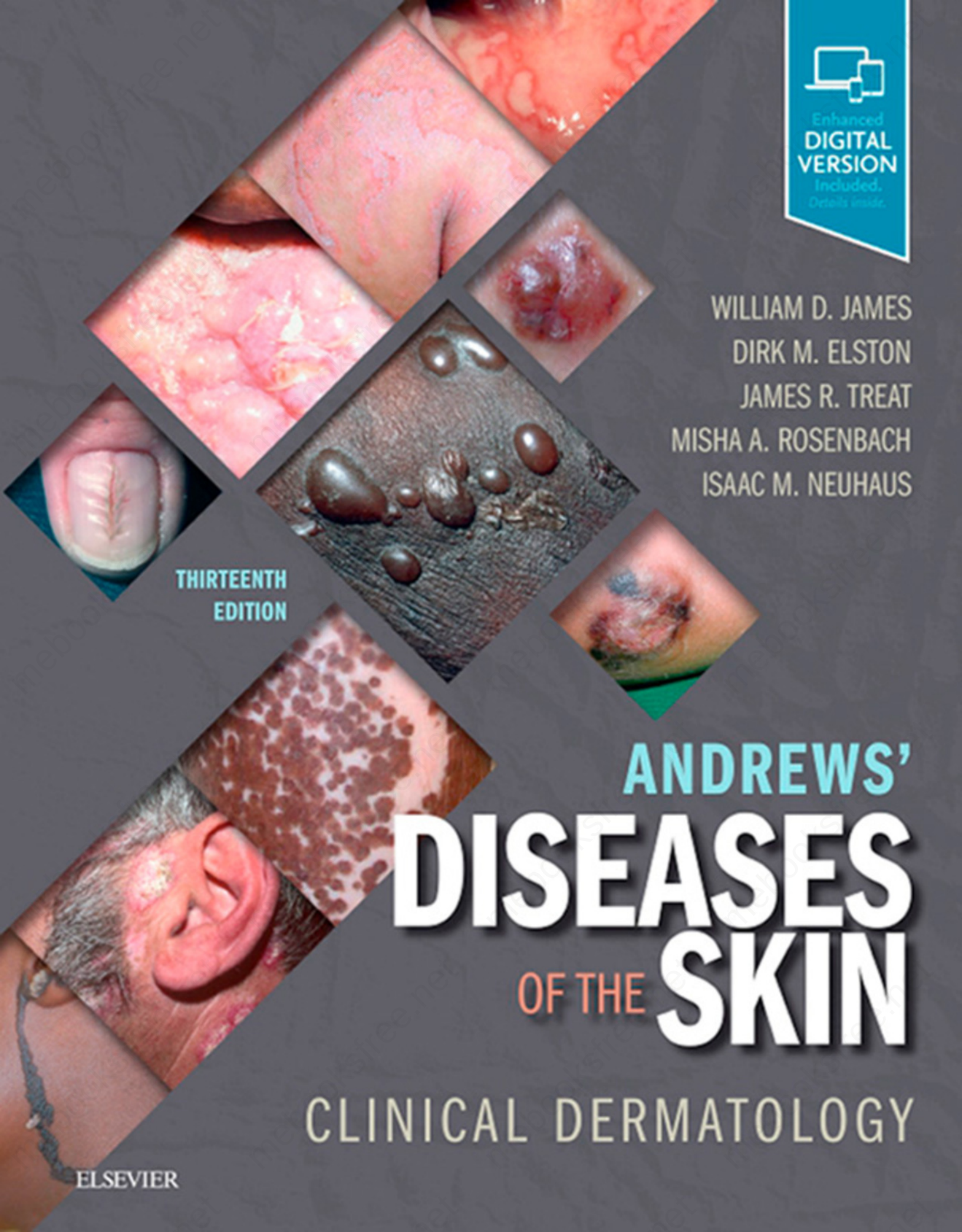
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Andrews' Diseases of the Skin
Clinical Dermatology

THIRTEENTH EDITION

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Video Contents

Preface and Acknowledgments to the Thirteenth Edition

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 are committed to keeping *Andrews'* as an excellent tool for anyone who needs help in diagnosing a patient with a clinical conundrum or treating a patient with a therapeutically challenging disease. This edition retains Drs. James, Elston and Neuhaus but we were saddened that Dr. Berger decided the 12th edition was his last. However, we are excited that two new experts have joined the team. Dr. Jim Treat is a superb pediatric dermatologist who was recruited to update many areas of the book. He is knowledgeable in investigations which have led to reclassification of diseases, insights into etiopathogenesis, and newer treatments. He also has updated the vascular anomalies portion of the text, reflecting the continuing improvements in our understanding of these important primarily pediatric conditions. Additionally, Dr. Misha Rosenbach agreed to add his expertise to *Andrews'*. He is a dually board certified internist and dermatologist who has prominent roles in the Medical Dermatology Society and Dermatology Hospitalist group. Dr. Rosenbach was able to update and revamp the adverse drug reaction section, as so many of the new chemotherapeutic agents and small molecular/targeted inhibitors are inducing novel eruptions. New diseases such as the interferonopathies and those along the JAK/STAT pathway, and updated therapeutics in such conditions as autoimmune blistering conditions are also described in his sections of the text.

Andrews' is primarily intended for the practicing dermatologist. It is meant to be used on the desktop of his or her clinic, giving consistent, concise advice on the whole spectrum of clinical situations faced in the course of a busy workday. While we have been true to our commitment to a single-volume work, we provide our text in a convenient online format as well. 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 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. On our collective trips around the world, we have been gratified to see our international colleagues studying *Andrews'*. Thousands of books have been purchased by Chinese and Brazilian dermatologists alone.

Many major changes have been made to this edition. The new authorship team has worked closely to continue to improve the quality of our text. The surgical chapters have been updated and expanded by Isaac Neuhaus. He has added more videos to complement those already online. He has as well information on new cosmetic procedures. We thank him for his continued work to improve this portion of our textbook. 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, netrophilic eccrine hidradenitis, for example, could be presented under drug eruptions, netrophilic reactive conditions, infection or cancer-associated disease, or with eccrine disorders. The final decisions are 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 the addition over 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 discoveries as new tools in the diagnosis and treatment of lymphoma; new staging, diagnostic modalities and treatment for melanoma and non-melanoma skin cancers; new treatment paradigms for hair disorders; and new biologics for psoriasis and JAK inhibitors for alopecia area and vitilago. We have attempted to define therapeutics 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. Not all are fully supported by formal evidence, yet are helpful to individual patients.

Extensive revisions were necessary to add this wealth of new information. We 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. A major effort in this edition was to reillustrate the text with hundreds of new color images. Many have been added to the printed text; you will also find a number only in the online version. Enjoy! We have looked to our own collections to accomplish this. Two years ago we published an Atlas to accompany this textbook. Many newer photos in our text are included in the Atlas. The Atlas has over 3000 images covering the depth and breadth of our specialty and is a superb companion to this textbook. We are able to present these photos due to 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.

All of the authors recognize the importance of our mentors, teachers, colleagues, residents, and patients in forming our collective expertise in dermatology. Dirk and Bill were trained in military programs, and our indebtedness to this fellowship of clinicians in unbounded. Jim and Misha were trained and continue to teach, see patients and publish at the University of Pennsylvania. Isaac is a

product of our sister institution, The University of California, San Francisco. The other institutions we have called home, including Walter Reed, Geisinger Medical Center, Brooke in San Antonio, the Cleveland Clinic, and the Medical University of South Carolina, nurtured us and expanded our horizons. Our friendship goes well beyond the limits of our profession; it is wonderful to work with people you not only respect as colleagues, but also enjoy as closely as family. Jennifer Lu and Barbara Lang provided expert assistance throughout the revision process to Bill. He is indebted to them for their hard work. Finally, we are proud to be a part of the Elsevier team and have such professionals as Charlotta Kryhl, Louise Cook, and Andrew Riley supporting us every step of the way.

WDJ
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For my wife Ann, my son Dan and his family Wynn, Declan and Driscoll and my daughter Becca. You make my life joy-filled with your love.

—WDJ

To my wife and best friend, Kathy, and our wonderful children, Carly and Nate.

—DME

To my incredible wife and our 2 amazing girls, thank you for filling our lives with joy and love.

—JRT

To Jake, Lara, and Anna, my loving and supportive family – thank you for your support and your patience with me during all those weekends I had to work. I love you all so very much.

—MAR

To my amazing ladies- Tammy, Leah, Josie and Anna.

—IMN

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1 Skin: Basic Structure and Function

Bonus images for this chapter can be found online at expertconsult.inkling.com

Skin is composed of three layers: the epidermis, dermis, and subcutaneous fat (panniculus) (Fig. 1.1). The outermost layer, the epidermis, is composed of viable keratinocytes covered by a layer of keratin, the stratum corneum. The principal component of the dermis is the fibrillar structural protein collagen. The dermis lies on the panniculus, which is composed of lobules of lipocytes separated by collagenous septa that contain the neurovascular bundles.

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 30–40 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 ADNEXA

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. An additional cell, the Merkel cell, can be found in the basal layer of the palms and soles, oral and genital mucosa, nail bed, and follicular infundibula. Located directly above the basement membrane zone, Merkel cells 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 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. 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 can be divided into the innermost basal layer (stratum germinativum), the malpighian or prickle layer (stratum spinosum), the granular layer (stratum granulosum), and the 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 (Fig. 1.3). 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. Histones appear to regulate epidermal differentiation, and histone deacetylation suppresses expression of profilaggrin. 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, as well as the hair bulge. 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, within its cytoplasm the keratinocyte accumulates intermediate filaments composed of a fibrous protein, keratin, arranged in an α-helical coiled pattern. These tonofilaments are fashioned into bundles, which converge on and terminate at the plasma membrane, where they end in specialized attachment plates called desmosomes. 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 called 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. Degradation of the mitochondrial network within keratinocytes occurs with aging. Oxidation injury to keratinocytes occurs with environmental exposure and thermal burns, and can be partially prevented by vitamin C in the form of L-ascorbic acid.

Premature programmed cell death, or apoptosis, appears in hematoxylin and eosin (H&E)–stained sections as scattered bright-red cells, some of which may contain small, black pyknotic nuclei. These cells are present at various levels of the epidermis, because 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. Lamellar granules contribute to skin cohesion and impermeability. Conditions such as lamellar ichthyosis and Flegel hyperkeratosis demonstrate abnormal lamellar granules. Glycolipids such as ceramides

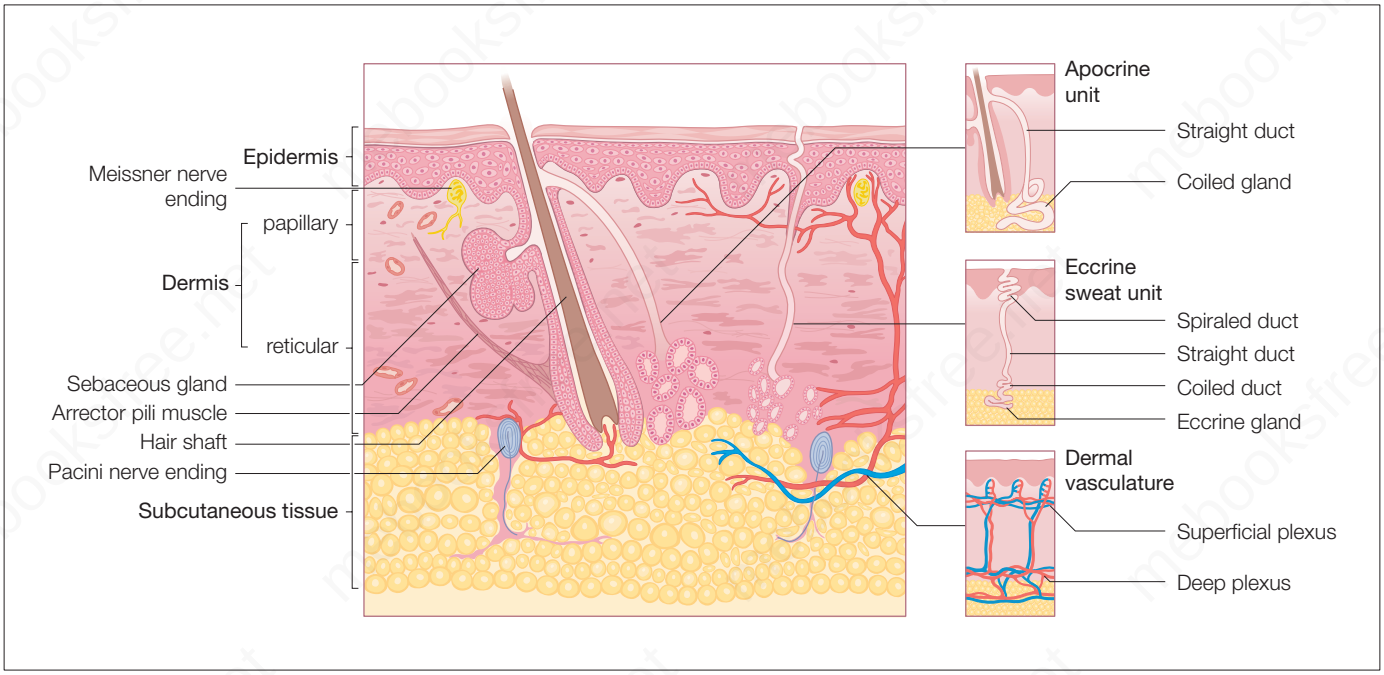

Fig. 1.1 Diagrammatic cross section of the skin and panniculus.

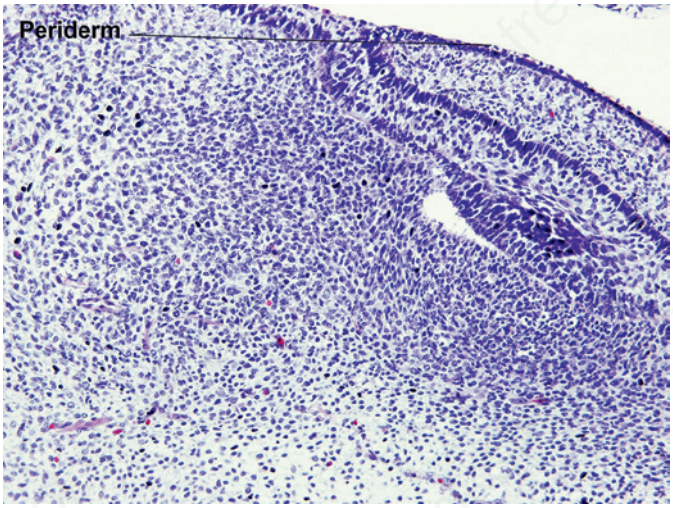

Fig. 1.2 In early fetal life, a cuboidal periderm is present, rather than an epidermis. Fetal skin, H&E × 40.

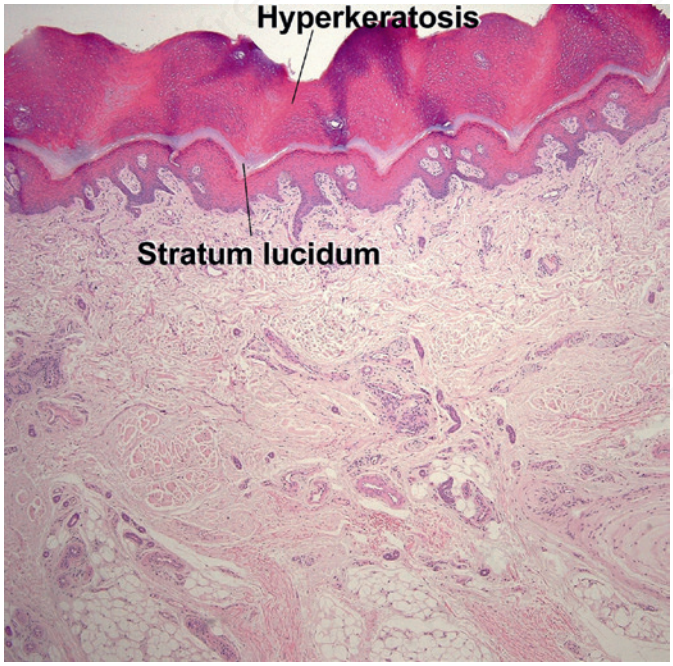

Fig. 1.3 Volar skin demonstrating a thick corneum and dermis, H&E × 100.

contribute a water-barrier function to skin and are typically found in topical products meant to restore the epidermal barrier. Lamellar bodies form abnormally in the absence of critical ceramides such as glucosylceramide, or there is disproportion of critical lipids. Desmosomal adhesion depends on cadherins, including the calcium-dependent desmogleins and desmocollins. Antibodies to these molecules result in immunobullous diseases, but desmogleins function not only in adhesion but also in differentiation. The binding of the desmoglein 1 cytoplasmic tail to the scaffolding-protein Erbin downregulates the Ras-Raf pathway to promote stratification and differentiation of keratinocytes in the epidermis.

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, 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. Kallikrein-related peptidase 5, a serine protease secreted from lamellar granules, appears to function in profilaggrin cleavage.

Keratohyalin 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, these cells participate in the induction of the immune response, rather than acting as passive casualties. Keratinocytes secrete a wide array of cytokines and inflammatory mediators, including tumor necrosis factor–alpha (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, suggesting that keratinocytes actively respond to immune effector signals.

During wound healing, epithelial cell migration occurs before dermal remodeling. Tight junction proteins claudin-1 and occludin are critical for effective migration. Downregulation of claudin-1 expression results in delayed migration and reduced epithelial proliferation. For occludin, downregulation impairs wound healing when cells are also subjected to mechanical stress. Wound healing occurs best in a moist environment but can be impaired by excessive maceration.

Melanocytes

Melanocytes 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 about 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 melanocyte/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. 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.

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. Melanocytes in red-haired individuals tend to be rounder and to produce more pheomelanin. The melanocortin 1 receptor (MC1R) is important in the regulation of melanin production. Loss-of-function mutations in the *MC1R* gene bring about a change from eumelanin to pheomelanin production, whereas activating gene mutations can enhance eumelanin synthesis. Most redheads are compound heterozygotes or homozygotes for a variety of loss-of-function mutations in this gene.

Antimicrobial peptides, including cathelicidin and β-defensins, are key components of the innate immune system. They protect against infection, are implicated in the pathogenesis of atopic dermatitis, and play a role in control of pigmentation. The β-defensins encompass a class of small, cationic proteins important to both the innate and the adaptive immune system. β-Defensin 3 also functions as a melanocortin receptor ligand.

Eumelanin production is optimal at pH 6.8, and changes in cellular pH also result in alterations of melanin production and the eumelanin/pheomelanin 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 pyrimidine dimer formation can be assessed using gas chromatography–mass spectrometry or enzyme-linked immunosorbent assays. Pigment within melanocytes also serves to protect the melanocytes themselves against photodamage, such as ultraviolet A (UVA)–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. Melanocytes and keratinocytes express neurotrophins (ectodermal nerve growth factors). Melanocytes release neurotrophin 4, but the release is downregulated by ultraviolet B (UVB) irradiation, suggesting neurotrophins as possible targets for therapy of disorders of pigmentation. Melanocytes express toll-like receptors (TLRs) and stimulation by bacterial lipopolysaccharides increases pigmentation. Melatonin and its metabolites protect melanocytes from UVB damage.

Langerhans Cells

Langerhans cells are normally found scattered among keratinocytes of the stratum spinosum. They constitute 3%–5% of the cells in this layer. As with melanocytes, Langerhans cells are not connected to adjacent keratinocytes by the desmosomes. The highest density of Langerhans cells in the oral mucosa occurs in the vestibular region, and the lowest density is in the sublingual region, suggesting the latter is a relatively immunologically "privileged" site.

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 CD1α or S-100 immunostains. Ultrastructurally, they are characterized by a folded nucleus and distinct intracytoplasmic organelles called Birbeck granules. In their fully developed form, the organelles are rod shaped with a vacuole at one end, resembling 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 as well as humoral immunity. 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. Langerhans cells express langerin, membrane adenosine triphosphatase (ATPase, CD39), and CCR6, whereas CD1α+ dermal dendritic cells express macrophage mannose receptor, CD36, factor XIIIa, and chemokine receptor 5, suggesting different functions for these two CD1α+ populations. 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-12 (IL-12), the macrophages found in the epidermis 72 hours 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.

Vaccine studies suggest the importance of various cutaneous dendritic cells. Microneedle delivery of vaccine into skin can provoke CD8+ T-cell expansion mediated by CD11c(+) CD11b(+) langerin-negative dendritic cells. Intradermal immunization is dependent on Langerhans cells to stimulate follicular T helper cells and germinal center formation.

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DERMOEPIDERMAL JUNCTION

The junction of the epidermis and dermis is formed by the basement membrane zone (BMZ). 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 periodic acid–Schiff (PAS)–positive basement membrane is composed of the fibrous components. The basal lamina is synthesized by the 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 BP230 (bullous pemphigoid antigen 1) and BP180 (bullous pemphigoid antigen 2, type XVII collagen).

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. Laminin 5 (laminin-332) is a component of the lamina lucida/lamina densa interface, and collagen IV is the major component of the lamina densa. 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, whereas abundant hemidesmosomes stabilize the upper portion of the follicle.

The 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 also helps regulate growth, adhesion, and movement of keratinocytes and fibroblasts, as well as apoptosis. Much of this regulation takes place through activation of integrins and syndecans. Extracellular matrix protein 1 demonstrates loss-of-function mutations in lipoid proteinosis, resulting in reduplication of the basement membrane.

Breitkreutz D, et al: Skin basement membrane. Biomed Res Int 2013; 2013: 179784.

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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. Hedgehog signaling by the transducer known as *smoothened* appears critical for hair development. Abnormalities in this pathway contribute to the formation of pilar tumors and basal cell carcinoma. In the absence of hedgehog signaling, embryonic hair germs may develop instead into modified sweat gland or mammary epithelium.

Although the various adnexal structures serve specific functions, all can function as reserve epidermis, in that reepithelialization occurs after injury to the surface epidermis, principally because 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 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 adnexa will slowly fill with granulation tissue until they are flush with the surrounding skin. In contrast, areas rich in adnexa will quickly be covered with epithelium. No more granulation tissue will form, and the contour defect created by the saucerization will persist.

The 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 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. 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 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: large, pale, glycogen-rich cells and smaller, darker-staining cells. The pale glycogen-rich cells are thought to initiate the formation of sweat. The darker cells may function similar to cells of the dermal duct, which actively reabsorb sodium, thereby modifying sweat from a basically isotonic to a hypotonic solution by the time it reaches the skin surface. Sweat is similar in composition to plasma, containing the same electrolytes, but 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. In most other mammals, the apocrine gland is the major sweat gland.

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.

The coiled secretory gland is located at the junction of the dermis and subcutaneous fat (Fig. 1.4). 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 apices 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 surrounds 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 apocrine secretion.

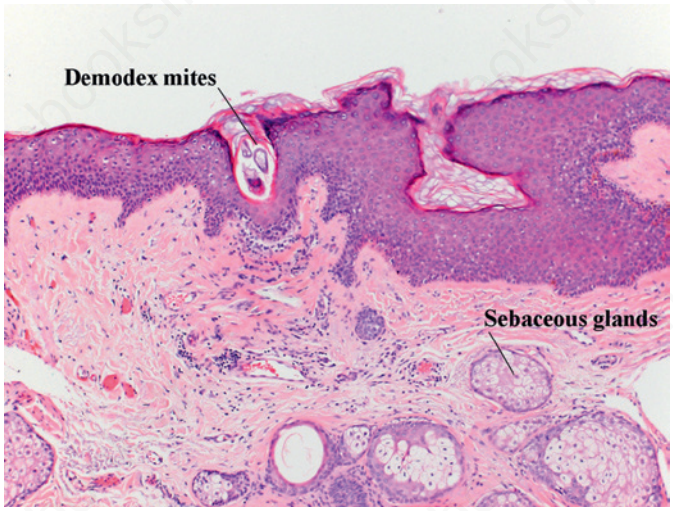

Fig. 1.4 Axillary skin is rugose and demonstrates large apocrine glands. Axillary skin, H&E × 40.

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 stroma of the sebaceous nevus 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, representing 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 bud develops into the sebaceous gland, and a lower bud 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

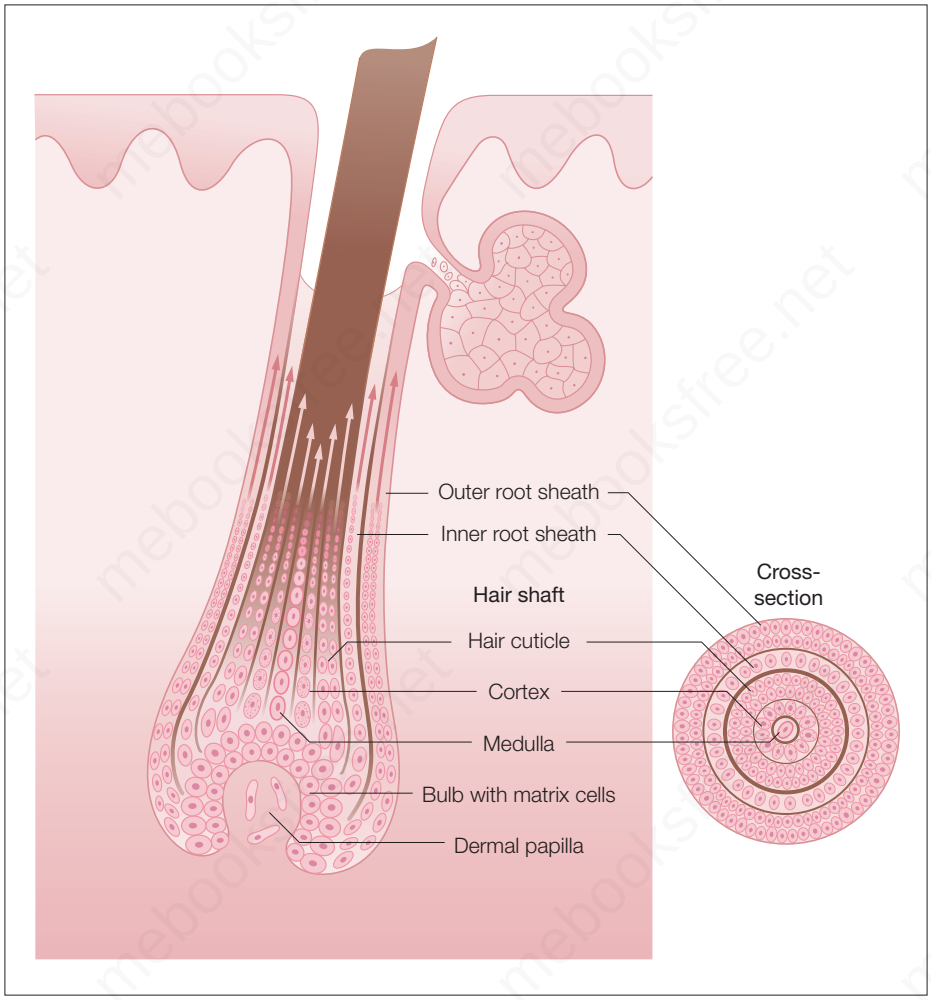

Fig. 1.5 Anatomy of the hair follicle. Additional eFigures are available.

units. The density of pilosebaceous units decreases throughout life, possibly because of dropout 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 an outer root sheath, is produced by the matrix portion of the hair bulb (Fig. 1.5). The sheaths and contained hair form concentric cylindrical layers. The hair shaft and inner root sheath move together as the hair grows upward 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 3–5 years. Normally, about 85%–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 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 3–5 months. Most sites on the body have a much shorter anagen and much longer telogen, resulting in short hairs that stay in place for long periods without growing longer. Prolongation of the anagen phase results in long eyelashes in patients with acquired immunodeficiency syndrome (AIDS).

Human hair growth is cyclic, but each follicle functions as an independent unit and regulatory T cells play a role in control of follicular stem cells and hair regeneration (Fig. 1.6). Humans do not 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.

Pregnancy is typically accompanied by retention of an increased number of scalp hairs in anagen, 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. Between 3 and 5 months later, a more profound effluvium is noted. Patients receiving 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 growing anagen hair is characterized by a pigmented bulb and an inner root sheath. Histologically, catagen hairs are best identified by the presence of many apoptotic cells in the outer root sheath. 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 flamethrower-like

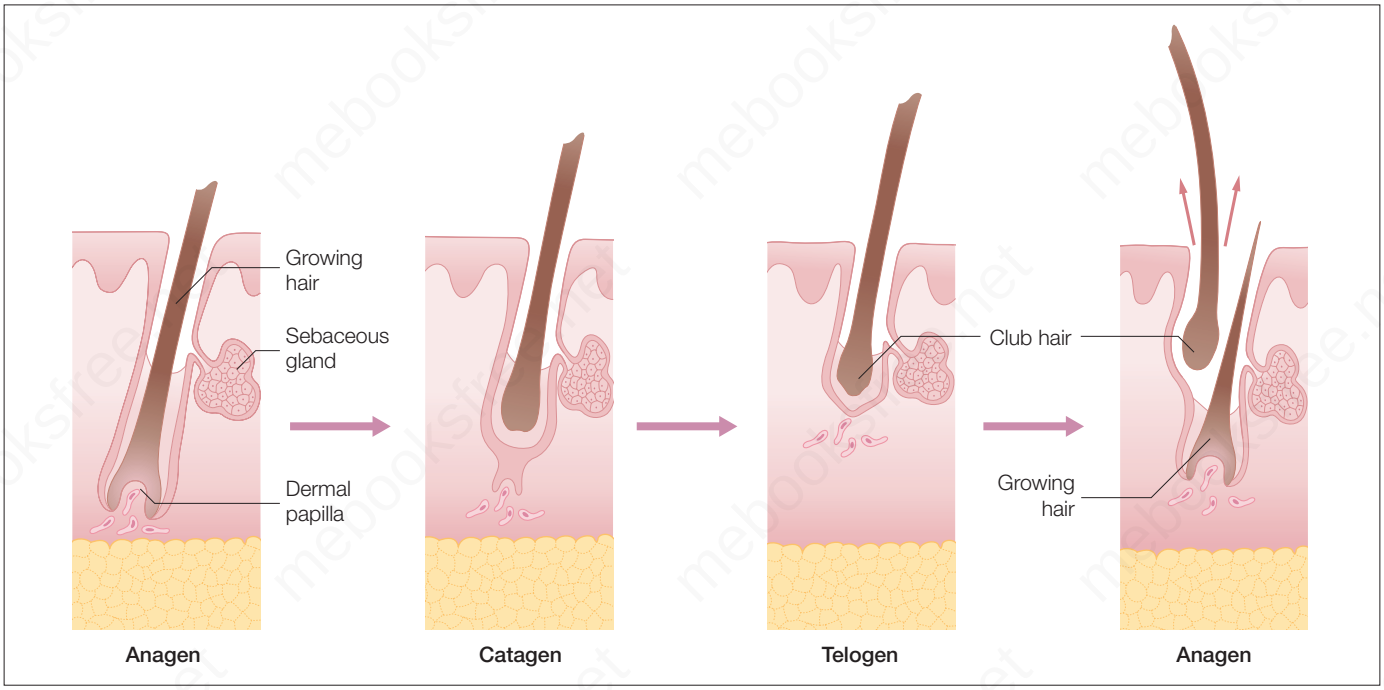

Fig. 1.6 Phases of the growth cycle of a hair.

appearance in vertical H&E sections. 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 this, along with curvature of the follicle just above the bulb, causes black hair to be curly. Uncombable hair is triangular with a central canal. Hair shape is at least partially controlled by the trichohyalin gene.

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 of hair results from a decreased number of melanocytes, which produces fewer melanosomes. Repetitive oxidative stress causes apoptosis of hair follicle melanocytes, resulting in normal hair graying. Premature graying is related to exhaustion of the melanocyte stem cell pool.

Although the genetics of balding is complex, it is known that polymorphisms in the androgen receptor gene are carried on the X chromosome, inherited from the mother. The genetics of female pattern hair loss is less clear, because polymorphisms in the androgen receptor do not appear to be associated with female-pattern hair loss, and adrenal androgens may play a larger role.

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 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 a shark's teeth. This same undulating cuticle is seen in steatocystoma and some dermoid cysts.

Sebaceous glands are found in greatest abundance on the face and scalp, although 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).

Most lipids produced by the sebaceous gland are also produced elsewhere in the body. Wax esters and squalene are unique secretory products of sebaceous glands. Sebocytes express histamine receptors, and antihistamines can reduce squalene levels, suggesting that antihistamines could play a role in modulating sebum production. Skin lipids contribute to the barrier function, and some have antimicrobial properties. Antimicrobial lipids include free sphingoid bases derived from epidermal ceramides and fatty acids (e.g., sapienic acid) derived from sebaceous triglycerides.

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Horsley V, et al: T(regs) expand the skin stem cell niche. Dev Cell 2017; 41: 455.
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Nails

Nails act to assist in grasping small objects and in protecting the fingertip from trauma and serve a sensory function. Pacinian corpuscle-like structures are present in the nail bed of human fetuses, but are difficult to identify in adults. Fingernails grow an average of 0.1 mm/day, requiring about 4–6 months to replace a complete nail plate. The growth rate is much slower for toenails, with 12–18 months required to replace the great toenail.

The keratin types found in the nail are a mixture of epidermal and hair types, with the hair types predominating. Nail isthmus keratinization differs from that of the nail bed in that keratin 10 is only present in nail isthmus. Brittle nails demonstrate widening of the intercellular space between nail keratinocytes on electron microscopy.

Whereas most of the skin is characterized by rete pegs that resemble an egg crate, the nail bed has true parallel rete ridges. These ridges result in the formation of splinter hemorrhages when small quantities of extravasated red blood 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 (distal portion of 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 nail bed. The location of a melanocytic lesion within the matrix can be assessed by the presence of pigment within the dorsal or ventral nail plate.

Baswan S, et al: Understanding the formidable nail barrier. Mycoses 2017; 60: 284.

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DERMIS

The constituents of the dermis are mesodermal in origin except for nerves, which, as with melanocytes, derive from the neural crest. Until the sixth week of fetal life, the dermis is merely a pool of scattered dendritic-shaped cells containing acid mucopolysaccharide, 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. During fetal development, Wnt/β-catenin signaling is critical for differentiation of ventral versus dorsal dermis, and the dermis then serves as a scaffold for the adnexal structures identified with ventral or dorsal sites.

Infant dermis is composed of small collagen bundles that stain deeply red. Many fibroblasts are present. In adult dermis, few fibroblasts persist; 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 dendrocytes 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. Collagen 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 (dermis below level of postcapillary venule). Collagen I messenger ribonucleic acid (mRNA) and collagen III mRNA are both expressed in the reticular and papillary dermis and are downregulated by UV light, as is the collagen regulatory proteoglycan decorin. This downregulation may play a role in photoaging.

Type IV collagen is found in the BMZ. Type VII collagen is the major structural component of anchoring fibrils and is produced predominantly 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 acid mucopolysaccharides and fibronectin. They can be stimulated to produce fibronectin by agents such as phytosphingosine-1-phosphate and epidermal growth factor.

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 mucopolysaccharides stain with colloidal iron and with alcian blue at both pH 2.5 and pH 0.5. They stain metachromatically with toluidine blue at both pH 3.0 and pH 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 toluidine blue (metachromatically), but only at the higher pH for each stain.

Collagen is the major stress-resistant material of the skin. Elastic fibers contribute 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 Marfan syndrome and pseudoxanthoma elasticum.

Vasculature

The dermal vasculature consists principally of two intercommunicating plexuses. The subpapillary plexus, or upper horizontal network, contains the postcapillary venules and courses at the junction of the papillary and reticular dermis (Fig. 1.7). 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.

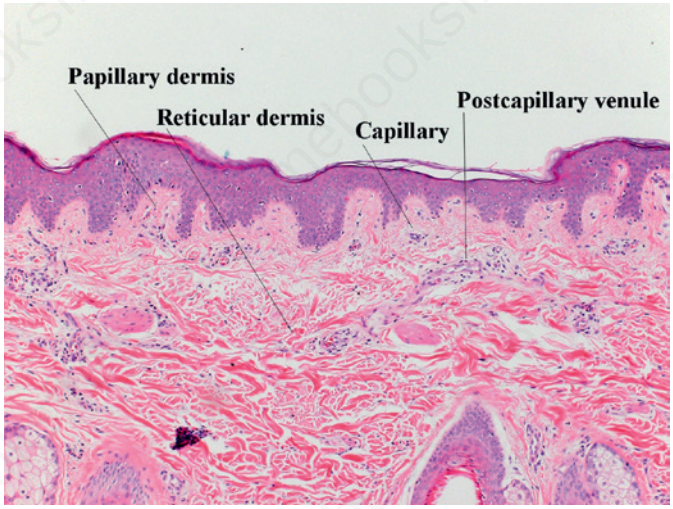

Fig. 1.7 Below the epidermis, the papillary dermis is composed of fine, nonbundled collagen. Capillaries are present within the papillary dermis, and the postcapillary venule sits at the junction of the papillary and reticular dermis. H&E × 40.

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 arrectores pilorum are attached to the hair follicles below the sebaceous glands and, in contracting, pull the hair follicle upward, producing gooseflesh. The presence of scattered smooth muscle throughout the dermis is typical of anogenital skin.

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 crisscross at right angles. Arterial smooth muscle forms a concentric, wreathlike 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. Most smooth muscle expresses desmin intermediate filaments, but vascular smooth muscle instead expresses vimentin. Smooth muscle actin is consistently expressed by all types of smooth muscle.

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

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 an important clue to the diagnosis of Hansen disease.

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: 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 that 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. Signal transduction differs for sensations of heat and cold and in peripheral nerve axons.

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

Mast cells play an important role in the normal immune response, as well as immediate-type sensitivity, contact allergy, and fibrosis. Measuring 6–12 microns in diameter, with ample amphophilic cytoplasm and a small round central nucleus, normal mast cells resemble fried eggs in histologic sections. In telangiectasia macularis eruptiva 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 0.6–0.7 micron in diameter. Coarse particulate granules, crystalline granules, and granules containing scrolls may be seen. On the cell's surface are 100,000–500,000 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 Giemsa 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 the 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 and then a 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 used to assess apoptosis and demonstrates decreased staining in mastocytomas. Proliferation usually is only moderately enhanced.

SUBCUTANEOUS TISSUE (FAT)

Beneath the dermis lies the panniculus, with lobules of fat cells or lipocytes separated by fibrous septa composed of collagen and large blood vessels (Fig. 1.8). 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. It is an important site of hormone conversion, such as that of androstenedione into estrone by aromatase. Leptin, a hormone produced in lipocytes, regulates body weight through the hypothalamus and influences how we react to flavors in food. Various substances can affect lipid accumulation within lipocytes. Obestatin is a polypeptide that

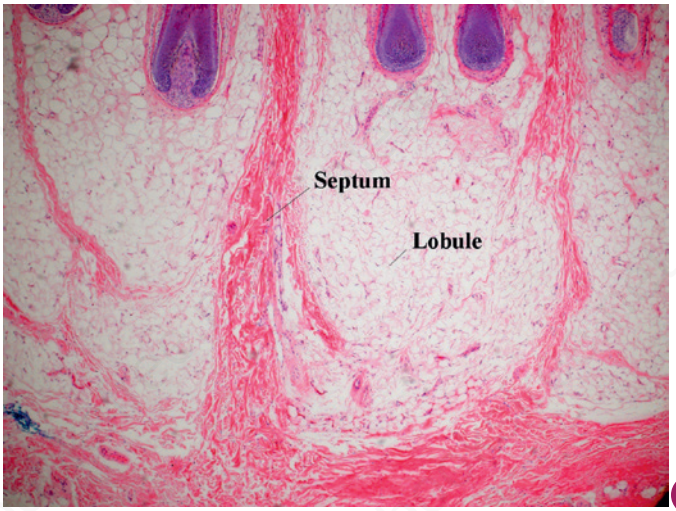

Fig. 1.8 The lobules of the subcutaneous fat are separated by fibrous septae. H&E × 40.

reduces feed intake and weight gain in rodents. (–)Ternatin, a highly *N*-methylated cyclic heptapeptide that inhibits fat accumulation, produced by the mushroom *Coriolus versicolor*; has similar effects in mice. Study of these molecules provides insight into the molecular basis of weight gain and obesity. 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 intraabdominal 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, serves to distinguish various conditions that may be clinically similar.

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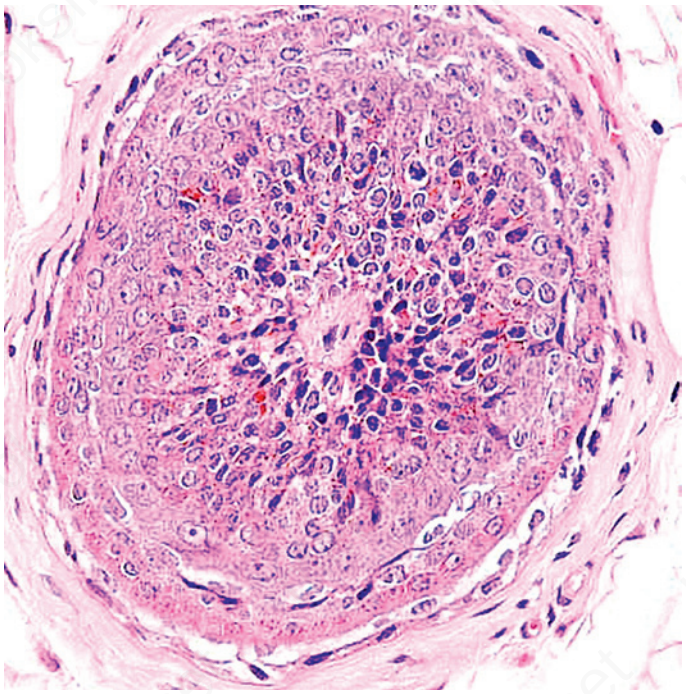
Bonus images for this chapter can be found online at **expertconsult.inkling.com**

eFig. 1.1 Cross section of anagen bulb demonstrating pigment within matrix.

eFig. 1.2 Cross section of isthmus of anagen follicle demonstrating glycogenated outer root sheath and keratinized inner root sheath.

eFig. 1.3 Catagen hair with many apoptotic keratinocytes within the outer root sheath.

eFig. 1.4 Vertical section of telogen hair demonstrating "flame-thrower" appearance of club hair.



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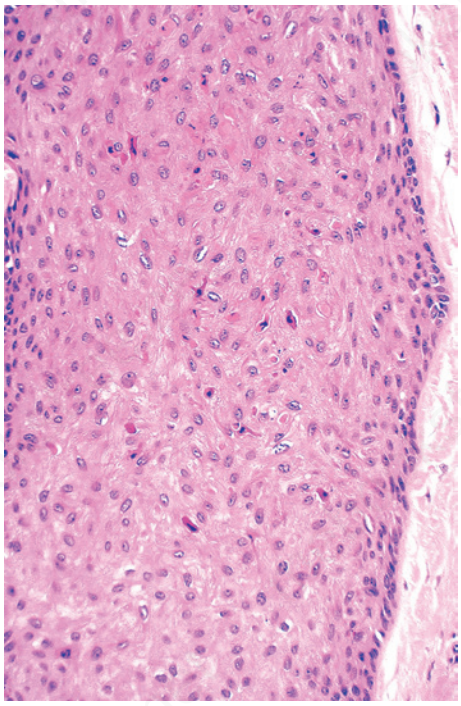

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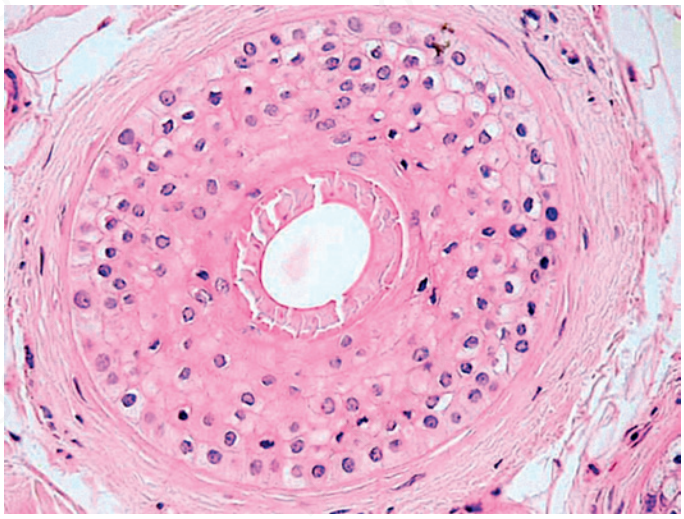

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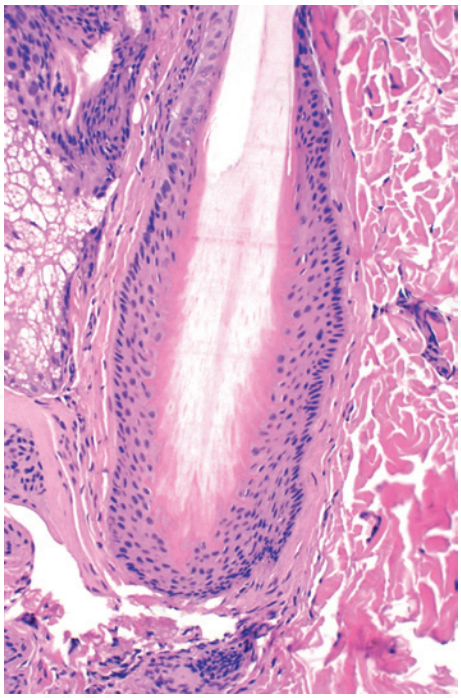

eFig. 1.4 Vertical section of telogen hair demonstrating "flamethrower" appearance of club hair. Additional eFigures are available in the electronic version.

2 Cutaneous Signs and Diagnosis

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In some patients, the appearance of skin lesions may be so distinctive that the diagnosis is clear at a glance. In others, subjective symptoms and clinical signs alone are inadequate, and a complete history and laboratory examination, 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, the diagnosis in dermatology 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 present with lesions that have distinct characteristics. They may be uniform or diverse in size, shape, and color or 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.

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 may fade into the surrounding skin. Macules may constitute the whole lesion or part of the eruption or may be merely an early phase. If the lesions become slightly raised, they are then designated papules or, in some cases, 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 (eczema), yellowish (xanthoma), or black (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.

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 or to pustules, or they may erode before regression takes place.

The term "maculopapular" should not be used. There is no such thing as a "maculopapule," although there may be both macules and papules in an eruption. 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.

Nodules

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

Tumors

Tumors are soft or firm, freely movable or fixed masses of various sizes and shapes, but usually are 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 cases are pedunculated (neurofibromas). 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, plateaulike elevations of various sizes (Fig. 2.4). They are usually oval or of arcuate contours, pink to red, and surrounded by a "flare" of macular erythema. Wheals may be discrete or may coalesce. These lesions often develop quickly (minutes to hours). Because the wheal is the prototypic lesion of urticaria, diseases in which wheals are prominent are frequently described as "urticarial" (e.g., urticarial vasculitis). Dermatographism, or pressure-induced whealing, may be evident.

Vesicles (Blisters)

Vesicles are circumscribed, fluid-containing elevations 1–0 mm in size (Fig. 2.5). They may be clear 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 (e.g., 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. They may break spontaneously or develop into bullae through coalescence or enlargement. The

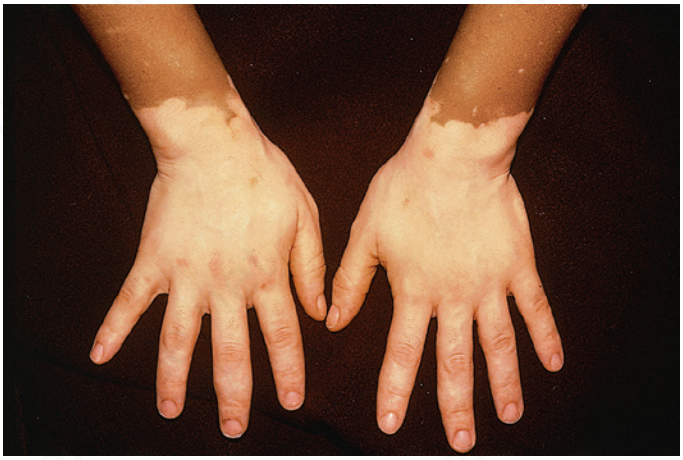


Fig. 2.1 Macular depigmentation, vitiligo.

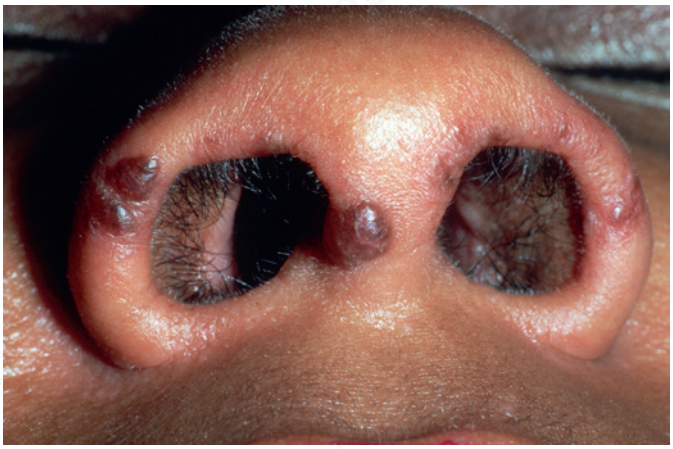


Fig. 2.2 Sarcoidosis (papules).

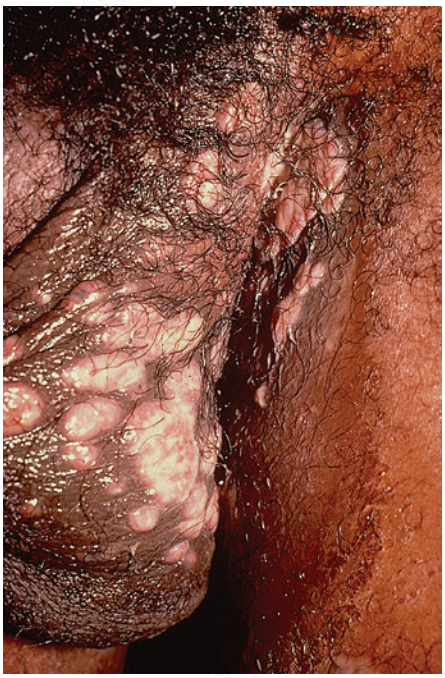


Fig. 2.3 Moist plaques of condyloma lata.

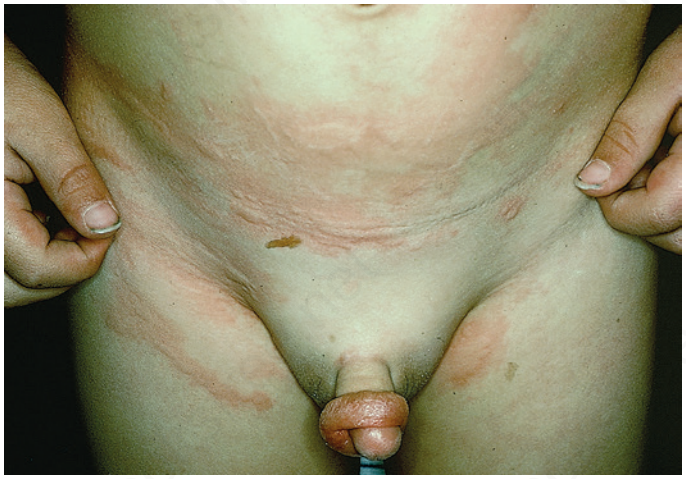


Fig. 2.4 Acute urticaria.

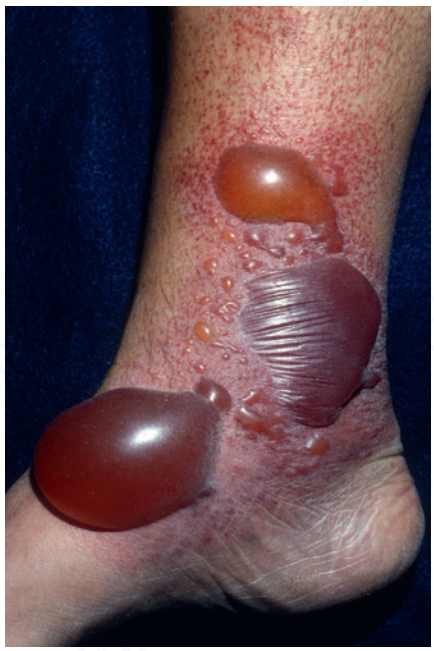


Fig. 2.5 Piroxicam hypersensitivity (vesicles and bullae, some with hemorrhage).

inflammatory process may lead to pustule formation. When the contents are of a seropurulent character, the lesions are known as vesicopustules. Vesicles have either a single cavity (unilocular) or several compartments (multilocular).

Bullae

Bullae are rounded or irregularly shaped blisters containing serous or serosanguineous fluid. They differ from vesicles only in size, being larger than 1 cm (see Fig. 2.5). They are usually unilocular but may be multilocular. Bullae may be located superficially in the epidermis, so 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. Alternatively the broken bleb may leave a raw and moist base, which may be covered with seropurulent or purulent exudate. Less frequently, irregular vegetations may appear on the base (as in pemphigus vegetans). When subepidermal, the bullae are tense, do not rupture easily, and are often present when the patient is examined.

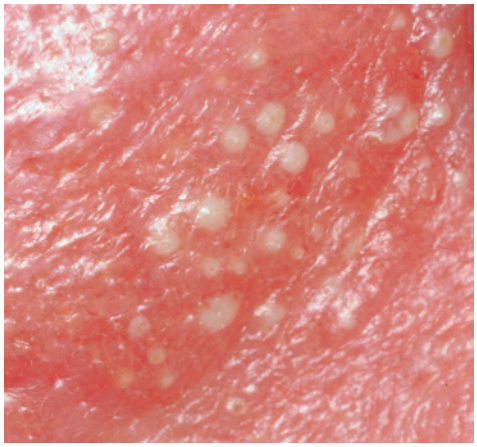


Fig. 2.6 Staphylococcal folliculitis (pustules).

Nikolsky sign refers to the diagnostic maneuver of putting lateral pressure on unblistered skin in a patient with a bullous eruption; a positive result occurs when the epithelium shears off. Asboe-Hansen sign refers to the extension of a blister to adjacent, unblistered skin when pressure is put on the top of the blister. Both these signs demonstrate the principle that in some diseases, the extent of microscopic vesiculation is more than what 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. 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. 2.6). They are similar to vesicles in shape and usually have an inflammatory areola. Pustules are usually white or yellow centrally but have a red tinge 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 types; 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 disturbed, pathologic exfoliation results, producing scales. These scales vary in size; some are fine, delicate, and branny, as in tinea versicolor, whereas others are coarser, as in eczema and ichthyosis, and still others are stratified, as in psoriasis. 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 suggests a pathologic process in the epidermis, and parakeratosis is often present histologically.

Crusts (Scabs)

Crusts are dried serum, pus, or blood, usually mixed with epithelial and sometimes bacterial debris. 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 sometimes reaching the papillary layer of the dermis. Excoriations are caused by scratching with the fingernails in an effort to relieve itching. 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 the excoriations, the more severe is 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 several centimeters in length with sharply defined margins. Fissures may be dry or moist, red, straight, curved, irregular, or branching. They occur most often 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 around 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.

Erosions

Loss of all or portions of the epidermis alone, as in impetigo, 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 centimeters (Fig. 2.7). Ulcers 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 deeply into the dermis, subcutaneous tissues, or deeper, as with leg ulcers. Ulcers heal with scarring.

Scars

Scars are composed of new connective tissue that has replaced lost substance in the dermis or deeper parts resulting from 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

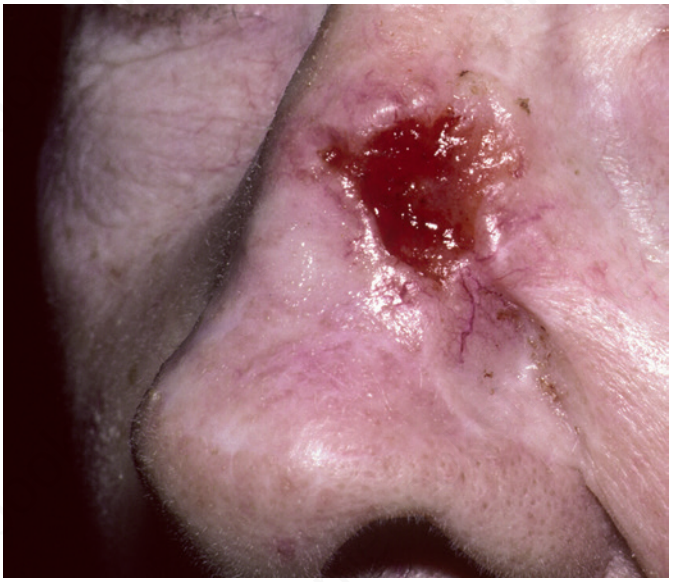


Fig. 2.7 Basal cell carcinoma (ulcer). (Courtesy Steven Binnick, MD.)

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 occurring on the scalp. Scars may be thin and atrophic, or the fibrous elements may develop into neoplastic overgrowths, as in hypertrophic scars or keloids. Some individuals and some areas of the body, especially the anterior chest and upper back, are especially prone to hypertrophic scarring. Scars first tend to be pink or violaceous, later becoming white, glistening, and, rarely, hyperpigmented. Scars are persistent but usually become softer, less elevated, and less noticeable over years.

GENERAL DIAGNOSIS

Interpretation of the clinical picture may be difficult because identical clinical lesions may have many different causes. Moreover, the same skin disease may give rise to diverse eruptions. Thus for each specific type of primary morphologic lesion, there is a differential diagnosis of the conditions that could produce that lesion. Also, there is a parallel list of all the variations that a single skin disease can cause; for example, lichen planus may have hyperpigmented patches, violaceous plaques, hypertrophic papules, and, rarely, minute papules.

Being superficial, skin lesions can be easily observed and palpated. Magnification may be easily applied, enhancing visualization of the fine details of the lesions. Smears and cultures may be readily obtained for bacteria and fungi. Biopsy and histologic examination of skin lesions are usually minor procedures, making histopathology an important component of many dermatologic evaluations. The threshold for biopsy should be low. This is especially true of inflammatory dermatoses, potentially infectious conditions, and skin disorders in immunosuppressed and hospitalized patients in whom 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, diet, and living conditions is important, as well as the onset, duration, and course of the disease and the response to previous treatment. 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, herbal products, eyedrops, and suppositories. Drug reactions are frequent and may simulate many different skin diseases clinically and histologically. It is equally important to inquire about topical agents that have been applied to the skin and mucous membranes for medicinal or cosmetic purposes, because these agents may cause cutaneous or systemic reactions.

A complete medical history that includes other medical diagnoses of the patient is essential. Certain skin diseases are specific to or associated with other conditions, such as cutaneous Crohn disease and pyoderma gangrenosum in Crohn disease. 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 factors in a dermatologic history. Habitation in certain parts of the world predisposes to distinctive diseases for that particular geographic locale, including San Joaquin Valley fever (coccidioidomycosis), Hansen disease, leishmaniasis, and histoplasmosis. Sexual orientation and practices may be relevant, as in genital ulcer diseases and human immunodeficiency virus (HIV) infection.

Examination

Examination should be conducted in a well-lit room. Natural sunlight is the ideal illumination. Abnormalities of melanin pigmentation (e.g., vitiligo, melasma) are more clearly visible under ultraviolet (UV) light. A Wood's light (365 nm) is most often 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, and scraping will reveal the nature of the lesion's base. Pigmented lesions, especially in infants, should be rubbed in an attempt to elicit Darier sign (whealing), as seen in urticaria pigmentosa. Dermoscopy is an important part of the examination of neoplasms.

The entire eruption must be seen to evaluate distribution and configuration. This is optimally done by having the patient completely undress and viewing 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 difficult 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.

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. Lesions may appear over the entire body or may follow the lines of cleavage (pityriasis rosea), dermatomes (herpes zoster), or lines of Blaschko (epidermal nevi) (Fig. 2.8). 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 remain the same during their entire existence (e.g.,

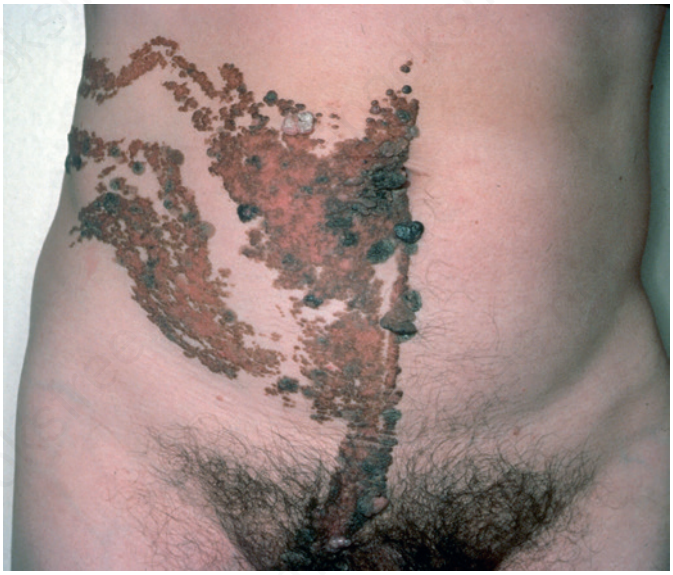


Fig. 2.8 Linear epidermal nevus (blaschkoid).

warts). When lesions succeed one another in a series of crops, as 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, as with 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 (corymbiform) arrangement. Concentric annular lesions are typical of borderline Hansen disease and erythema multiforme. These are sometimes said to be in a "cockade" pattern, referring to 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 called 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 with normal-appearing skin centrally (annular) or a portion of a circle (arcuate or gyrate), 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 (Fig. 2.9). 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.

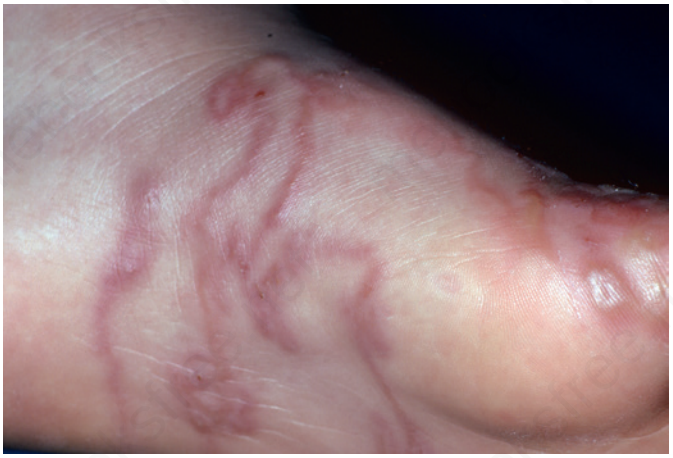


Fig. 2.9 Cutaneous larva migrans (serpiginous).

Color

The color of the skin is determined by melanin, oxyhemoglobin, reduced hemoglobin, lipid, and carotene. Not only do the proportions of these components affect the color, but also their depth within the skin, the thickness of the epidermis, and hydration 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.

The color of lesions may be valuable as a diagnostic factor. Dermatologists should be aware that there are many shades of pink, red, and purple, each of which tends to suggest a diagnosis or disease group. Interface reactions such as lichen planus or lupus erythematosus are described as violaceous. Lipid-containing lesions are yellow, as in xanthomas (Fig. 2.10) or steatocystoma multiplex. The orange-red (salmon) color of pityriasis rubra pilaris is characteristic. The constitutive color of the skin determines the quality of the color one observes with a specific disorder. In dark-skinned persons, erythema is difficult to perceive. Pruritic lesions in African Americans may evolve to be small, shiny, flat-topped papules with a violaceous hue, from the combination of erythema and pigment incontinence. These lichenified lesions would be suspected of being lichenoid by the untrained eye, but may be in fact eczematous.

Patches lighter in color than the normal skin may be completely depigmented or may have lost only part of their pigment (hypopigmented). This is an important distinction because certain conditions are or may be hypopigmented, such as tinea versicolor, Hansen disease, ash-leaf 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.

Hyperpigmentation may result from epidermal or dermal causes. It may be related to either 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 frequently the result of dermal melanin deposition, but in some conditions, such as lichen aureus, is caused

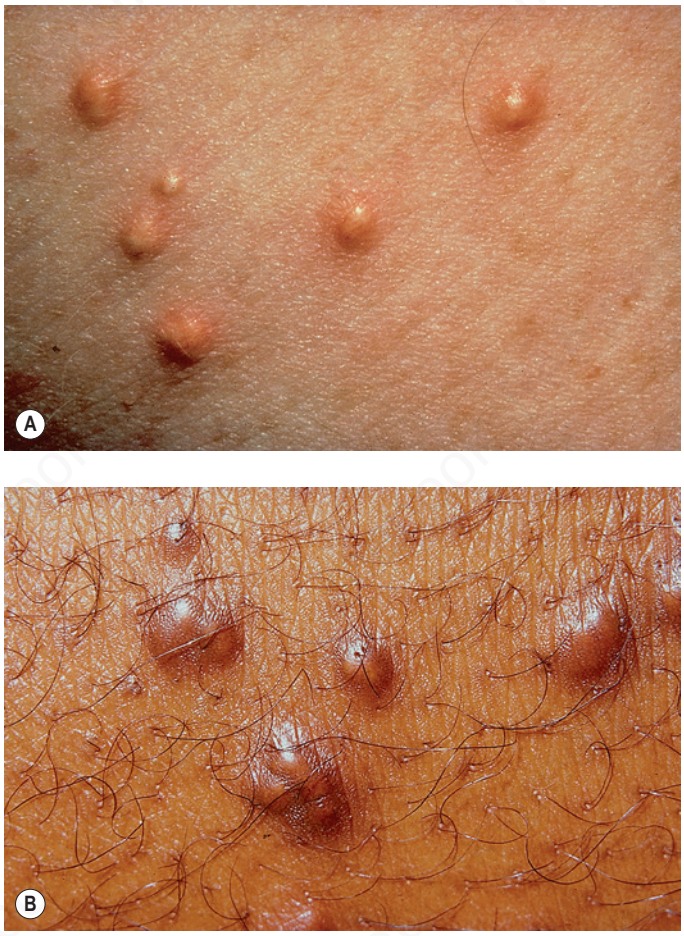


Fig. 2.10 Eruptive xanthoma. (A) Yellow color easily discerned on white skin. (B) Yellow color subtler in brown or black skin.

by iron. Dermal iron deposition appears more yellow-brown or golden than dermal melanin.

Texture/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. 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?

Hyperesthesia/Anesthesia

Certain conditions may be associated with increased or decreased sensation. For example, the skin lesions of borderline and tuberculoid Hansen disease typically are anesthetic in their centers. In complex regional pain syndrome spontaneous pain and tenderness on palpation are characteristic. In other neuropathic conditions such as notalgia paresthetica, the patient may perceive both pruritus and hyperesthesia. Neurally mediated itch may be accompanied by other neural sensations, such as heat or burning. The combination of pruritus with other neural symptoms suggests the involvement of nerves in the pathologic process.

Hair, Nails, and Oral Mucosa

Involvement of hair-bearing areas by certain skin disorders causes characteristic lesions. Discoid lupus, for example, causes scarring alopecia with characteristic dyspigmentation (Fig. 2.11). 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 suggest the diagnosis, such as the alopecia seen in the tumid plaques of follicular mucinosis.

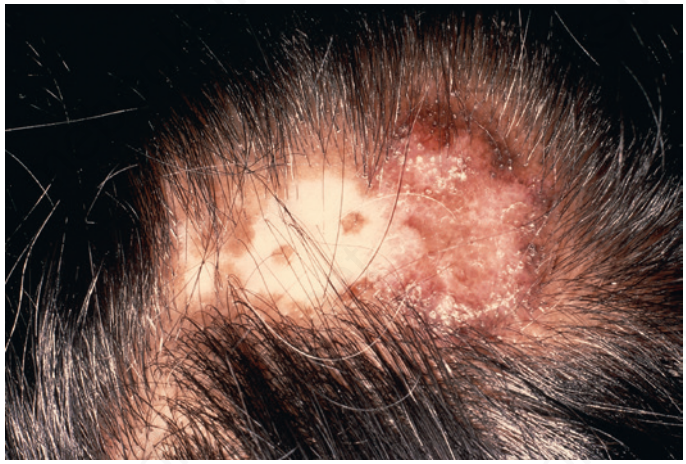


Fig. 2.11 Scalp plaque with scarring alopecia hyperpigmentation and depigmentation, discoid lupus erythematosus.

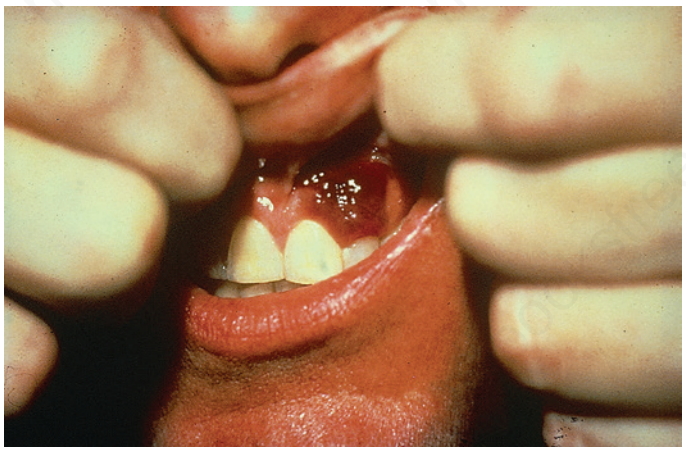


Fig. 2.12 Oral Kaposi sarcoma.

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.

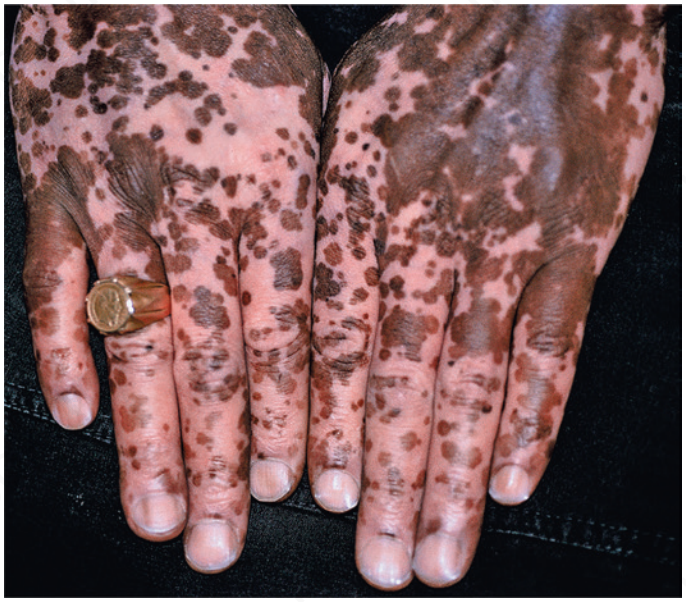
The complete skin examination includes examination of the oral mucosa. Oral lesions are characteristically found in viral syndromes (exanthems), lichen planus, HIV-associated Kaposi sarcoma (Fig. 2.12), and autoimmune bullous diseases (pemphigus vulgaris).

Self-Examination

Patients at risk for the development of skin cancer should be taught the correct method of skin self-examination, specifically, the ABCDEs of melanoma detection and the types of lesions that might represent basal cell carcinoma or squamous cell carcinoma.

Bonus images for this chapter can be found online at expertconsult.inkling.com

eFig. 2.1 Macular depigmentation, vitiligo.
eFig. 2.2 Whitish grouped papules of lichen nitidus.
eFig. 2.3 Vesicles, bullae, and erosions; bullous pemphigoid.
eFig. 2.4 Erythematous plaques studded with sheets of pustules, pustular psoriasis.
eFig. 2.5 Ulcer of the lip, chancre of primary syphilis.
eFig. 2.6 Annular, arcuate, and polycyclic configurations; granuloma annulare.
eFig. 2.7 Acral small blue papule, blue nevus.
eFig. 2.8 Scalp plaque with scarring alopecia hyperpigmentation and depigmentation, discoid lupus erythematosus.



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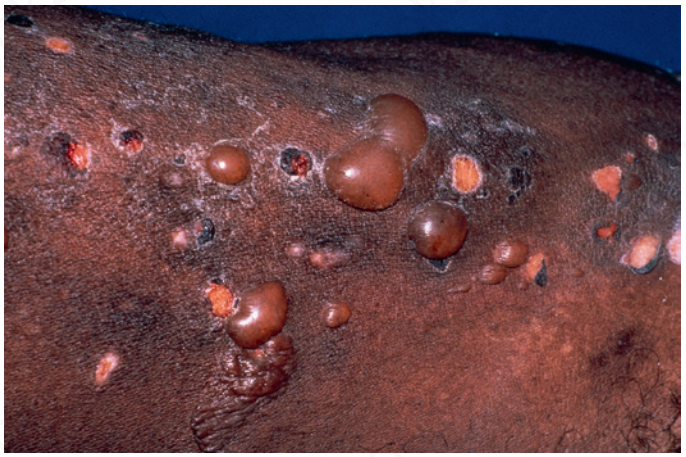
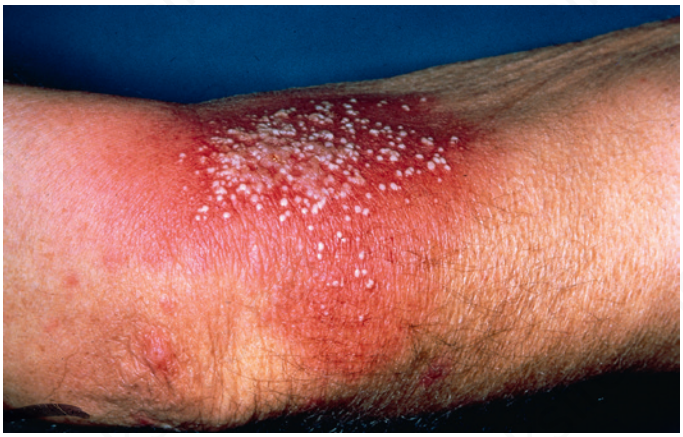
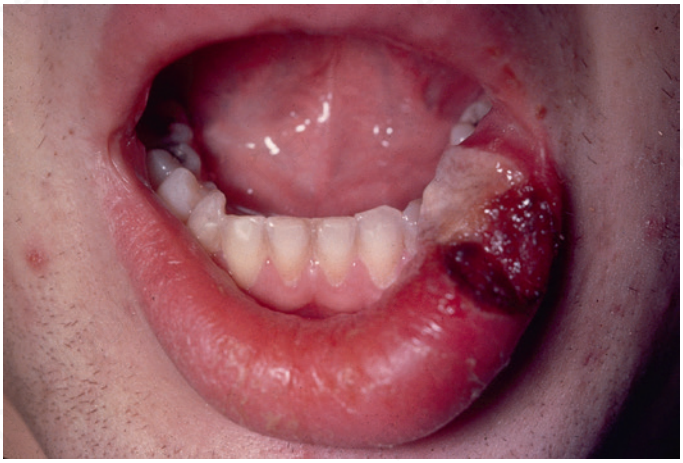


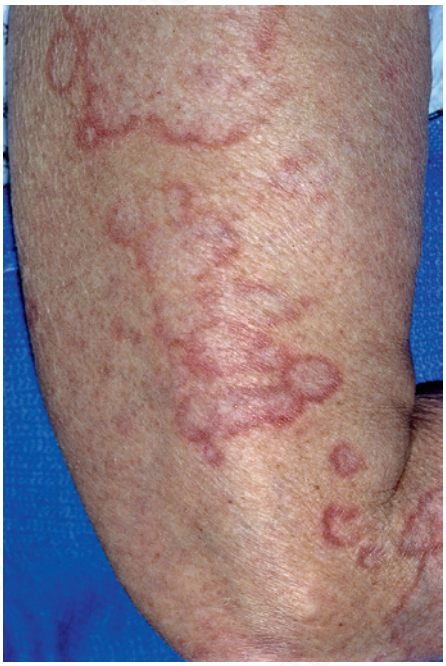
eFig. 2.3 Vesicles, bullae, and erosions; bullous pemphigoid.



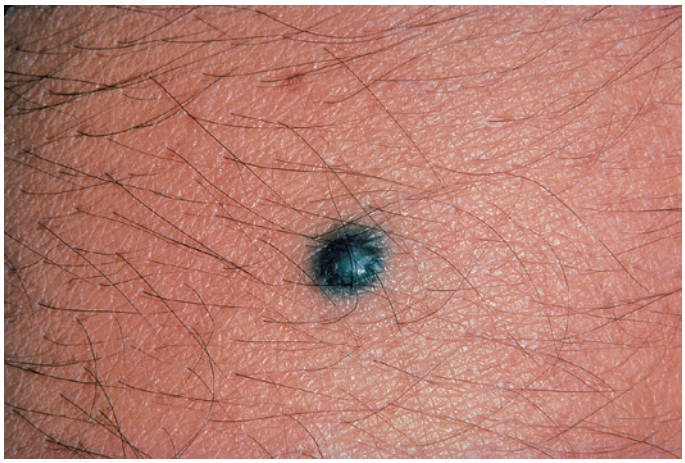
eFig. 2.4 Erythematous plaques studded with sheets of pustules, pustular psoriasis.



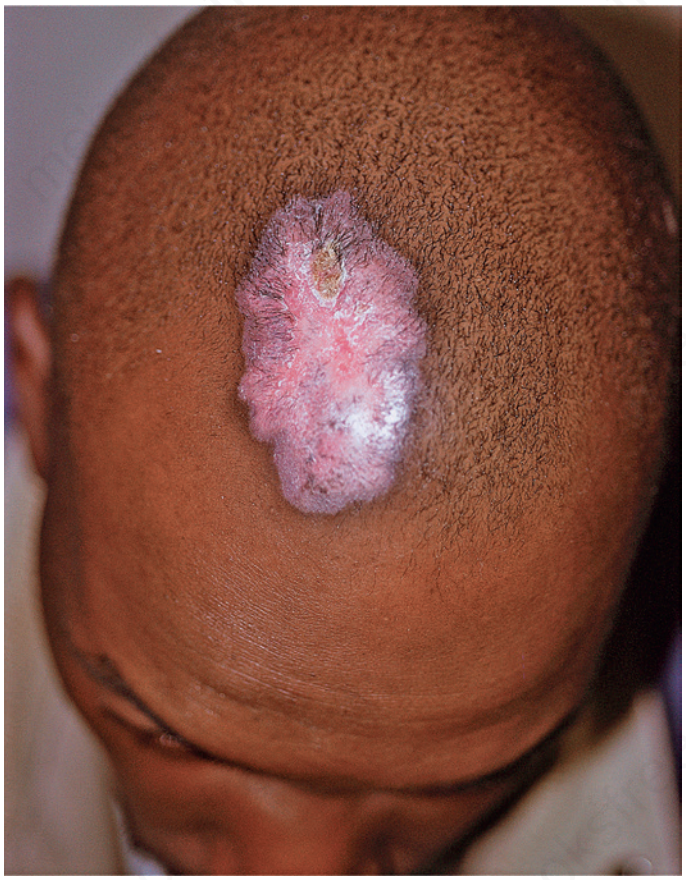
eFig. 2.5 Ulcer of the lip, chancre of primary syphilis.



eFig. 2.6 Annular, arcuate, and polycyclic configurations; granuloma annulare.



eFig. 2.7 Acral small blue papule, blue nevus.



eFig. 2.8 Scalp plaque with scarring alopecia hyperpigmentation and depigmentation, discoid lupus erythematosus.

3 Dermatoses Resulting From Physical Factors

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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; 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 this radiation than any other organ.

HEAT INJURIES

Thermal Burns

Injury of varying intensity may be caused by the action of excessive heat on the skin (Fig. 3.1). 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, as follows:

- *First-degree burns* of the skin result 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 some constitutional reaction can occur if the involved area is large.
- *Second-degree burns* are subdivided into superficial and deep forms.
  - In the superficial second-degree burn, there is a transudation of serum from the capillaries, which causes edema of the superficial tissues. Vesicles and bullae are formed by the serum gathering beneath the outer layers of the epidermis. Complete recovery without scarring is usual in patients with superficial burns.
  - The deep second-degree burn is pale and anesthetic. Injury to the reticular dermis compromises blood flow and destroys appendages, so healing takes more than 1 month and results in scarring.
- *Third-degree burns* involve loss of the full thickness of the dermis and often some of the subcutaneous tissues. Because the skin appendages are destroyed, there is no epithelium available for regeneration of the skin. An ulcerating wound is produced, which on healing leaves a scar.
- *Fourth-degree burns* involve the destruction of the entire skin, including the subcutaneous fat, and any underlying tendons.

Both third-degree and fourth-degree burns require grafting for closure. All third- and fourth-degree burns are followed by constitutional symptoms of varying severity, depending on the size of the involved surface, the depth of the burn, and particularly the location of the burned surface. The more vascular the involved area, the more severe are the symptoms.

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. Women, infants, and toddlers all have a greater risk of death from burns than men. Excessive scarring, with either keloid-like scars or flat scars with contractures, may produce deformities and dysfunction of the joints, as well as chronic ulcerations from impairment of local circulation. Delayed postburn blistering may occur in partial-thickness wounds and skin graft donor sites. It is most common on the lower extremities and is self-limited. Although burn scars may be the site of development of carcinoma, evidence supports only the possibility of a modest excess of squamous cell carcinomas in burn scars. With modern reconstructive surgery, this unfortunate end result 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 available), which are continued until pain does not return on stopping them.

The vesicles and bullae of second-degree burns should not be opened but should be protected from injury because 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 it with a sterile needle, allowing collapse onto the underlying wound. Excision of full-thickness and deep dermal wounds that will not reepithelialize within 3 weeks (as soon as hemodynamic stability is achieved, normally 2–3 days) reduces wound infections, shortens hospital stays, and improves survival. Additionally, contractures and functional impairment may be mitigated by such intervention. Skin grafting, or coverage with biologic dressings such as allograft or xenograft skin, cultured epidermal autografts, or skin substitutes also assist in healing. The role of early ablative laser treatments to prevent disabling scars and its use in improving fully formed scars is an area of active investigation. The most superficial wounds may be dressed with greasy gauze, whereas silver-containing dressings are used for their antibiotic properties in intermediate wounds.

Fluid resuscitation, treatment of inhalation injury and hypercatabolism, monitoring and early intervention of sepsis, pain control, environmental control, and nutritional support are key components of the critical care of burns. Intensive care management in a burn center is recommended for patients with partial-thickness wounds covering more than 10% of the body surface, if involving the face, hands, feet, genitalia, perineum, or joints; if secondary to electrical, chemical, or inhalation injury; in patients with special needs; and for any full-thickness burn.

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. Oral commissure burns may require reconstructive procedures (Fig. 3.2). High-voltage burns are often occupational; internal damage may be masked by minimal surface skin change and may be complicated by subtle and slowly developing sequelae. 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, where an entrance and an exit wound are visible. This is the most lethal type of strike, and cardiac arrest

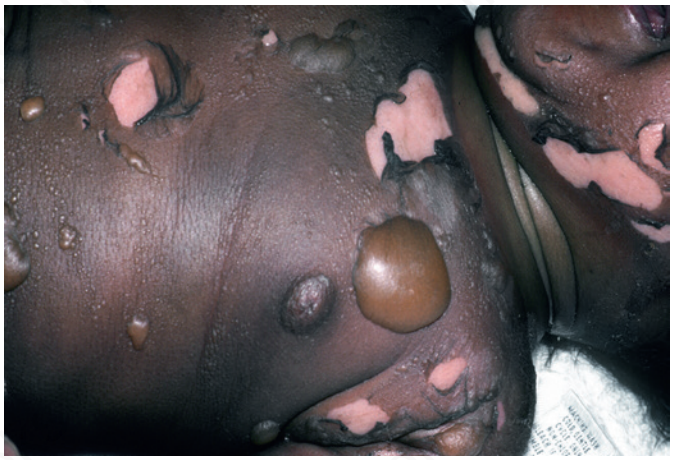

Fig. 3.1 Hot water burn. (Courtesy Steven Binnick, MD.)

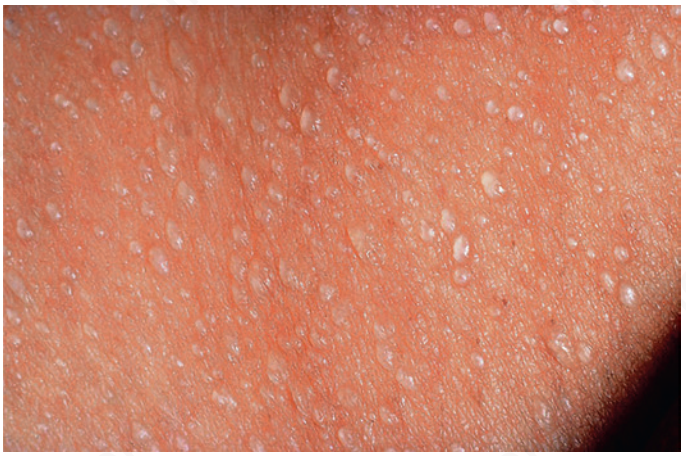

Fig. 3.3 Miliaria crystallina.

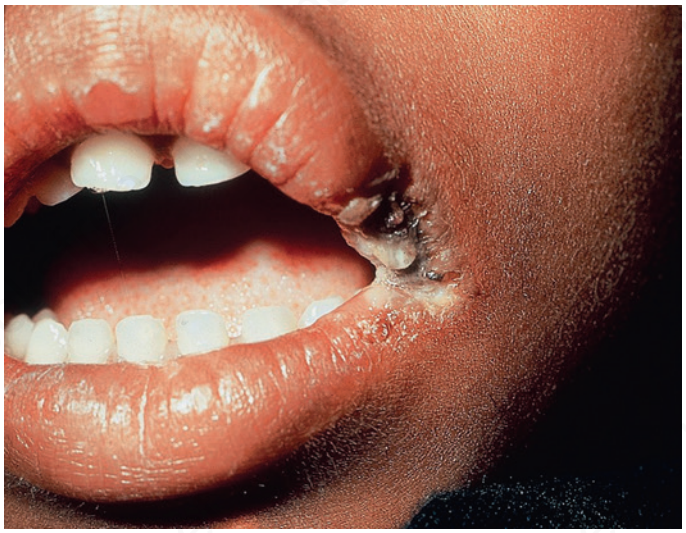

Fig. 3.2 Electrical burn from biting electrical cord. (Courtesy Paul Hong, MD.)

or other internal injuries may occur. Other types of lightning strike are indirect and result in the following burns:

- Linear burns in areas on which sweat was present
- Burns in a feathery or arborescent pattern, which is believed to be pathognomonic
- Punctate burns with multiple, deep, circular lesions
- Thermal burns from ignited clothing or heated metal, which may occur if the patient was speaking on a cell phone or listening to an iPod or similar device when struck

Hot Tar Burns

Polyoxyethylene sorbitan in bacitracin zinc–neomycin–polymyxin B (e.g., Neosporin) ointment, vitamin E ointment, and sunflower oil are excellent dispersing agents that facilitate the removal of hot tar from burns.

Alemayehu H, et al: Management of electrical and chemical burns in children. J Surg Res 2014; 190: 210.
Carta T, et al: Use of mineral oil Fleet enema for the removal of a large tar burn. Burns 2015; 41: e11.
Compton CC: The delayed postburn blister. Arch Dermatol 1992; 128: 24.
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Esteban-Vives R, et al: Second-degree burns with six etiologies treated with autologous noncultured cell-spray grafting. Burns 2016; 42: e99.
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Saracoglu A, et al: Prognostic factors in electrical burns. Burns 2014; 40: 702.
Sheridan RL, Greenhalgh D: Special problems in burns. Surg Clin North Am 2014; 94: 781.
Sokhal AK, et al: Clinical spectrum of electrical burns. Burns 2017; 43: 182.
Wallingford SC, et al: Skin cancer arising in scars: a systematic review. Dermatol Surg 2011; 37: 1239.
Wang KA, et al: Epidemiology and outcome analysis of hand burns. Burns 2015; 41: 1550.

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 in the tropics and during the hot summer months in temperate climates. *Staphylococcus epidermidis*, which produces an extracellular polysaccharide substance, induces miliaria in an experimental setting. This polysaccharide substance may obstruct the delivery of sweat to the skin surface. The occlusion prevents normal secretion from the sweat glands, and eventually 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 Crystallina

Miliaria crystallina is characterized by small, clear, superficial vesicles with no inflammatory reaction (Fig. 3.3). It appears in bedridden patients whose fever produces increased perspiration or when clothing prevents dissipation of heat and moisture, as in bundled children. Hypernatremia without fever may induce it.

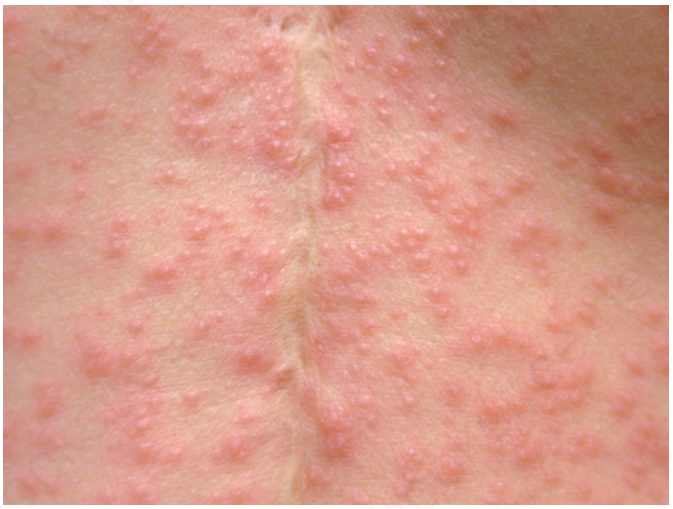

Fig. 3.4 Miliaria rubra.

The lesions are generally asymptomatic, and their duration is short-lived because they tend to rupture at the slightest trauma. Drugs such as isotretinoin, adrenergic/cholinergic drugs, and doxorubicin may induce it. The lesions are self-limited; no treatment is required.

Miliaria Rubra (Prickly Heat)

The lesions of miliaria rubra appear as discrete, extremely pruritic, erythematous papulovesicles (Fig. 3.4) 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. Exercise-induced itching or that of atopic dermatitis may also be caused by miliaria rubra. The site of injury and sweat escape is in the prickle cell layer, where spongiosis is produced.

Miliaria Pustulosa

Miliaria pustulosa is preceded by another dermatitis that has produced injury, destruction, or blocking of the sweat duct. The pustules are distinct, superficial, and independent of the hair follicle. The pruritic pustules occur most frequently on the intertriginous areas, flexural 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, because salt-losing crises may precipitate miliaria pustulosa or rubra, with resolution after stabilization.

Miliaria Profunda

Nonpruritic, flesh-colored, deep-seated, whitish papules characterize miliaria profunda. It is asymptomatic, usually lasts only 1 hour 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. Miliaria profunda 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 it 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. Sweating may be depressed to half the normal amount for as long as 3 weeks.

Tropical Anhidrotic Asthenia

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

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. Circulating air fans can also be used 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 colloidal oatmeal or cornstarch are beneficial if used in moderation. Patients with mild cases may respond to dusting powders, such as cornstarch or baby talcum powder.

Chao CT: Hypernatremia-related miliaria crystallina. Clin Esp Nephrol 2014; 18: 831.

Haque MS, et al: The oldest new finding in atopic dermatitis. JAMA Dermatol 2013; 149: 436.

Mowad CM, et al: The role of extracellular polysaccharide substance produced by *Staphylococcus epidermidis* in miliaria. J Am Acad Dermatol 1995; 20: 713.

Onal H, et al: Miliaria rubra and thrombocytosis in pseudohypoaldosteronism. Platelets 2012; 23: 645.

Erythema Ab Igne

Erythema ab igne 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. 3.5). 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. Interface dermatitis and epithelial atypia may be noted.

Erythema ab igne on the legs results from habitually warming them in front of open fireplaces, space heaters, or car heaters. Similar changes may be produced on the lower back or at other sites of an electric heating pad application, on the upper thighs with laptop computers, or on the posterior thighs from heated car seats. The reason for chronically exposing the skin to heat may be pain from an underlying cancer, or from a condition which predisposes to a feeling of cold, such as anorexia nervosa. The condition occurs also in cooks, silversmiths, and others exposed over long periods to direct moderate heat.

Epithelial atypia, which may lead to Bowen disease and squamous cell carcinoma, has rarely been reported to occur overlying erythema

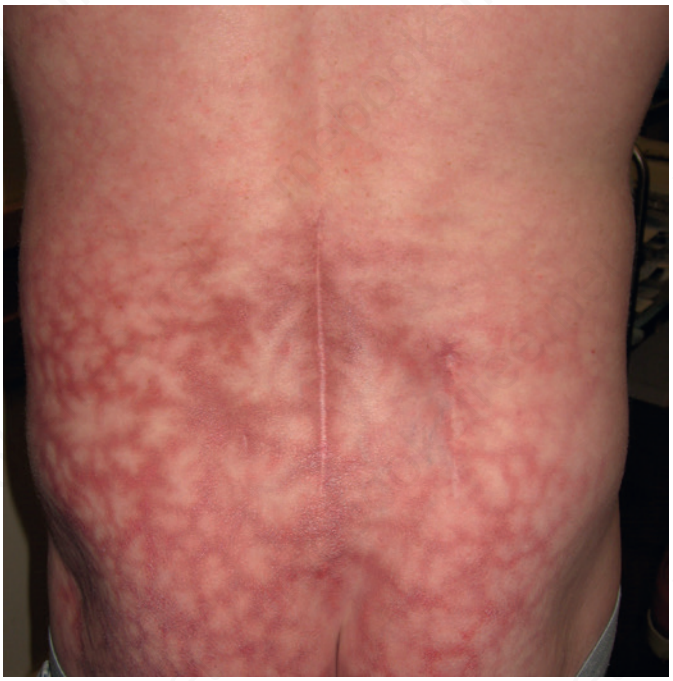

Fig. 3.5 Erythema ab igne.

ab igne. In remote areas of Kashmir, Kangri fire pots can induce erythema ab igne and cancer within the affected area. Treatment with 5-fluorouracil (5-FU), imiquimod, or photodynamic therapy 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, as may treatment with the Q-switched neodymium-doped yttrium-aluminum-garnet (Nd:YAG) laser.

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Dessinoti C, et al: Erythema ab igne in three girls with anorexia nervosa. Pediatr Dermatol 2016; 333: e149.
Kim HW, et al: Erythema ab igne successfully treated with low fluenced 1,064-nm Q-switched neodymium-doped yttrium aluminum garnet laser. J Cosmet Laser Ther 2014; 16: 147.
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Wani I: Kangri cancer. Surgery 2010; 147: 586.
Wharton JB, et al: Squamous cell carcinoma in situ arising in the setting of erythema ab igne. J Drugs Dermatol 2008; 7: 488.

COLD INJURIES

Exposure to cold damages the skin by at least three mechanisms:

- Reduced temperature directly damages the tissue, as in frostbite and cold immersion foot.
- Vasospasm of vessels perfusing the skin 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 because of fat composition or location (cold panniculitis; see Chapter 23).

Outdoor workers and recreationalists, military service members, alcoholic persons, and homeless people are particularly likely to sustain cold injuries. Maneuvers to treat orthopedic injuries or heatstroke and cooling devices for other therapeutic use may result in cold injuries ranging from acrocyanosis to frostbite. Holding ice coated with salt (salt and ice challenge) will induce cold-induced blistering.

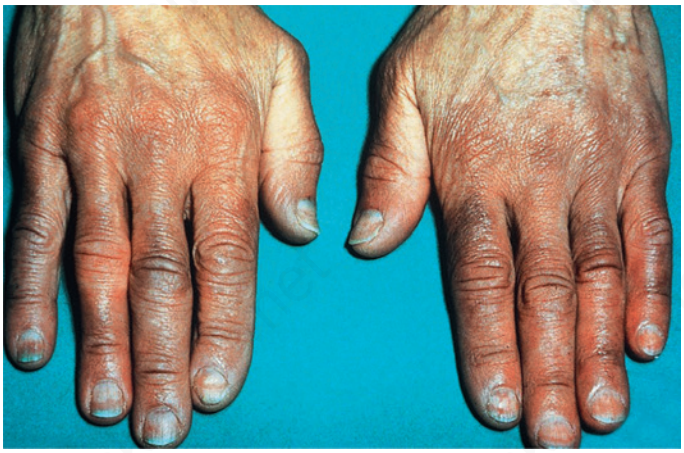

Fig. 3.6 Acrocyanosis.

Heil K, et al: Freezing and non-freezing cold weather injuries. Br Med Bull 2016; 117: 79.
Roussel LO, et al: Tweens feel the burn. Int J Adolesc Med Health 2016; 28: 217.

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. 3.6). 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 (rather than episodic) nature and lack of tissue damage (ulceration, distal fingertip resorption).

Acrocyanosis with swelling of the nose, ears, and dorsal hands may occur after inhalation of butyl nitrite. Interferon alpha-2a and beta may induce it. Repeated injection of the dorsal hand with narcotic drugs may produce lymphedema and an appearance similar to the edematous phase of scleroderma. This so-called puffy hand syndrome may include erythema or a bluish discoloration of the digits. Patients with anorexia nervosa frequently manifest acrocyanosis as well as perniosis, livedo reticularis, and acral coldness. It may improve with weight gain. Approximately one third of patients with skin findings of POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M component, skin changes) have acrocyanosis. Also, in patients with a homozygous mutation in *SAMDH1* and cerebrovascular occlusive disease, acrocyanosis was frequent.

Acral vascular syndromes, such as gangrene, Raynaud phenomenon, and acrocyanosis, may be a sign of malignancy. In 47% of 68 reported cases, the diagnosis of cancer coincided with the onset of the acral disease. If such changes appear or worsen in an elderly patient, especially a man, without exposure to vasoconstrictive drugs or prior autoimmune or vascular disorders, a paraneoplastic origin should be suspected.

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Miest RY, et al: Cutaneous manifestations in patients with POEMS syndrome. Int J Dermatol 2013; 52: 1349.
Poszepczynska-Guigné E, et al: Paraneoplastic acral vascular syndrome. J Am Acad Dermatol 2002; 47: 47.
Xin B, et al: Homozygous mutation in *SAMHD1* gene causes cerebral vasculopathy and early onset stroke. Proc Natl Acad Sci USA 2011; 108: 5372.

Pernio (Chilblains, Perniosis)

Pernio constitutes 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, antiphospholipid antibodies, or cold agglutinins may be present and pathogenic. Chilblain-like lesions may occur in discoid and systemic lupus erythematosus (SLE; chilblain lupus), particularly the TREX1-associated familial type, as a presenting sign of leukemia cutis, or if occurring in infancy may herald the Nakajo-Nishimura syndrome or the Aicardi-Goutières and Singleton-Merten syndrome. The chronic use of crack cocaine and its attendant peripheral vasoconstriction will lead to perniosis with cold, numb hands and atrophy of the digital fat pads, especially of the thumbs and index fingers, as well as nail curvature.

Pernio occur chiefly on the feet, hands, ears, and face, chiefly in women; onset is enhanced by dampness (Fig. 3.7). In surgery technicians, the hands are affected if an orthopedic cold therapy system is used; the skin under the device develops the lesions. The lateral thighs are involved in women equestrians who ride on cold, damp days and the hips in those wearing tight-fitting jeans with a low waistband. Wading across cold streams may produce similar lesions. Nondigital lesions of cold injury can be nodular.

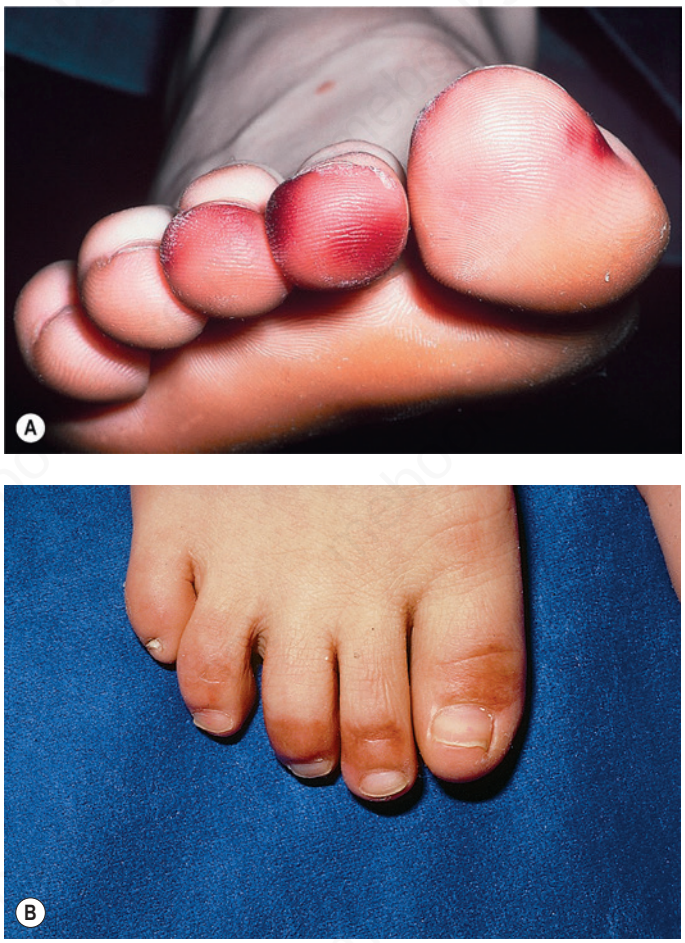

Fig. 3.7 Chilblains (pernio) in adult (A) and child (B).

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, with the color partially or totally disappearing on pressure, and are cool to the touch. Sometimes the extremities are clammy because of excessive sweating. As long as the dampness and cold exposure continues, new lesions will continue to appear. Investigation into an underlying cause should be undertaken in patients with pernio that is recurrent, chronic, extending into warm seasons, or poorly responsive to treatment.

Pernio 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 and is accompanied by characteristic "fluffy" edema of the vessel walls.

Treatment

The affected parts should be protected against further exposure to cold or dampness. If the feet are involved, woolen socks should be worn at all times during the cold months. Because patients are often not conscious of the cold exposure that triggers the lesions, appropriate dress must be stressed, even if patients say they do not sense being cold. Because 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 effective. Vasodilators such as nicotinamide, 500 mg three times a day, or dipyridamole, 25 mg three times a day, or the phosphodiesterase inhibitor sildenafil, 50 mg twice daily, may be used to improve circulation. Pentoxifylline and hydroxychloroquine may be effective. Spontaneous resolution occurs without treatment in 1–3 weeks. Systemic corticoid therapy is useful in chilblain lupus.

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Baker JS, Miranpuri S: Perniosis a case report with literature review. J Am Podiatr Med Assoc 2016; 106: 138.
Ferrara G, Cerroni L: Cold-associated perniosis of the thighs ("equestrian-type" chilblain). Am J Dermatopathol 2016; 38: 726.
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Kanazawa N: Nakajo-Nishimura syndrome. Allergol Int 2012; 61: 197.
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Mireku KA, et al: Tender macules and papules on the toes. JAMA Dermatol 2014; 150: 329.
Payne-James JJ, et al: Pseudosclerodermatous triad of perniosis, pulp atrophy and parrot-beaked clawing of the nails. J Forensic Leg Med 2007; 14: 65.
Tran C, et al: Chilblain-like leukaemia cutis. BMJ Case Rep 2016 Apr 19; 2016.
Weismann K, et al: Pernio of the hips in young girls wearing tight-fitting jeans with a low waistband. Acta Derm Venereol 2006; 86: 558.

Frostbite

When soft tissue is frozen and locally deprived of blood supply, the damage is called frostbite. The ears, nose, cheeks, fingers, and

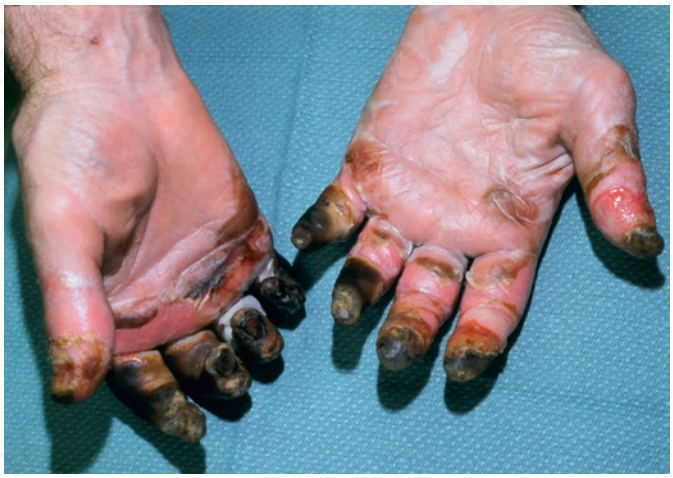

Fig. 3.8 Frostbite.

toes are most often affected. The frozen part painlessly becomes pale and waxy. Various degrees of tissue destruction similar to that 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. 3.8). The degree of injury is directly related to the temperature and duration of freezing. African Americans are at increased risk of frostbite. Arthritis of the small joints of the hands and feet may appear months to years later.

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°C and 43°C (100°F and 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 should be administered because of the considerable pain experienced with rapid thawing. When the skin flushes and is pliable, thawing is complete. The use of tissue plasminogen activator to lyse thrombi decreases the need for amputation if given within 24 hours of injury. Infusion of the vasodilator iloprost may be used if available. 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.

The use of anticoagulants to prevent thrombosis and gangrene during the recovery period has been advocated. Pentoxifylline, 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 preventive against repeated episodes. Arthritis may be a late complication.

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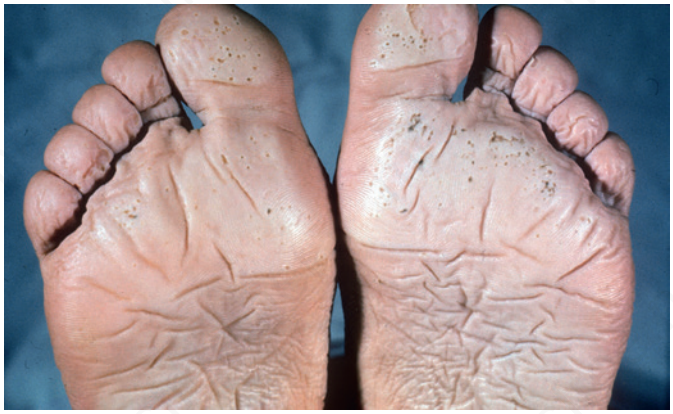

Fig. 3.9 Tropical immersion foot. (Courtesy Steven Binnick, MD.)

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Wang Y, et al: Frostbite arthritis. Am J Phys Med Rehabil 2016; 95: e28.

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. Fishermen, sailors, and shipwreck survivors may be seen with this condition. The lack of circulation produces edema, paresthesias, and damage to the blood vessels. Similar findings may complicate the overuse of ice, cold water, and fans by patients trying to relieve the pain associated with erythromelalgia. 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.

Warm Water Immersion Foot

Exposure of the feet to warm, wet conditions for 48 hours or more may produce a syndrome characterized by maceration, blanching, and wrinkling of the soles and sides of the feet (Fig. 3.9). Itching and burning with swelling may persist for a few days after removal of the cause, but disability is temporary. This condition was often seen in military service members in Vietnam but has also been seen in persons wearing insulated boots.

Warm water immersion foot should be differentiated from tropical immersion foot, seen after continuous immersion of the feet in water or mud at temperatures above 22°C (71.6°F) for 2–10 days. This was known as "paddy foot" in Vietnam. It involves erythema, edema, and pain of the dorsal feet, as well as fever and adenopathy (Fig. 3.10). Resolution occurs 3–7 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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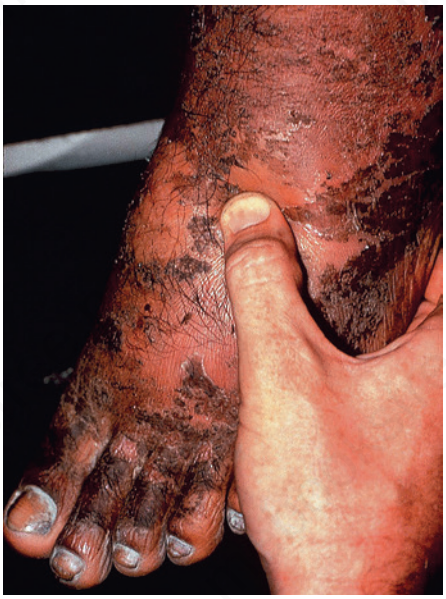

Fig. 3.10 Tropical immersion foot. (Courtesy James WD [ed]: Textbook of Military Medicine, Office of the Surgeon General, United States Army, 1994.)

Davis MD: Immersion foot associated with the overuse of ice, cold water, and fans. J Am Acad Dermatol 2013; 69: 169.
Olson Z, Kman N: Immersion foot. J Emerg Med 2015; 49: e45.

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, 320–400 nm; UVB, 280–320 nm; and UVC, 200–280 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). Although the amount of UVA radiation is 100 times greater than UVB radiation during midday hours, UVB is up to 1000 times more erythemogenic than UVA, and so essentially all solar erythema is caused by UVB. The most biologically effective wavelength of radiation from the sun for sunburn is 308 nm. Although it does not play a significant role in solar erythema, UVA is of major importance in patients with drug-induced photosensitivity and also play a role in photoaging and cutaneous immunosuppression.

The amount of UV exposure increases at higher altitudes, is substantially larger in temperate climates in the summer months, and is greater in tropical regions. UVA may be reflected somewhat more than UVB from sand, snow, and ice. Whereas sand and snow reflect as much as 85% of the UVB, water allows 80% of the UV to penetrate up to 3 feet. Cloud cover, although blocking substantial amounts of visible light, is a poor UV absorber. During the middle 4–6 hours of the day, the intensity of UVB is 2–4 times greater than in the early morning and late afternoon.

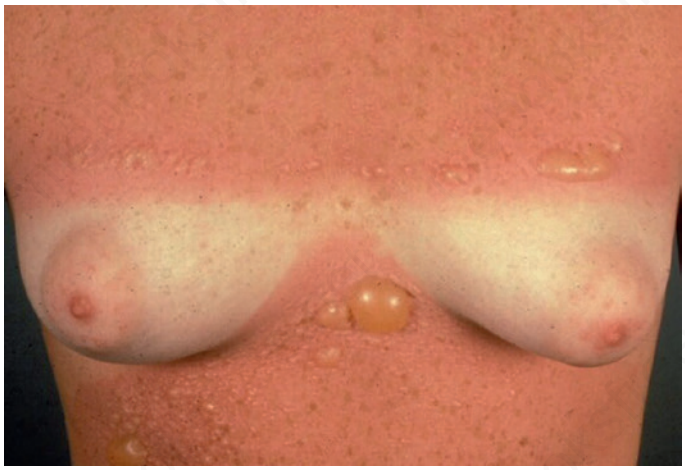

Fig. 3.11 Acute sunburn. (Courtesy Dr. L. Lieblich.)

Clinical Signs and Symptoms

Sunburn is the normal cutaneous reaction to sunlight in excess of an erythema dose. UVB erythema becomes evident at around 6 hours after exposure and peaks at 12–24 hours, 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 (Fig. 3.11). Discomfort may be severe; edema typically 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 1 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 2–3 days after exposure, and lasts 10–14 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. Tanning is not recommended for sun protection. Commercial tanning bed–induced tanning, while increasing skin pigment, does not increase UVB MED and is therefore not protective for UVB damage. Such tanning devices have been shown to cause melanoma, and their use for tanning purposes should be banned. An individual's inherent baseline pigmentation, ability to tan, and susceptibility to burns are described as the person's "skin type." Skin type is used to determine starting doses of phototherapy and sunscreen recommendations and reflects the risk of development of skin cancer and photoaging (Table 3.1).

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

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

cascades are triggered. Prostaglandins, especially of the E series, are important mediators. Aspirin (acetylsalicylic acid [ASA]) and nonsteroidal antiinflammatory drugs (NSAIDs), including indomethacin, have been studied, as well as topical and systemic steroids. Medium-potency (class II) topical steroids applied 6 hours after the exposure (when erythema first appears) provide a small reduction in signs and symptoms. Oral NSAIDs and systemic steroids have been tested primarily before or immediately after sun exposure, so there is insufficient evidence to recommend their routine use, except immediately after solar overexposure. Therefore 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.

Prophylaxis

Sunburn is best prevented. Use of the UV index 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 United States and Western Europe, especially in white persons under age 30, more than 50% of whom report at least one sunburn per year. Sun protection programs have the following four main messages:

- Avoid midday sun.
- Seek shade.
- Wear sun-protective clothing.
- Apply a sunscreen.

The period of highest UVB intensity, between 9 AM and 3–4 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 degrees, or when a person's shadow is shorter than his or 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) 4–50, 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, UPF correlates well with the actual protection the product provides in vivo. In general, denser weaves, washed older clothing, and loose-fitting clothes 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 4-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 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. Sunscreen 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 (e.g., *p*-aminobenzoic acid [PABA], PABA esters, cinnamates, salicylates, anthranilates, benzophenones, benzylidene camphors such as ecamsule [Mexoryl], dibenzoylmethanes [Parsol 1789, in some products present as multicompound technology Helioplex], and Tinosorb [S/M]) and physical agents (zinc oxide or titanium dioxide). Sunscreens are available in numerous formulations, including sprays, gels, emollient creams, and wax sticks. Sunscreens may be water resistant, with some maintaining their SPF after 40 minutes of water immersion and others maintaining their SPF after 80 minutes of water immersion.

For skin types I to III (see Table 3.1), daily application of a broad-spectrum sunscreen with an SPF of 30 in a facial moisturizer, foundation, or aftershave is recommended. For outdoor exposure, a sunscreen of SPF 30 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 minutes before and 30 minutes after sun exposure has begun is recommended. This dual-application approach will reduce the amount of skin exposure by twofold to threefold over a single application. Sunscreen should be reapplied after swimming or vigorous activity or toweling. Sunscreen failure occurs mostly in men, from 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 is recommended with the most stringent sun protection practices. The dose is 600 IU daily for those 70 and younger and 800 IU for older patients.

Photoaging and cutaneous immunosuppression are mediated by UVA as well as UVB. For this reason, sunscreens with improved UVA coverage have been developed. Those containing excellent protection for both UVB and UVA are identified on the label by the words "broad spectrum," and these sunscreens should be sought by patients.

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Thompson AE: Suntan and sunburn. JAMA 2015; 314: 638.

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 redheads with blue eyes and of Celtic origin (skin types I or II) are especially susceptible. Ephelides may be genetically determined and may

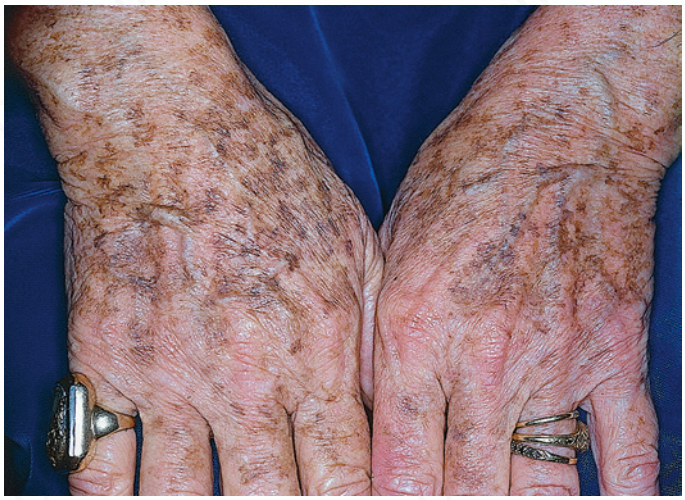

Fig. 3.12 Solar lentigines.

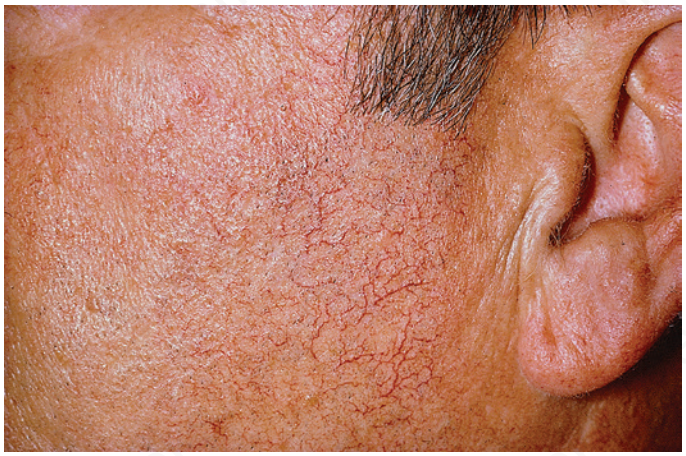

Fig. 3.13 Dermatoheliosis.

recur in successive generations in similar locations and patterns. They usually appear at about age 5 years.

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 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 (Fig. 3.12).

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 solar lentigines are best prevented by appropriate sun protection. Cryotherapy, topical retinoids, hydroquinone, intense pulse light, undecylenoyl phenylalanine, and lasers are effective in the treatment of solar lentigines.

Hafner C, et al: The absence of *BRAF, FGFR3*, and *PIK3CA* mutations differentiates lentigo simplex from melanocytic nevus and solar lentigo. J Invest Dermatol 2009; 129: 2730

Imhof L, et al: A prospective trial comparing Q-switched ruby laser and a triple combination skin-lightening cream in the treatment of solar lentigines. Dermatol Surg 2016; 42: 853.

Praetorius C, et al: Sun-induced freckling. Pigment Cell Melanoma Res 2014; 27: 339.

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 the person's skin type (see Table 3.1). Risk for melanoma and nonmelanoma skin cancer is also related to skin type. The persons 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 develop photoaging have the genetic susceptibility and have had sufficient actinic damage to develop skin cancer, and they therefore require more frequent and careful cutaneous examinations.

Chronic sun exposure and chronologic aging are additive. Cigarette smoking is also important in the development of wrinkles, resulting in the inability of observers to distinguish solar-induced from smoking-induced skin aging accurately. 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 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 (Fig. 3.13). These persons are 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; in addition, dermal hemosiderosis occurs from actinic purpura. 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, 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 (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 thirties or early forties. 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. The ears may exhibit one or more firm nodules on the helix, known as weathering nodules. Biopsy reveals fibrosis and cartilage metaplasia.

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. This is known as dermatoporosis. Most

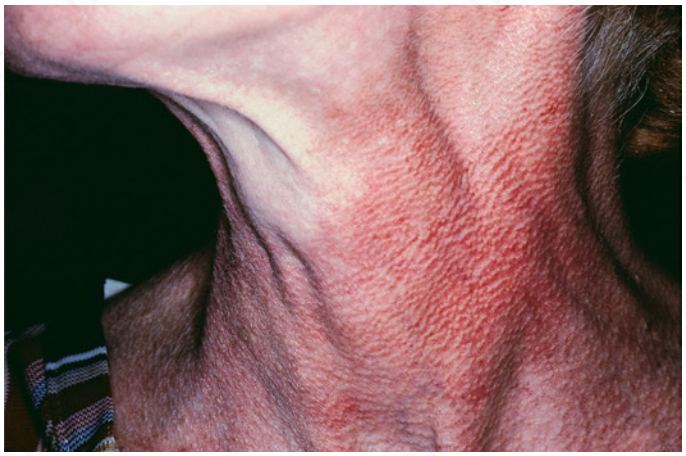

Fig. 3.14 Poikiloderma of Civatte.

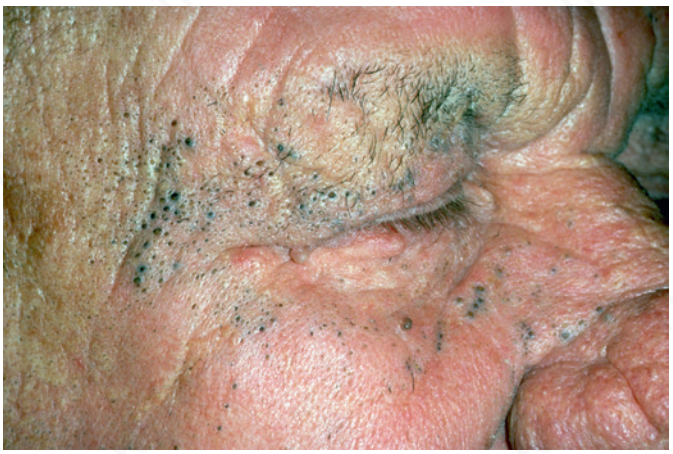

Fig. 3.16 Favre-Racouchot.

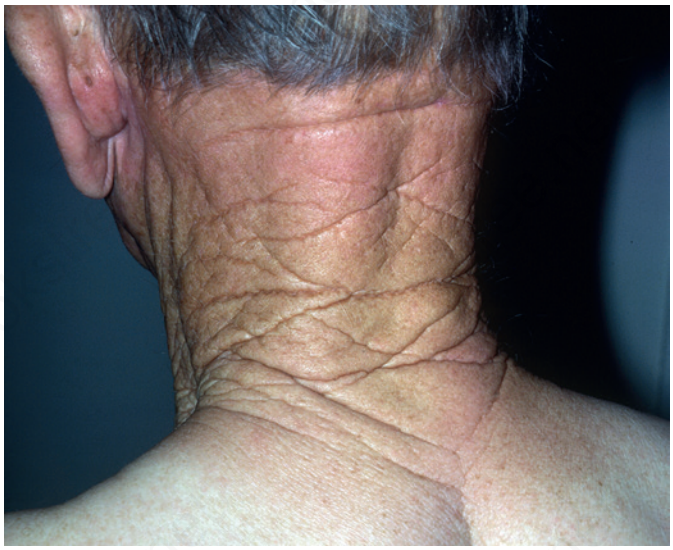

Fig. 3.15 Cutis rhomboidalis nuchae.

frequently, 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. Deep dissecting hematomas may result as well, causing large areas of necrosis. Again, minor trauma may lead to a painful deep bruise or simply erythema, without fever. This severe complication of dermatoporosis occurs primarily on the legs of elderly women, many of whom are taking anticoagulants or systemic steroids. Slowly growing erythematous plaques called acquired elastotic hemangiomas, which show horizontal proliferation of capillary blood vessels in the upper dermis, may also appear on the sun-damaged skin of the arms and neck. White stellate pseudoscars on the forearms are a frequent complication of this enhanced skin fragility. 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).

Both UVB and UVA radiation induce reactive oxygen species (ROS) and hydrogen peroxide. Acting through activator protein 1 (AP-1), transcription of various matrix-degrading enzymes is upregulated, specifically matrix metalloproteinase 1 (MMP-1; collagenase), MMP-3 (stromelysin 1), and MMP-9 (gelatinase). 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, MMP-1 levels are also increased through AP-1. 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. In both the adult and the juvenile form of colloid milium, the primary skin lesion is a translucent, flesh colored or slightly yellow, 1–5 mm papule. Minimal trauma may lead to purpura from 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-age and older adults, usually men. Lesions often coalesce into plaques and may rarely be verrucous. Petrochemical exposures have been associated with adult colloid milium. Pigmented forms of colloid milium are associated with hydroquinone use. Lesions have been induced by tanning bed exposure, and they 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.

Treatment with fractional photothermolysis or MAL-photodynamic therapy may be effective for colloid milium.

Prevention and Treatment

Because 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 the primary prevention required against photoaging. Because photoaging, as with other forms of radiation damage, appears to be cumulative, reducing the total lifetime UV exposure is the goal. The guidelines previously outlined for sunburn prophylaxis should be followed.

The regular use of emollients or moisturizing creams on 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. Chemical peels, resurfacing techniques, laser and other light technologies (for vascular alterations, pigmented lesions, and dermal alterations), botulinum toxins, and soft tissue augmentation are all used to treat the consequences of photoaging. The surgical and laser treatments of photoaging are discussed in Chapter 38.

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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 production of endogenous photosensitizers), idiopathic, and light exacerbated (genetic and acquired). Phototoxicity and the idiopathic disorders are discussed here; the other conditions are covered in later chapters.

Chemically Induced Photosensitivity

A number of substances known as photosensitizers may induce an abnormal reaction in skin exposed to sunlight or its equivalent. The result may be a greatly increased sunburn response without allergic sensitization called phototoxicity. Phototoxicity may occur from both externally applied (phytophotodermatitis and berloque dermatitis) and internally administered chemicals (phototoxic drug reaction). In contrast, photoallergic reactions are true allergic sensitizations triggered by sunlight, produced either by 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. Phototoxicity occurs on initial exposure, has an onset of less than 48 hours, 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, the period of initial sensitization), and shows histologic features of allergic contact dermatitis.

Action Spectrum

Chemicals known to cause photosensitivity (photosensitizers) are usually resonating compounds with a molecular weight of less than 500 daltons. Absorption of radiant energy (sunlight) by the photosensitizer produces an excited state; 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 that produces phototoxicity 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 when 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 generally 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

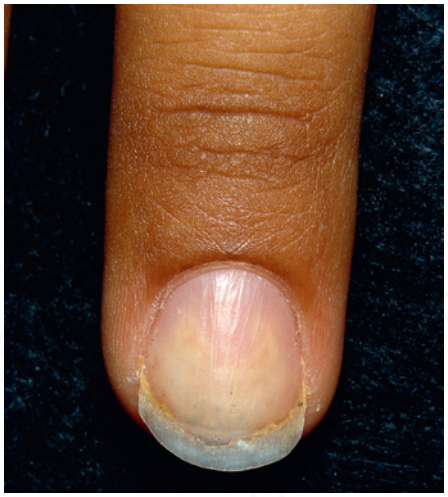

Fig. 3.17 Photo-onycholysis from minocycline.

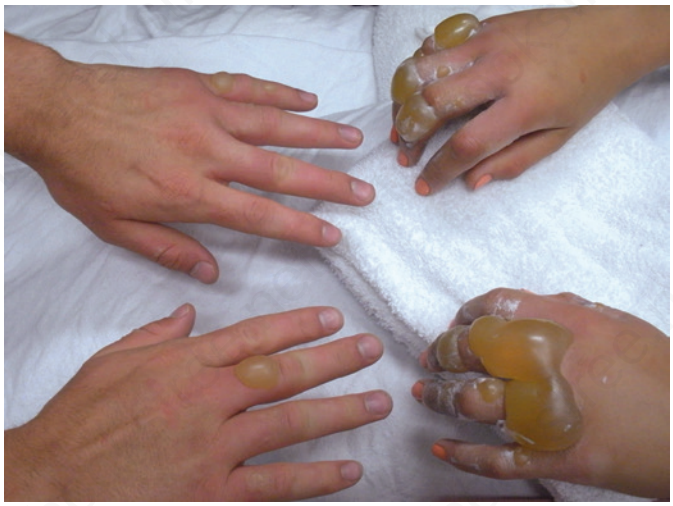

Fig. 3.18 Two friends who made limeade in the sun to sell in the summer.

varies widely. In general, to elicit a phototoxic reaction, a considerably greater amount of the photosensitizing substance is necessary than that needed to induce a photoallergic reaction. The erythema begins, as with any sunburn, within 2–6 hours but worsens for 48–96 hours before beginning to subside. Exposure of the nail bed may lead to onycholysis, called photo-onycholysis (Fig. 3.17). Phototoxic reactions, especially from topically applied photosensitizers, may cause marked hyperpigmentation, even without significant preceding erythema.

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. These volatile hydrocarbons may be airborne, so the patient may give no history of touching tar products. The burning and erythema may continue for 1–3 days. Although up to 70% of white persons exposed to such a combination develop this reaction, persons with type V or VI skin are protected by their constitutive skin pigmentation. After 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. Furocoumarins in many plants may cause a phototoxic reaction when they come in contact with skin that is 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. Fragrance products containing bergapten, a component of oil of bergamot, will produce this reaction. If a fragrance containing this 5-methoxypsoralen or other furocoumarin is applied to the skin before exposure to the sun or tanning lights, berloque dermatitis may result. This hyperpigmentation, which may be preceded by redness and edema, occurs primarily on the neck and face. Artificial bergapten-free bergamot oil and laws limiting the use of furocoumarins in Europe and the United States have made this a rare condition. However, "Florida Water" and "Kananga Water" colognes, formerly popular in the Hispanic, African American, and Caribbean communities, contain this potent photosensitizer and can still be ordered online, as can other aromatherapy products containing furocoumarins.

Most phototoxic plants are in the Umbelliferae, Rutaceae (rue), Compositae, and Moraceae families. Incriminated plants include

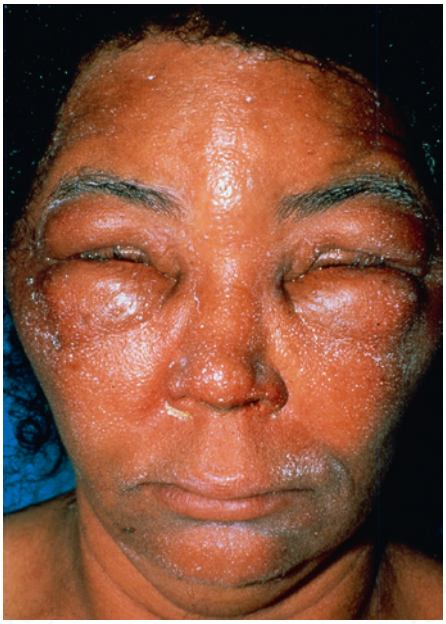

Fig. 3.19 Severe phytophototoxicity.

agrimony, angelica, atrillal, bavachi, buttercup, common rice, cowslip, dill, fennel, fig, garden and wild carrot, garden and wild parsnip, gas plant, goose foot, zabon, lime and Persian lime (Fig. 3.18), 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 (mokihana burn). It is a member of the rue family. Exposure through limes used to flavor gin and tonics and Mexican beer may result in phototoxic reactions in outdoor bartenders and their customers. Home tanning solutions containing fig leaves can produce phytophotodermatitis. These conditions may be widespread and severe enough to require burn unit management (Fig. 3.19).

Occupational disability from exposure to the pink rot fungus *(Sclerotinia sclerotiorum)*, present on celery roots, occurs in celery farmers. In addition, disease-resistant celery contains furocoumarins and may produce phytophotodermatitis in grocery workers. Usually, insufficient sensitizing furocoumarin is absorbed from dietary exposure; however, ingested herbal remedies may cause systemic phototoxicity.

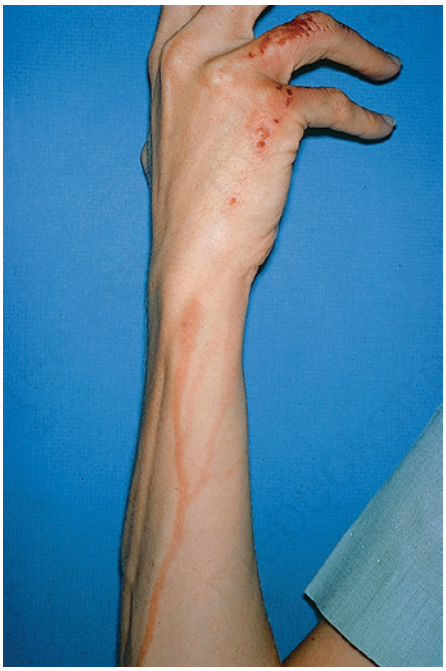

Fig. 3.20 Phytophotodermatitis; the patient had rinsed her hair with lime juice on the beach in Mexico.

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 may rinse their hair with lime juice outdoors, and streaky hyperpigmentation of the arms and back will result where the lime juice runs down (Fig. 3.20).

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 hours, and marked hyperpigmentation results. The asymmetry, atypical shapes, and streaking of the lesions are helpful in establishing the diagnosis. These features may lead to a misdiagnosis of child abuse.

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

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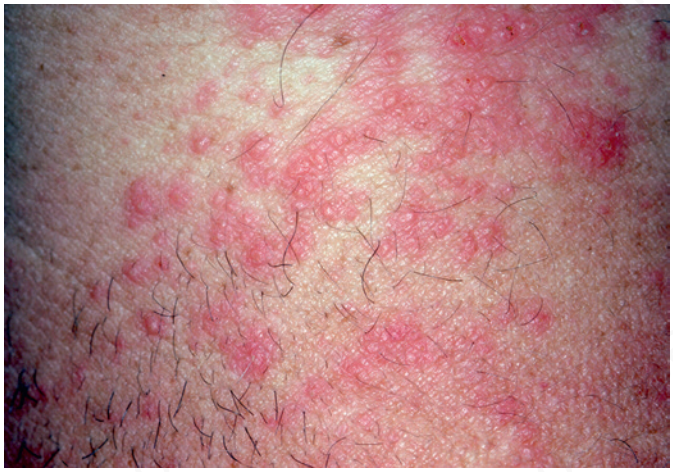

Fig. 3.21 Polymorphous light eruption, papular type.

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Idiopathic Photosensitivity Disorders

This idiopathic group includes the photosensitivity diseases for which no cause is known. These disorders 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 of 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 four decades of life, and females outnumber males by 2 : 1 or 3 : 1. The pathogenesis is unknown, but a family history may be elicited in 10%–50% of patients. Some investigators report that 10%– 20% of patients with PLE may have positive antinuclear antigens (ANAs) and a family history of lupus erythematosus. Photosensitive 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 plaquelike lesions also occur (Fig. 3.21). Plaquelike lesions are more common in elderly patients and may closely simulate lupus erythematosus, with indurated, erythematous, fixed lesions. In African Americans, a pinpoint papular variant has been observed, closely simulating lichen nitidus but showing spongiotic dermatitis histologically (Fig. 3.22). Scarring and atrophy do not occur; in darkly pigmented races, however, marked postinflammatory hyperpigmentation or hypopigmentation may be present. In some patients, pruritus only, without an eruption, may be reported (PLE sine eruptione). Some of these patients will develop typical PLE later in life.

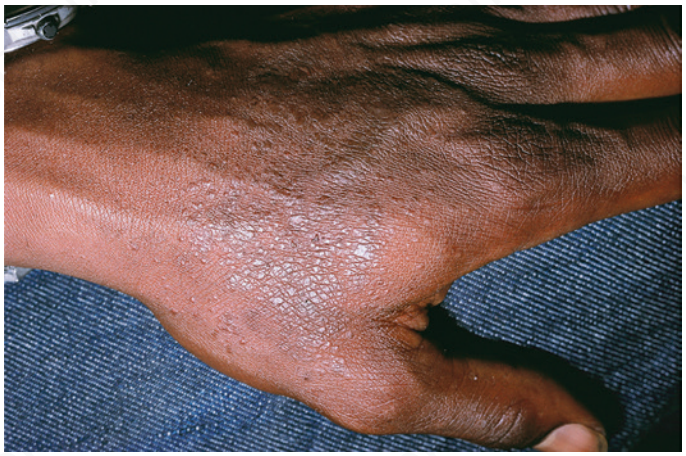

Fig. 3.22 Polymorphous light eruption, micropapular variant resembling lichen nitidus.

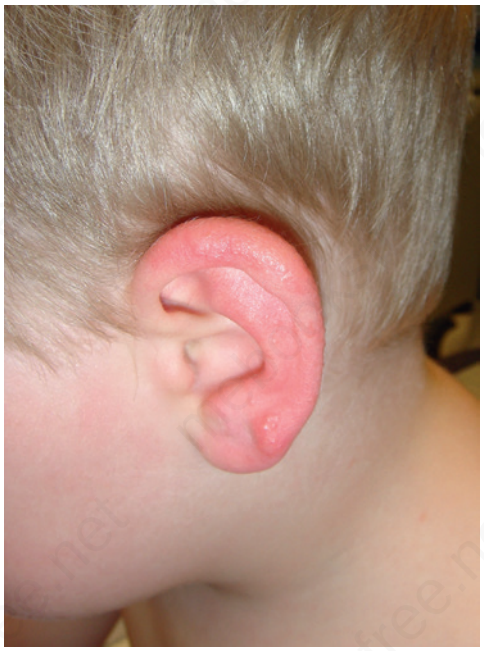

Fig. 3.23 Juvenile spring eruption of the ears.

The lesions of PLE appear most often 1–4 days after exposure to sunlight, although patients may report itching and erythema during sun exposure and development of lesions within the first 24 hours. 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. Typically, however, 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 frequently in the spring. The eruption often improves with continued sun exposure (hardening), so patients may be clear of the condition in the summer or autumn.

An unusual variant of PLE is juvenile spring eruption of the ears (Fig. 3.23). This occurs most frequently in boys age 5–12 years but may also be found in young adult males. It presents in the spring, often after sun exposure on cold but sunny days. The typical lesions are grouped small papules or papulovesicles on the helices. Lesions may form visible vesicles and crusting. Juvenile spring eruption of the ears 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. Another localized variant of PLE is spring and summer eruption of the elbows, but this occurs in adults, equally in men and women.

Histologically, a perivascular, predominantly T-cell infiltrate is present in the upper and middle dermis. There is often edema and endothelial swelling, with occasional neutrophils. Epidermal changes are variable, with spongiosis and exocytosis most often observed. Occasionally, a virtual absence of findings microscopically may paradoxically be reported and has been referred to as pauci-inflammatory photodermatitis.

The reported action spectrum of PLE varies, possibly depending on the different ethnic backgrounds of reported populations. UVA is most often responsible; however, UVB and both wavelengths in combination are also frequently necessary. Patients often report eruptions following sun exposure through window glass. Although rare, visible light sensitivity can also occur. Typically, women are more sensitive than men to UVA only, and men are more sensitive to visible light. Men, although the minority of PLE patients, tend to have more severe PLE and broader wavelengths of sensitivity. Most patients react more in affected sites, and in some, lesions can only be induced in affected areas. Phototesting produces variable results. One protocol produced positive results in 83% of tested patients using four exposures of UVB, UVA, or a combination in previously affected sites. However, the light sources are not readily available, and reported protocols vary widely. In clinical practice, the diagnosis is usually made clinically.

The differential diagnosis of PLE includes 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. Serologic testing alone may not distinguish PLE from SLE because of the possibility of positive ANA tests in PLE patients. Lupus erythematosus may present initially with photosensitivity before other features of lupus occur. Sebaceous neutrophilic adenitis, is characterized by erythematous circinate plaques on the head, neck, and upper chest and has been reported in the first to second month of spring. Histologically, neutrophilic infiltration of the sebaceous glands occurs, sometimes forming microabscesses. Although it may be photoinduced, it may also be idiopathic as in the cases reported in the genital area. Acute pustular folliculitis is a recurrent eruption of the head and neck that may be photoinduced, viral associated, or idiopathic. It resolves in most cases spontaneously in several days. The presence of follicular pustules distinguishes the photoinduced cases from PLE.

Therapeutically, most patients with mild PLE 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 or blockers (ecamsule, avobenzone, titanium dioxide, zinc oxide) of long-wave UVA because this is the most common triggering wavelength. Sunblocks containing more than one of these agents are more effective. DermaGard film can be applied to windows at home and in the car to block the transmission of almost all UVB and UVA rays while allowing visible light to be transmitted. Degradation does occur, so the film should be replaced every 5 years. These measures of photoprotection are critical for all patients, because they are free of toxicity and reduce the amount and duration of other therapies required. Patient education is important in the management of PLE. Phototesting may be required to convince patients that they are UV sensitive and will also determine the action spectrum.

The use of topical tacrolimus ointment at night or twice daily, combined with the previous measures for sun avoidance and the use of sunscreens, controls PLE in many patients. At times, topical steroids, frequently of super or high potency and in several daily