 3 weeks to 3 months after the uveitis appears, usually as it begins to improve. This phase is characterized by alopecia, vitiligo, and poliosis of scalp, eyebrows, eyelashes, and hairs of the axillae. The fourth phase is one of recurrent attacks of uveitis. Most ocular complications occur as a result of this phase of the disease, and include permanent decreased visual acuity, cataracts, and glaucoma. Revised diagnostic criteria have been developed.

VKHS is a cell-mediated autoimmune disease with the autoantigen(s) felt to be solely expressed in melanin-containing cells. The target antigens may be the tyrosinase family proteins, as immunization of mice with several of these proteins can induce a syndrome similar to VKHS. Supporting this hypothesis are the rare observations that skin trauma that was followed by vitiligo, erythroderma, interferon therapy for hepatitis C, and melanoma can all be associated with the appearance of VKHS. Treatment of the ocular inflammatory disease with immunosuppressives may prevent ocular complications.

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ALEZZANDRINI SYNDROME

Alezzandrini syndrome is a very rare syndrome characterized by a unilateral degenerative retinitis, followed after several months by ipsilateral vitiligo on the face and ipsilateral poliosis. Deafness may also be present.

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LEUKODERMA

Postinflammatory leukoderma may result from many inflammatory dermatoses, such as pityriasis rosea, psoriasis, herpes zoster, secondary syphilis, and morphea. Sarcoidosis, tinea versicolor, mycosis fungoides, scleroderma, and pityriasis lichenoides chronica may all present with hypopigmented (only rarely, actually depigmented) lesions, as may leprosy. Burns, scars, postdermabrasion, and intralesional steroid injections with depigmentation are other examples of leukoderma.

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ALBINISM

Albinism is a partial or complete congenital absence of pigment in the skin, hair, and eyes (oculocutaneous albinism), or the eyes alone (ocular albinism). The cutaneous phenotype of the various forms of albinism is broad, but the ocular phenotype is reasonably constant in most forms. This includes decreased visual acuity, nystagmus, pale irides that transilluminate, hypopigmented fundi, hypoplastic foveae, and lack of stereopsis. The recent discovery of the genetic basis of many of the forms of albinism has dramatically changed the classification scheme. Genetic disorders of pigment cells can now be defined as caused by 1) disruption of melanoblast migration to target tissues during development (Waardenburg syndrome and piebaldism); 2) disruption of melanin synthesis (oculocutaneous albinism, ocular albinism); 3) disruption of melanosome formation (Chédiak-Higashi and Hermansky-Pudlak syndromes); or 4) disruption of melanosome transport and melanin transfer to keratinocytes (Griscelli syndrome). The most serious sequelae of albinism are gross visual disturbances and the increased risk for the development of skin cancer. A number of syndromes associated with albinism can also cause premature mortality due to impairment of the functioning of other involved organs and systems.

Disorders of Melanin Synthesis

Oculocutaneous Albinism Four types of oculocutaneous albinism (OCA) have been described, all caused by disruption of melanin synthesis and all autosomal-recessive disorders. Historically, the term tyrosinase-negative OCA was used if the mutation was in the tyrosinase gene (encoding an enzyme absolutely required for pigment synthesis). However, some "tyrosinase-positive" patients were found to be compound heterozygotes for mutations in tyrosinase as well (Fig. 36-6).

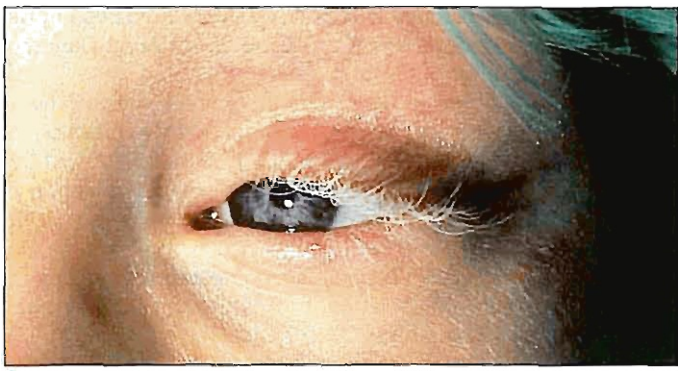

Fig. 36-6 Albinism, with light skin, blue eyes and white hair.

Oculocutaneous Albinism 1

Oculocutaneous albinism 1 (OCA1) results from mutations in the tyrosinase gene and accounts for approximately 40% of OCA worldwide. Affected patients are homozygous for the mutant gene or are compound heterozygotes for different mutations in the tyrosinase gene. OCA1 is divided into two forms: OCA1A and OCA1B. At birth they are indistinguishable. OCA1A is the most severe form, with complete absence of tyrosinase activity and complete absence of melanin in the skin and eyes. Visual acuity is decreased to 20/400. In OCA1B, tyrosinase activity is greatly reduced but not absent. Affected patients may show increase in skin, hair, and eye color with age and can tan. OCA1B was originally called "yellow mutant" albinism. Temperature-sensitive OCA (OCA1-TS) results from mutations in the tyrosinase gene that produce an enzyme with limited activity below 35° C (95° F) and no activity above this temperature. Affected patients have white hair, skin, and eyes at birth. At puberty, dark hair develops in cooler acral areas.

Oculocutaneous Albinism 2

Oculocutaneous albinism 2 (OCA2) has a prevalence of 1 in 15,000 and is the most common form of OCA, accounting for approximately 50% of OCA worldwide, most frequently in Africa. Patients were formerly called "tyrosinase-positive" albinos. Inheritance is autosomal recessive and results from mutations in the P gene. The P gene codes a putative membrane transport protein that spans melanocyte internal membranes, likely the endoplasmic reticulum. The cutaneous phenotype of OCA 2 patients is broad, from nearly normal pigmentation to virtually no pigment. Pigmentation increases with age and visual acuity improves from infancy to adolescence. Prader-Willi and Angleman syndromes are caused by deletions in the chromosomal region contiguous to and sometimes including the P gene. One percent of patients with these syndromes also have OCA2.

Oculocutaneous Albinism 3

Oculocutaneous albinism 3 (OCA3) is caused by mutations in the tyrosine-related protein 1 (TRP-1) gene, located on chromosome 9. To date, this form of OCA has only been described in African patients and is characterized by light brown hair, light brown skin, blue–brown irides, nystagmus, and decreased visual activity. Brown rather than black

melanin is formed. This type of albinism was previously referred to as "rufous" albinism.

Oculocutaneous Albinism 4 (OCA4)

Oculocutaneous albinism 4 (OCA4) is due to mutations in the MATP gene on chromosome 5 encoding a membrane-associated transporter protein, predicted to span the membrane 12 times and to function as a transporter. Patients are hypopigmented to a variable degree, similar to patients with OCA2. Visual acuity is decreased and nystagmus is found in many but not all patients. This is the most common form of tyrosinase-positive albinism in Japan; it has also been reported in a Turkish patient and several German patients.

Ocular Albinism There are multiple forms of ocular albinism, which are clinically similar. Ocular albinism type 1 (OA1) is X-linked, and characterized by depigmented fundi, with resultant strikingly apparent choroidal vessels; associated findings can include nystagmus, head nodding and impaired vision. Female carriers have "mud-splattered" or mosaic pigmentation of the fundi due to lyonization of the X chromosomes. Macromelanosomes are found in the skin, so skin biopsy may be used to help establish this diagnosis; patients may present with lighter skin than expected. It is suggested that "ocular" albinism may be somewhat of a misnomer and that cutaneous involvement is present but clinically subtle. Data suggest that the melanocyte-specific OA1 gene product is the first described G-protein coupled receptor to reside exclusively on an intracellular membrane, likely an endosomal compartment. In one large South African kindred, OA1 is associated with late-onset deafness.

Disorders of Melanosome Formation

These are multisystem syndromes that are associated with albinism. These syndromes are caused by genes that function in intracellular organelle formation and movement in a variety of specialized cell types, such as melanocytes, neurons, immune cells, and type II epithelial cells in lungs.

Chédiak-Higashi Syndrome Chédiak-Higashi syndrome is an autosomal-recessive disorder characterized by oculocutaneous albinism and immunologic deficiency, including defective phagocyte, lymphocyte, and natural killer (NK) cell function. Antibody-dependent cellular cytotoxicity is also defective. Early childhood is marked by recurrent bacterial infections. Eighty-five percent of Chédiak-Higashi syndrome patients develop an accelerated phase characterized by a lymphocyte and macrophage activation syndrome. The results of liver function tests will be abnormal, and fever, hepatosplenomegaly, lymphadenopathy, pancytopenia, and infiltration of the CNS occur. Although the accelerated phase may respond to etoposide plus systemic steroid and intrathecal methotrexate, relapses invariably occur. These relapses are less responsive to treatment and are eventually fatal. Unless patients undergo successful stem cell transplantation, most die in childhood.

The causative gene is LYST (lysosome trafficking regulator), located on chromosome 1; its function is unknown. Lysosomal protein transport is defective and giant intracytoplasmic inclusion bodies are seen in most granulated cells. Giant melanosomes are observed and cause pigment dilution (hypopigmentation of skin, hair, and fundi), possibly secondary to impaired melanin transport. The hair has a metallic gray sheen. Microscopic examination of hair samples reveals multiple small granules of pigment dispersed throughout the shaft.

Hermansky-Pudlak Syndrome Hermansky-Pudlak syndrome (HPS) is an autosomal-recessive disorder consisting of oculocutaneous albinism, a hemorrhagic diathesis secondary to the absence of dense bodies in platelets, and accumulation of a ceroid-like material in the reticuloendothelial system, visceral organs, oral mucosa, and urine. Patients with this disorder have a history of easy bruisability, epistaxis, gingival bleeding, hemoptysis, and bleeding after various surgical procedures and childbirth.

Currently, seven human genes (HPS1–7) have been identified, which when independently mutated, lead to a clinical picture consistent with HPS. It is anticipated that more HPS genes will be identified in humans since in mice there are at least 14 non-allelic genes that when singly defective give rise to HPS. While the HPS subtypes 1 to 7 all share the clinical signs and symptoms noted above, a few subtypes have additional unique features that serve to distinguish them from the other HPS subtypes.

The most common subtype is HPS1, and together with HPS4, comprises 50% of the known worldwide cases of HPS. HPS1 and HPS4 are clinically very similar (reflecting the biochemical studies that demonstrate that HPS1 and 4 proteins are associated together in a complex) and are the most severe forms of HPS. Interstitial pulmonary fibrosis, inflammatory bowel disease, renal failure, and cardiomyopathy are late complications and can cause premature mortality between the ages of 20 and 50 years old. A recent study suggests that pirfenidone, an antifibrotic agent, can slow the progression of pulmonary fibrosis in HPS1 patients with significant residual lung function (initial forced ventilatory capacity >50%). One in 21 Puerto Ricans has a mutation (usually a 16-bp duplication) in the HPS1 gene, which is located at 10q23. HPS accounts for 80% of albinos in Puerto Rico, and 1 in 1800 Puerto Ricans in the northwest region of the country has HPS. Patients may have completely absent to normal pigmentation and the majority have the ocular findings typical of albinism. Atypical nevi, acanthosis nigricans-like lesions in the axillae and neck, and trichomegaly also occur. Solar damage as evidenced by solar lentigines, actinic keratoses, and nonmelanoma skin cancers occurs in 80% of patients with the 16-bp duplication in HPS1 (Fig. 36-7).

HPS2 is caused by a mutation in the gene coding for a subunit of AP3, a molecule necessary for normal protein trafficking to the lysosome. HPS2 is notable for immunodeficiency and persistent neutropenia, with patients suffering recurrent bacterial infections of the upper respiratory system and middle ear, possibly due to the lack of antigen presentation by the CD1b molecule, since CD1b fails to gain access to the lysosome. Mild pulmonary fibrosis and a mild balance defect are also associated with HPS2.

HPS3, HPS5, and HPS6 have mild clinical findings, without reported pulmonary or gastrointestinal involvement. Patients with HPS3 have been reported to be initially misdiagnosed as having ocular albinism.

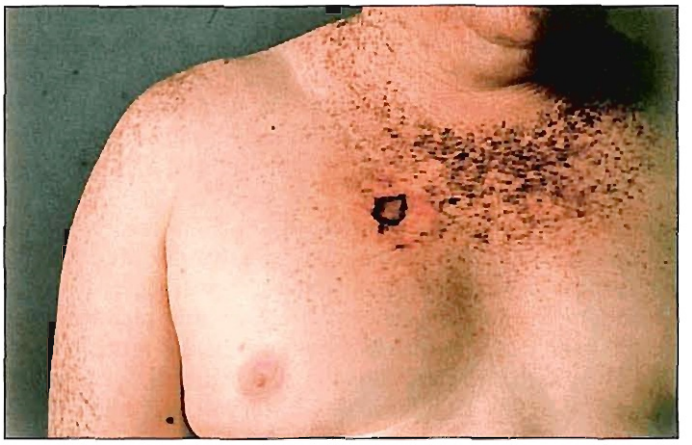

Fig. 36-7 Hermansky-Pudlak syndrome, freckling of the "V" of the neck, and a basal cell carcinoma in a Puerto Rican man.

The clinical similarity found for HPS3, HPS5, and HPS6 also reflects the biochemical observation that the respective proteins associate together in a complex.

Only a single patient has been reported with HPS7—a 48-year-old Portuguese woman with OCA, ease of bruising, and a bleeding tendency, who had mild pulmonary symptoms and reduced lung compliance, but otherwise normal pulmonary function and no evidence of fibrosis on high-resolution computed tomography (CT) chest scans. The HPS7 gene encodes dysbindin, a protein of unknown function.

Disorders of melanosome transport

Griscelli Syndrome (Partial Albinism with Immunodeficiency) Some groups refer to this disorder as *Griscelli Syndrome, type 2 (GS2)*. GS2 is a rare autosomal-recessive syndrome characterized by variable pigmentary dilution, hair with a silvery metallic sheen, frequent pyogenic infections, neutropenia, and thrombocytopenia. Defective NK cell function, impaired delayed-type hypersensitivity, and hypogammaglobulinemia are present. Patients develop an accelerated phase termed hemophagocytic syndrome characterized by an uncontrolled, life-threatening activation of T-cells and macrophages. Some patients have severe neurologic involvement, thought to be secondary to infiltration of immune cells into the CNS. Bone marrow transplantation is the only effective therapy for GS2.

Histologically, melanocytes are hyperpigmented and filled with stage IV melanosomes, whereas adjacent keratinocytes contain only sparse melanosomes. The giant cytoplasmic granules seen in Chédiak-Higashi syndrome are absent. Giant melanosomes are not seen. On microscopic examination, hair samples contain uneven clumps of aggregated melanin pigment in the medulla of the shaft.

The gene defective in this disorder encodes Rab27a, a small GTPase molecule in the Ras family, which associates with melanosomes in a molecular complex together with the motor protein myosin Va (defective in Griscelli syndrome type 1/Elejalde syndrome) and the linker protein melanophilin (defective in Griscelli syndrome type 3). This complex facilitates movement of melanosomes on actin filaments located at the periphery of melanocytes; disruption of the complex blocks transfer of melanin to neighboring keratinocytes and results in hypopigmentation. Similarly, the movement of cytoplasmic organelles in immune cells is impaired, leading to immune dysfunction.

Elejalde Syndrome Also referred to as *Griscelli Syndrome, type 1 (GS1)*, Elejalde syndrome is a rare autosomal-recessive syndrome consisting of moderate pigment dilution, profound primary neurologic defects, no immune defects, and hair with a metallic silvery sheen. This syndrome was first reported as *neuroectodermal melanolysosomal* disease. Patients have severe developmental delay and mental retardation early in life. Many patients do not survive into the second decade of life. Microscopic examination of hair shafts reveals irregular clumps of pigment, similar to that seen in Griscelli syndrome type 2. Skin biopsy reveals an increased melanization of the epidermal basal layer detected with Fontana-Masson staining, due to the retention of melanin in melanocytes.

The gene underlying this disorder encodes myosin Va, a motor protein involved in the movement of melanosomes along actin filaments at the periphery of the melanocyte. When transport to the cell periphery is disrupted, melanin cannot be transferred to keratinocytes, resulting in a pigment dilution phenotype. The myosin Va protein is also found in brain tissue, functions in the short-range axonal/dendritic transport in neuronal cells, and binds to synaptic vesicles; the neurologic manifestations are likely due to impaired movement of intracellular organelles/vesicles in neuronal tissue.

Griscelli Syndrome, Type 3 The two patients reported in the literature to have Griscelli syndrome, type 3 (GS3), aged 16 and 12 years old, have only manifested hypopigmentation. Whether late-onset signs and symptoms involving other organs and systems will develop has yet to be determined. The gene underlying this disorder encodes melanophilin, which associates on melanosomes in a complex with Rab27a and myosin Va (see above); gene mutations result in a block in the transfer of melanin to neighboring keratinocytes; hypopigmentation results.

Disorders of Melanoblast Migration and Survival

These disorders cause "spotting," i.e. patches of white hair and/or unpigmented skin.

Waardenburg Syndrome Four genotypic variants of Waardenburg syndrome exist, with overlapping phenotypic features; all are autosomal dominant. Types 1 and 3 are caused by mutations in the PAX3 gene, encoding a transcription factor. Type 2 is caused by mutations in the MITF gene, also encoding a transcription factor, and type 4 is due to either a heterozygous mutation in the SOX10 gene (encoding a transcription factor), or homozygous mutations in the endothelin-3 (EDN3) or the endothelin B receptor (EDNR3) gene. These mutations impair the ability of melanoblasts to reach their final target sites (inner ear, eye, skin) during embryogenesis.

Patients with this syndrome have features of piebaldism, with a white forelock, hypopigmentation, premature graying, and other characteristic findings including synophrys, congenital deafness, dystopia canthorum (broad nasal root),

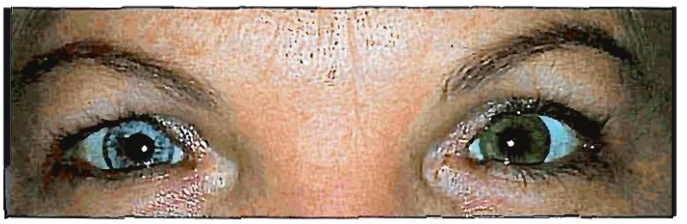

Fig. 36-8 Waardenburg syndrome with heterochromia irldis.

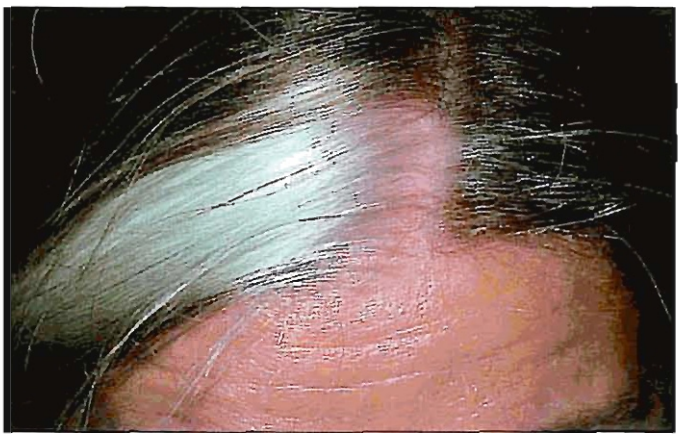

Fig. 36-9 Piebaldism, white forelock.

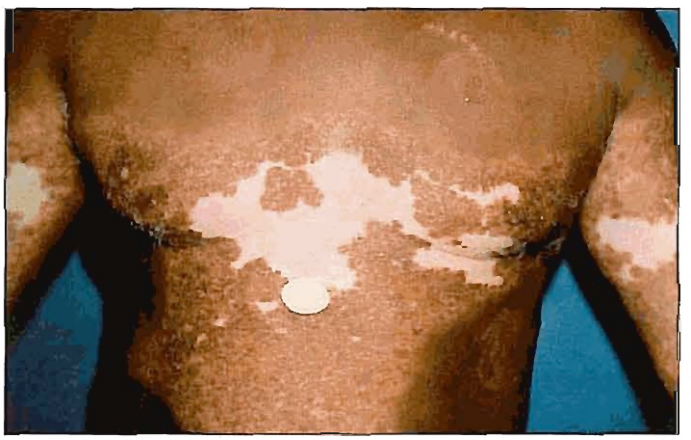

Fig. 36-10 Piebaldism, vitiligo-like depigmentation.

and ocular changes, including heterochromia irides (Fig. 36-8). Type 1 and 3 are both characterized by dystopia canthorum, but in type 1 white forelock and depigmented skin patches are more frequent while in type 3, limb anomalies occur. In type 2, no dystopia canthorum is observed, but hearing loss and heterochromia irides are more frequent. In type 4, aganglionic megacolon can occur.

Piebaldism Piebaldism is a rare, autosomal-dominant syndrome with variable phenotype, presenting at birth. The characteristic clinical features are a white forelock and patchy absence of skin pigment (Figs 36-9 and 36-10). The depigmented lesions are static and characteristically occur on the anterior and posterior trunk, mid-upper arm to wrist, mid-thigh to mid-calf, and shins. A characteristic feature of piebaldism is the presence of hyperpigmented macules within the areas lacking pigmentation and also on normally pigmented skin. The white forelock is a triangular or diamond-shaped midline white macule on the frontal scalp or forehead. The medial portions of the eyebrows and eyelashes may be white. Histologically, melanocytes are completely absent in the white macules.

Piebaldism is caused by mutations in the KIT gene, encoding a cell surface membrane receptor for the stem cell growth factor. The phenotypic differences between families are caused by different locations of mutations in the gene. A mild phenotype occurs in cases associated with mutations in the ligand-binding region, whereas more severe phenotypes occur from mutations in the tyrosine-kinase region of the receptor. The white lesions may respond to surgical corrections (see discussion under vitiligo).

Cross-McKusick-Breen Syndrome Also known as *Cross syndrome*, *oculocerebral-hypopigmentation syndrome*, or *hypopigmentation and microphthalmia*, this extremely rare disorder is characterized by white skin, blond hair with a yellow–gray metallic sheen, small eyes with cloudy corneas, jerky nystagmus, gingival fibromatosis, and severe mental and physical retardation. The genetic basis of Cross-McKusick-Breen syndrome remains undetermined.

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CHAPTER

37 Dermatologic Surgery

Dermatology has always been a surgically oriented field, including such procedures as curettage, biopsy, destruction, and excision. Over the years, the practice of dermatology has evolved to include a greater number and extent of surgical procedures. This evolution has been due to many factors, including dermatologists' greater understanding of cutaneous pathology and the fact that outpatient dermatologic surgery is more cost-effective, safer, and provides a greater degree of patient convenience. As a result, the American Board of Dermatology mandates certain surgical exposure and experience for all residents in dermatology residency programs. Furthermore, with the recent ACGME accreditation of Procedural Dermatology fellowships, dermatologic surgery has become recognized as a main stream medical option for patients. This chapter and Chapter 38 provide a survey of procedures, indications, and appropriate management within the spectrum of dermatologic surgery.

PREPARATION FOR SURGERY

Before any surgical procedure, preoperative evaluation should include a detailed medical history. Questions about drug allergies, medications, herbal supplements, presence of a pacemaker or implantable cardioverter-defibrillator, prior wound infections, recently implanted prosthetics, or history of endocarditis are critical in order to appropriately manage the surgical patient.

Anticoagulants

There is much debate regarding the role of antiplatelet and/or anticoagulants and surgical bleeding. Dermatologists are frequently presented with the dilemma of whether to discontinue blood thinners in the setting of surgery. Data suggest that continuous treatment with blood thinners perioperatively in patients undergoing Mohs and cutaneous surgery is not associated with an increase in surgical complications. However, discontinuation of these medications may increase the risk of cerebral and cardiovascular complications. Kovich and Otley reported a series of thrombotic complications in a group of patients who had discontinued aspirin or warfarin prior to surgery, including stroke, transient ischemic attack, myocardial infarction, pulmonary embolus, and death. Furthermore, West et al demonstrated that blinded cutaneous surgeons were unable to intraoperatively identify which patients were taking a blood thinning agent based on the subjective amount of surgical oozing. As such, it is recommended to maintain patients on all medically necessary blood thinners during cutaneous surgery. Patients taking aspirin for primary prevention may discontinue it 2 weeks prior to any surgical procedure.

Ginkgo, garlic, ginseng, ginger, and vitamin E may increase the risk of perioperative bleeding. As these herbal supplements are not medically necessary, patients should discontinue them for several weeks prior to undergoing dermatologic surgery.

Antibiotic Prophylaxis

Dermatologists performing cutaneous surgery are often faced with the decision of whether to prescribe prophylactic antibiotics. Wounds are categorized into four groups. Clean wounds (class I) are created on normal skin using clean or sterile technique. Examples include excision of neoplasms, noninflamed cysts, biopsies, and most cases of Mohs surgery. The majority of dermatologic surgery falls into this category. The infection rate of these wounds is less than 5%. Clean-contaminated wounds (class II) are created on contaminated skin or any mucosal or moist intertriginous surface, such as the oral cavity, upper respiratory tract, axilla, or perineum. The infection rate of these wounds is 10%. Contaminated wounds (class III) involve visibly inflamed skin with/without nonpurulent discharge and have an infection rate of 20% to 30%. Examples included inflamed cysts or traumatic wounds. Infected wounds (class IV) have contaminated foreign bodies, purulent discharge or devitalized tissue. Examples included necrotic tumors, ruptured cysts, or active hidradenitis suppurativa. These wounds have an infection rate of 40%.

Clean (class I) wounds do not require antibiotic prophylaxis. Antibiotics are not routinely required in clean-contaminated (class II) wounds in dermatologic surgery. It is preferable to treat infections as they arise, rather than expose all patients to antibiotics and the increased rate of drug-related adverse events. The exception to this would be those surgery cases which violate mucosal membranes (i.e. oral and nasal mucosa), anogenital and inguinal areas, patients with heavily colonized skin (i.e. atopic dermatitis or infected skin), patients with a history of prior wound infection, as well as in those patients in whom a wound infection would result in significant morbidity (Table 37-1). In contaminated (class III) and infected (class IV) wounds, antibiotics serve a therapeutic role and should be used.

First-generation cephalosporins are a good initial choice for the treatment of wound infection because of their coverage of staphylococcal organisms, common Gram-negative organisms such as *Escherichi coli*, and certain *Proteus* species. Macrolides are an alternative for patients who are allergic to penicillin or cephalosporins. Culture should be performed to identify the infectious agent and ensure that appropriate antibiotic therapy is used.

Risk factors associated with wound infections include impaired immune status, poor glucose control in diabetics, alcoholism, and chronic medical problems, such as renal failure or chronic obstructive pulmonary disease.

The American Heart Association (AHA) has divided patients into high, medium, and low endocarditis risk

Table 37-1 Antibiotic prophylaxis for heavily colonized or high risk patients

Situation	Antibiotic	Regimen (1 hour pre-operative dose)
Skin	cephalexin	1 g orally
	dicloxacillin	1 g orally
	clindamycin	300 mg orally
	vancomycin	500 mg IV
Oral/Respiratory mucosa	cephalexin	1 g orally
	amoxicillin	1 g orally
	clindamycin	300 mg orally
Gastrointenstial/Genitourinary mucosa	cephaexin	1 g orally
	trimethoprim/sulfamethoxazole	1 double strength tablet orally
	ciprofloxacin	500 mg orally

Box 37-1 Endocarditis risk

High-risk category
- Prosthetic cardiac valves
- Previous bacterial endocarditis
- Complex cyanotic congenital heart disease (e.g. single ventricle states, transposition of the great arteries, tetralogy of Fallot)
- *Surgically constructed systemic pulmonary shunts or conduits*

Moderate-risk category
- *Most other congenital cardiac malformations* (other than listed above)
- Acquired valvular dysfunction (e.g. rheumatic heart disease)
- Hypertrophic cardiomyopathy
- Mitral valve prolapse with valvular regurgitation or thickened leaflets

Low-risk category
- Physiologic heart murmurs
- Mitral valve prolapse without valvular regurgitation
- Cardiac pacemakers and implanted defibrillators
- Isolated secundum atrial septal defect
- Surgical repair of atrial septal defect, ventricular septal defect, or patent ductus arteriosus (without residua beyond 6 months)
- Previous rheumatic fever without valvular dysfunction
- Previous coronary artery bypass graft surgery
- Previous Kawasaki's disease without dysfunction

(Box 37-1). The AHA recommends that incision or biopsy of surgically scrubbed skin does not require antibiotic prophylaxis, even if the patient is categorized as being at high risk for endocarditis. However, if surgery is performed on contaminated or heavily colonized skin, and violates respiratory, oral, or genitourinary mucosa, antibiotics are indicated (Table 37-2). *Standard antibiotic recommendation* for endocarditis prophylaxis in procedures involving oral or respiratory mucosa is amoxicillin 2.0 g (in children, 50 mg/kg) 1 h prior to the procedure. Revised AHA guidelines do not require repeat antibiotic dosing several hours later. Cephalexin is an appropriate alternative for procedures involving skin only. Penicillin allergic patients can be treated with clindamycin 600 mg (in children, 20 mg/kg) at the same timepoints.

There are no formal guidelines regarding the use of antibiotics in patients with orthopedic prosthetic devices. Patients with joint replacement probably do not need prophylactic antibiotics for clean wounds. If mucosa is invaded, prophylaxis is appropriate and reasonable in these cases. Consultation with orthopedic surgery is appropriate in determining whether antibiotic prophylaxis is necessary.

Preoperative Antisepsis

Many surgical preparations are available. Alcohol is commonly used for minor clean procedures such as biopsies. However, since it has only weak antimicrobial activity, it is not recommended for more extensive sterile procedures. Chlorhexidine has a broad spectrum against Gram-positive and -negative organism, has a rapid onset of activity, sustained residual activity, and is nonstaining. Chlorhexidine has been reported to cause both ototoxicity and keratitis from direct ocular contact. However, this is mainly in patients under general anesthesia who cannot respond to immediate irritation associated with ocular contact. Betadine and all iodine-containing preparations are often irritating to the skin, leave a residual color, can be absorbed in very premature infants, and must dry before the procedure to act as an effective antimicrobial agent. Hexachlorophene should not be used on children or pregnant women, because of potential neurotoxicity and teratogenicity, respectively. Hydrogen peroxide has no significant antiseptic properties, and thus it is not suitable for sterile skin preparation.

If hair must be removed prior to surgery, this should be performed in a manner that does not leave open skin (i.e. cuts or scratches) which can serve as a conduit for infection. Preoperative shaving has been associated with a higher rate of bacterial infection secondary to cutting of the skin surface.

Anesthesia

Anesthetics work by blocking sodium influx into neurons and preventing depolarization and blockage of action potential. Small unmyelinated C-fibers, which carry pain and temperature, are more easily blocked than larger myelinated A-fibers, which carry pressure sensation and motor function. Local anesthetics are divided into two group, amides and esters, based on the structural linkage between the aromatic hydrophobic portion and the hydrophilic amine end. Amides are metabolized by hepatic microsomal enzymes. Esters are metabolized in plasma by pesudocholinesterase and excreted by the kidney. The workhorse anesthetic of dermatologic surgery is lidocaine. Longer-acting anesthetics, such as bupivacaine, are also employed for special procedures such as nerve and digital blocks.

Table 37-2

Situation	Antibiotic	Regimen (1 hour pre-operative dose)
Contaminated skin	cephalexin	Adults: 2 g; children: 50 mg/kg orally
	dicloxacillin	Adults: 2 g; children: 50 mg/kg orally
	clindamycin	Adults: 600 mg; children: 20 mg/kg orally
	vancomycin	Adults:1 g; children: 20 mg/kg IV
Oral/Respiratory mucosa	amoxicillin	Adults: 2 g; children: 50 mg/kg orally
	ampicillin	Adults: 2 g; children: 50 mg/kg IM/IV
	clindamycin	Adults: 600 mg; children: 20 mg/kg orally
	cephalexin	Adults: 2 g; children 50 mg/kg orally
	azithromycin/clarithromycin	Adults: 500 mg; children: 15 mg/kg orally
Gastrointestinal/Genitourinary mucosa		
High risk patients	ampicillin + gentamicin	Adults: 2 g + 1.5 mg/kg IM/IV
		Children: 50 mg/kg + 1.5 mg/mg IM/IV
	vancomycin + gentamicin	Adults: 1 g IV + 1.5 mg/kg IM/IV
		Children: 20 mg/kg IV + 1.5 mg/kg IM/IV
Moderate risk patients	amoxicillin	Adults: 2 g; children: 50 mg/kg orally
	ampicillin	Adults: 2 g; children: 50 mg/kg IM/IV
	vancomycin	Adults:1 g; children: 20 mg/kg IV

All local anesthetics, with the exception of cocaine and prilocaine, cause vasodilation due to relaxation of smooth muscle. This results in increased surgical bleeding and shorter duration of action as the anesthesia is cleared from the surgical site due to vasodilation. Epinephrine, which causes vasoconstriction, is often added to local anesthetics in order to decrease bleeding and increase duration of anesthesia. The vasoconstrictive effect of epinephrine takes 15 min for onset. Large amounts of epinephrine are contraindicated in patients with hypertension, hyperthyroidism, and pheochromocytoma, and in the digits. Epinephrine is safe to use in well vascularized areas, such as the ear, nose, and genitals.

Sodium bicarbonate (8.3%) can be added (1:10 ratio) in order to reduce the pain and burning associated with the lower pH of lidocaine. However, sodium bicarbonate can reduce epinephrine activity with time, thus requiring freshly mixed preparations on a regular basis.

The issues of maximum dosages are not well documented. Maximum dosage of anesthesia has traditionally been accepted as 5 mg/kg of 1% plain lidocaine and 7 mg/kg of 1% lidocaine with epinephrine. These numbers have been based on old industry-based studies, not found in the medical literature. Experience with tumescent liposuction has taught that dosages up to 55 mg/kg are well tolerated and safe in certain clinical situations. Bupivacaine has a greater risk of cardiac toxicity than lidocaine, because of its longer duration of action.

Allergic reactions to local amide anesthetics are quite rare. The metabolite *p*-aminobenzoic acid (PABA) is responsible for ester allergies. Therefore, ester types are rarely used today. There is no cross-reactivity between ester and amide classes of anesthetics. True systemic amide allergy is extremely rare. Thorough questioning of patients who report allergy often reveals a vasovagal reaction or epinephrine sensitivity. If local anesthetics use is precluded, intradermal injection with diphenhydramine can be used. Drowsiness can be a side effect when large doses of this agent are used. Bacteriostatic saline, with the benzyl alcohol preservative acting as the anesthetic agent, is often sufficient to provide brief anesthesia needed to perform small procedures.

Topical anesthetics can be effectively used for many laser procedures, as well as decreasing pain associated from pinpricks of local anesthesia. Eutectic mixture of 2.5% lidocaine and 2.5% prilocaine is one such agent. In addition, there are numerous lidocaine-containing products on the market. Prilocaine-induced methemoglobinemia has been reported in children due to the increased systemic absorption of prilocaine with certain topical products. All agents are applied thickly for about an hour prior to the procedure. The level of anesthesia obtained with these topical agents is often inconsistent.

Equipment

The choice of instruments and suture depends on the procedure being performed. Most simple, in-office biopsies are performed in a "clean" rather than sterile manner, and require minimal instrumentation. More complex excisional and reconstructive surgery is generally performed with sterile technique and employs a surgical tray with a wider range of instruments (Box 37-2). For procedures requiring sutures, absorbable material is used for deeper, layered closures, whereas surface sutures are generally nonabsorbable or fast-absorbing (Box 37-3). The large number of suture choices relates to both the type of procedure performed and anatomic location treated. Choices include absorbable and nonabsorbable, synthetic and nonsynthetic, monofilament and braided. All have appropriate applications and a detailed discussion is beyond the scope of this chapter. In general, for procedure requiring buried suture, a synthetic braided suture is the standard choice. The 50% tensile strength for this class of suture is about 3 months. Additionally, they are less palpable under the skin. For procedures on the trunk and extremities (i.e. areas under tension), a monofilament absorbable suture may be a better choice as the tensile strength may last for a greater length of time. The thicker skin in these areas may hide the palpability of this class of suture, making it more acceptable to patients. Epidermal approximation in more delicate areas is more appropriately closed with smaller 5-0 or 6-0 sutures. Absorbable sutures (i.e. gut), may be considered in sensitive areas where suture removal may be painful or difficult (i.e. eyelids) and children. Facial sutures are often taken out in 4 to 7 days to decrease the chance of forming track marks from epitheliazation of the

Box 37-2 Cutaneous surgical instruments and supplies

- Scalpel handle (flat No 3)
- Blade (No 15)
- Needle holder (appropriate size)
- Sharp curved iris scissors, tissue cutting scissors
- Blunt undermining scissors
- Skin hook (dull tipped, 2–4 prong)
- Hemostats
- Forceps (1 × 2 teeth, with suture platform)
- Skin preparatory scrub in sterile basin
- Sterile towels
- Sterile gauze and cotton-tipped swabs
- Hyfrecator cover
- Suture
- Suture scissors
- Blade remover

Box 37-3 Examples of common skin suture material

Absorbable	
■ Gut (chromic, plain)	*twisted*
■ Polyglycolic acid (Dexon®)	*braided*
■ Polygalactin 910 (Vicryl®)	*braided*
■ Polydioxanone (PDS®)	*monofilament*
■ Polytrimethylylene carbonate (Maxon®)	*monofilament*
■ Poliglecaprone 25 (Monocryl®)	*monofilament*
■ Glycomer 631 (Biosyn®)	*monofilament*
Nonabsorbable	
■ Silk (braided)	
■ Nylon (Ethilon®, Dermalon®)	*monofilament*
■ Nylon (Surgilon®, Nurolon®)	*braided*
■ Polypropylene (Prolene®, Surgipro®)	*monofilament*
■ Polyester (Ethibond®, Mersilene®, Dacron®)	*braided*
■ Polybutester (Novafil®)	*monofilament*

suture puncture site, whereas sutures on the scalp, neck, and body are often left in for 2 weeks. Running subcuticular sutures can be left in for 3 weeks to add tensile strength to wounds without the risk of track marks.

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Kovich O, Otley CC: Thrombotic complications related to discontinuation of warfarin and aspirin therapy perioperatively for cutaneous operation. J Am Acad Dermatol 2003;48:233.

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BIOPSIES

When performing a skin biopsy, the clinician should consider the lesion, reason for biopsy (e.g. diagnostic versus cosmetic), and site. Shave biopsies can range from a superficial scissor snip of an epidermal growth to deep shave excisions of papillary dermal processes. Punch biopsies are most often used for dermal lesions, sampling deeper than shave biopsies, but requiring sutures. Excisional biopsies remove an entire clinical lesion and are the biopsy of choice for pigmented lesions suspicious for melanoma. Incisional biopsies remove a portion of a clinical lesion and are often performed on larger plaques or patches when an excisional biopsy is not cosmetically acceptable or feasible. A wedge biopsy is a deep incisional biopsy that can sample pathologic tissue and adjacent normal tissue, and is especially useful for pathologic *diagnosis of certain inflammatory conditions (e.g.* panniculitis, fasciitis).

Shave biopsies are best suited for pedunculated, papular, or otherwise exophytic lesions. However, using a deep or rolled shave, samples can also be obtained of macular or indurated lesions, provided the necessary histologic changes reside in the epidermis or papillary dermis. Infiltration of local anesthesia distends and elevates the lesion, increases skin turgor, affords greater resistance to the blade, and facilitates undercutting the lesion. Using either a 15 blade scalpel or a razor blade, which can be flexed to achieve the desired depth, a horizontal incision is made and the lesion removed with sweeping strokes (Fig. 37-1). Hemostasis is

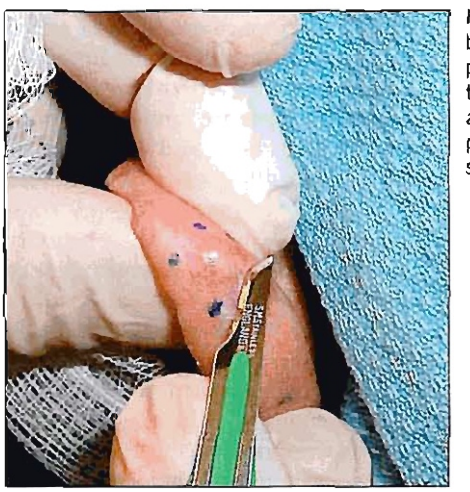


Fig. 37-1 Shave biopsy, lesion is pinched up with thumb and finger and biopsy performed with sweeping strokes.

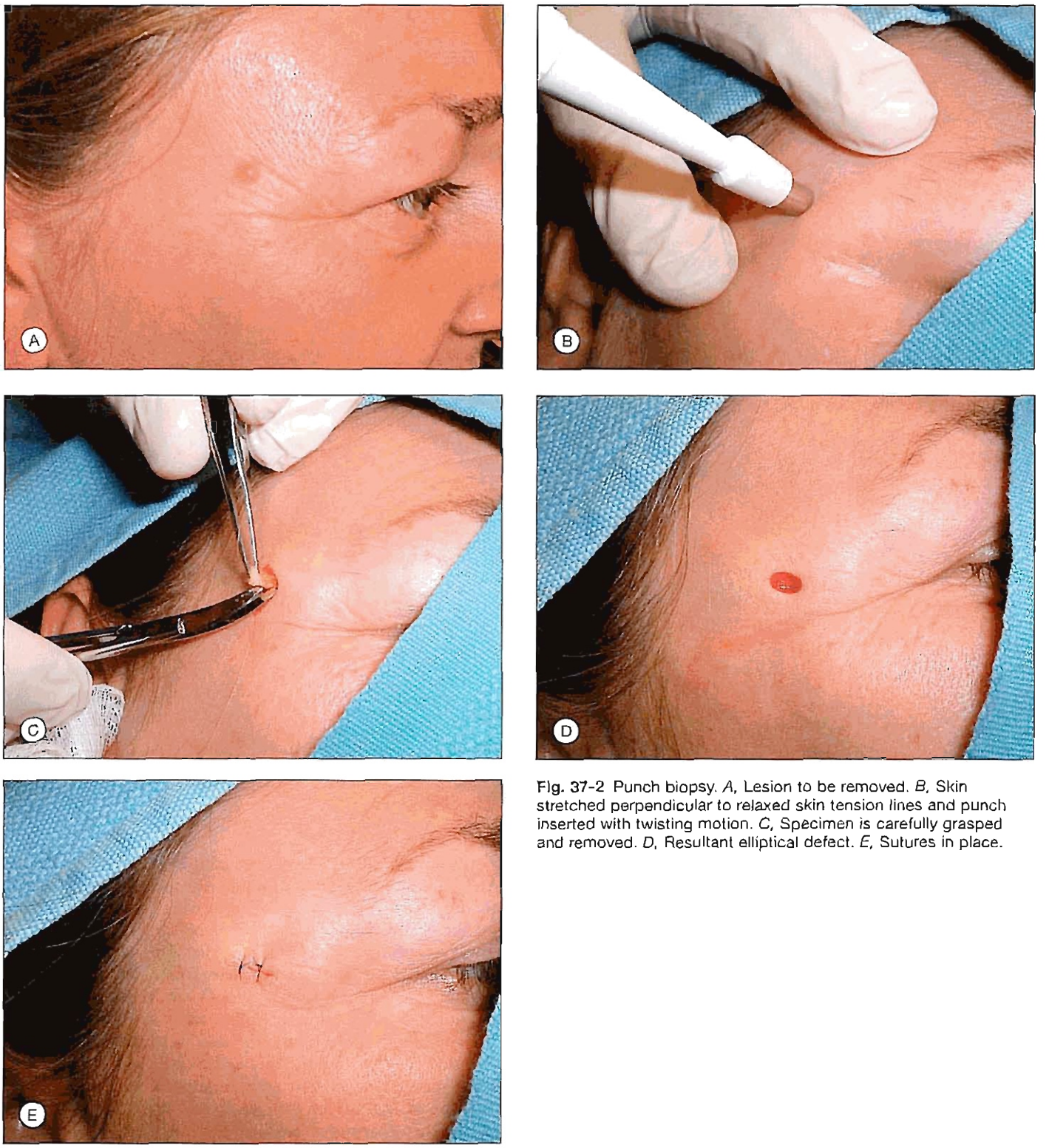


Fig. 37-2 Punch biopsy. *A*, Lesion to be removed. *B*, Skin stretched perpendicular to relaxed skin tension lines and punch inserted with twisting motion. *C*, Specimen is carefully grasped and removed. *D*, Resultant elliptical defect. *E*, Sutures in place.

easily attained with 35% aluminum chloride solution. Sharp scissor excision is a variant of shave excisions and is best suited for pedunculated lesions.

The dermatologic punch is commonly used for both excisional and incisional biopsies (Fig. 37-2). When performing a punch biopsy, the skin should be stretched perpendicular to the relaxed skin tension lines. The elliptical wound resulting from the release of the tension can be suture closed in a linear fashion without redundancy or puckering associated with circular wounds. The punch is placed on the skin perpendicular to the surface. While applying gentle pressure, it is rotated back and forth and advanced to the hub. The specimen is carefully grasped to avoid crush artifact and the base is cut.

Narrow hole extrusion is a surgical technique that uses a punch biopsy to make a small cutaneous portal through which larger benign growths (e.g. lipoma) can be extruded (Fig. 37-3). This technique allows the evacuation of large subcutaneous growths with a relatively small surface incision.

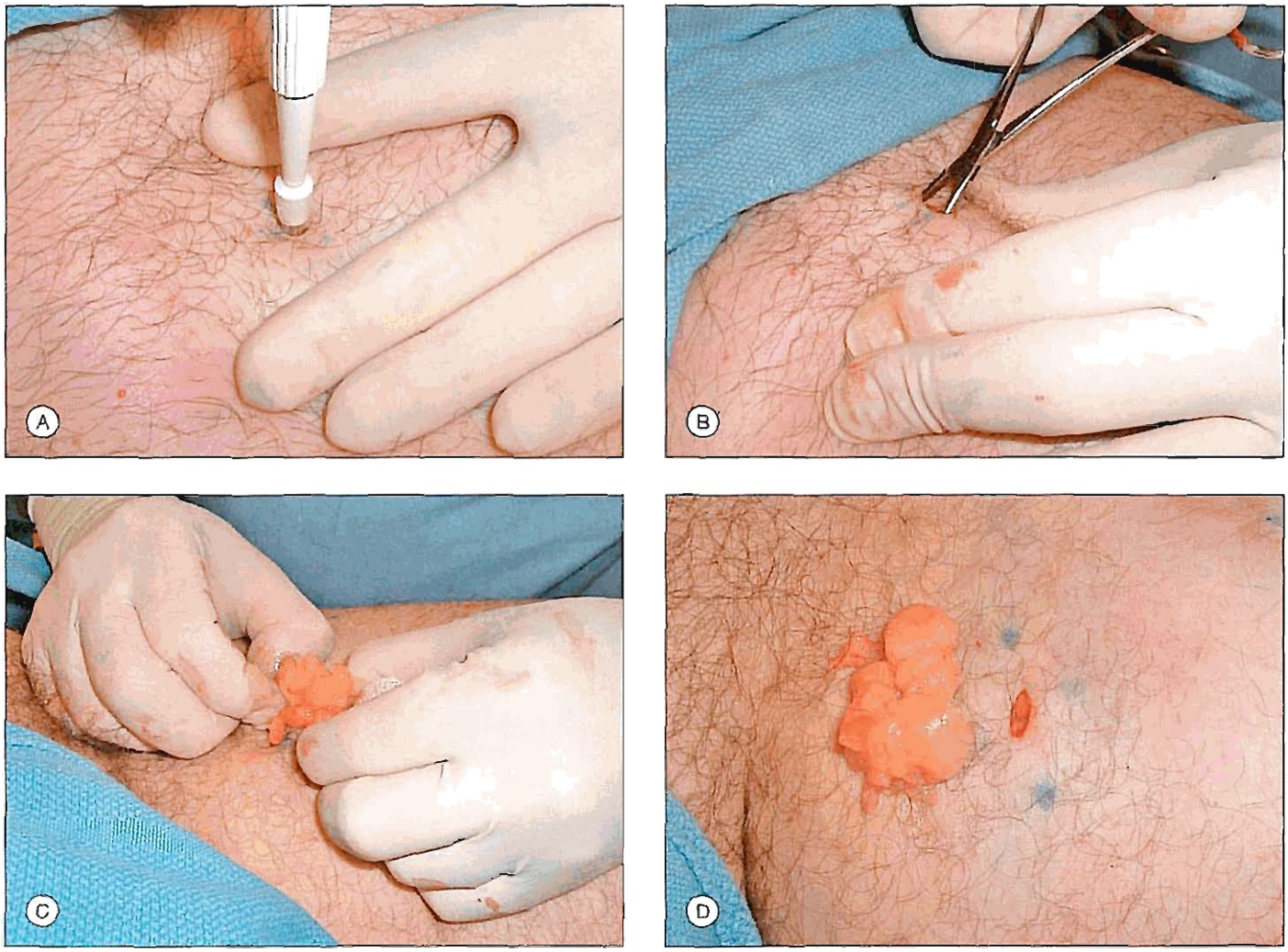


Fig. 37-3 Narrow hole extrusion of lipoma. *A*, 4 mm punch in center of lipoma. *B*, Hemostat used to loosen lipoma. *C*, Extrusion of lipoma through narrow hole. *D*, Entire lipoma removed.

CRYOSURGERY

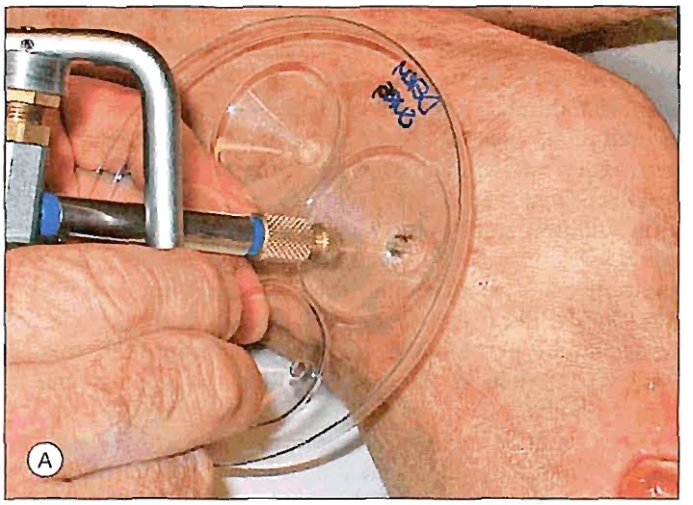
Cryosurgery is used for the treatment of numerous benign, premalignant, and malignant skin lesions. This modality is extensively used by almost every dermatologist owing to its ease of use, cost-effectiveness, and versatility. Postoperative wound care is relatively simple and complications are infrequent. Although a number of cryogens have been used (including ethyl chloride, CO_2, and NO), liquid nitrogen, with a boiling point of –195.6° C, is most widely utilized.

The mechanism of injury in cryosurgery is the result of multiple factors, including mechanical damage to cells resulting from intra- and extra-cellular ice crystal formation, exposure to high electrolyte concentrations in surrounding nonfrozen or thawing fluid, recrystallization patterns during thaw, and ischemia caused by vascular stasis and damage. Rapid freezing causes intracellular ice crystals which are more destructive than the extracellular crystals formed during slow freezing. Tissue damage is maximized with a slow thaw time, which causes increased solute gradients and greater cell destruction. Multiple freeze–thaw cycles can further increase damage to the target lesion.

There are several techniques for cryosurgery. The simplest is the use of a cotton-tipped applicator. Varying the amount of pressure applied and the length of contact by the applicator to the skin can control the depth of freeze. Additionally, the volume of liquid nitrogen can be increased or decreased by adding or removing cotton from the applicator tip. As viruses have been shown to survive in liquid nitrogen, cotton-tipped applicators should never be reintroduced to the storage container. Rather, a small amount of liquid nitrogen should be transferred to an individual container and discarded after use.

Spray application is one of the most commonly used methods of cryosurgery. This technique uses a hand-held liquid nitrogen spray unit with an adjustable nozzle to vary the size of the stream delivered. An insulating cone or a disposable otoscope speculum can be used to focus the delivery of liquid nitrogen, resulting in a deeper freeze and finer control (Fig. 37-4).

Basal cell carcinomas (BCCs) can effectively be treated with cryosurgery. Freezing to reach a target temperature of approximately –50° C, as measured by a thermocouple, is appropriate for management of these tumors. This translates to a thaw time of approximately 60 seconds, with a freeze margin of approximately 5 mm (Fig. 37-5). It is important to recognize that the pain associated with such treatment requires local anesthesia. In a review of published data, Kokoszka et al found a recurrence rate of less than 10% for



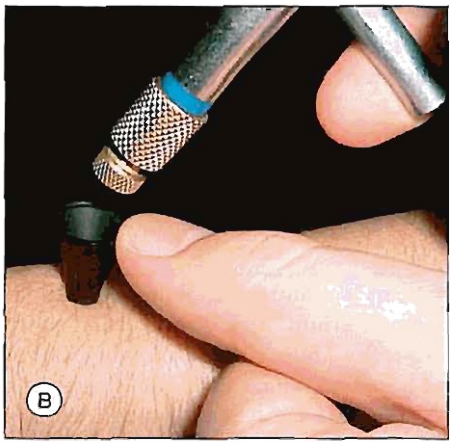
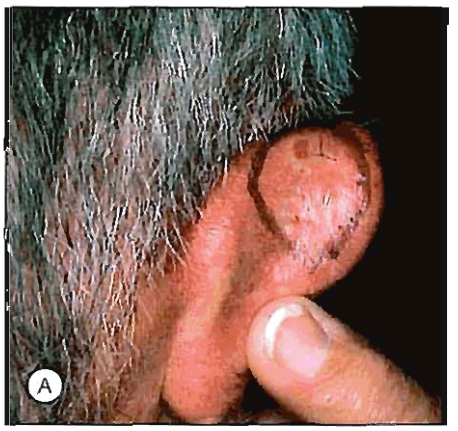
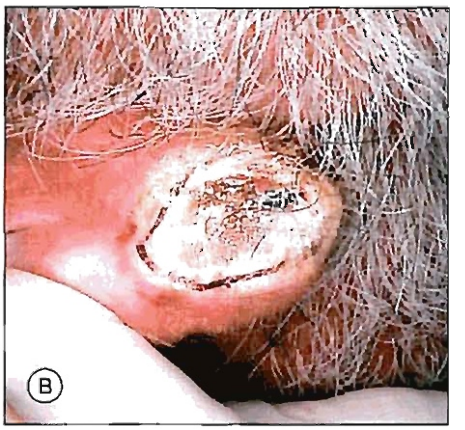
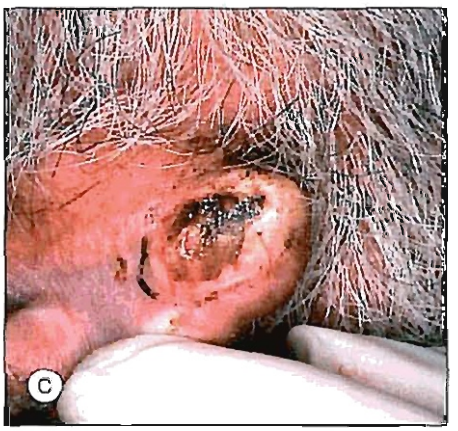


Fig. 37-4 *A*, Cryoplate with multiple sized openings. *B*, Disposable otoscope speculum with tip cut off.







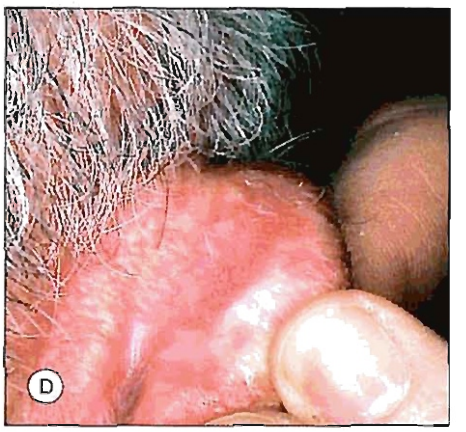


Fig. 37-5 Cryosurgery. *A*, Basal cell carcinoma on the posterior helix. *B*, Cryosurgery to neoplasm. *C*, 1 week later with necrosis and sloughing of treatment area. *D*, Final result several months later.

primary small, noninfiltrating (i.e. superficial and nodular) BCC treated with cryosurgery. Some have suggested that initially treating the tumor with curettage, following this with cryosurgery with a 1-min thaw time, can lead to cure rates consistent with curettage and electrodessication.

Side effects of cryosurgery are similar to other ablative procedures (i.e. curettage and electrodessication), and include blistering, crusting, pain, a 3- to 4-week healing period, and scaring. As melanocytes are more susceptible to thermal damage than keratinocytes, hypopigmentation can often be seen, especially in individuals with darker skin tones. While pigment alterations are more frequently seen with longer freeze–thaw times, these changes can be observed even with very brief treatment cycles. A self-limited hyperplastic or pseudoepitheliomatous healing response may occur approximately 2 to 4 weeks after freezing. Nerve injury can occur during cryosurgery. Anatomic locations with superficial nerves (e.g. lateral aspects of the fingers, ulnar groove of the elbow, pre- and post-auricular skin) are especially susceptible to this complication. Techniques to limit this risk include tenting the skin up and away from the nerve, ballooning the skin with lidocaine, or sliding the skin back and forth over the underlying fascia during treatment. Alopecia can occur when treating hair-bearing areas. Both atrophic and hypertrophic scars can be seen following cryosurgery.

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CURETTAGE

The curette has long been a standard tool in the dermatologist's surgical armamentarium. This round, semi-sharp knife is available in sizes from 0.5 to 10 mm, allowing for the removal of a variety of lesions. Since it is not as sharp as a scalpel, the curette does not easily cut through normal epidermis and will not enter the dermis. Therefore, it is best suited for use on soft or friable lesions, such as warts, seborrheic and actinic keratoses, the papules of molluscum contagiosum, or selected basal and squamous cell carcinomas. The proper selection of lesion, its location, and the size of the curette, combined with the surgeon's technique, all play a role in both the therapeutic and cosmetic outcome.

The skin should be stabilized with the nondominant hand while the curette is held like a pencil. Curettage should be performed in a centripetal manner (from the outside in) to avoid stripping sun-damaged skin and creating a larger wound. To ensure complete excision, curettage should be performed in multiple directions to produce symmetrical wound margins. A large curette is used for initial debulking, followed by a smaller curette to remove any residual foci or extensions. Curettage is complete when the "gritty," firm sensation of normal dermis is felt and slight punctuate dermal bleeding occurs.

Curettage, combined with electrodessication (C&E), is widely used for the treatment of BCC and squamous cell carcinomas (SCC) (Fig. 37-6). Silverman et al reviewed the cure rates of primary BCC treated with C&E over a 27-year period at New York University. This experience stratified low-, middle-, and high-risk anatomic locations and the risk of recurrence following C&E of primary BCC. Low-risk anatomic sites (neck, trunk, and four extremities) had a 5-year recurrence rate of 3.3%. Middle-risk sites (scalp, forehead, pre- and post-auricular, and malar areas) had an overall recurrence rate of 12.9%, but this was reduced to 5% when limited to noninfiltrative carcinomas of less than 1 cm. High-risk sites (nose, paranasal, nasal–labial groove, ear, chin, mandibular, and peri-oral and -ocular areas) had an overall recurrence rate of 17.5%, but a more acceptable 5% recurrence rate was achieved when treatment was limited to lesions of less than 6 mm.

In addition to size and anatomic location, the histologic subtype is an important factor in the effectiveness of C&E. Infiltrative and micronodular carcinomas are not appropriate for C&E, while it is a therapeutic option in superficial and nodular subtypes. SCC in situ may be appropriately treated with C&E, while invasive SCC would not be amenable to this modality.

There is little agreement regarding the requisite number of cycles of C&E. Indeed, treating all lesions identically with a particular number of cycles may lead to overtreatment of some lesions and undertreatment of others. In general, accepted therapy employs three cycles to treat most malignant lesions. However, smaller superficial malignancies may be treated with fewer cycles; the rational is to improve cosmetic outcome, while still achieving acceptable cure rates. Nonetheless, the success of C&E relies on the operator's ability to identify by feel and appearance the tissue to be ablated. Kopf et al demonstrated that physician experience is an important factor in the cure rate of carcinomas treated by C&E, with residents having a higher rate of recurrence as compared to attendings. Finally, C&E should be replaced by excision if curettage extends into subcutaneous tissue. As such, lesions that have been biopsied using a punch which has extended into the subcutaneous fat, may be less amenable to C&E.

Goldman G: The current status of curettage and electrodesiccation. Dermatol Clin 2002;20:569.

Kopf AW, et al: Curettage–electrodesiccation treatment of basal cell carcinomas. Arch Dermatol 1977;113:439.

Sheridan AT, Dawber RP: Curettage, electrosurgery and skin cancer. Australas J Dermatol 2000;41:19.

Silverman MK, et al: Recurrence rates of treated basal cell carcinomas. Part 2: Curettage–electrodesiccation. J Dermatol Surg Oncol 1991;17:720.

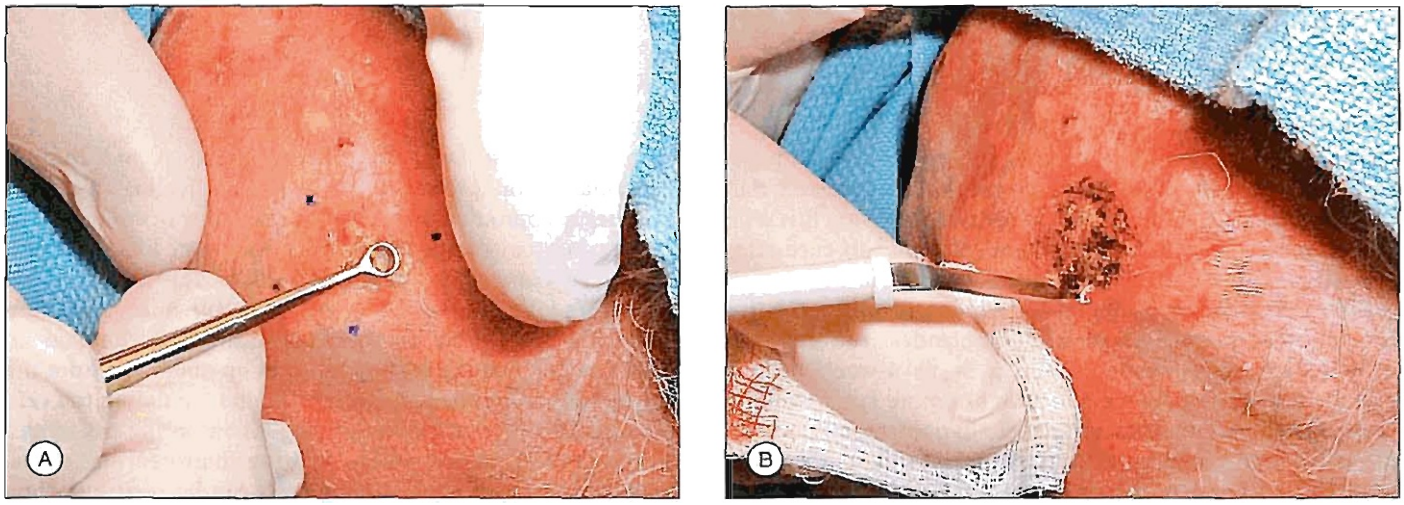

Fig. 37-6 Curettage and electrodessication. A, Curettage of squamous cell carcinoma in situ. B, Electrodessication immediately following.

60Hz Alternating current		Unaltered sine wave	
Spark gap circuit			
Modality	Electrode configuration		Waveform
Electrodesiccation	Monoterminal	Markedly damped	
Electrofulguration	Monoterminal	Markedly damped	
Electrocoagulation	Biterminal	Moderately damped	
Electronic circuit			
Modality	Electrode configuration		Waveform
Electrocoagulation	Biterminal	Partially rectified	
Electrosection, with coagulation	Biterminal	Fully rectified	
Electrosection, pure cutting	Biterminal	Fully rectified, filtered	

Fig. 37-7 Electrosurgery waveforms.

ELECTROSURGERY

Electrosurgery comprises a variety of surgical techniques, applications, and apparatus. In general, the tissue effect is created by heat delivered to or generated in the tissue as a result of an electrical current. Some form of electrosurgery is routinely used by dermatologists for destruction, hemostasis, excisions, and cosmetic procedures. An understanding of the different modalities and their applications can improve the surgical outcome (Fig. 37-7).

Electrocautery

Electrocautery is most often performed today with battery-powered, hand-held, disposable units. Direct current is passed through a metal treatment tip. Resistance to the flow of current causes heat to be generated, which can be adjusted by the intensity of the current. Hemostasis is achieved by direct heating of the tissue; no electrical current passes through the patient. As such, this device may be considered in patients with implantable devices sensitive to electric current.

Electrodesiccation, Electrofulguration

Electrodesiccation (from the Greek *dessicate*, meaning "dry") and electrofulguration (from the Greek *fulgur*, meaning "lightning") represent the most commonly employed uses of electrosurgery in dermatology. In electrodesiccation, the electrode tip is in contact with the tissue; with electrofulguration, a 1- to 2-mm separation between the tip and the tissue produces a spark. Electrodessication causes a deeper wound, while electrofulguration is more superficial.

A highly damped (decreasing amplitude) waveform is produced, of high voltage and low amperage produced by a spark-gap generator. As this is a monoterminal current, a grounding electrode on the patient is not required. Electrodesiccation/fulguration produces superficial destruction as the carbonization on the treated surface limits damage to deeper tissue.

This type of electrosurgery has numerous applications in the daily practice of dermatology. Superficial, small dermal tumors, such as syringomas or seborrheic keratoses, may be treated with electrodesiccation. Insertion of the fine epilating needle into the tumor is followed by the application of low current until a surface bubbling occurs. The small amount of char is then removed with a curette, resulting in a smooth surface appearance. In addition, skin tags, warts, and fine telangiectases may all be effectively removed by this technique. Electrodesiccation or fulguration is commonly employed in treatment of many BCCs and SCCs (see above section on curettage). It is also useful in excisional surgery to obtain hemostasis. The field must be dry, since the destruction by this current is superficial and will not be transmitted through blood.

Electrocoagulation

Electrocoagulation employs moderately damped current with a lower voltage and higher amperage. The patient is incorporated into biterminal circuit. Electrocoagulation causes greater tissue damage and deeper penetration than electrodessication or electrofulguration.

Electrosection

Electrosection employs an undamped, low-voltage, high-amperage current in a biterminal fashion. This technique has the advantage of cutting with simultaneous hemostasis. As such, it is used for bloodless excisional surgery of protuberant masses and growths, such as rhinophyma. There is vaporization of tissue with little heat spread. Care must be taken with this technique, as maintaining an appropriate depth can be difficult given the ease with which the device

can cut through skin. When properly used, fine surgical excisions can be produced with minimal trauma to surrounding tissue and excellent hemostasis. Various handpiece attachments, including scalpels, needles, wire loops, and balls, can further adapt the instrument to the specific procedure.

Care must be taken when using electrosurgery in a patient with a pacemaker or implantable cardioverter-defibrillator, especially if the procedure is performed within a few centimeters of the device. Although modern devices are better shielded and less likely to respond to external electrical interference, it is always prudent to deliver current in short bursts of less than 5 s. Additionally, consideration should be given to the use of electrocautery (heat only, no electrical transmission) or a bipolar device (current transmitted between two tips) when treating these patients. Yu et al recently reviewed the use of electrosurgery in patients with cardiac devices and offer a complete discussion of the subject.

Aferzon M, Millman B: Excision of rhinophyma with high-frequency electrosurgery. Dermatol Surg 2002;28:735.

El-Gamal HM, et al: Electrosurgery, pacemakers and ICDs: a survey of precautions and complications experienced by cutaneous surgeons. Dermatol Surg 2001;27:385.

LeVasseur JG, et al: Dermatologic electrosurgery in patients with implantable cardioverter-defibrillators and pacemakers. Dermatol Surg 1998;24:233.

Rex J, et al: Surgical management of rhinophyma: report of eight patients treated with electrosection. Dermatol Surg 2002; 28:347.

Wagner RF Jr: Medical and technical issues in office electrolysis and thermolysis. J Dermatol Surg Oncol 1993;19:575.

Yu SS, et al: Cardiac devices and electromagnetic interference revisited: new radiofrequency technologies and implications for dermatologic surgery. Dermatol Surg 2005;31:932.

EXCISIONAL TECHNIQUE

The fusiform or elliptical excision is the workhorse procedure used to treat invasive skin cancers as well as benign skin lesions needing extirpation (Fig. 37-8). The basic principle of the fusiform ellipse is excision of a specimen oriented with its longest axis along skin tension lines and its width not exceeding one-third of its length. The ellipse can be curved in a crescentic or "lazy-S" pattern to better align the final scar with skin tension lines. If performed with the correct dimensions (usually length-to-width ratio of 3:1) and a 30° angle at each pole, standing cutaneous cones at the two extremes of the excision is generally avoided. Standing cutaneous cones represent excess tissue bunching at the poles of a skin closure and should be "sewn out" or excised by triangulation or M-plasty if needed. Undermining, using sharp or blunt dissection of the skin from underlying subcutaneous tissue, reduces wound tension and creates wound edge eversion.

SKIN FLAPS AND GRAFTS

Choosing whether to close a wound by linear closure, local skin flap, skin graft, or allow it to heal by second intention can be complex. Important considerations include patient concerns, local tissue movement, consideration of adjacent anatomic structural preservation and function, and cosmetic outcome.

Second Intention

Years ago, second intention healing was common and accepted. In the current medical climate, patients desire more cosmetically elegant reconstruction. As there is contraction in wound healing, wounds that are adjacent to a free margin may result in a pull and distortion. This may effect surrounding anatomic structures (i.e. pull on a nasal rim or eyelid). The wounds may heal with hypertrophic or pigmentary changes. However, there are areas and situations where allowing a wound to heal by second intention is appropriate. These include superficial wounds in concave areas (i.e. medial canthus, conchal bowl, and junction between the nose and cheek) or certain clinical situations, such as elderly or frail patients without cosmetic concerns. Wound care is simple and postoperative restrictions are minimized.

Flaps

Local skin flaps are geometric segments of tissue contiguous with a skin defect that are advanced, rotated, or transposed to close a wound. Advantages of flaps include better approximation of skin texture and color, hiding incision lines, redirecting tension vectors, and covering exposed cartilage and bone. Flap survival is based on the preservation of the random blood supply along the pedicle. It is important to consider both the primary movement of the flap (the actual movement of the flap into the defect) and secondary movement (movement of surrounding tissue in reaction to the flap movement) (Fig. 37-9).

An advancement flap moves almost entirely in one linear direction (Fig. 37-10). Variations of this flap are often named by the appearance of the final defect and are frequently termed the O-T, O-L, O-Y, and island pedicle flap (Fig. 37-11). The rotation flap is often used to close large defects when there is insufficient tissue laxity (Fig. 37-12). The flap has the advantage of good survival secondary to the large pedicle and the ability to borrow skin from a great distance. A back cut can be used to reduce pivotal restraint and provide greater tissue movement, but may compromise the vascular pedicle. Variations include O-Z (Fig. 37-13) or dorsal nasal rotation flap (Fig. 37-14). Advancement and rotation flaps are best described as sliding flaps which are pulled into position over the primary defect in either a linear (advancement) or arcuate (rotation) manner. Tension vectors resulting from this pulling action are directed 180° back in advancement flaps or along the arc of rotation in reverse fashion for rotation flaps.

In the case of the transposition flap, the flap in elevated, transposed over intervening tissue, and sutured into the primary defect (Fig. 37-15). The tension vector is directed across the closure of the secondary defect (i.e. the area originally occupied by the flap), and thus is a useful flap to redirect the wound tension. The prototype of this flap is the rhombic flap (Fig. 37-16). Other examples include bilobed flaps, nasolabial/melolabial flaps, banner flap, Z-plasty, and Webster's 30° flap (Fig. 37-17).

Choice of a particular type of flap must take multiple factors into consideration, including location of defect, availability of tissue movement, surrounding structures, effects of tissue movement, and blood supply. Full discussion of flaps is available in multiple referenced texts and decisions regarding their use requires appropriate and extensive training.

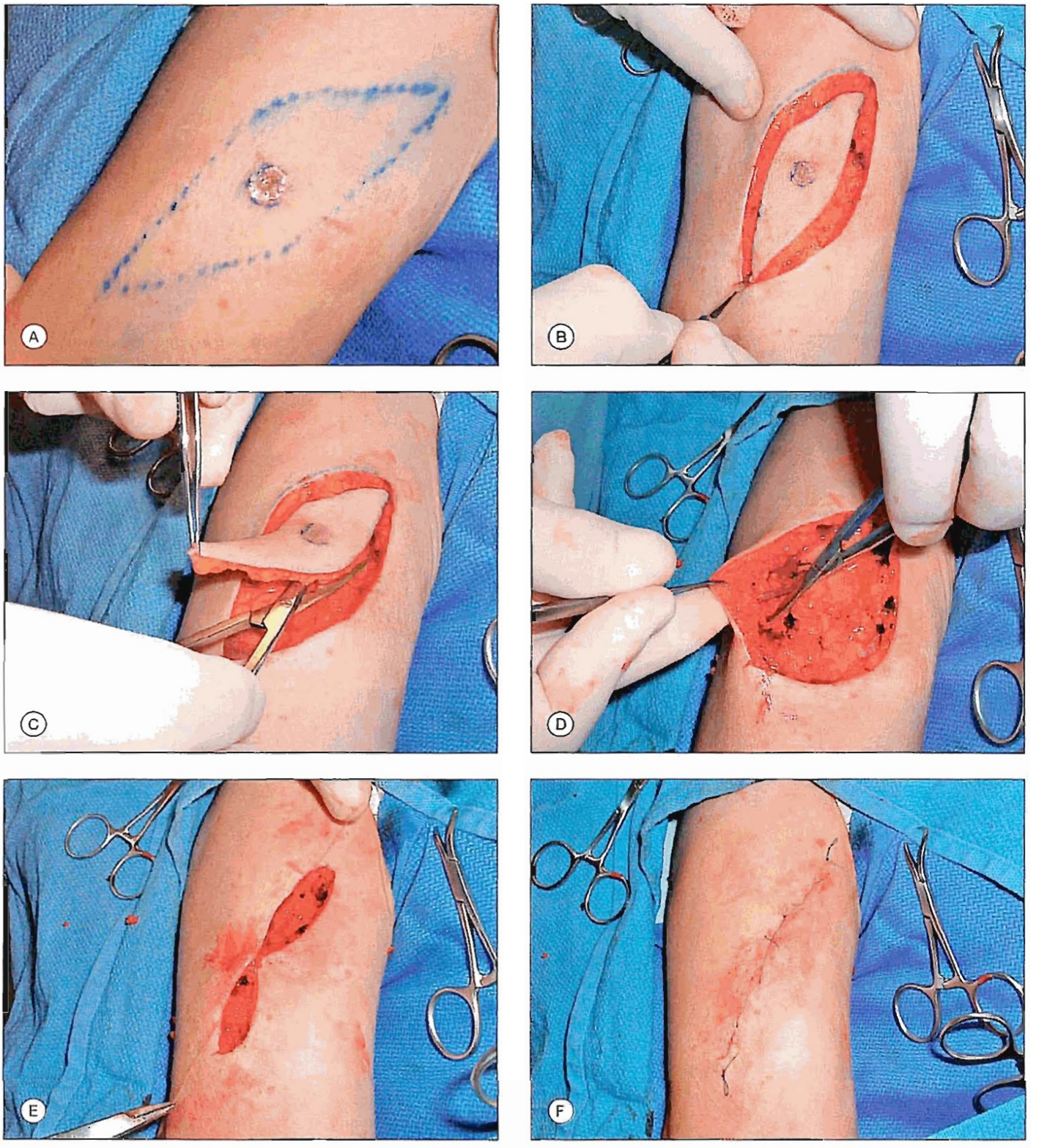

Fig. 37-8 Elliptical excision. *A*, Ellipse is designed along relaxed skin tension lines with a 3:1 length-to-width ratio. *B*, Incision made into subcutaneous tissue. *C*, Removal using tissue scissors in even plane. *D*, Blunt undermining of skin edges using skin hook. *E*, Buried interrupted tension-bearing absorbable sutures placed. *F*, Epidermal approximation using nonabsorbable running subcuticular sutures, with interruption in center of wound for easier removal.

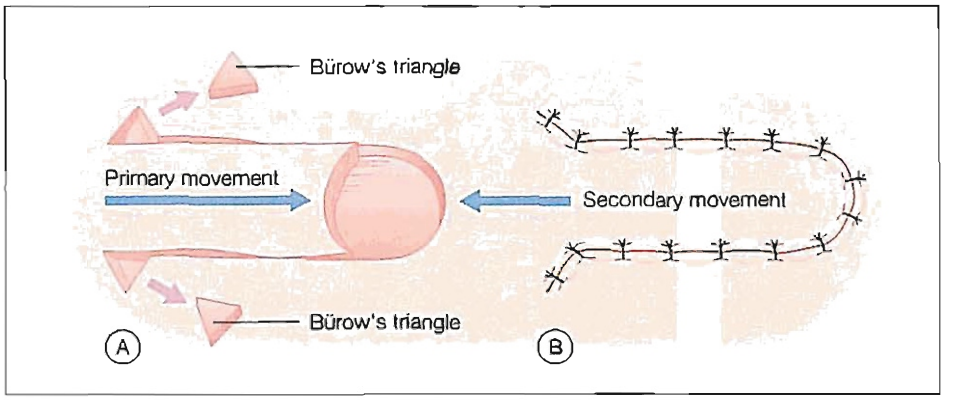

Fig. 37-9 Diagrams of flaps.

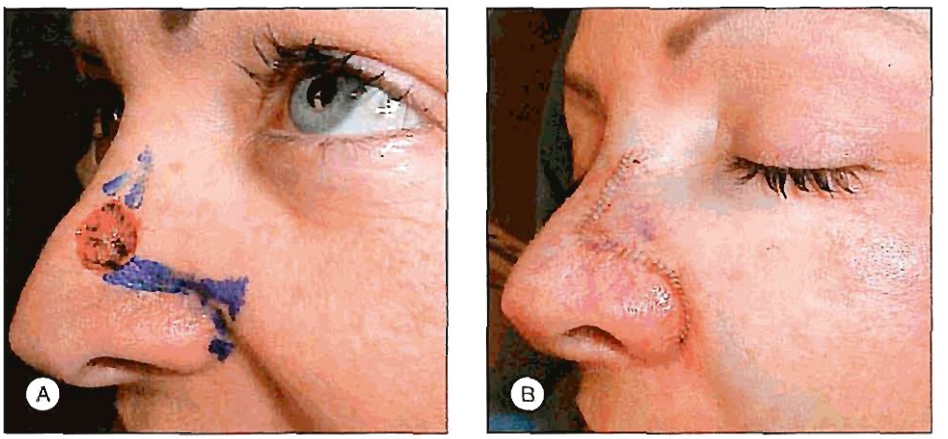

Fig. 37-10 Single arm advancement flap. *A*, Advancement flap designed on nasal sidewall. *B*, Final wound closure.

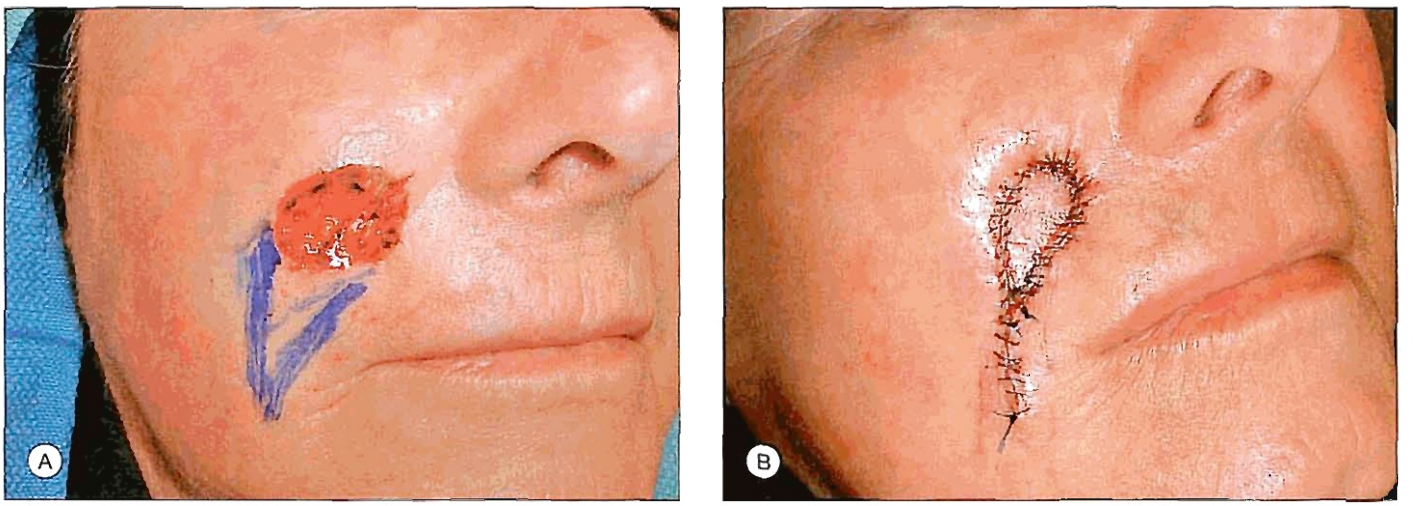

Fig. 37-11 Island pedicle flap. *A*, Island pedicle flap designed. *B*, Final wound closure.

Skin Grafts

Skin grafts are employed when primary closure or flap closure is not an available option. By definition, a graft is completely excised from the donor site and is devitalized (i.e. no intrinsic blood supply). Success is predicated on the reattachment of vascular supply to the graft from the defect. Grafts offer the advantage of less local scaring as compared to local flaps. However, the lack of color and texture match due to the remote donor location of grafts is a potential disadvantage.

Grafts can be categorized as full, split, and composite. Choice for using each of these depends on the depth of the defect, vascular supply, and concern of recurrence of skin cancer. Full-thickness skin grafts have a full dermis and are the most common grafts used in dermatologic surgery. The graft is defatted, trimmed to fit the defect, anchored in place with peripheral and basting sutures, and secured with a tie-over dressing (Fig. 37-18).

Split thickness skin grafts have only a partial dermis and are useful for covering large areas or for improved surveillance in tumors with a high risk of recurrence (Fig. 37-19 and 37-20). In comparison to full-thickness skin grafts, they have a higher rate of survival, shorter healing time, do not require repair of the donor site, and are a good choice for poorly

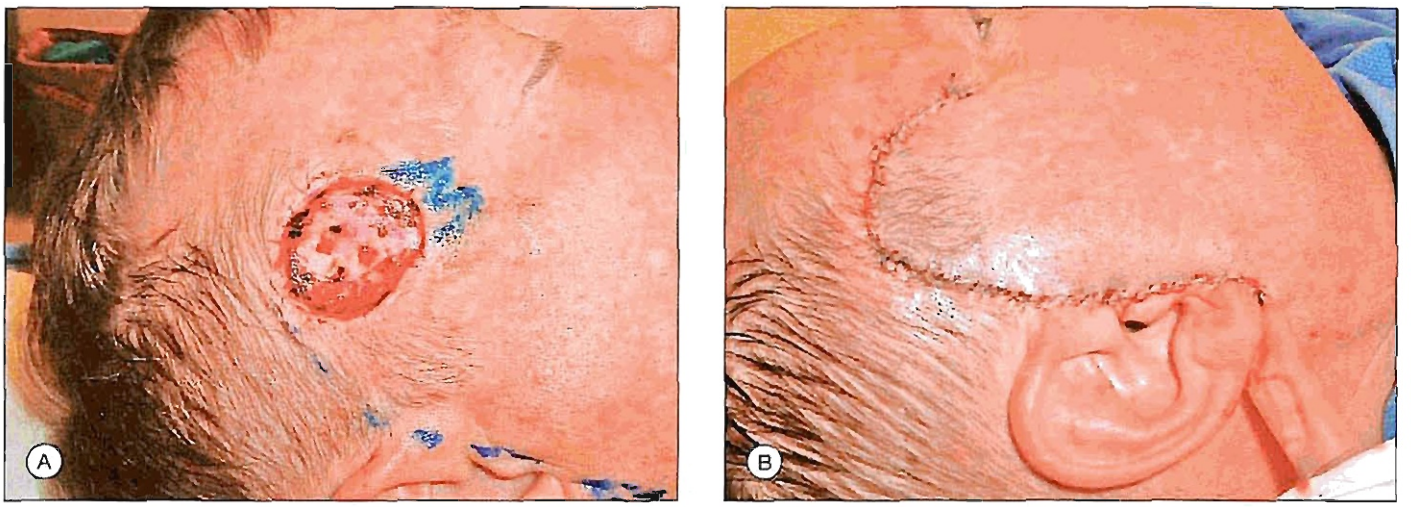

Fig. 37-12 Rotation flap. A, Rotation flap designed. Redundant skin from cheek is borrowed to repair defect. B, Final wound closure.

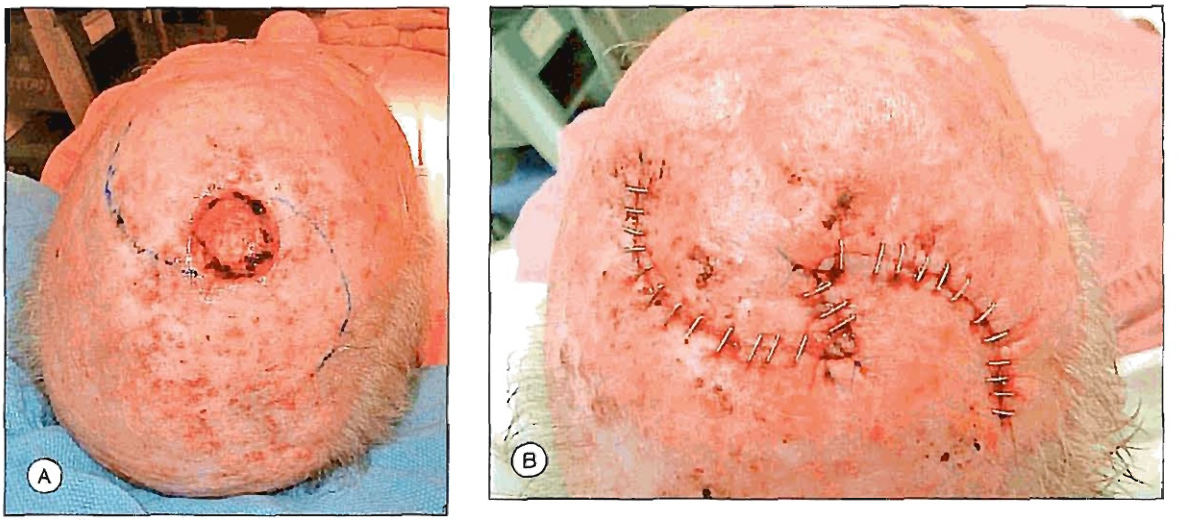

Fig. 37-13 O-Z rotation flap. *A*, Flap designed. *B*, Final wound closure.

vascularized areas. However, they have a higher degree of contraction and provide a poorer cosmetic match

Composite grafts most commonly consist of skin and underlying structure (i.e. cartilage) and are predominately used to repair such wounds as full-thickness alar rim defects. These grafts have an increased nutrient requirement and thus are more likely to fail. Free cartilage grafts can be used for reconstruction of the ear, and nasal ala or tip.

MOHS MICROGRAPHIC SURGERY

Frederic Mohs initially developed this technique at the University of Wisconsin in the 1930s. The original technique used zinc chloride paste to fix tissue in vivo followed by surgical excision. Drs Theodore Tromovitch and Samuel Stegman modified this in the 1970s to a fresh-frozen tissue variant which continues to be used today. While the basic surgical principles in Mohs micrographic surgery are similar to those used in standard excision, there are unique challenges encountered with Mohs surgery. A complete understanding of pathology, anatomy, cutaneous oncology, advanced surgical reconstruction, and management of surgical complications are critical to a successful patient outcome. Any dermatologist performing Mohs micrographic surgery should be well trained in this technique and all the surrounding challenges of surgical and post-operative care.

Mohs micrographic surgical excision is a tissue-sparing technique that employs frozen-section control of 100% of the surgical margin. This evaluation of the entire surgical margin using horizontal sections (not vertical as used in standard sectioning), combined with precise mapping, allows for the highest cure rate of cutaneous neoplasms (Fig. 37-21). In addition, the sparing of normal adjacent tissue can improve cosmesis and decrease the risk of functional defects in a sensitive anatomic location. Any tumor that has a contiguous growth pattern would be a candidate for Mohs micrographic surgical excision.

There are multiple indications for Mohs micrographic surgical excision (Box 37-4, Fig. 37-22). Mohs surgery provides cure rates of 99% for primary and 95% for recurrent BCCs. SCCs on the skin and lip treated with Mohs surgery have a 5-year recurrence rate of 3.1% (vs 10.9% for other modalities). SCC on the ear treated with Mohs surgery had a 5-year recurrence rate of 5.3% (vs18.7% for other

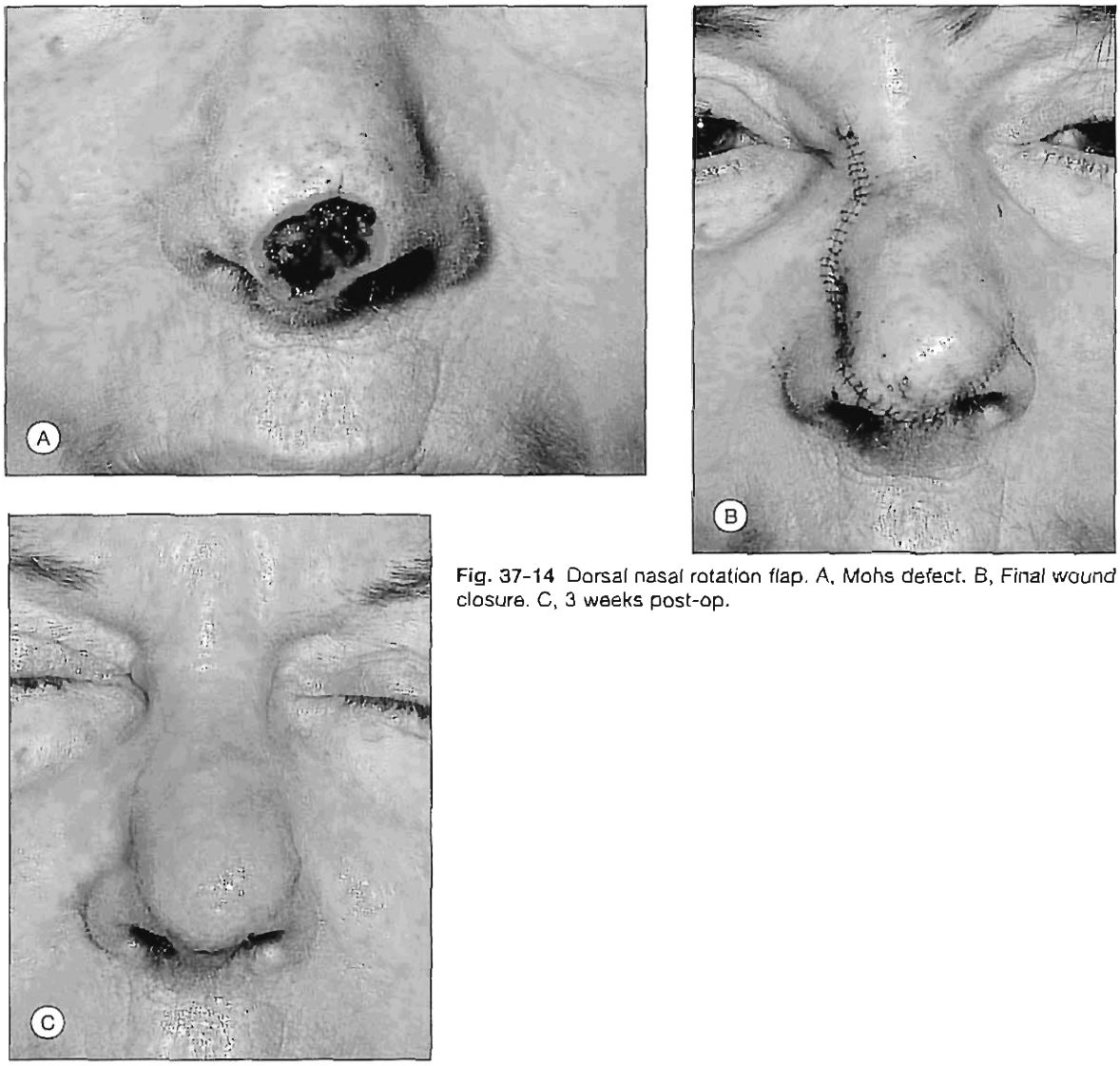

Fig. 37-14 Dorsal nasal rotation flap. A, Mohs defect. B, Final wound closure. C, 3 weeks post-op.

modalities). Locally recurrent SCC also had a reduced recurrence rate when treated with Mohs surgery as compared to other modalities (10% vs 23.3%). Other tumors which can be successfully treated by Mohs surgery include dermatofibrosarcoma protuberans, atypical fibroxanthoma, and microcystic adenexal carcinoma. Mohs micrographic surgical excision of melanoma continues to be debated. Bricca et al demonstrated comparable 5-year local recurrence rates, metastasis rates, and disease-specific survival rates in head and neck melanomas treated with Mohs micrographic surgery as compared to standard excision.

Barlow RJ, et al: Mohs' micrographic surgery using frozen sections alone may be unsuitable for detecting single atypical melanocytes at the margins of melanoma in situ. Br J Dermatol 2002;146:290.

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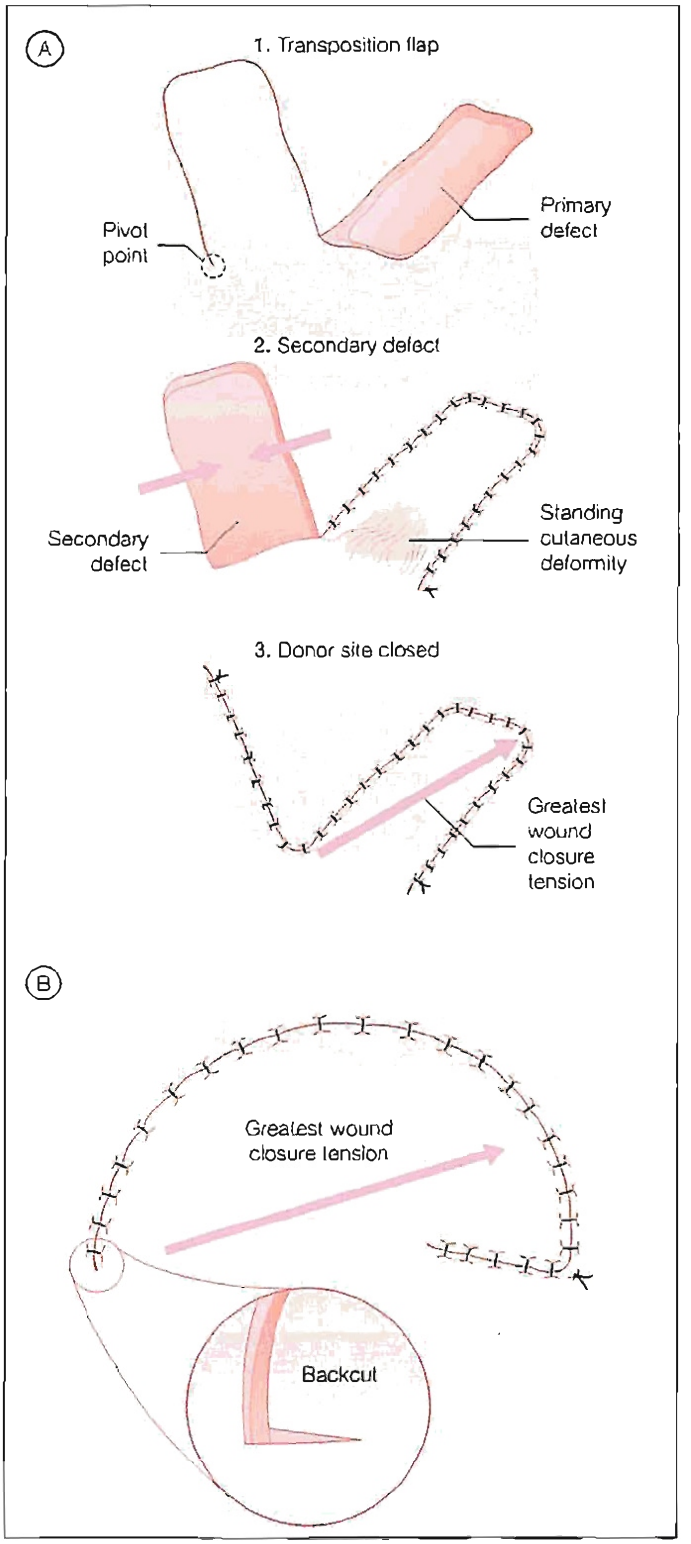

Fig. 37-15 Diagram of flaps.

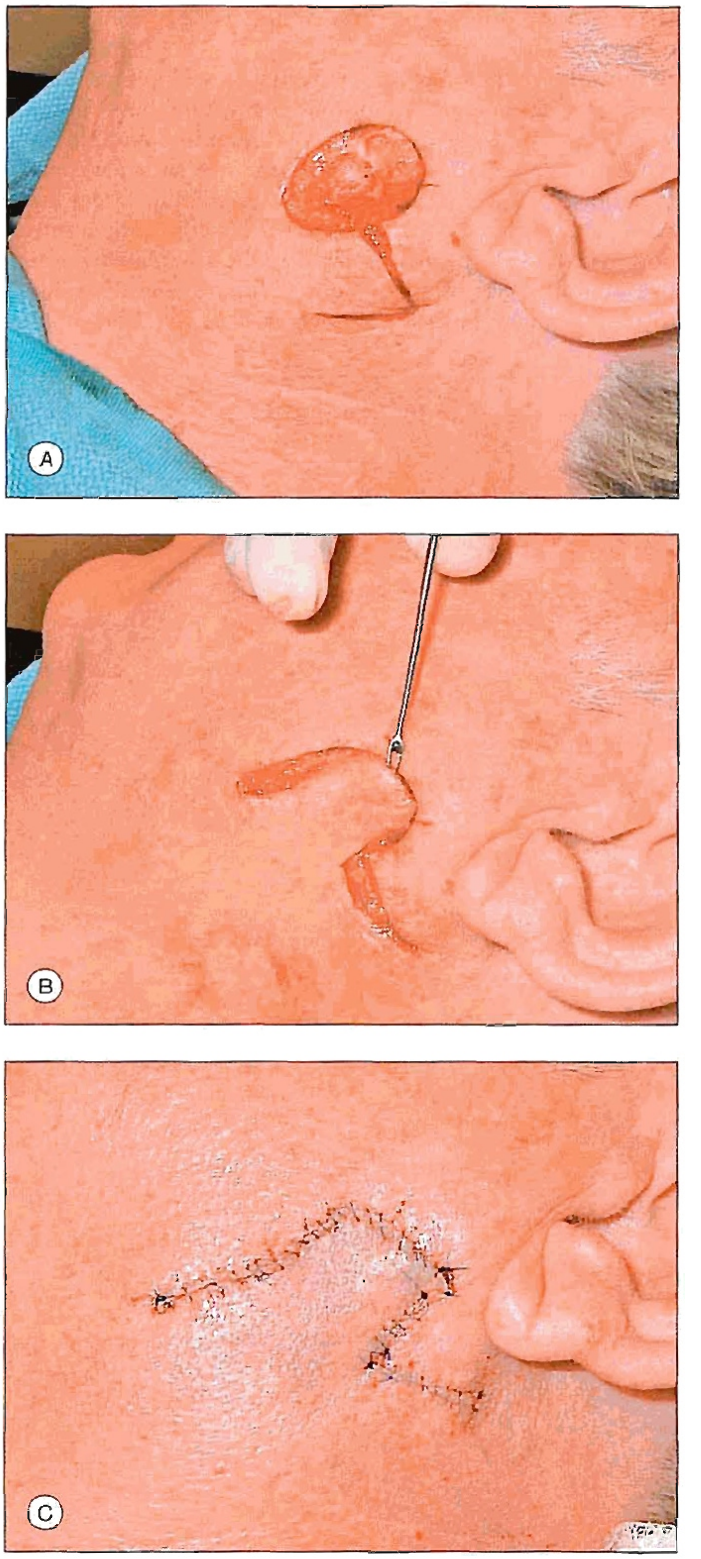

Fig. 37-16 Transposition flap. *A*, Rhombic flap designed and incised. *B*, Flap is moved into position. *C*, Final wound closure. (Photographs courtesy of Christopher B Zachary, MD)

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) involves the activation of a photosensitizer by visible light in the presence of oxygen, resulting in the activation of reactive oxygen species, which selectively destroy the target tissue.

The first requirement for PDT is delivery of either a systemic or topical photosensitizing drug. Systemic photosensitizing molecules are large, lipophilic molecules that require intravenous administration to reach the target site. One of the major disadvantages of these systemic drugs is the prolonged period of phototoxicity. Examples include porfimir sodium and hematoporphyrin derivative. The benzoporphyrin derivative monoacid ring A (verteporfin)

has a shorter period of photosensitivity (<72 h) compared to other systemic agents.

Topical agents offer the advantage of limiting photosensitivity to only the application site and have become widely used in dermatology. Delta-aminolevulinic acid (ALA) is applied and left on the skin for a sufficient period of time to allow for accumulation within the target cells. ALA is subsequently converted to the photosensitizer protoporphyrin IX (PpIX), which can then be stimulated through the controlled use of a light source. Tumor cells are thought to be selectively targeted by increased penetration of ALA

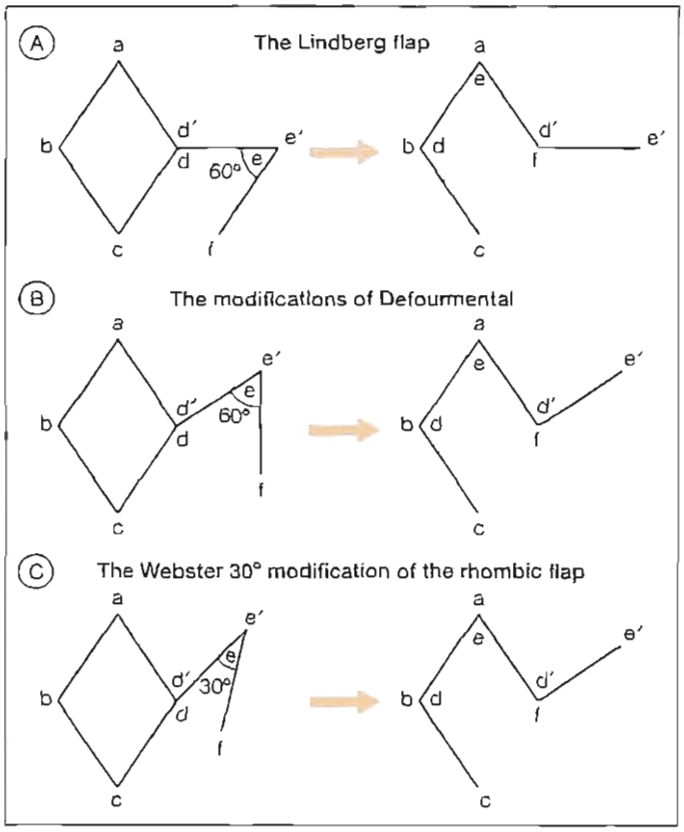

Fig. 37-17 Diagram of flaps.

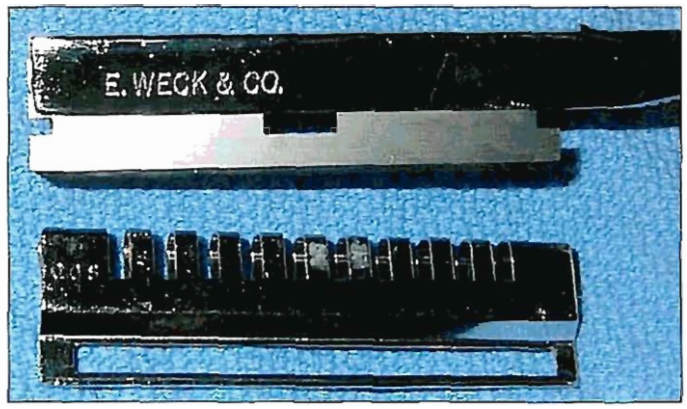

Fig. 37-19 Weck blade. Hand-held blade with various sized guards can be used to obtain split thickness skin grafts of desired thickness.

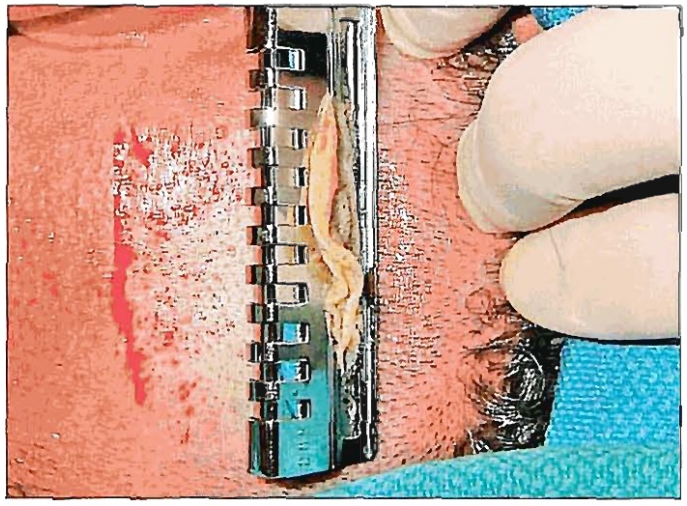

Fig. 37-20 Harvesting of split thickness skin graft. Mastoid process is an excellent source. Hair will regrow at donor site and hide the wound. Hairs remaining in the graft are above the level of the bulb and will not persist once the graft takes.
(Photographs courtesy of Christopher B Zachary, MD)

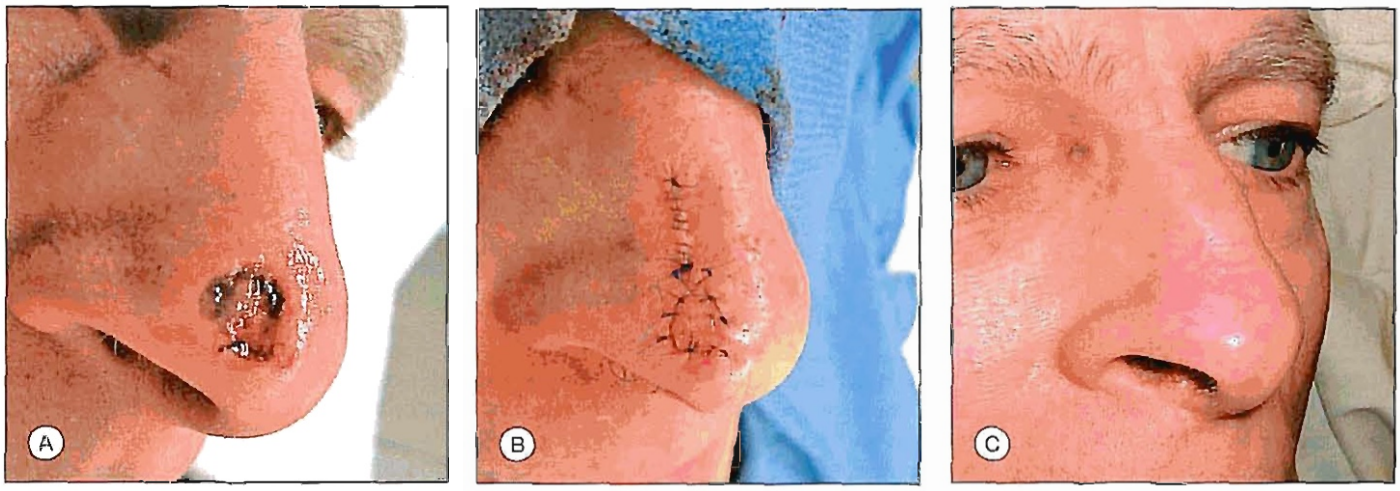

Fig. 37-18 Full thickness skin graft. *A*, Mohs surgery defect. Proximity to eye and concern for pull on lower lid make a full-thickness skin graft an appropriate closure choice. *B*, Final wound closure.

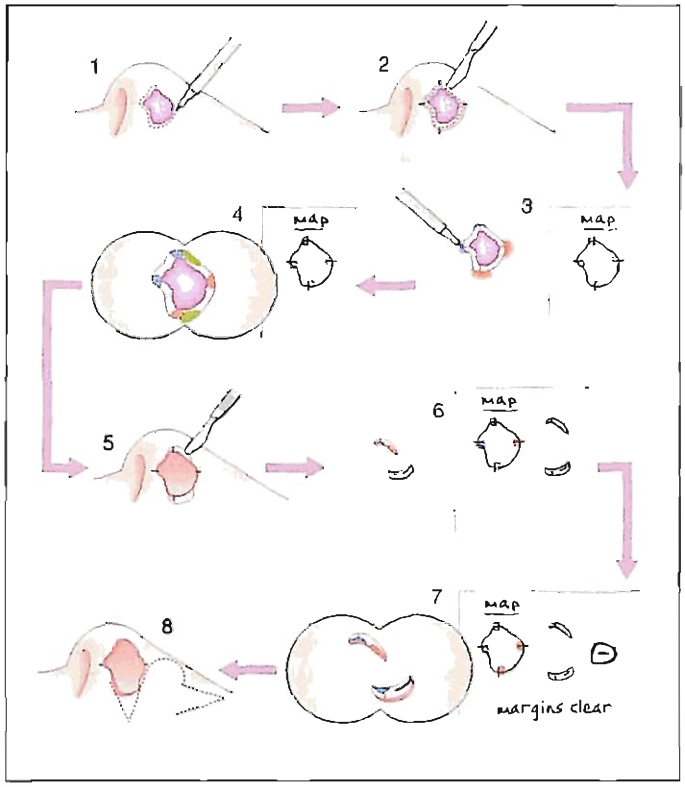

Fig. 37-21 A diagram of the Mohs Surgery process.

Box 37-4 Indications for Mohs surgery

- Recurrent or incompletely excised nonmelanoma skin cancer
- Tumors with aggressive histologic subtypes (i.e. infiltrative, morpheaform, micronodular, perivascular or perineural involvement)
- Tumors with poorly defined clinical margins
- High-risk location >0.4 cm (H-zone of the face, eyes, ears, nose)
- Large tumors (>1.0 cm on face; >2.0 cm on trunk or extremities)
- Cosmetically and functionally important areas, including genital, anal, perianal, hand, foot, and nail units
- Tumors arising in immunosuppressed patients
- Tumors arising in previously irradiated skin or scar
- Genetic conditions with increased risk of neoplasms (i.e. basal cell nevus syndrome or xeroderma pigmentosa)

through the abnormal epidermis overlying the tumor cells. In addition, the iron-deficient, rapidly proliferating tumor cells have an increased production of PpIX as compared to normal epidermal cells, resulting in selective photosensitivity and damage to the target site. Methyl aminolevulinate (mALA) is also used as a topical photosensitizing agent. Gentle scraping or curettage prior to application is performed to increase penetration. Once absorbed, mALA is converted to ALA within the target tissue.

The second requirement of PDT is an appropriate light source to activate the photosensitizer. The light source must match the absorption peak of the photosensitizer. Lasers,

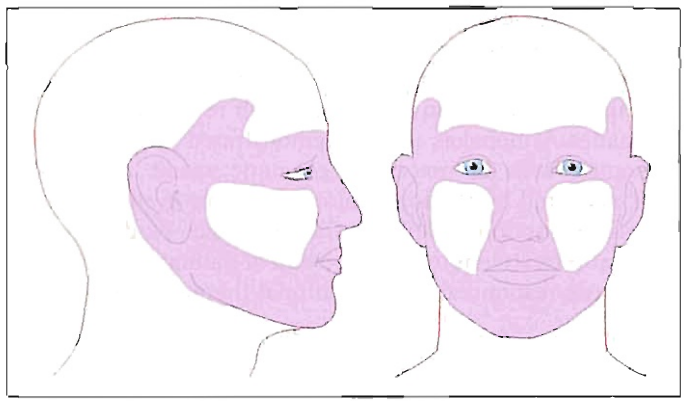

Fig. 37-22 H-zone of the face.

intense pulsed light devices, and an incoherent light source can be used. Red light uses the 630-nm peak of PpIX as its target, and has a deeper penetration, which is appropriate for dermal processes. Blue light targets the 417-nm peak and has a more superficial penetration, making it an appropriate choice for the treatment of epidermal lesions like actinic keratoses.

Following absorption of light, the photosensitizer is converted from a stable ground state to a short-lived excited triplet state, which may then be converted to a longer-lived excited triplet state. The excited triplet state electrons interact with tissue oxygen, creating singlet oxygen. Singlet oxygen causes oxidative damage to cellular membranes (i.e. mitochondria and other cellular organelles) and direct cell death, the key mechanism of action in topical PDT. This entire process occurs in the course of microseconds. In comparison, PDT using systemic photosensitizers predominantly causes destruction of target sites via vascular injury that leads to tissue ischemia.

Actinic Keratosis

Numerous studies have demonstrated the efficacy of PDT in the treatment of actinic keratoses. Acral lesions do not appear to respond as well to PDT as facial lesions. Several studies have demonstrated that a topical ALA applied for 14 to 18 h, followed by activation with a variety of light sources is an effective treatment of actinic keratoses on the scalp and face. Touma et al showed that short incubation periods of 1 to 3 h with ALA may be an effective protocol for the treatment of actinic keratoses, vastly improving the convenience of this therapy. Kurwa et al demonstrated similar reduction in dorsal actinic keratoses with a single ALA PDT and red light treatment as compared to a 3-week course of twice a day topical 5-fluorouracil (5-FU) (70% vs 73% reduction).

mALA may offer several advantages over ALA, including improved skin penetration due to its increased lipophilic quality, greater selectivity for neoplastic cells, and possibly less pain and discomfort associated with treatment. However, there are no comparative studies for ALA and mALA PDT in the treatment of actinic keratosis. Pariser et al showed the mALA applied for 3 h followed by noncoherent red light resulted in an almost 90% response rate in the treatment of actinic keratosis. Szeimies et al demonstrated a similar response rate for mALA PDT compared to cryotherapy, although PDT gave better cosmetic results and had a higher degree of patient satisfaction.

Given the absence of a stratum corneum on the lips and the increased penetration of topical ALA, PDT has effectively been used for the treatment of actinic cheilitis. This may be an option in patients with recalcitrant disease. Alexiades-Armenakas et al demonstrated about a 70% clearance with an excellent cosmetic result using ALA PDT activated by the long-pulsed dye laser in patients with refractory actinic cheilitis. Stender and Wolf reported successful treatment in a small group of patients who had not previously responded to conventional therapy.

Basal Cell Carcinoma

Studies suggest that topical PDT for the treatment of BCC can have initial clearing and excellent cosmetic result, but often have a higher recurrence rate with long-term follow-up. Rhodes et al compared topical mALA PDT and excision surgery for the treatment of nodular BCC. Seventy-five percent of cancers treated with PDT cleared with one cycle, while the remaining 25% required a second cycle of treatment. Complete response rates were similar at 3 months (91% for PDT vs 98% for excision) and a better cosmetic result was seen with PDT. However, PDT resulted in a higher rate of recurrence at 2-year follow-up. Additionally, more frequent visits and treatments were required with PDT, raising the question of practicality for this modality.

Haller et al demonstrated effective treatment of superficial BCC with two sessions of ALA PDT using red light spaced 1 week apart, and had a 96% clearance rate at over 2-year follow-up. Morton et al used the same double treatment methods for the treatment of large and/or multiple BCC and reported an 85% clearance rate at a mean 34-month follow-up. Soler et al conducted a follow-up study of superficial and nodular BCCs that had responded completely to mALA PDT alone and with prior curettage. Of 350 treated BCCs followed for a mean period of 35 months, the overall cure rate was 79%.

Lui et al demonstrated that systemic PDT using verteporfin could effectively treat patients with multiple nonmelanoma skin cancers. Histopathologic clearance rates up to 93% were seen. At 2-year follow-up, a clinical complete response of up to 95% was seen in patients.

Squamous Cell Carcinoma in Situ

SCC in situ is quite responsive to PDT. In a randomized study, Salim et al compared topical ALA PDT with 5-FU. At 1-year follow up, PDT achieved an 82% clinical response rate compared to 48% with 5-FU. Morton et al demonstrated a 78% clearance rate of large patches of Bowen's disease (diameter >20 mm) with ALA PDT. Additionally, ALA PDT results in a clearance rate of 89% for patients with multiple patches of Bowen's disease. Varma et al showed initial clearing in 88% of Bowen's disease lesions using ALA PDT. However, at 12-month follow-up, complete response decreased to 69%.

There are few reports of the use of PDT for invasive cutaneous SCC. Given the limited success in treating these tumors, PDT is not recommended as standard therapy for invasive SCC.

Alexiades-Armenakas MR, Geronemus RG: Laser-mediated photodynamic therapy of actinic cheilitis. J Drugs Dermatol 2004;3:548.

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Jeffes EW, et al: Photodynamic therapy of actinic keratoses with topical aminolevulinic acid hydrochloride and fluorescent blue light. J Am Acad Dermatol 2001;45:96.

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RADIATION THERAPY FOR SKIN CANCER

Radiation therapy (XRT) has a long history of use for treatment of both benign and malignant skin conditions. Ionizing radiation in dermatologic therapy of benign conditions has decreased markedly owing to highly effective medical therapies, balanced against the potential genetic and somatic hazards of radiation. However, XRT for malignant skin conditions continues to remain an important primary

and adjuvant therapeutic modality. When used in the proper clinical situation, XRT can provide effective treatment while sparing normal tissue and eliminating the need for surgical reconstruction.

XRT is an appropriate primary treatment for skin cancer in patients who refuse surgery or are poor surgical candidates secondary to numerous medical comorbidities. In contrast, patients who are relatively young should not be candidates for XRT due to the increased risk of developing additional primary tumors within the radiation field and the long-term cosmetic complications associated with this therapy. Tumors located on the eyelids, nose, ears, and lips do well with XRT, while lesions on the extremities are better treated by surgical excision. Treatment of primary BCC with XRT can produce cure rates of greater than 90%, while primary SCC may have a slightly higher recurrence rate. It is important to stress that Mohs micrographic surgical excision of primary tumors can achieve cure rates of 97% to 99%, often with excellent long-term cosmetic outcomes.

XRT may also be considered if margins show microscopic evidence of residual tumor following surgical excision. Recurrent BCC and SCC that had been treated previously by nonradiologic methods can be treated by radiation, although not with the same success as primary tumors. Caccialanza et al demonstrated an 84% 5-year cure rate for recurrent BCC and SCC in a group of nearly 250 recurrent tumors, with almost all having an acceptable cosmetic result. Locke et al showed that primary tumors treated with radiation had a response rate of 93% as compared to an 80% control rate for recurrent neoplasms. Mohs micrographic surgical excision of recurrent nonmelanoma skin cancer produces higher cure rates (95%).

In a prospective, randomized trial, Avril et al demonstrated that primary facial BCCs treated by surgical excision (almost all with frozen tissue examination) had a 4-year recurrence rate of 0.7%, as compared to 7.5% with XRT. In addition, a cosmetic result of "good or better" was achieved in 87% of surgically treated patients, as compared to 69% with XRT.

Several studies indicate that recurrence of nonmelanoma skin cancer after primary XRT may be more aggressive and invasive than recurrence after primary surgical treatment. Smith et al treated BCCs recurrent following radiotherapy and subsequently excised by Mohs micrographic surgery to a control group of BCC recurrent following other treatment modalities and similarly excised. They demonstrated that BCCs that recurred following primary radiation therapy had deeper subcutaneous tissue invasion and larger percentage increase between clinical preoperative tumor area and final postoperative defect area, as compared to recurrent tumors that had initially been treated with other modalities.

XRT offers a valuable adjunctive treatment option for particularly aggressive perineural SCC and BCC. Detection of single-cell tumor spread may be particularly difficult following excisional surgery. In addition, perineural carcinoma may spread more rapidly along nerve sheaths than by contiguous growth. Given the increased risk of metastasis and recurrence in this group of tumors, adjuvant XRT should be considered as prophylactic treatment following surgical excision.

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CHAPTER

38 Laser Surgery and Cosmetic Dermatology

CUTANEOUS LASER SURGERY

Almost no area of dermatology is changing as rapidly as that of cutaneous laser surgery. Development of new lasers, as well as improvements in existing lasers, continues to advance the field. As a result of this progress, laser surgery has become an effective therapeutic modality for a variety of dermatologic conditions.

Laser is an acronym for light amplification by stimulated emission of radiation. The first laser, a ruby laser, was operated in 1960 by Theodore Maiman. Medical applications were quickly recognized, and Leon Goldman pioneered their dermatologic use. While technology has advanced through the years, several distinctive characteristics have remained in all lasers. As compared to other light sources, laser light is defined as monochromatic, collimated (i.e. nondivergent) and in phase (i.e. peaks and troughs of the light are all aligned) (Fig. 38-1). The wavelength is determined by the active medium of each particular laser. Active medium can consist of a gas (i.e. argon or CO_2), liquid (i.e. dye), or a solid (i.e. ruby or yttrium–aluminum–garnet crystal) (Table 38-1; Fig. 38-2).

Light can interact with incident targets in one of three ways: transmitted, reflected, or absorbed (Fig. 38-3). In the first two cases, the light has no effect. When absorbed, the light energy is transformed into heat. In most cases of laser therapy, it is the heat generated by absorption that produces the desired effect. One notable exception is photodynamic therapy (see Chapter 37).

Lasers in cutaneous surgery are selected by matching their particular wavelength with the absorption spectrum of a desired target. The goal is to deliver a wavelength that is specifically absorbed by the chromophore (the most common in skin being water, hemoglobin, and melanin), inducing heat build up and destruction of that target. In an ideal situation, that wavelength would have little or no absorption by surrounding structures. By controlling exposure times and energy delivered (fluence), the amount of heat build up can be confined to the desired target with minimal or no damage to surrounding structures (a property defined as thermal relaxation time). This concept of selective photothermolysis was originally promoted by Parish and Anderson and is the basis for all laser–tissue interactions.

The laser is a technologically advanced instrument. However, as with any surgery, side effects can occur. Hypertrophic scarring and pigmentary changes are the most common, but infection, pain, and lack of efficacy are possible. Appropriate instruction and supervision in the use of lasers must be obtained by dermatologic surgeons in order to ensure optimum safety and surgical outcome.

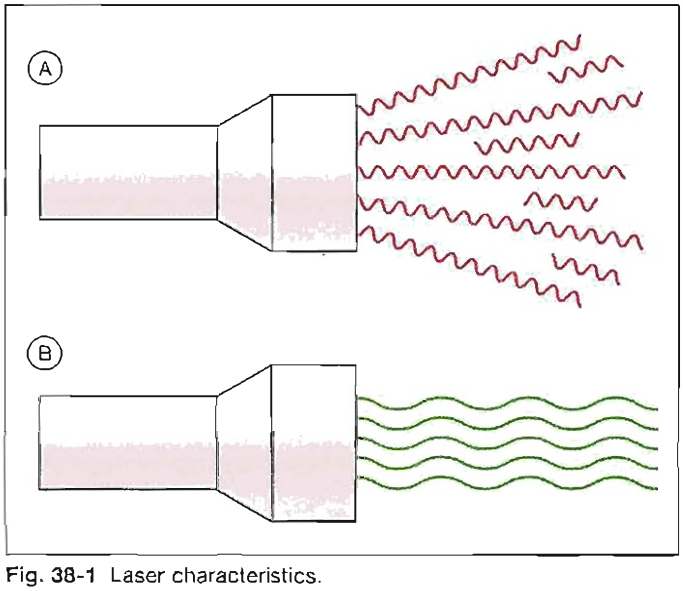

Fig. 38-1 Laser characteristics.

Argon Laser

The argon laser was one of the first lasers used for the treatment of vascular and pigmented lesions. Because its wavelengths (488 and 514 nm) do not precisely correspond to absorption peaks of either hemoglobin or melanin, and also because of its continuous-wave nature, thermal damage to surrounding tissue may be significant. Other lasers have been developed which have largely replaced the argon laser, due to their greater efficacy and improved side effect profile (i.e. less scarring and dyspigmentation). In addition, the newer technology has resulted in smaller and more reliable laser devices.

Copper Vapor/Copper Bromide Laser

These devices with wavelengths of 578 and 511 nm were effective in treating vascular and pigmented lesions, respectively. Due to technical concerns regarding size of the device, reliability, and cost of maintenance, they have been replaced by several of the lasers discussed below.

Pulsed Dye Laser

The pulsed dye laser (PDL) was the first laser developed to specifically take advantage of the theory of selective photothermolyis. The laser medium is a rhodamine dye which initially was developed to deliver a wavelength of 577 nm, coinciding with a specific hemoglobin absorption peak. Older lasers used a wavelength of 585 nm, but for various technical and clinical reasons, the wavelength has evolved in the current generation of PDL to be 595 nm. Initial pulse durations were in the order of 500 μs/pulse. This was based on calculations that the target, hemoglobin, had a thermal

Table 38-1 Dermatologic lasers

Laser	Wavelength (nm)	Color	Applications
Argon	488–514	Blue–green	Vascular lesions
Intense pulsed light (IPL)	515–1200	Green–red and infrared	Vascular lesions, pigmented lesions, epilation, photodamage
Potassium titanyl phosphate (KTP)	532	Green	Vascular lesions, pigmented lesions
Q-switched Nd:YAG (frequency doubled)	532	Green	Vascular lesions, pigmented lesions, tattoo–red
Copper vapor	578/511	Yellow–green	Vascular lesions, pigmented lesions
Flashlamp pumped pulsed dye (PDL)	585–600	Yellow	Vascular lesions
Q-switched ruby	694	Red	Deep and superficial pigmented lesions; tattoo–black, blue, green
Long pulsed ruby	694	Red	Epilation
Q-switched alexandrite	755	Infrared	Tattoo–blue, black, green
Long pulsed alexandrite	755	Infrared	Epilation
Diode	810	Infrared	Epilation
Q-switched Nd:YAG	1064	Infrared	Deep and superficial dermal pigment; tattoo–black, blue
Long pulsed Nd:YAG	1064	Infrared	Epilation, vascular lesion
Er:YAG	2940	Infrared	Superficial skin resurfacing and destruction of superficial growths
Carbon dioxide	10,600	Infrared	Skin resurfacing and destruction of warts, keloids, superficial cancers, and benign growth

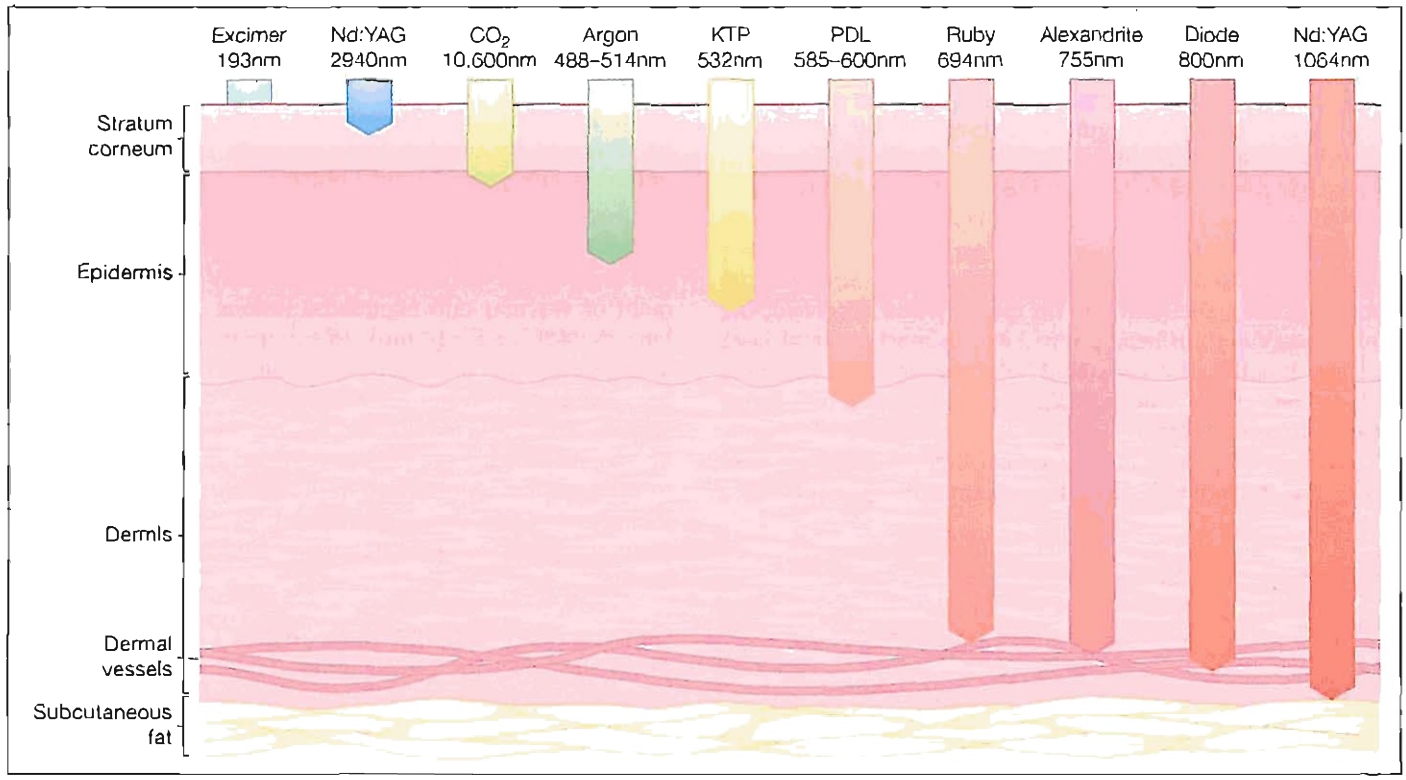

Fig. 38-2 Laser penetration.

relaxation time of 1 ms or less. Newer configurations of the laser allow for pulse durations from 0.45 to 40 ms, based on newer understandings of thermal relaxation times in the context of the size of the target (e.g. capillaries vs larger vessels) and clinical effects (purpuric vs nonpurpuric treatments). By using longer pulse durations, more gentle and uniform heating results in reduced or absent post-treatment purpura (more acceptable to patients) than the earlier PDL configurations, while still maintaining clinical efficacy.

The PDL is an extremely useful instrument for the treatment of vascular lesions. These lasers have traditionally been used for port-wine stains, telangiectasias, erythematotelangiectatic rosacea, and hemangiomas. The risk of scarring and pigment change is very slight, and infants as young as a few weeks old can be treated. The newer long pulsed and longer wavelength lasers allow for treatment of larger and deeper vessels. By associating these treatments with surface cooling devices, the epidermis can be protected, which

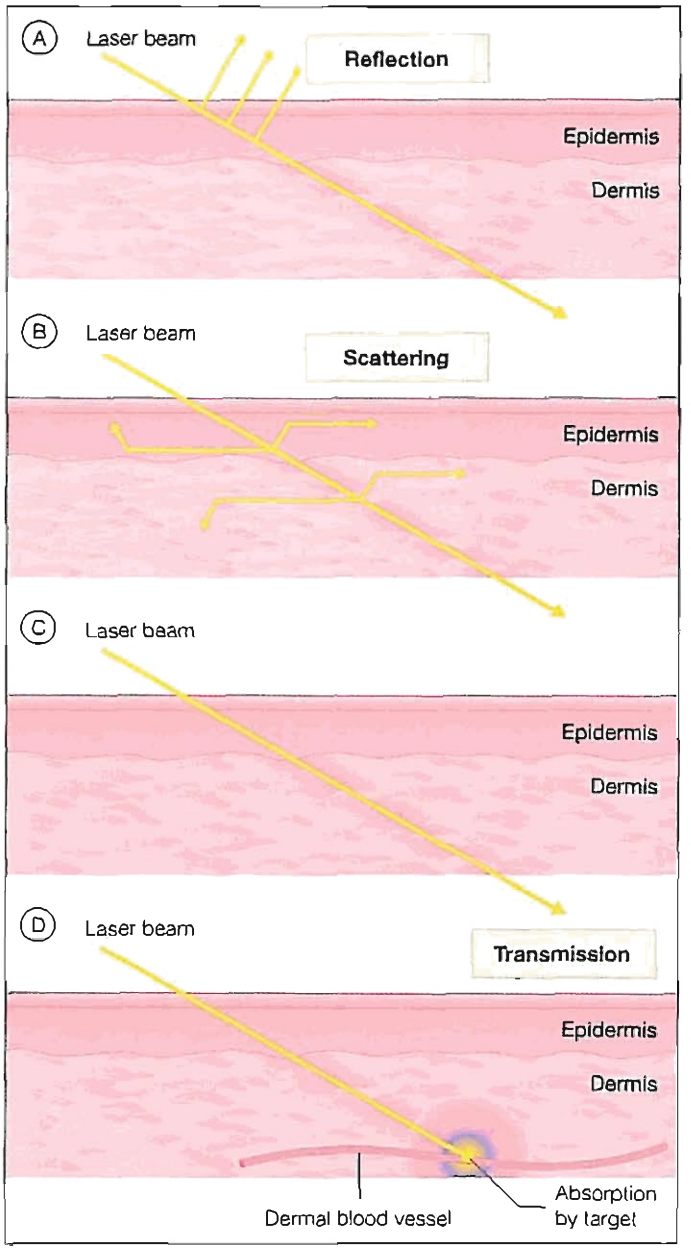

Fig. 38-3 Laser interaction with skin.

allows for delivering greater energy in a safer and less painful manner.

PDL has been effectively used for the treatment of warts, producing similar cure rates as traditional therapy. Several reports address the use of PDL for hypertrophic scars. Manuskiatti and Fitzpatrick demonstrated that PDL, intralesional corticosteroid, and 5-fluorouracil (5-FU) produced similar beneficial effects in the treatment of hypertrophic sternotomy scars. The mechanism of action in both incidences is not clear. It may be related to injury to vessels supporting the lesions or simply heat-related injury. As with other treatment modalities for these two conditions, results are variable.

KTP (Potassium Titanyl Phosphate) Laser

The KTP laser produces a visible green beam of 532 nm. Since there is significant hemoglobin and melanin absorption of this wavelength, KTP can be used to treat both vascular and superficial pigmented lesions. The KTP laser is actually an Nd:YAG (see below) laser which emits a wavelength of 1064 nm. The beam is passed through a crystal of KTP which reduces the wavelength by 50%, producing the 532 nm wavelength. The laser can be Q-switched (quality switched), emitting a beam in the range of 10 to 50 ns, and is useful for treating superficial pigment lesions and red tattoos. Alternatively, it can be delivered in a quasi-continuous mode (pulse durations as high as 50 ms), which can be used for the treatment of both vascular and pigmented lesions. In the longer continuous mode, they need to be delivered in a very narrow beam or in conjunction with a cooling device in order to minimize surface injury. Since individual vessels must be traced out using a narrow beam diameter, there are limitations to the number of vessels treated in any given session. In addition, the 532 nm wavelength has a limited depth of penetration, making it an excellent choice for the treatment of fine facial vessels.

Many KTP lasers employ a cooling tip to limit surface epidermal damage. This permits delivery of wide beam diameters and pulse durations, allowing for deeper penetration and more rapid treatment of a larger area. Unlike PDLs, KTP lasers do not produce postoperative purpura. KTP lasers can be quite compact, allowing for easy transport between various locations. With few moving parts they are relatively maintenance free.

These lasers are best suited for treatment of individual telangiectasias of the face, cherry angiomas, small spider angiomas, and small pigmented lesions, such as lentigos, ephileds, and thin seborrheic keratosis, including dermatosis papulosa nigra.

Q-Switched Ruby Laser

The Q-switched ruby laser emits a red 694 nm beam. The first laser developed was a ruby laser; however, this long pulsed laser was shown to have little application in dermatology due to excessive cutaneous injury. The development of Q-switching allowed for production of extremely high energies and short nanosecond pulse durations. This technology resulted in damage to the selected target while minimizing injury to surrounding tissue. The Q-switched ruby laser can effectively treat tattoos with black, blue, and green pigment. In addition, the ruby laser is successful in treating macular pigmented lesions, such as lentigines, ephelids, and nevus of Ota (Figs 38-4 and 38-5). For unknown reasons, other lesions such as café-au-lait macules, Becker nevus, and postinflammatory pigment alteration can respond, but the success is unpredictable. Treatment of melasma is very disappointing, with some patients improving, some showing no response, and others with temporary worsening. The main immediate side effects include crusting, which takes approximately 7 to 10 days to resolve. Longer-term side effects can include both hypo- and hyper-pigmentation.

Q-Switched Alexandrite Laser

This laser uses the semiprecious stone, alexandrite, as the active medium. In addition to the Q-switched ruby and Q-switched Nd:YAG lasers, the Q-switched alexandrite laser effectively treats tattoos. The long wavelength (755 nm) penetrates deeply into the dermis with absorption by blue, black, and green tattoo pigment. These lasers show a similar therapeutic profile to the Q-switched ruby laser. One advant-

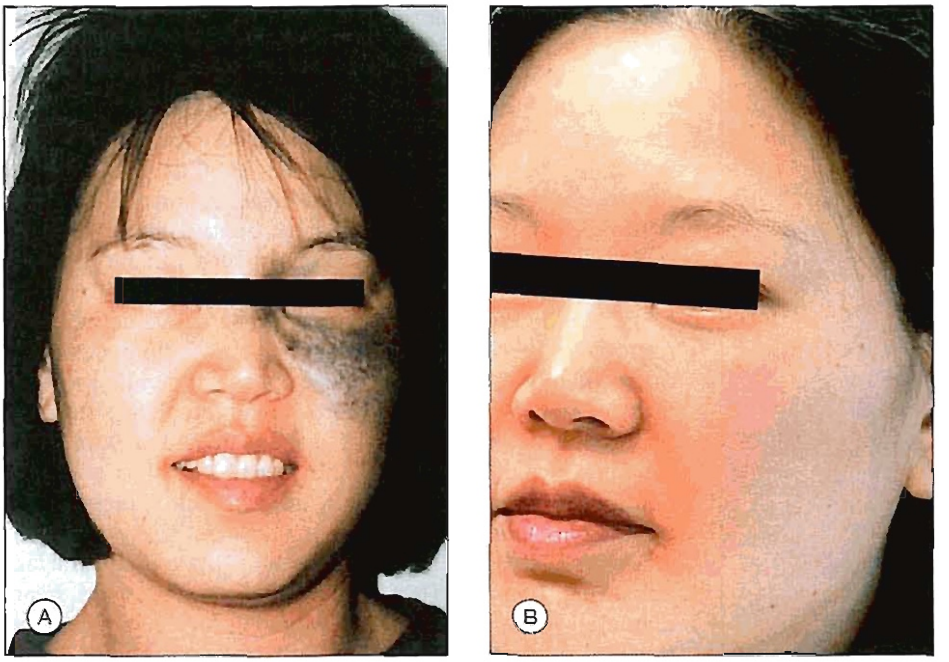

Fig. 38-4 Nevus of Ota *A*, prior to treatment and *B*, after treatment with a Q-switched ruby laser.

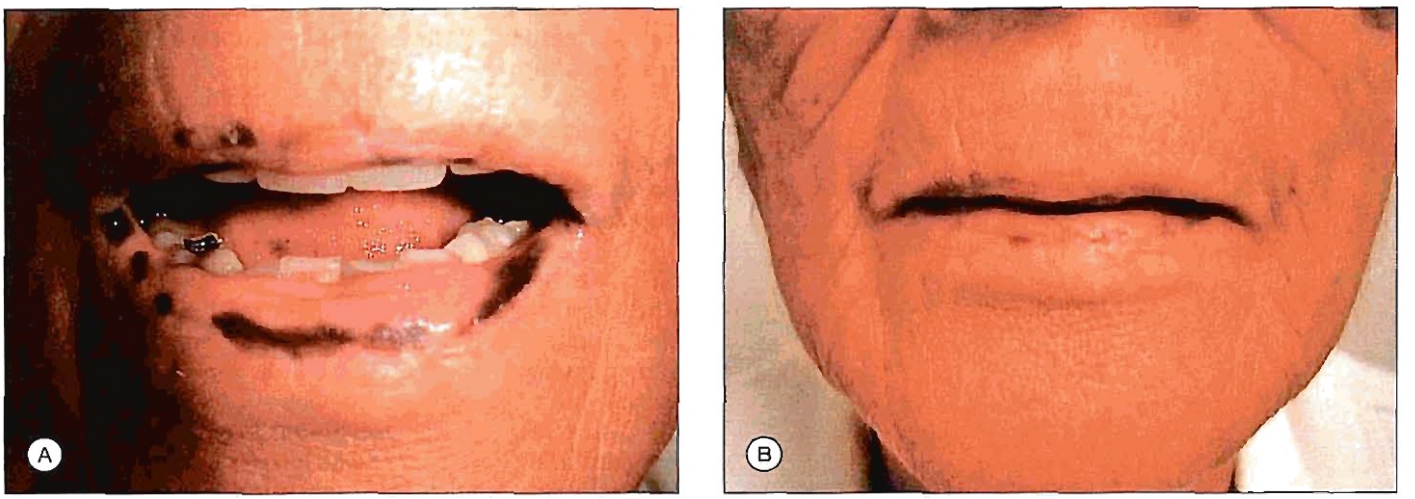

Fig. 38-5 Peutz-Jeghers syndrome *A*, prior to treatment and *B*, after treatment with a Q-switched ruby laser.

age, however, is the ability to deliver the alexandrite laser at 10 pulses/s, allowing for more rapid therapy compared with the single pulse/s delivery with the ruby laser. Disadvantages include a smaller beam diameter and less power.

Neodymium:Yttrium–Aluminum–Garnet Laser

The neodymium:yttrium–aluminum–garnet (Nd:YAG) laser can be used in three modes: continuous wave, Q-switched, and frequency doubled (KTP, see above). Both continuous and Q-switched modes emit an invisible near-infrared beam (1064 nm). As compared to shorter wavelength energies, the Nd:YAG laser is poorly absorbed by hemoglobin and melanin. Therefore, much higher fluences are required to treat lesions containing these chromophores. Because of the longer wavelength, the Nd:YAG laser penetrates much deeper and therefore is useful in treating more deeply seated or thicker lesions compared to shorter wavelength lasers.

In the Q-switched mode, it is highly effective for black and blue tattoos. In its frequency doubled mode, the green 532 nm beam, it treats red tattoos (Fig. 38-6). The Q-switched Nd:YAG laser can also be used to treat nevus of Ota, and in the frequency doubled mode, superficially pigmented lesions (i.e. vertigos, upholds, CALM).

The continuous or long pulsed mode extends the applications for the Nd:YAG laser. By extending the pulse duration, this laser can safely be used for hair removal in darkly pigmented patients (see below). In addition, as hemoglobin has a small peak at 1064 nm, the longer pulsed Nd:YAG laser has been used for vascular lesions, especially larger and deeper vessels. Hemangiomas, vascular malformations such as port-wine stains, and deeper larger caliber vessels have all been treated with this technology. Groot et al reviewed an algorithm for use of the long pulsed Nd:YAG laser for the effective treatment of vascular lesions of various type, size, and depth.

Intense Pulsed Light

The intense pulsed light (IPL) is a device that uses a flashlamp which emits a noncoherent broad spectrum of light (from 400–>1200 nm) at various pulse durations and

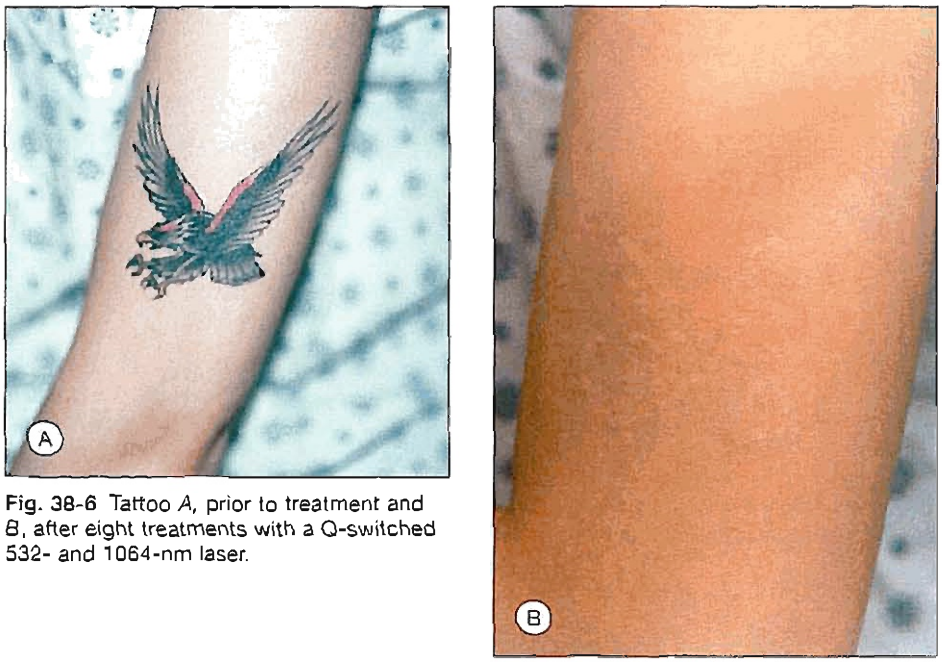

Fig. 38-6 Tattoo *A*, prior to treatment and *B*, after eight treatments with a Q-switched 532- and 1064-nm laser.

intervals. By employing filters to eliminate the lower wavelengths, light from 560 nm and above can be used to treat various cutaneous conditions. This technology has the advantage of treating more than one specific chromophore at a time.

IPL has been used for the rejuvenation of photoaged skin. Weiss et al demonstrated significant improvement in telangiectasias, pigment, and skin texture of the face, neck, and chest with IPL. IPL has been combined with topical aminolevulinic acid for photodynamic rejuvenation. By using IPL as the activating light source, patients benefit from the treatment of actinic keratoses as part of photorejuvenation. IPL has also been effectively used for hair removal (see below).

Laser Hair Removal

Laser hair removal is widely used for the permanent reduction of hair and this is one of the most popular laser procedures performed. Most lasers for hair removal target the melanin within the follicle, although some believe that they may work by targeting hemoglobin and damaging the microvasculature of the follicle. White, blond, and grey hairs generally respond poorly. As melanin is the target for these lasers, care must be taken in treating more darkly pigmented patients to avoid epidermal damage. In this patient population, the longer pulsed Nd:YAG laser has allowed safe treatment with fewer complications.

As hair is the target, patients must avoid waxing, electrolysis, or plucking of hairs prior to laser hair removal. Shaving prior to laser treatment is acceptable (and is mandatory immediately prior to treatment to avoid epidermal injury) and will not interfere with efficacy. It appears that only hairs in the anagen growth phase are permanently injured. Therefore, sufficient time must elapse between treatments for hair to regrow and provide an appropriate chromophore for subsequent laser treatment, generally 8 to 12 weeks.

Currently used devices for hair removal include the long pulsed ruby, alexandrite, diode, and Nd:YAG lasers, and the IPL. In addition, these longer pulsed lasers can produce a significant reduction in both hair and papules/pustules in patients with pseudofolliculitis barbae.

Effective laser treatment of white and blond hairs remains a challenge. Early evidence by Sadick et al demonstrated an approximately 50% reduction in the number of blond and white hairs using combined radiofrequency and IPL. Further research is necessary to evaluate the long-term success of this technology.

Ablative Laser Resurfacing

Both CO_2 and erbium:YAG (Er:YAG) lasers are absorbed by water. Since water makes up 72% of the skin, they effectively ablate the skin to varying depths depending on the energy delivered. They can be used therapeutically to treat conditions such as warts, adnexal tumors, and skin cancers. They may also be employed to remove very superficial external layers and resurface the skin for cosmetic enhancement.

Early systems employed a continuous wave mode of emission, which lead to a greater degree of thermal damage and risk of scarring. Newer high energy ultra-pulsed and computerized scanning systems have allowed a greater degree of control with laser ablation, resulting in more predictable outcomes.

Carbon Dioxide Lasers The CO_2 laser emits an invisible infrared beam of 10,600 nm and can be used in continuous-wave or super-pulsed mode. Water nonselectively absorbs laser energy, turning it instantly into steam, and producing ablative and thermal damage. Used in the super-pulsed mode, the laser beam can be delivered in short bursts, allowing thermal destruction of the epidermis and papillary dermis while limiting deeper thermal damage. Delivery in this mode is more uniform and markedly faster when the optomechanical scanner is employed. Super-pulsed CO_2 lasers are extremely useful in the treatment of actinic damage and photoaging. The thermal injury causes conformational changes within the collagen, leading to clinical tightening. As such, ablative laser resurfacing is extremely effective at

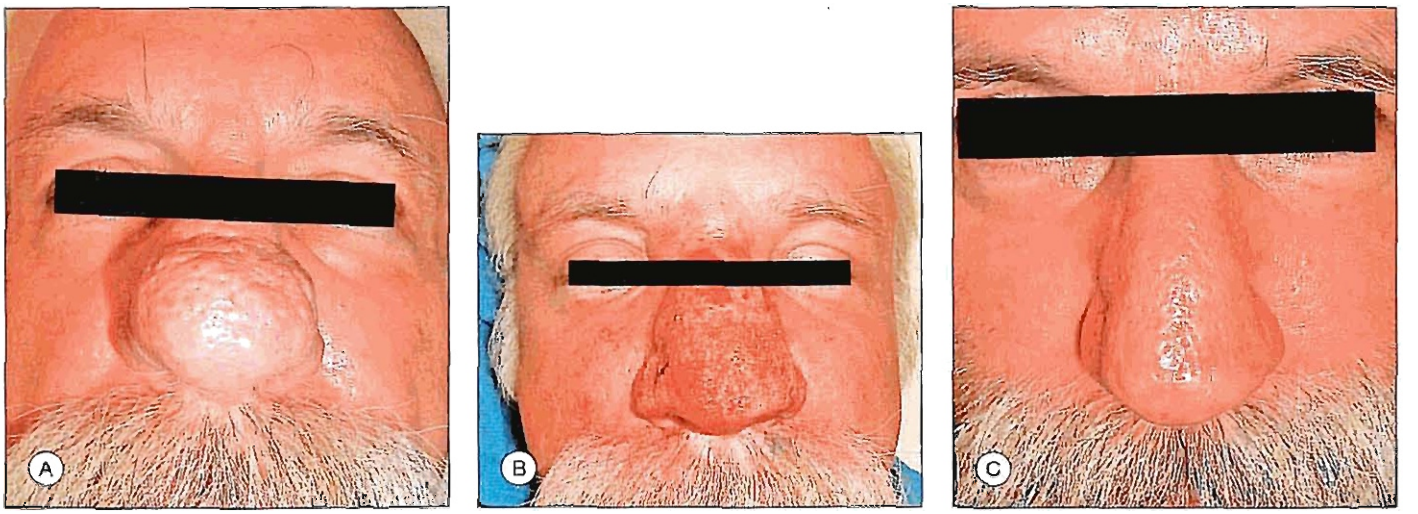

Fig. 38-7 Rhinophyma *A*, prior to treatment and *B*, immediately following treatment with a Er:YAG laser. *C*, Final result 3 months later, with marked improvement in shape and appearance.

improving wrinkling, scarring, and skin tone. Side effects include postinflammatory pigmentary changes, scarring and textural changes, and prolonged erythema. In addition, patients must be educated regarding the morbidity of the postoperative course and prolonged recovery associated with ablative resurfacing.

Used in the quasi continuous-wave mode, it is an excellent therapeutic choice for very large plantar and periungual warts, which have failed to respond to routine office modalities. Both a cutting mode and a defocused ablative mode can be used with these systems to effectively excise the visible verrucae and treat any residual human papillomavirus in surrounding skin. The CO_2 laser is also an excellent treatment option for ear lobe keloids but may not be as successful for keloids elsewhere. Other benign lesions amenable to CO_2 laser ablation include xanthelasma, rhinophyma, and syringomas. Various malignant and premalignant lesions also are effectively treated by laser ablation, including actinic chelitis, and superficial basal and squamous cell carcinomas.

Erbium:Yttrium–Aluminum–Garnet Laser The Er:YAG laser emits an invisible near-infrared beam of 2940 nm, resulting in significantly more efficient absorption (16 times) by water, and a more explosive ablative effect, as compared to the CO_2 laser. As such, the Er:YAG laser results in tissue ablation with less surrounding thermal damage. In addition, this wavelength is close to a collagen absorption peak, thus allowing for collagen ablation much more efficiently than the CO_2. The decreased thermal injury and collagen ablation is an advantage for treatment of scars, photodamaged skin, and rhytids (Fig. 38-7). Some maintain that healing may be slightly faster, with less risk of prolonged erythema and scarring (especially below the jawline). Nonetheless, depth of injury is the primary determinant for prolonged erythema and scarring. The decreased thermal damage can result in poor hemostasis with the Er:YAG laser. To address this limitation, certain systems have a coagulation feature to limit the amount of intraoperative bleeding. In addition, the collagen-tightening effect may not be as pronounced as with the CO_2 laser. However, when similar clinical injuries and depth are achieved, studies have shown that the Er:YAG and CO_2 lasers have comparable photorejuvinating effects, and similar postoperative healing times and complication profiles.

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COSMETIC DERMATOLOGY

Dermatologists have been leaders in the field of cosmetic surgery. Many procedures, products, and technologies in cosmetic dermatologic surgery have been advanced and researched by dermatologists. Patients are increasingly turning to dermatologists for the management and treatment of cosmetic issues. As a result, dermatologists must continue to be at the forefront of cosmetic procedures and remain committed to advancing the field through innovation and scientific progress.

Soft-Tissue Augmentation

Soft-tissue augmentation has been gaining popularity in recent years as patients seek cosmetic improvement without undergoing major surgery. There are numerous fillers available to correct soft-tissue contour abnormalities and provide cosmetic enhancement. While they provide numerous advantages over surgical techniques, the temporary nature of most fillers requires repeated treatment to maintain a desired outcome. While some find the temporary nature of these agents to be a problem, any undesired reactions that occur are also temporary. In the last few years, there has been an increase in the number of available agents. In Europe there are as many as 30 different filler choices. In contrast, in the US the FDA has approved very few, although in the past few years several more have become available.

Bovine Collagen

Bovine-derived collagen has been used for over 20 years and is the gold standard against which all filler substances are compared. There are three FDA-approved products for use in soft-tissue augmentation: Zyderm I, Zyderm II, and Zyplast. The source for all three types is a closed herd in the US, and there have been no cases of bovine spongiform encephalopathy associated with these products. All are composed of 95% type I collagen and the remainder type III collagen, suspended in buffered saline and 0.3% lidocaine. Zyderm I consists of 35 mg/mL of collagen, while Zyderm II has a higher concentration of 65 mg/mL of collagen. Zyplast is cross-linked with glutaraldehyde, making it more resistant to proteolytic degradation which provides longer duration. Preexisting bovine collagen hypersensitivity occurs in about 3% of the population. As such, a skin test is required prior to using this product. Additionally, 1% to 2% of patients with a negative skin test will subsequently develop an allergic reaction following treatment. Therefore, many dermatologists recommend a second skin test after an initial negative test. However, patients may develop allergy after multiple treatments. In patients who have previous experience with bovine collagen, but not in the previous 2 years, a single skin test is recommended. Patients can expect 3 to 5 months of improvement, depending on the location of placement. Dynamic rhytids (i.e. due to muscular activity) may have a shorter duration of correction, as opposed to more static conditions (i.e. acne scars). Zyplast may have a longer duration due to its relative protection from enzymatic degradation. However, it must be placed deeper in the dermis to avoid a beaded surface appearance and is therefore less useful for correction of superficial rhytids. Zyplast placed in the glabellar complex has resulted in vascular occlusion and necrosis. This may be due to the deeper placement required of this product and the associated adverse pressure-related effects on cutaneous vasculature.

Human Collagen

Cosmoderm I and II, and Cosmoplast are FDA-approved bioengineered human collagen derived from neonatal foreskin. Their concentrations correspond to those of Zyderm and Zyplast. The main advantage of these products is that they do not require a pretreatment test for hypersensitivity. They do not have any greater longevity than the bovine-derived products.

Autologous Fat Transplantation

Autologous lipotransfer allows for soft-tissue augmentation without the risk of allergy, rejection, or infectious transmission. Unlike other filler techniques, fat transfer is truly a grafting procedure. As such, its success is predicated on the survival of the transferred adipocytes. Fat is harvested from a choice of donor sites, typically the abdomen, buttock, thigh, or knee. There is no consensus as to the advantages of harvesting with a liposuction cannula, syringe extraction with a large-bore needle, or open surgical method. The fat is then separated from anesthetic fluid and blood, and then injected through a large-bore needle (16- to 18-gauge) into the desired location. Any remaining fat can be frozen for use at a later time with varying claims regarding loss of efficacy. Storage requires a –70° C freezer.

However, the variable rate of graft survival, the recipient site reaction (i.e. bruising, swelling), and the added morbidity of a donor site are limiting factors in patient satisfaction with this technique. In some instances, partial survival results in uneven correction which may require additional treatments. Some argue that multiple, smaller volume injections spaced out over two to three treatments are more effective than single large volume lipotransfer. If the fat survives, it certainly provides the most natural correction. However, local factors such as motor activity and gravitational effects will mitigate against permanent correction. This technique is not useful for the correction of superficial rhytids, and mainly corrects deeper defects such as the nasolabial folds, hypolabium, buccal depression, and deep scars.

Hyaluronic Acid

Hyaluronic acid, a natural polysaccharide, is a component of human connective tissue. A member of the family of glycosaminoglycans, hyaluronic acid is composed of repeating disaccharide units. This molecule has the advantage of being identical across all species. As such, hypersensitivity reactions should not occur and skin testing is not required prior to treatment. However, Friedman et al demonstrated a local hypersensitivity reaction in 1 in every 1400 patients treated,

although the incidence has declined with the introduction of a more purified product. Hyaluronic acid avidly binds water and patients may experience redness, swelling, and bruising in the first few days after treatment. Most of the volume is maintained following placement and over correction is not necessary when injecting. Hyaluronic acid products consist of a clear gel and contain no lidocaine. As such, local anesthesia and regional blocks are often used for patient comfort.

There are two types of hyaluronic acid filler substances. Streptococcal derived, which includes Restylane®, Restylane Fine Line®, Perlane® (the latter two are not yet FDA approved at the time of this publication) and Captique®. The other source is the rooster comb, which includes Hylaform® and Hylaform Plus® gel. There is a difference between these products based on their viscosity, which is determined by the size and concentration of the molecule within each preparation. The denser products are effective for the treatment of deeper contour abnormalities. Hyaluronic acid fillers can produce a more durable aesthetic improvement as compared to collagen, often lasting from 5 to 8 months (Fig. 38-8).

Synthetic Fillers

Microparticles of poly-L-lactic acid (Sculptra) are used as an injectable implant that is FDA approved for correcting facial lipoatrophy in patients with human immunodeficiency virus (HIV). This is a biodegradable, biocompatible, and immunologically inert product that does not require skin testing. Polylactic acid has been used as absorbable suture material (i.e. Vicryl). Polylactic acid is absorbed gradually in the skin, inducing a fibroblastic response that leads to collagen formation. Repeat injections can be given at 4-week intervals. Side effects include foreign body granulomas at injection sites, which can occur at a delayed time point. Injections of 5-FU or triamcinolone (10 mg/mL) may be used for the treatment of these papules.

Hydroxyapatite (Radiesse) are fine particles (30 μm) of material traditionally used to reconstruct bone. Injected into the dermis or subcutaneous tissue, it stimulates a fibrotic reaction which results in correction of soft-tissue depressions and enhancement of hypolabium. Experience with this product is limited and long-term risks and length of time of correction are not well known. Caution must be exercised as any product that requires a fibrotic reaction in order to be effective can result in a hyperraction leading to an untoward result.

Silicon has been used in the past for soft-tissue augmentation by dermatologists. This product was never FDA approved and issues of purity and safety limited its widespread use. In 1994 it was removed from the market by the FDA. Recently, 1000 centistoke liquid silicone (Silikon 1000) has been approved by the FDA for the treatment of retinal detachment. It is currently being used off-label as a permanent filler for HIV-associated facial lipoatrophy, scars, and rhytids. The potential for delayed and severe complications with this permanent filler, as well as legal concerns and restrictions, has limited its use. Adverse reactions associated with silicone injections include granuloma formation and migration of implant, which are compounded by the permanent nature of the product. Many of the past reported complications of silicone injection are the result of either using an impure and nonmedical grade substance or the failure to use a multisession, microdroplet technique. One precaution is that the current FDA-approved product is more concentrated than the older silicone products previously used. Further study is needed to evaluate the long-term safety and efficacy of silicon oil injections for correction of soft-tissue contour deficiencies.

Expanded polytetrafluoroethylene (ePTFE) is a synthetic solid material that is soft and pliable, is not degraded, and has the advantage of being permanent. The material is placed through a small skin incision and positioned in the desired location. Areas commonly treated with this include lip margins or the muscular portion of the vermillion for enhancement, nasolabial folds, and soft-tissue depressions. Some complications associated with ePTFE include extrusion, migration, shrinkage, and hardening.

Other Fillers

Many other filler substances are available outside the US. Artecoll® (FDA approved) is a suspension containing 20% polymethylmethacrylate (PMMA) microspheres of 30 to 40 μm in diameter suspended in 80% bovine collagen for soft-tissue augmentation. The carrier collagen is degraded over several months, leaving the permanent PMMA microspheres, which serve as a framework for connective tissue deposition. Technique is critical to successful outcomes. If injected too deeply, the implant is ineffective, while superficial placement can cause prolonged erythema. Granuloma formation and hypertrophic scarring can occur and have been reported as a delayed reaction. Intralesional triam-

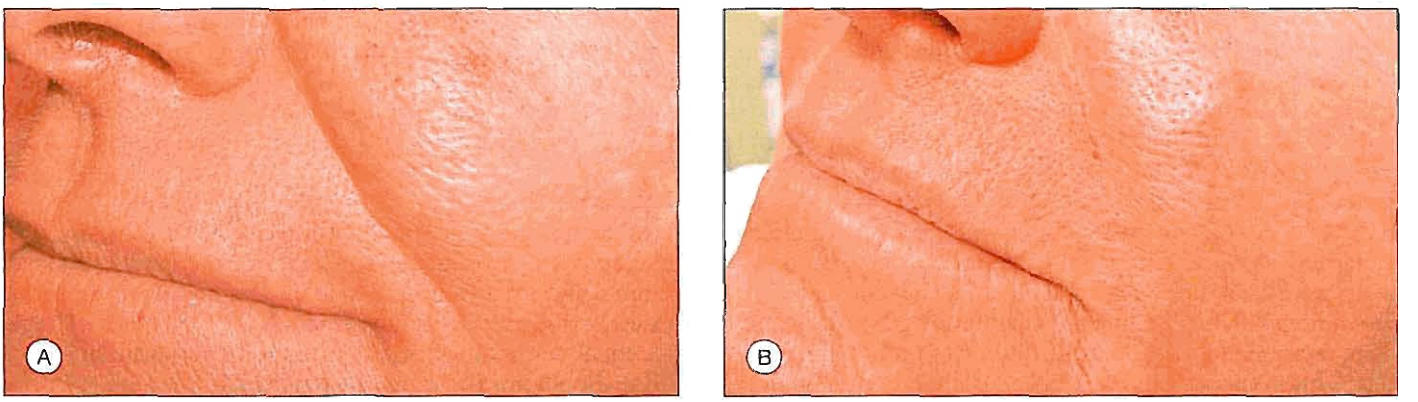

Fig. 38-8 Hyalurinic acid filler. Nasolabial fold *A*, prior to treatment and *B*, immediately following placement of hyaluronic acid with marked improvement and reduction of rhytids.

cinolone can be used for treatment of these reactions. Additionally, a patient who developed a delayed foreign body granuloma 6 years after injection with Artecoll® was successfully treated with a 24-week course of 600 mg/day of allopurinol.

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BOTULINUM TOXIN

The use of botulinum toxin in dermatology has rapidly increased over the years, and at present is the most common cosmetic procedures performed in the US. Produced by *Clostridium botulinum*, there are seven different serotypes of botulinum neurotoxin (BTX): A, B, C1, D, E, F, and G. All these serotypes inhibit the release of acetylcholine from the presynaptic motor neuron, resulting in chemodenervation and paralysis of the treated muscle.

Botulinum toxin type A (Botox Cosmetic®; Dysport®) is the most commonly used serotype. Its mechanism of action is via the cleavage of the SNAP-25, a presynaptic membrane protein required for fusion of neurotransmitter-containing vesicles. Effect is generally noted 2 to 5 days after treatment with botulinum toxin type A (BTX-A), but can be as long as 2 weeks in some cases. Results can last from 3 to 6 months. For dosing purposes, 1 U of Botox® is equivalent to about 3 to 5 U of Dysport®.

The only other serotype that is commercially available is botulinum toxin type B (Myobloc)®. Its mechanism of action is via the cleavage of a vesicle-associated membrane protein (VAMP), also known as synaptobrevin. This serotype has a much more rapid onset of effect as compared to BTX-A. In addition, differences in potency suggest that approximately 100 U of Myobloc are equivalent to 1 U of Botox.

Given the efficacy, experience, FDA approval and safety profile of Botox®, it has emerged as the leading choice of botulinum toxin amongst practitioners. Botox® is distributed as a vacuum dried powder in 100-U vials, which is reconstituted with 1.0 to 5.0 mL of saline. Despite package insert recommendations, experience suggests that there is little loss of potency over an extended period of time following reconstitution. The use of preserved saline for reconstitution reduces the burning and pain associated with injection. This is due to the benzyl alcohol in preserved saline which has anesthetic properties.

Botulinum toxin is predominantly used in dermatology for treatment of dynamic rhytids on the upper third of the face. The key for successful treatment is an understanding of the anatomy involved in facial expression, rather than performing the procedure by rote. Having the patient frown, squint, and raise their brows prior to treatment, helps identify the active muscles and serves as a guide for proper placement.

For the treatment of the glabellar brow furrow, approximately 20 to 35 U of BTX-A are typically injected into the corrugators and procerus (Figs 38-9 and 38-10). Ptosis of the upper lid is a rare complication, but can be quite problematic for the patient. These effects are temporary and generally occur from the diffusion of the toxin. The use of apraclonidine 0.5% or phenylephrine 2.5% eye drops can stimulate Müller's muscles in the lid, providing some relief until the effects of the botulinum toxin disappear.

Horizontal forehead lines can be treated with BTX-A as well. The frontalis is a brow elevator and care must be taken to avoid brow ptosis when treating this area. One way to limit this effect is to only paralyze a portion of the frontalis muscle, maintaining activity. For instance, injection may be limited to the superior half of the frontalis; 10 to 25 U, delivered in multiple injections across the forehead, is typically used for this area.

Crow's feet are dynamic rhytids produced from contraction of the lateral orbicularis oculi. Superficial blebs are raised approximately 1 cm lateral to the lateral canthus (Fig. 38-11). Bruising is limited by injecting superficially and limiting the total number of injections. Other sites that can be treated with BTX-A include platysmal bands, diagonal creases along the nasal sidewall (i.e. "sniff lines" or "bunny lines"), mental crease, and depressor anguli oris (for frowning of the lateral corners of the mouth). Care must be taken when treating the lower third of the face to avoid complications with mouth and lip control.

In addition to cosmetic uses, BTX-A is FDA approved for the treatment of hyperhidrosis. Axillary hyperhidrosis can effectively be treated with doses of 50 U/axilla. A starch iodine test can map the area of activity prior to treatment (Fig. 38-12). Intradermal injections are spaced 1 cm apart over the entire area. The effect generally lasts between 6 and 12 months, and appears to be related to the dosage used. Treatment of palmar hyperhidrosis with BTX-A requires higher doses due to the greater surface area involved, typically 100 to 150 U/palm. The pain associated with palmar injections requires the use of wrist nerve blocks. Lastly, a slight muscle weakness of the hands is typically seen for several weeks following treatment. Although this weakness is typically not functionally significant, patients must be informed of this.

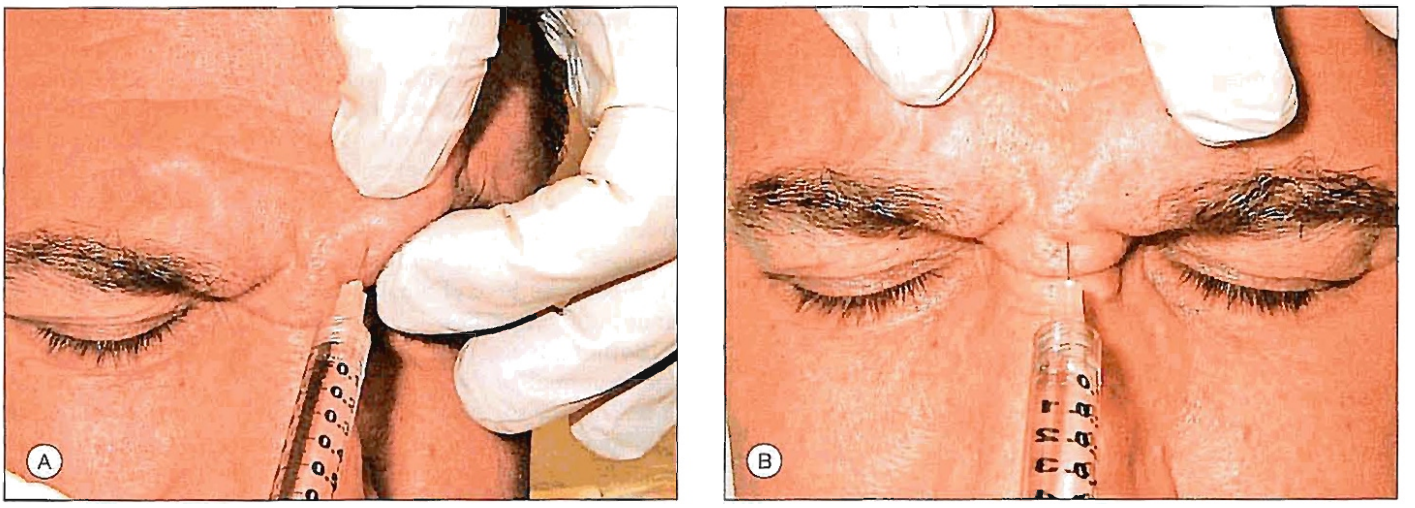

Fig. 38-9 Botulinum toxin injection technique for glabellar complex. *A*, Patient frowns and muscle is grasped between thumb and index finger, and the injection is placed directly into the belly of the corrugator supercilii. *B*, Injection into the procerus muscle. (Courtesy of Christopher B Zachary, MD)

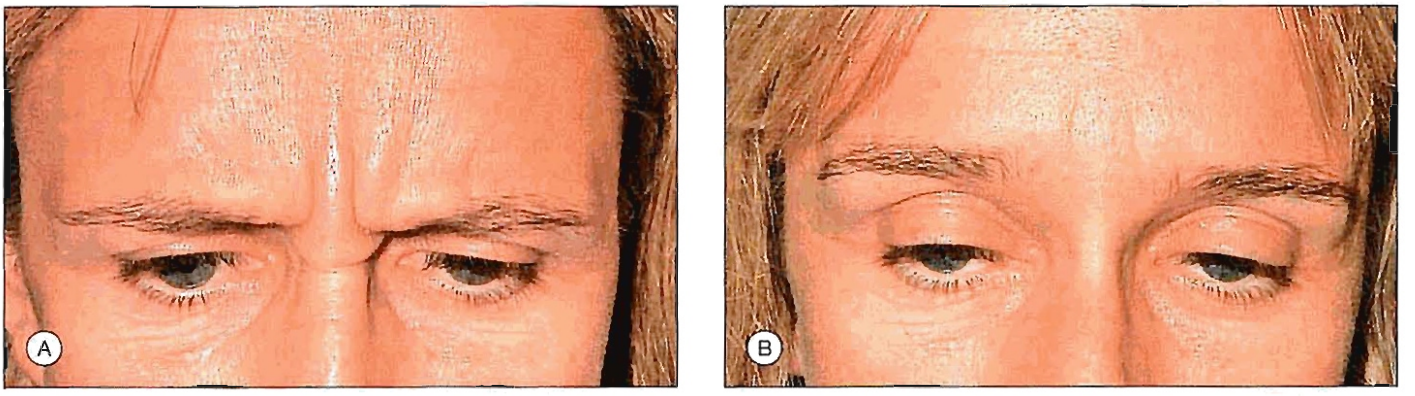

Fig. 38-10 Botulinum toxin for glabellar frown furrow. *A*, Glabellar lines with frowning. *B*, Patient attempting to frown after botulinum toxin. (Courtesy of Christopher B Zachary, MD)

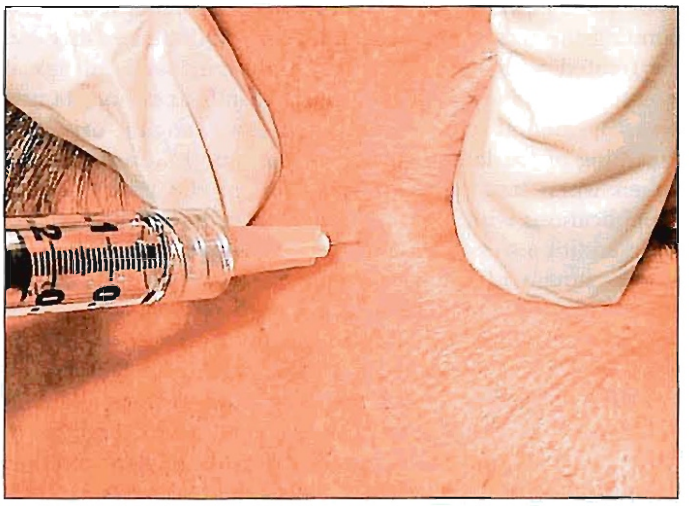

Fig. 38-11 Botulinum toxin injection technique for crow's feet, superficial injection approximately 1 cm from the orbital rim.

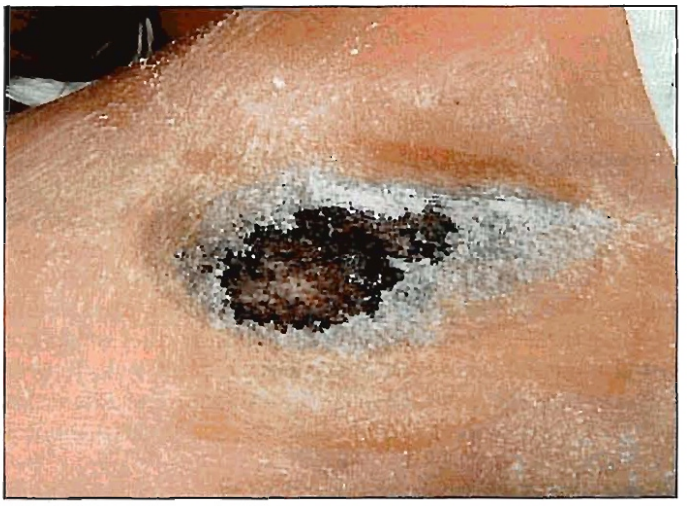

Fig. 38-12 Starch iodine test, developing positive test with darkening in areas of hyperhidrosis.

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VARICOSE AND TELANGIECTATIC VEINS

Sclerotherapy

Patients frequently present to dermatologists seeking treatment of telangiectasias and reticular veins in the lower extremity. The treatment of choice for telangiectatic and reticular veins is sclerotherapy (Fig. 38-13). Despite recent technologic advances, laser treatment for lower extremity telangiectasias should be reserved for those vessels which can not be cannulated with a needle. In addition, laser therapy can be considered in patients who have failed to respond to sclerotherapy or had significant complications from sclerotherapy.

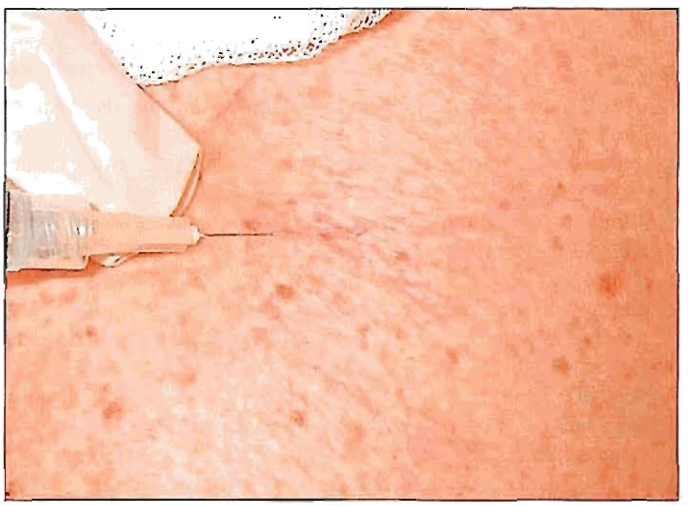

Fig. 38-13 Sclerotherapy, injection technique using fine needle to cannulate vein.

There are three broad classes of sclerosing agents available to dermatologists—hyperosmotic agents, detergents, and chemical irritants (Table 38-2).

Hypertonic saline is an FDA-approved agent that is commonly used in sclerotherapy. Used in concentrations of 10% to 30%, this agent has the advantage of a complete lack of allergenicity when used alone. The disadvantage of hypertonic saline is the pain associated with injections and the ulcerogenic potential. Often, anesthetic agents such as lidocaine are added to the mixture to minimize the discomfort involved, both by decreasing the concentration of the saline and by the direct anesthetic effect. The authors' formulation is to mix two parts hypertonic saline (23.4%) with one part 1% lidocaine, resulting in an approximate concentration of 16% NaCl.

Hypertonic saline (10%) and dextrose (25%) is another hyperosmolar agent that has been used in vein sclerosing. This agent has the advantages of low allergenicity and decreased pain compared to higher concentrations of plain hypertonic saline. However, this mixture is currently not FDA approved and is a relatively weak sclerosant as compared to other options available.

Sodium tetradecyl sulfate (STS) is a detergent sclerosant that has been FDA approved for over 50 years. Typical concentrations used for superficial telangiectasias and reticular veins are 0.1% to 0.5%. One advantage of STS is the lack of pain with injections; however, extravascular injection can be painful. Also, as with all detergents, STS can be made into a foam. This is typically done with a three-way stopcock and a syringe filled with air (Fig. 38-14). Foam can increase contact between the agent and the vessel wall and result in more effective sclerosis at a lower concentration. One disadvantage with this agent is the isolated reports of anaphylaxis and death associated with STS.

Polidocanol, a detergent, is not currently FDA approved for use in sclerotherapy. It possesses many of the same advantages as STS, including lack of pain with injection and the ability to use it as a foam. Goldman demonstrated comparable efficacy and a similar adverse event profile between polidocanol and STS.

Sodium morrhuate is a detergent approved by the FDA for treatment of varicose veins. However, this sclerosing agent is not generally used for the treatment of cutaneous telangiectasias due to its highly caustic nature and higher anaphylaxis potential.

Table 38-2 Sclerotherapy agents

Agent	Class	FDA approved	Comments
Hypertonic saline	Hyperosmotic	Yes	No allergenicity, painful
Hypertonic saline (10%) + dextrose (25%)	Hyperosmotic	No	Lower allergenicity, painful
Sodium tetradecyl sulfate	Detergent	Yes	Can use as foam, painless except with extravascular injection
Polidocanol	Detergent	No	Painless, can use as foam
Sodium morrhuate	Detergent	Yes	High risk of allergic reaction
Chromated glycerin	Chemical irritant	No	Weak agent
Polyiodinated iodine	Chemical irritant	No	Highly caustic

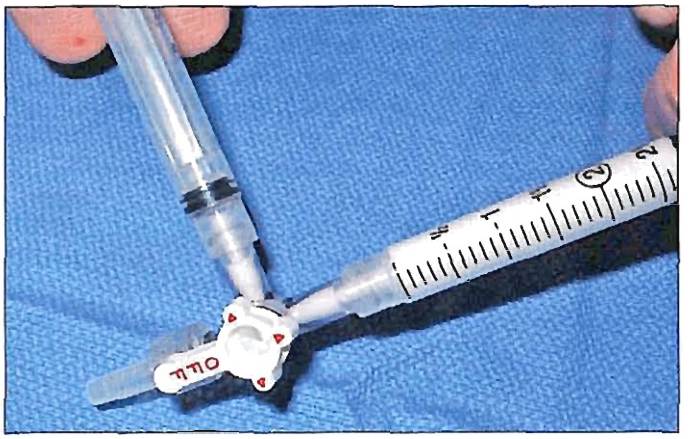

Fig. 38-14 Sclerosing foam, sodium tetradecyl sulfate foam made by mixing air with liquid using a three-way stopcock and two syringes.

Glycerin and polyiodide iodide are chemical irritants used as sclerosing agents. Though not FDA approved for sclerotherapy, these act as corrosive agents and cause a direct injury to the vessel endothelium. Leach and Goldman report a significant decrease in bruising, swelling, and postprocedural hyperpigmentation with glycerin as compared to STS.

Side effects and complications can be associated with all types of sclerotherapy agents. Ulceration can occur despite the meticulous technique of the dermatologist and regardless of the sclerosing agent used. Extravasation of sclerosing solution from the vein may occur or injection into a dermal arteriole or arteriovenous anastomosis may result in cutaneous necrosis. If it is suspected that extravasation has occurred, injection of normal saline to dilute the sclerosing agent may prevent ulceration. Alternatively, application of 2% nitroglycerin ointment may prove beneficial. If ulceration does occur, conservative wound management should be undertaken until healed.

Hyperpigmentation along the course of treated veins has been reported to occur in 10% to 30% of patients. This pigmentation is due to hemosiderin deposition and has been reported with a variety of sclerosing agents, including hypertonic saline, polidocanol, and STS. Pigmentation often improves with time, with approximately 70% improvement over a 6-month period. Treatment options include trichloracetic acid, hydroquinone, retinoic acid cream and intense pulsed light, and laser treatments. Tafazzoli et al report excellent results with the Q-switched ruby laser.

Telangiectatic matting is the appearance of fine telangiectatic blush at the site of previously treated veins. This has been reported in 10% to 15% of patients treated with sclerotherapy. Risk factors associated with this include estrogen therapy, obesity, and a family history of telangiectasia. Low injection pressures and limiting the amount of sclerosant per injection site may help reduce the incidence of telangiectatic matting. Spontaneous resolution often occurs within 3 to 12 months. Treatment options include intense pulsed light, pulsed dye laser, and injection of sclerosant into the matted vessels.

Arterial injection of sclerosant is the most feared complication of vein sclerosing. While extremely rare, it has significant morbidity and immediate action must be undertaken. Classically, the patient reports significant pain immediately following injection, accompanied by significant pallor and cyanosis. If arterial injection occurs, the physician should immediately apply ice and attempt to dilute the vessel with injections of normal saline. Procaine can be used to inactivate STS. Intravenous heparin and thrombolysis should be considered.

Ambulatory Phlebectomy

Ambulatory phlebectomy is an outpatient procedure used to remove varicose veins. This is a highly technical procedure which has been pioneered by dermatologists and requires additional training. A series of stab incisions are made along the course of the varicosity. Various hooks and clamps are used to remove the vein (Fig. 38-15). Sclerotherapy can follow for any remaining reticular veins.

Endovenous Ablation

Endovenous ablation should be considered in patients with greater saphenous incompetence and is rapidly replacing traditional vein stripping. Radiofrequency or laser (810 or 1320 nm) can be used to heat and damage the vein (Fig. 38-16). A catheter is placed under ultrasound guidance. Tumescent anesthesia allows the procedure to be performed painlessly, surrounds the vein and allows for greater contact between the catheter and vessel wall, and distends the skin away from the heat source and prevents cutaneous damage. The catheter is slowly withdrawn along the length of the vein, and the thermal injury leads to vessel occlusion.

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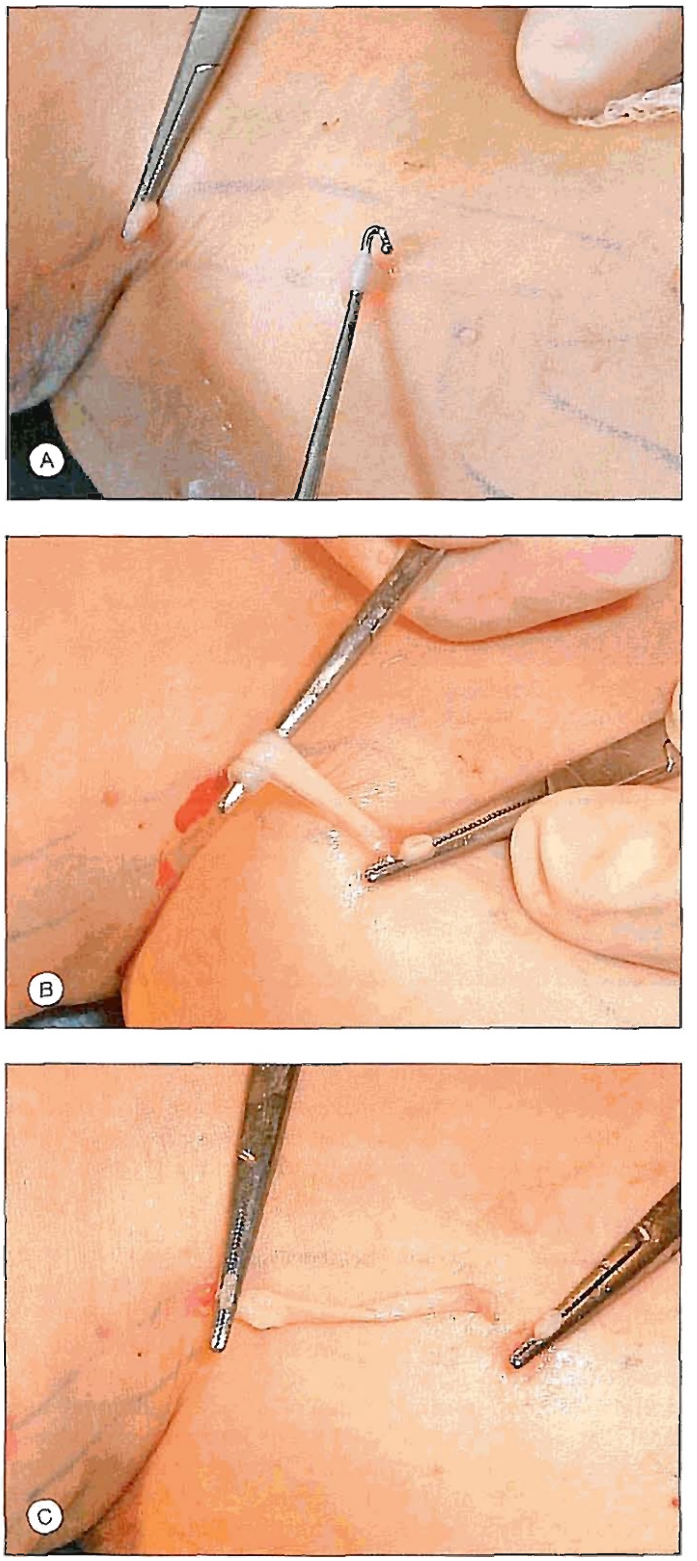

Fig. 38-15 Ambulatory phlebectomy. *A*, Hook used to secure the vein. *B*, Vein is clamped on either side and severed. Clamp is then used to remove the vein using a rolling and pulling technique. *C*, Removed vein segment. The distal end can be tied off using absorbable suture or additional segments can be removed using the same technique.

Fig. 38-16 Endovenous ablation, a radiofrequency catheter with deployable electrodes at the tip causes thermal destruction of the vein wall.

LIPOSUCTION

Liposuction is used for the removal of local areas of adipose and to improve the patient's body contour. Liposuction is not a treatment for obesity and should not be used as a weight loss mechanism. The most common areas treated in women are the abdomen and thighs. Other frequently treated sites include the neck, jowls, knees, ankles, and breasts. Other conditions such as gynecomastia, buffalo hump, lipoma, lipodystrophy, and axillary hyperhidrosis are all conditions that can be treated by liposuction.

The current technique employed by dermatologists involves infiltrating the treated area with dilute anesthesia and aspirating the fat via cannulas attached to a vacuum. Tumescent anesthesia typically consists of 0.05% to 0.1% lidocaine with 1:1,000,000 epinephrine and sodium bicarbonate. The total safe concentration of lidocaine that can be used is 55 mg/kg.

Much discussion has been raised regarding the safety of liposuction. It is important to stress that the serious complications seen in liposuction are associated with general anesthesia, and not with procedures performed with local tumescent anesthesia. While there have been reports of deaths occurring during liposuction, no reports have occurred when patients were treated with tumescent anesthesia alone. Office-based tumescent liposuction performed by dermatologic surgeons is safe and has a lower complication rate than hospital-based procedures.

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CHEMICAL PEELS

Superficial Peels

Peels are categorized by the level of injury they cause. Superficial peels cause wounding to the epidermis and may reach the papillary dermis. These peels are well tolerated by patients who have limited "down time" after treatment. Superficial peels are used in the treatment of photoaging, actinic keratoses, solar lentigenes, and pigmentary dyschromias. Given the limited nature of the injury induced by these peels, patients often need multiple treatments on a weekly or monthly basis to reach a desired result. However, patients need to understand that superficial peels cannot provide the improvement in wrinkles and deep furrows that may be possible with deeper injury peels.

Alpha-hydroxy acids (AHA) are naturally occurring agents found in foods, and glycolic and lactic acid are the

Table 38-3 Jessner's solution

Resorcinol	14 g
Salicyclic acid	14 g
85% lactic acid	14 g
95% ethanol qs ad	100 mL

most commonly used for peeling. The depth of injury is determined by the pH, the concentration of the acid, the amount applied, and the length of treatment time. Glycolic acid, in concentrations up to 70%, is commonly used for melasma, acne, and photoaging. Following rapid application to the entire face, it must be neutralized with sodium bicarbonate or plain water. Glycolic acid has been used in combination with 5-FU for the treatment of actinic keratoses, a so-called "fluor-hydroxy pulse peel."

Salicylic acid, a beta-hydroxy acid, can be used in concentrations of 20% to 30% for the treatment of acne and mild photoaging. It is also used in combination with other agents as part of the Jesnner's solution. Following application, patients experience some mild stinging and discomfort. A whitening of the skin is noted after 5 min. Salicylic acid does not require neutralization, although cool compresses after application can soothe the skin.

Trichloroacetic acid (TCA) in concentrations of 10% to 35% is used extensively as a light peel. The agent is applied and erythema and a white frost are noted within 1 min. Repeated applications can be used to achieve a deeper peel. TCA does not require neutralization after application.

Jessner's solution combines resourcinol, salicylic acid, and lactic acid in ethanol (Table 38-3). This superficial peel has keratolytic activity and is commonly used for acne or hyperkeratotic lesions. It is self neutralizing and multiple applications can be performed to obtain a deeper injury.

Solid CO_2 (dry ice) has been used alone and in combination with TCA to obtain a deeper peel. It has been proposed as an effective treatment for acne scars and as a way to potentiate the effect of TCA to achieve a deeper peel.

Medium Depth Peel

Medium depth chemical peeling is defined as a controlled wound to the epidermis and deep papillary dermis, often with some extension into the upper reticular dermis. In contrast to the multiple treatments that are often performed with superficial peels, medium depth peels are generally done as a single procedure due to the more significant injury produced. These peels cause epidermal necrosis and significant dermal injury, which results in increased collagen production during the wound healing process over the next several months. Medium depth peels are indicated for the treatment of mild-to-moderate photodamage, rhytids, pigmentary dyschromias, actinic keratoses, solar lentigenes, and other epidermal growths. Lawrence et al demonstrated a similar efficacy with Jessner's/35% TCA medium depth peel as compared to 5-FU in the treatment of widespread facial actinic keratoses.

The classic medium depth peel is 50% TCA. However, it is generally not used as a single-agent peel due to the increased incidence of complications, namely scarring and dyspigmentation. Rather, combining 35% TCA with an initial application of another agent, such as Jessner's solution or glycolic acid, can produce a medium depth injury without the complication associated with the higher concentration of TCA alone. As a result of the damage to the epidermis produced with the initial peel, the TCA is able to penetrate deeper and produce a more significant and even result.

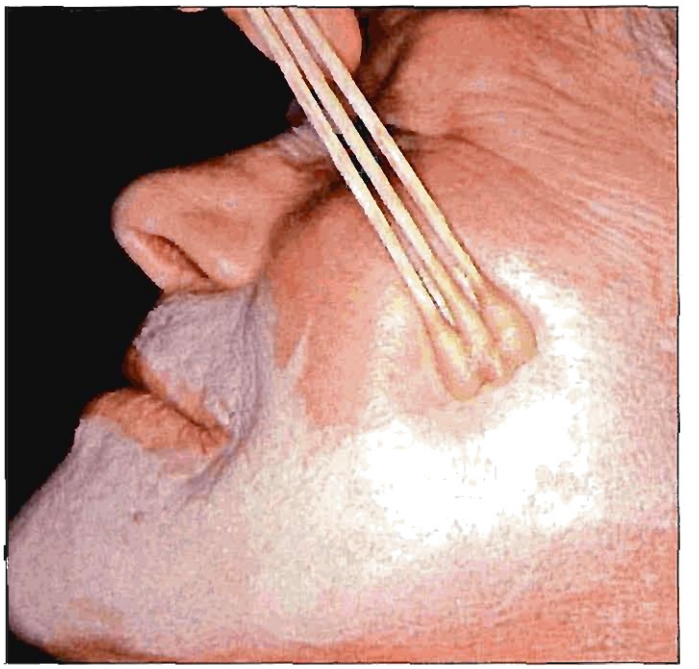

Fig. 38-17 Baker-Gordon phenol peel, white frosting following application. (Courtesy of Richard G Glogau, MD)

Table 38-4 Baker-Gordon formula

88% liquid phenol, USP	3 mL
Tap water	2 mL
Septisol® liquid soap	8 drops
Croton oil	3 drops

Deep Peel

Deep chemical peels are defined as an injury down to the mid-reticular dermis. These peels are indicated for patients with moderate-to-severe photodamage and advanced rhytids. These peels produce significant injury and patients have an extended period of healing following treatment.

Baker-Gordon formula phenol peel is the traditional deep peel (Fig. 38-17). Undiluted 88% phenol does not produce a deep or consistent injury because it causes complete coagulation of epidermal keratin proteins, thus blocking further penetration. The Baker-Gordon formula (Table 38-4) reduces the concentration of phenol to 55%; the croton oil acts as a keratolytic and potentiates the depth of penetration of the phenol. Cardiac monitoring is required since phenol can produce arrhythmias. Intravenous fluids are given before and during the peel to limit the serum concentrations of phenol. In addition, the face is divided into smaller cosmetic units which are treated individually. An approximately 15-min wait is required between treating each subunit, spreading the entire procedure over 1 to 2 h, and further limiting the systemic concentration of phenol. Following application, occlusive tape can be applied if a deeper wound is desired.

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