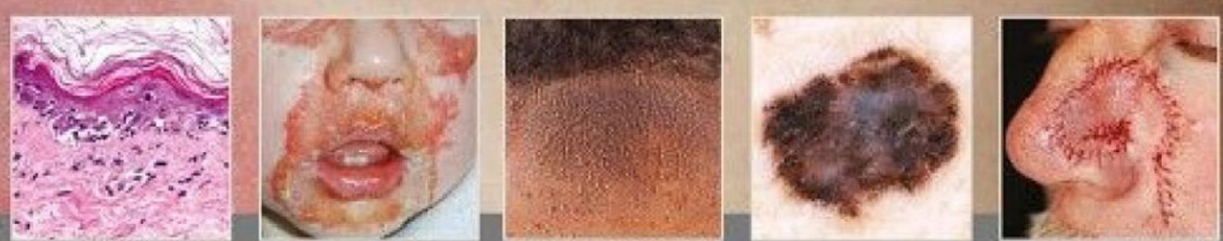
Fourth Edition

Dermatology

JEAN L. BOLOGNIA
JULIE V. SCHAFFER
LORENZO CERRONI



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ELSEVIER

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Preface

The practice of dermatology is based upon a visual approach to clinical disease, with the development of an appreciation of recurrent patterns and images. The entire spectrum of our discipline, from the generation of differential diagnoses to the orientation of rotational flaps, relies upon imagery. As a result, visualization also plays a critical role in how we integrate new information into pre-existing frameworks that serve as the hard drives of our medical memory.

In the textbook *Dermatology* there is a strong emphasis on visual learning. This commitment is reflected in the use of schematic diagrams to convey the principles of skin biology as well as cutaneous surgery, in addition to the inclusion of algorithms, which provide a logical as well as practical approach to commonly encountered clinical problems. The majority of the basic science is integrated throughout the book and appears as introductory chapters to the various sections. In this edition, even more emphasis has been placed on clinicopathologic correlations, with photomicrographs demonstrating key histologic findings adjacent to clinical images of the same disorder. The chapters also contain tables that attempt to provide weighted differential diagnoses and a "ladder" approach to therapeutic interventions. Lastly, color-coding of sections allows an easy and rapid access to required information.

The ultimate goal of *Dermatology* is for it to never make its way to the bookshelf because it is being used on a weekly, or perhaps even daily, basis. Hopefully, this book will function as a colleague, albeit a non-verbal one, who is easily approachable and possesses the necessary expertise to provide succinct, up-to-date information that is both precise and practical. It is also our hope that the organization is intuitive and information can therefore be quickly retrieved. Realizing this goal required the time and energy of our contributors, who have unselfishly shared their knowledge and experience with literally thousands of patients from around the world, and we thank them.

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VOLUMES, SECTIONS AND COLOR CODING

Dermatology is divided into two volumes. The book is divided into 22 sections, which are color-coded as follows for reference:

VOLUME ONE

- **Section 1** Overview of basic science
- **Section 2** Pruritus
- **Section 3** Papulosquamous and eczematous dermatoses
- **Section 4** Urticarias, erythemas and purpuras
- **Section 5** Vesiculobullous diseases
- **Section 6** Adnexal diseases
- **Section 7** Rheumatologic dermatology
- **Section 8** Metabolic and systemic diseases
- **Section 9** Genodermatoses
- **Section 10** Pigmentary disorders
- **Section 11** Hair, nails, and mucous membranes

VOLUME TWO

- **Section 12** Infections, infestations, and bites
- **Section 13** Disorders due to physical agents
- **Section 14** Disorders of Langerhans cells and macrophages
- **Section 15** Atrophies and disorders of dermal connective tissues
- **Section 16** Disorders of subcutaneous fat
- **Section 17** Vascular disorders
- **Section 18** Neoplasms of the skin
- **Section 19** Medical therapy
- **Section 20** Physical treatment modalities
- **Section 21** Surgery
- **Section 22** Cosmetic surgery

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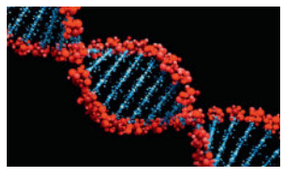

Therapeutic Ladders

Rx

Therapeutic ladders have been standardized for measuring levels of evidence.

Key to evidence-based support:
(1) prospective controlled trial
(2) retrospective study or large case series
(3) small case series or individual case reports.

Dermatology Website

Additional 'e' references in Chapters 8, 24, 65, 116, 145 and 150 can be found in full at http://www.expertconsult.com, which includes all of the book's content plus supplementary images and tables in a searchable format.

Expert CONSULT

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Dedication

Dedication

This book is dedicated to our families, in particular Dennis Cooper, MD, Andrew Schaffer and Ricarda Cerroni, who endured our work on this project and who unwittingly were part of the team, and to all the rest of the team at Elsevier who made it all happen.

Acknowledgments

We are grateful to the authors for sharing their expertise and putting forth their best efforts to bring up-to-date educational material to the readers. In addition, we wish to acknowledge the invaluable contributions of Joanne Scott and Glenys Norquay, both of whom invested years of focused work into this project. The expertise of team members Trinity Hutton (development), Joanna Souch (production), Lesley Frazier (illustrations), and Susan Stuart (production) ensured a top-quality textbook. We also want to thank Russell Gabbedy, who was there in the early days of the first edition and then rejoined us for the third and fourth editions.

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We would like to acknowledge and offer grateful thanks for the input of all previous editions' editors, without whom this new edition would not have been possible

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Basic Principles of Dermatology 0

Whitney A. High, Carlo Francesco Tomasini, Giuseppe Argenziano and Iris Zalaudek

Chapter Contents

INTRODUCTION TO CLINICAL DERMATOLOGY

The skin represents the largest organ of the human body. The average adult has 1.75 m^2 (18.5 ft^2) of skin that contains a variety of complex adnexal structures, including hair follicles, nails, glands and specialized sensory structures, all of which function in protection, homeostasis, and the transmission of sensation. Dermatology is the field of medicine that deals with the macroscopic study of skin, adjacent mucosa (oral and genital) and cutaneous adnexa, while dermatopathology deals with the microscopic study of the same structures. The two fields are closely allied, as they are complementary and requisite to one another.

Multiple studies have shown that a dermatologist is the most effective diagnostician with regard to skin disease[1,2]. This enhanced acumen reflects experience in recognizing distribution patterns and configurations as well as subtle variations in morphology and colors, in addition to appreciating associated histopathologic findings. This chapter will not only serve as an introduction to the classification schemes, descriptive terminologies and diagnostic tools utilized in dermatology, it will also highlight additional means for studying the skin, including dermoscopy (dermatoscopy) and dermatopathology, with clinicopathologic correlation between macroscopic and microscopic findings.

Etiologic Premises

All students of dermatology, whether beginners or advanced scholars, require a basic conceptual framework upon which to organize thousands of skin diseases. A useful arrangement is one that is analogous to a tree, with a trunk, major branches, minor branches, twigs and, ultimately, leaves (Fig. 0.1). Instead of memorizing thousands of leaves, a logical, progressive movement along the limbs will allow for a more complete and sophisticated differential diagnosis.

Inflammatory versus neoplastic

An early and major "branch point" in classifying skin diseases is deciding simply if a skin condition is "neoplastic" (either benign or malignant) or "inflammatory" (either infectious or non-infectious) (see Fig. 0.1). However, an experienced clinician knows that one must consider possible diagnoses along multiple limbs before narrowing the differential diagnosis, because both overlap and mimicry can occur. For example, mycosis fungoides, the most common form of cutaneous T-cell lymphoma, is a clonal lymphoproliferative disorder (a "neoplasm"), yet its clinical presentation resembles an inflammatory disorder (Fig. 0.2), especially in its early stages. Conversely, sarcoidosis is an inflammatory condition, but it may present as an isolated infiltrated plaque or nodule that may mimic a neoplasm (Fig. 0.3).

Morphology

To an engineer or material scientist, the word "*morphology*" refers to the structure and appearance of a material without regard to function. In dermatology, this term is used analogously to refer to the general appearance of a skin lesion or lesions, irrespective of the etiology or underlying pathophysiology. For example, a small cutaneous blister is referred to as a "vesicle", regardless of whether it is due to an infectious process, such as herpes zoster, or an autoimmune process, such as

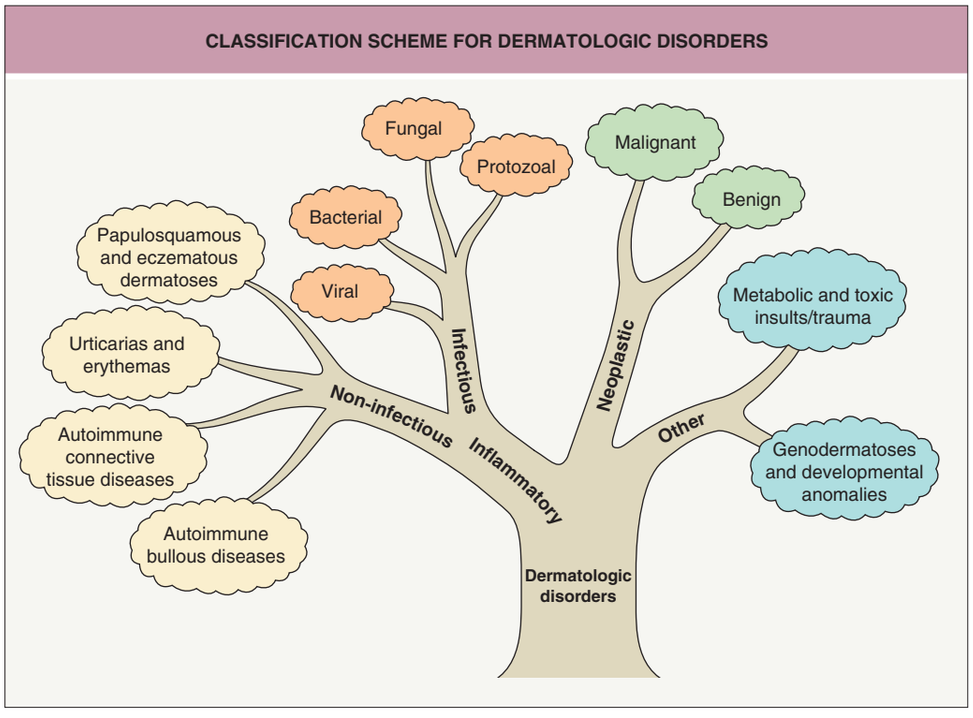

Fig. 0.1 Classification scheme for dermatologic disorders. The "trunk" of dermatology divides into the major etiologic "branches" of inflammatory, neoplastic, and other. Branches narrow and further subdivide, e.g. inflammatory into infectious and non-infectious. Branches ultimately terminate as clustered leaves, representing specific disorders.

ABSTRACT

All students of dermatology need a basic foundation and framework upon which to accumulate knowledge. In this chapter, the basic tenets of disease classification in dermatology are introduced. This includes division of disease processes into basic etiologic origins, most commonly inflammatory diseases versus neoplasms, with further subdivision of the former into infectious versus non-infectious. Further subcategorizations eventually result in an appropriate differential diagnosis. Descriptive terms are also introduced which represent the lexicon of dermatology and serve as the building blocks of a specialty-specific language. The principles of morphology, configuration, and distribution are stressed as is the utility of these concepts in the generation of a logical differential diagnosis. The importance of histopathologic examination of diseased skin, especially when an appropriate and representative biopsy specimen is obtained, is emphasized, as is clinicopathologic correlation. However, the latter may require both special stains and immunohistochemical stains. Advanced clinical examination techniques, in particular dermoscopy, are also outlined. In sum, this introductory chapter foreshadows a more detailed discussion of the myriad aspects of the clinical practice of dermatology and dermatopathology that follow in the remainder of the tome. In this regard, metaphorically, the chapter represents footings, placed into bedrock and designed to secure the "dermatologic skyscraper" that the remainder of the text represents.

Dermatopathology combines two separate, although intimately related disciplines, clinical dermatology and general pathology. Both of these fields share the same root, i.e., morphology. The secret for learning dermatopathology is to adapt the same skill sets that enable you to recognize primary and secondary skin lesions clinically and apply them to the microscopic slide. The chapter starts with the basic principles of performing a skin biopsy, including proper selection of a clinical lesion, biopsy techniques and handling of specimens, emphasizing the prerequisites for maximizing the results of the procedure. It then describes an algorithmic approach to pattern recognition for the histopathologic diagnosis of inflammatory skin diseases. Ancillary techniques that may help in the pathologic diagnosis of skin diseases, particularly immunohistochemistry, are also discussed.

KEYWORDS:

morphology,
distribution,
configuration,
skin color,
clinicopathologic correlation,
temporal course,
dermatopathology,
dermoscopy,
dermatoscopy,
skin biopsy,
special stains,
immunohistochemical stains,
clinicopathologic correlation,
dermatology lexicon,
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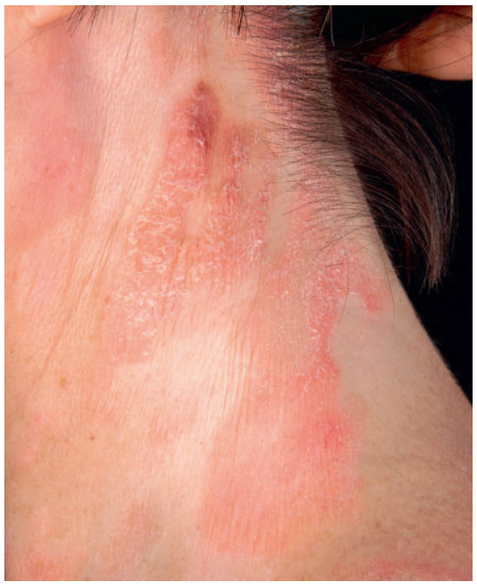


Fig. 0.2 Mycosis fungoides, the most common form of cutaneous T-cell lymphoma. Mycosis fungoides represents a neoplastic proliferation of monoclonal lymphocytes, but it presents clinically in a manner akin to that of inflammatory disorders. *Courtesy, Lorenzo Cerroni, MD.*

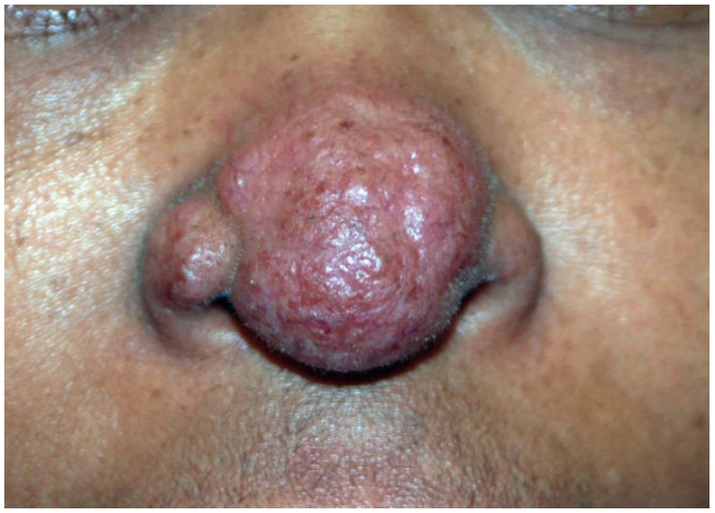


Fig. 0.3 Sarcoidosis. It is an inflammatory disorder of uncertain etiology, most prevalent in African-Americans from the southern United States, but sarcoidosis can present as a papulonodule or infiltrated plaque, mimicking a neoplastic disorder.

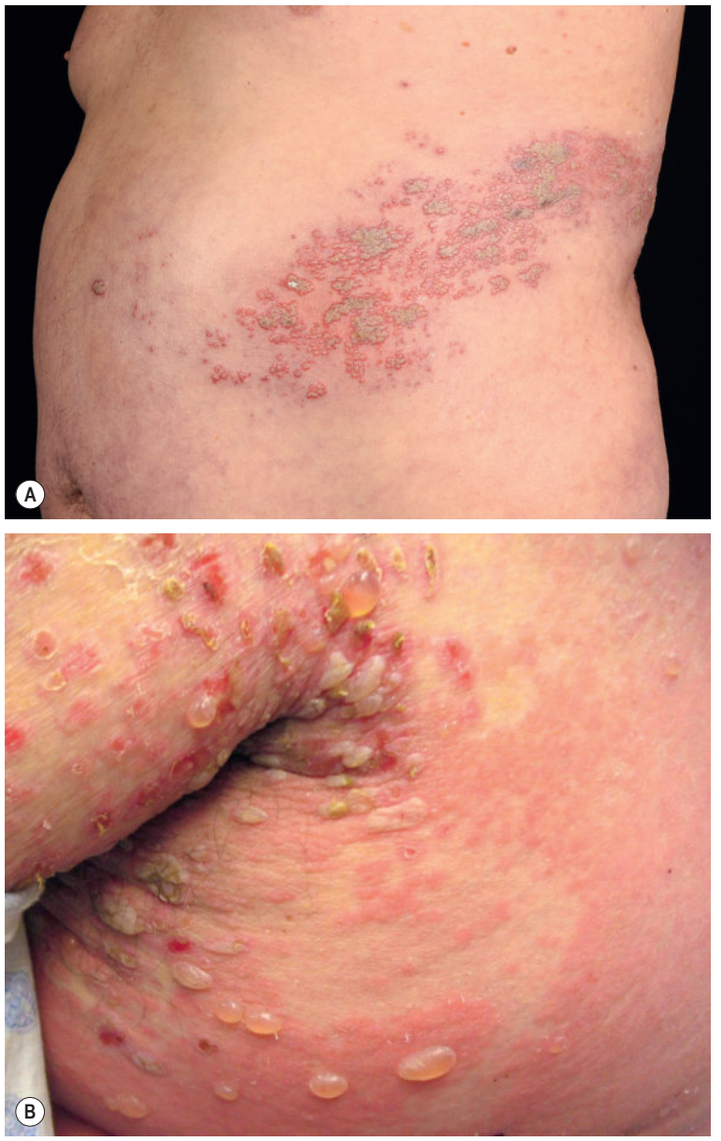


Fig. 0.4 Herpes zoster, an infectious disease, versus bullous pemphigoid, an autoimmune bullous disease. While disparate in etiology, herpes zoster (**A**) and bullous pemphigoid (**B**) result in a similar morphology – namely, cutaneous vesicles and bullae. *A, Courtesy, Lorenzo Cerroni, MD.*

bullous pemphigoid (Fig. 0.4). Therefore, the proper use of morphologic terms establishes a structural framework for grouping skin diseases based upon their macroscopic appearance[3].

In essence, morphologic terms become a "native language" by which dermatologists, and other health professionals, communicate with each other to *describe* skin lesions. As such, they are key elements of a lexicon. Without a basic working knowledge of morphology, it is impossible to describe cutaneous observations in a consistent manner. Therefore, one of the initial steps in studying dermatology is to learn basic morphologic definitions inherent to the specialty.

There exist both *primary* morphologic terms (Table 0.1), which refer to the most characteristic, representative or native appearance of skin lesions (e.g. a "papule"), as well as *secondary* morphologic terms (Table 0.2), which can augment or even supplant primary morphologic terms. Secondary morphologic terms often reflect the effects of exogenous factors or temporal changes (e.g. "scales", "crusts") that evolve during the course of a skin disease.

Secondary changes must be considered when performing, or examining histologically, a biopsy of a skin lesion. An astute clinician will generally attempt to biopsy a well-developed but "fresh" lesion that demonstrates the expected primary pathology, free of secondary changes such as erosions, excoriations, and lichenification. This allows the dermatopathologist to evaluate the histologic features of the lesions in their native state, without potentially confounding alterations.

Lastly, the skin is a three-dimensional structure, and like the cartographers who construct maps, there are certain descriptors used by dermatologists to describe the topography of individual skin lesions. Examples include flat-topped (lichenoid), dome-shaped, verrucous, umbilicated, filiform, and pedunculated[3].

Palpation and appreciation of textural changes

Any discussion of morphology must include textural change, and palpating a lesion often provides important diagnostic clues. In dermatology, palpation can prove useful in several ways. Firstly, it helps in making a distinction amongst primary morphologies (see Table 0.1). For example, the key difference between macules and papules, or patches versus plaques, is that macules and patches are flush with the surrounding skin and cannot be appreciated by palpation. On the other hand, papules and plaques, by definition, must be palpable (Table 0.3). Secondly, palpation may augment the examination and appreciation of a disease process for which visual changes are absent, unimpressive, or nonspecific. For example, in morphea, an autoimmune connective tissue disease that leads to sclerotic collagen within the dermis, the skin feels indurated (very firm) while only nonspecific hyperpigmentation may be evident with visual inspection. The same is true for other fibrotic disease processes, such as nephrogenic systemic fibrosis and systemic sclerosis. Likewise, atrophy, be it epidermal, dermal or subcutaneous, also serves as a diagnostic clue (Fig. 0.5).

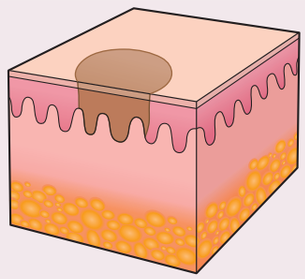
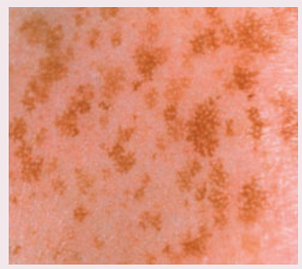
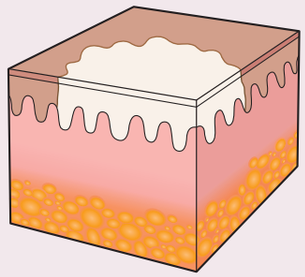
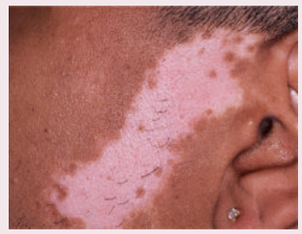
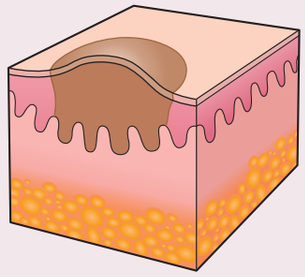
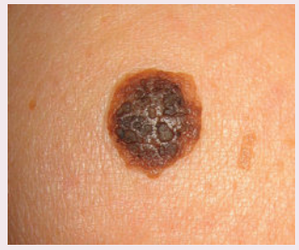
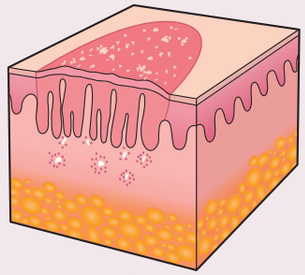
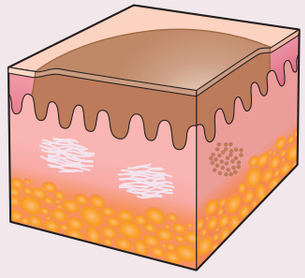
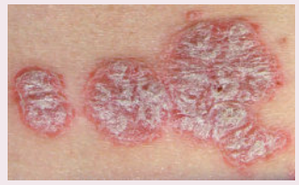
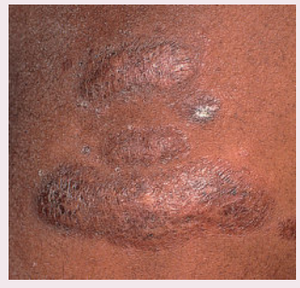
PRIMARY LESIONS – MORPHOLOGICAL TERMS				
Term	**Clinical features**		**Clinical example**	**Clinical disorders**
Macule	• Flat (non-palpable), circumscribed, differs in color from surrounding skin • <1 cm in diameter • Often hypo- or hyperpigmented, but also other colors (e.g. pink, red, violet)		 Solar lentigines	• Ephelid (freckle) • Lentigo • Idiopathic guttate hypomelanosis • Petechiae • Flat component of viral exanthems
Patch	• Flat (non-palpable), circumscribed, differs in color from surrounding skin • >1 cm in diameter • Often hypo- or hyperpigmented, but also other colors (e.g. blue, violet)		 Vitiligo	• Vitiligo • Melasma • Dermal melanocytosis (Mongolian spot) • Café-au-lait macule • Nevus depigmentosus • Solar purpura
Papule	• Elevated (palpable), circumscribed • <1 cm in diameter • Elevation due to increased thickness of the epidermis and/or cells or deposits within the dermis • May have secondary changes (e.g. scale, crust) • The profile can be flat-topped (lichenoid), dome-shaped, umbilicated, or verrucous		 Seborrheic keratosis	• Seborrheic keratosis • Cherry hemangioma • Compound or intradermal melanocytic nevus • Verruca • Molluscum contagiosum • Lichen nitidus • Elevated component of viral exanthems • Small vessel vasculitis
Plaque	• Elevated (palpable), circumscribed • >1 cm in diameter • Elevation due to increased thickness of the epidermis and/or cells or deposits within the dermis • May have secondary changes (e.g. scale, crust) • Occasionally, a plaque is palpable but not elevated, as in morphea	 	 Psoriasis  Sarcoidosis	*Primarily epidermal* • Psoriasis • Lichen simplex chronicus • Nummular dermatitis *Dermal* • Granuloma annulare • Sarcoidosis • Hypertrophic scar, keloid • Morphea • Lichen sclerosus

Table 0.1 Primary lesions – morphological terms. *Some of the photos courtesy, Jean L Bolognia, MD; Lorenzo Cerroni, MD; Louis A Fragola, Jr, MD; Julie V Schaffer, MD; Kalman Watsky, MD.*

Continued

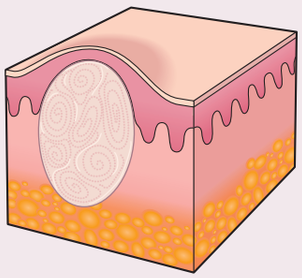
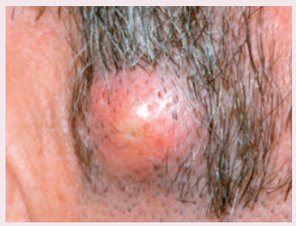
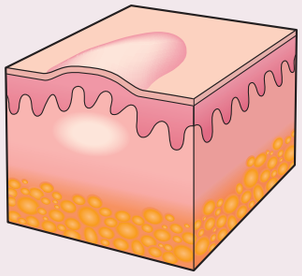
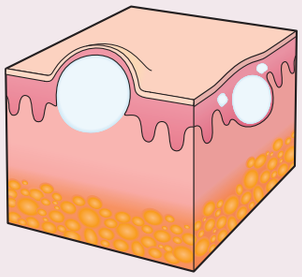
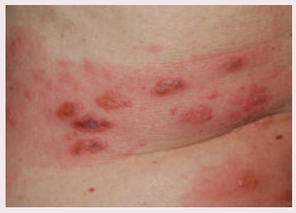
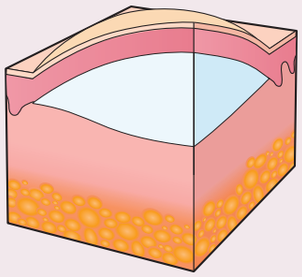
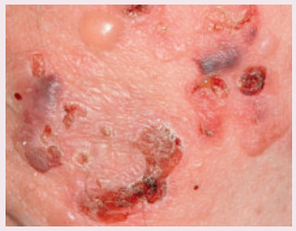
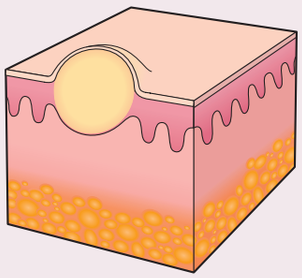
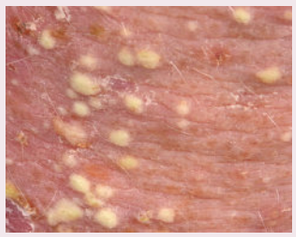
PRIMARY LESIONS – MORPHOLOGICAL TERMS				
Term	**Clinical features**		**Clinical example**	**Clinical disorders**
Nodule	• Palpable, circumscribed • Larger volume than papule, usually >1 cm in diameter • Involves the dermis and/or the subcutis • Greatest portion may be beneath the skin surface or exophytic		 Epidermoid cyst	• Epidermoid and tricholemmal cysts • Lipomas • Metastases • Neurofibromas • Panniculitis, e.g. erythema nodosum • Lymphoma cutis
Wheal	• Transient elevation of the skin due to dermal edema • Often pale centrally with an erythematous rim		 Acute annular urticaria	• Urticaria
Vesicle	• Elevated, circumscribed • <1 cm in diameter • Filled with fluid – clear, serous, or hemorrhagic • May become pustular, umbilicated or an erosion		 Herpes zoster	• Herpes simplex • Varicella or zoster • Dermatitis herpetiformis • Dyshidrotic eczema
Bulla	• Elevated, circumscribed • >1 cm in diameter • Filled with fluid – clear, serous, or hemorrhagic • May become an erosion		 Bullous pemphigoid	• Friction blister • Bullous pemphigoid • Linear IgA bullous dermatosis • Bullous fixed drug eruption • Coma bullae • Edema bullae
Pustule	• Elevated, circumscribed • Usually <1 cm in diameter • From its onset, filled with purulent fluid		 Folliculitis	*Follicularly centered* • Folliculitis • Acne vulgaris *Non-follicularly centered* • Pustular psoriasis • Acute generalized exanthematous pustulosis • Subcorneal pustular dermatosis

Table 0.1 Primary lesions – morphological terms. (cont'd)

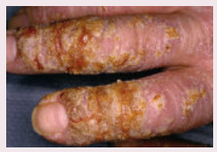
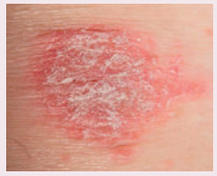
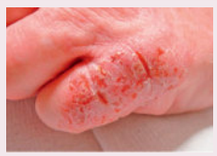
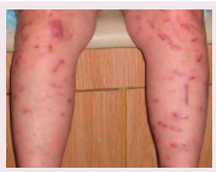
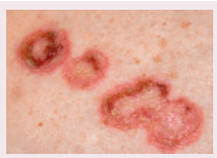
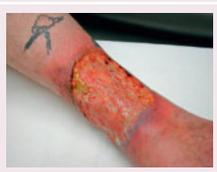
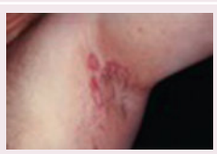
SECONDARY FEATURES – MORPHOLOGICAL TERMS			
Feature	**Description**		**Disorders**
Crust	• Dried serum, blood or pus on the surface of the skin • May include bacteria (usually *Staphylococcus*)	 Secondarily infected hand dermatitis	• Eczema/dermatitis (multiple types) • Impetigo • Later phase of herpes simplex, varicella or zoster • Erythema multiforme
Scale	• Hyperkeratosis • Accumulation of stratum corneum due to increased proliferation and/or delayed desquamation	 Psoriasis	• Psoriasis (silvery [micaceous] scale) • Tinea (leading scale) • Erythema annulare centrifugum (trailing scale) • Pityriasis (tinea) versicolor (powdery [furfuraceous] scale) • Actinic keratoses (gritty scale) • Pityriasis rosea (peripheral collarette of scale and central scale)
Fissure	• Linear cleft in skin • Often painful • Results from marked drying, skin thickening, and loss of elasticity	 Hand dermatitis	• Angular cheilitis • Hand dermatitis • Sebopsoriasis (intergluteal fold) • Irritant cheilitis
Excoriation	• Exogenous injury to all or part of the epidermis (epithelium) • May be linear or punctate	 Neurotic excoriations	• A secondary feature of pruritic conditions, including arthropod bites and atopic dermatitis • Neurotic excoriations • Acne excoriée
Erosion	• Partial loss of the epidermis (epithelium)	 Pemphigus foliaceus	• Impetigo • Friction • Trauma • Pemphigus, vulgaris and foliaceus
Ulcer	• Full-thickness loss of the epidermis (epithelium) • May have loss of the dermis or even subcutis • The size, shape and depth should be described as well as the characteristics of the border, base and surrounding tissue	 Pyoderma gangrenosum	• Stasis ulcer • Pyoderma gangrenosum • Ecthyma • Neuropathic ulcer
Infarct	• Ischemia of tissue • Color can vary from gray–white to purple to black	 Antiphospholipid syndrome	• Can be due to vascular compromise (e.g. atherosclerosis, calciphylaxis), thrombosis, vasculitis, emboli (infectious or non-infectious), or vasospasm (see Table 0.5)
Atrophy	• Epidermal atrophy – thinning of the epidermis, leading to wrinkling and a shiny appearance • Dermal atrophy – loss of dermal collagen and/or elastin, leading to a depression (see Table 0.3)	 Striae secondary to potent topical corticosteroids	• Lichen sclerosus • Poikiloderma • Striae • Anetoderma • Focal dermal hypoplasia (Goltz syndrome)

Table 0.2 Secondary features – morphological terms. *Some of the photos courtesy, Louis A Fragola, Jr, MD; Jeffrey P Callen, MD; Luis Requena, MD.*

Continued

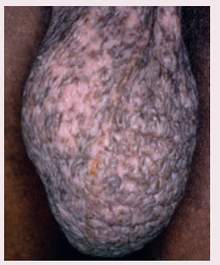
SECONDARY FEATURES – MORPHOLOGICAL TERMS			
Feature	**Description**		**Disorders**
Lichenification	• Accentuation of natural skin lines, reflecting thickening (acanthosis) of the epidermis • Often due to rubbing	 Lichen simplex chronicus	• Lichen simplex chronicus, isolated or superimposed on a pruritic condition, e.g. atopic dermatitis

Table 0.2 Secondary features – morphological terms. (**cont'd**)

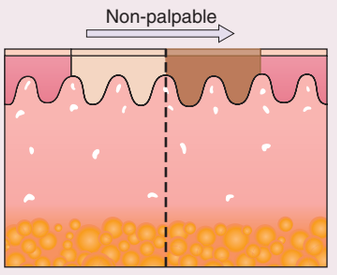
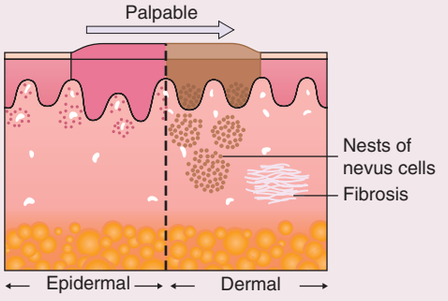
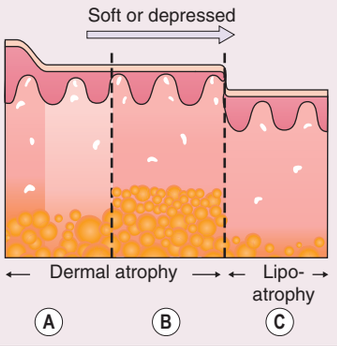
USE OF PALPATION IN DEFINING CUTANEOUS LESIONS			
Types of lesion			**Examples**
Macules & patches (non-palpable)			• Solar lentigines • Idiopathic guttate hypomelanosis • Melasma • Vitiligo • Petechiae • Dermal melanocytosis
Papules & plaques (palpable)			• Psoriasis • Lichen planus • Dermatitis • Intradermal or compound melanocytic nevus • Hypertrophic scar, keloid • Morphea
Atrophy – dermal & subcutaneous		(A) (B) (C)	• Anetoderma • Focal dermal hypoplasia (Goltz syndrome) • Lipoatrophy due to corticosteroid injections • Lipoatrophy due to panniculitis

Table 0.3 Use of palpation in defining cutaneous lesions.

Lastly, purpura is often classified as palpable or non-palpable, and this division implies different underlying etiologies (e.g. small vessel vasculitis aligned more with palpable purpura than macular purpura). Examples of useful distinctions that can be gleaned via palpation are outlined in Table 0.4.

Color

The color of skin lesions can provide important clues as to the nature of the disease process. Sometimes our perception of color may be modified by palpation (see Table 0.4). For example, while many dermatological processes appear red–purple in color, it is important to ascertain whether this is a blanchable erythema (i.e. it disappears with pressure), which suggests the color is due to vasodilation, or whether it is due to extravasation of red blood cells into the tissue (purpura), which does not blanch. Also, it is not uncommon for exogenous sources of pigment, such as topical medicaments, oral drugs and other ingestants, to be implicated in producing discoloration of the skin. Table 0.5 lists the more frequently observed colors of skin lesions and examples of associated disorders.

Variation in skin color within the human population

Many racial and ethnic descriptors are used in common parlance, including African, African-American, Asian, Middle Easterner, Northern European, Southern European, Native American, Pacific Islander

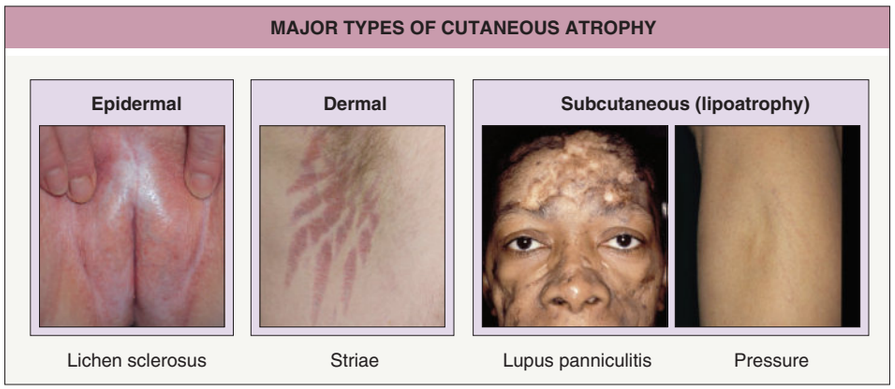


Fig. 0.5 Major types of cutaneous atrophy. *Photos courtesy, Jean L Bolognia, MD.*

PALPATION OF CUTANEOUS LESIONS
• Soft (e.g. intradermal nevus) versus firm (e.g. dermatofibroma) versus hard (e.g. calcinosis cutis, osteoma cutis)
• Compressible (e.g. venous lake) versus noncompressible (e.g. fibrous papule)
• Tender (e.g. inflamed epidermoid inclusion cyst, angiolipoma, leiomyoma) versus nontender
• Blanchable (e.g. erythema due to vasodilation) versus nonblanchable (e.g. purpura)
• Rough versus smooth
• Mobile versus fixed to underlying structures
• Dermal versus subcutaneous
• Temperature – normal versus warmer versus cooler
• Other, e.g. thrill, pulsatile

Table 0.4 Palpation of cutaneous lesions.

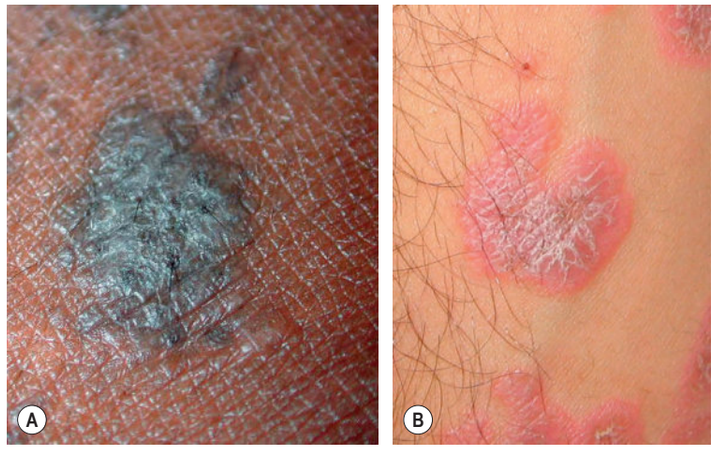


Fig. 0.6 Lichen planus presents differently in darkly pigmented versus lightly pigmented skin. A,B The erythematous to violaceous hue seen in lightly pigmented skin is more muted in darkly pigmented skin and the lesions appear brown–black in color. Wickham striae (lacy white pattern) are more easily seen in **B**.

and Hispanic, to describe individuals with similar cutaneous characteristics as well as heritage. Yet even within racial and ethnic groups, gradations exist with regard to skin pigmentation. Sometimes the term "skin of color" is used to describe all skin tones darker than those of white (Caucasian) skin[4]. However, this term encompasses more than skin color and its response to ultraviolet irradiation, as is assessed by the Fitzpatrick Scale (skin phototypes I–VI; Table 0.6). It also refers to other shared characteristics, such as hair color, hair texture, and a tendency toward certain reaction patterns in the skin as a response to an insult. The practice of dermatology requires a solid understanding of the differences in clinical features (e.g. hues of red) amongst individuals with different levels of skin pigmentation.

Variations in skin color are due to differences in the amount and distribution of melanin within epidermal melanocytes and keratinocytes[5], rather than the number of melanocytes (see Ch. 65). In addition, the ratio of eumelanin (brown–black) to pheomelanin (yellow–red) influences skin color, with pheomelanin the predominant pigment in those with freckles and red hair. Exposure to ultraviolet radiation also significantly impacts melanin production (tanning).

Pigmentation of the skin clearly influences the prevalence of certain cutaneous findings and disorders. For example, individuals with darkly pigmented skin are more likely to develop multiple streaks of longitudinal melanonychia (see Ch. 71)[6,7], pigmentation of the oral mucosa[8], persistent postinflammatory hyperpigmentation (see Ch. 67), and obvious pigmentary demarcation lines[9] (Futcher lines or Voigt lines; see Fig. 67.12). Whether postinflammatory hypopigmentation[10] is more common or just more clinically apparent is a matter of debate. In addition, discoid lupus erythematosus and keloids are seen more often in patients with darkly pigmented skin and African ancestry, but the relationship of these disorders to melanocyte function is not clear.

There can also be differences in the physiologic properties of the skin. For example, the stratum corneum of black skin often retains more layers and is more compact and cohesive than that of white skin. In addition, darker skin produces less vitamin D_3 in response to equivalent amounts of sunlight, and this is postulated to have been a driving force in the evolution of paler skin as early humans migrated away from the equator[11].

Perhaps the most important point to remember is that erythema (redness) can be difficult to appreciate in darkly pigmented skin. Erythema is caused by vasodilation and/or increased blood flow within the dermis, and if the epidermis is deeply pigmented, the red hues of oxyhemoglobin are often less obvious. For this reason, diseases that are classically described as erythematous (e.g. cellulitis) or violaceous (e.g. lichen planus) may present more subtly in darker skin types (Fig. 0.6)[12]. Diagnostic procedures that depend upon the development of erythema, such as patch testing for the evaluation of allergic contact dermatitis, can be more challenging to interpret in dark skin. Lastly, cyanosis (blue hues indicative of poor oxygenation and a critical clinical sign) is also more difficult to appreciate when the skin is darkly pigmented.

Configuration and Distribution

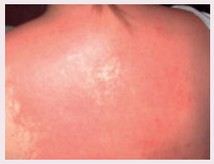
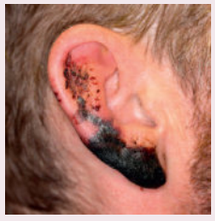
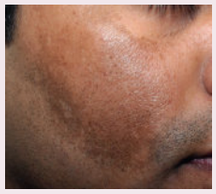
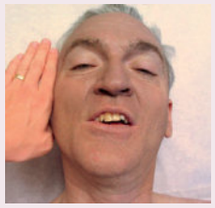
After carefully considering the morphology and color of skin lesions, the dermatologist must next analyze two closely related properties – configuration and distribution – in order to hone in on the correct diagnosis. For example, pruritic and fragile vesicles on the elbows and knees would prompt consideration of dermatitis herpetiformis, whereas grouped vesicles on an erythematous base confined to a single dermatome would mandate consideration of herpes zoster (Fig. 0.7) or zosteriform herpes simplex.

Configuration

Appreciation of the configuration or arrangement of skin lesions can provide important clues as to the diagnosis. Examples include *annular* (e.g. tinea corporis, granuloma annulare; see Ch. 19), *serpiginous* (e.g. cutaneous larva migrans), *clustered/grouped* (e.g. piloleiomyomas, herpetiform vesicles), *reticulated* (e.g. erythema ab igne), and *retiform* (e.g. purpura fulminans, purpura due to calciphylaxis [Fig. 0.8]; see Ch. 22). The latter pattern reflects occlusion of the cutaneous vasculature[13].

It also important to note if the cutaneous lesions are in a *linear* configuration (Fig. 0.9). The lesions may follow the lines of Blaschko, which reflect patterns of embryonic development (see Fig. 62.1)[14], or

COLOR AS A CLUE TO THE CLINICAL DIAGNOSIS

Color	Examples of diseases with this color
Erythema (pink to red–brown, depending upon the skin phototype)  Morbilliform (exanthematous) drug eruption	• Dermatitis • Psoriasis • Morbilliform drug eruption • Viral exanthems • Any insult that causes vasodilation
Black  Necrosis secondary to vasculopathy from levamisole-contaminated cocaine	• Necrosis of the skin due to: - Vasculitis (granulomatosis with polyangiitis) - Thrombosis (e.g. DIC, monoclonal cryoglobulinemia) - Emboli (e.g. ecthyma gangrenosum) - Vasospasm (e.g. severe Raynaud phenomenon) - Vascular compromise (e.g. atherosclerosis, calciphylaxis) • Eschar (e.g. anthrax) • Cutaneous melanoma • Traumatic tattoos (e.g. asphalt)
Blue (ceruloderma)  Dermal melanocytosis	• Dermal melanocytosis (e.g. Mongolian spot, nevus of Ota) • Dermal melanocytomas (e.g. blue nevi) • Cyanosis • Ecchymoses • Venous congestion (e.g. venous malformations) • Drugs/deposits (e.g. minocycline, traumatic tattoos)
Brown  Melasma	• Pigmented lesions - Lentigines - Seborrheic keratoses - Junctional, compound and congenital melanocytic nevi - Café-au-lait macules - Dermatofibromas - Melanoma - Pigmented AKs, Bowen disease • Postinflammatory hyperpigmentation – epidermal (see Ch. 67) • Melasma • Phytophotodermatitis • Drug-induced hyperpigmentation (e.g. cyclophosphamide) • Metabolic (e.g. Addison disease, hemochromatosis)
Gray  Argyria	• Postinflammatory hyperpigmentation – dermal (e.g. erythema dyschromicum perstans; see Ch. 67) • Drugs/deposits (e.g. argyria, chrysiasis) • Combined melanocytic nevus • Traumatic tattoos • See Blue (above)

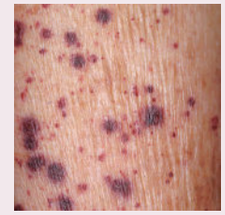
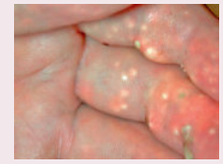
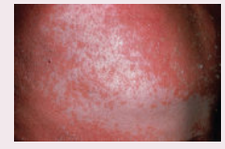
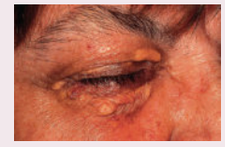
Color	Examples of diseases with this color
Purple (violaceous)  Palpable purpura of cutaneous small vessel vasculitis	• Purpura, non-palpable (e.g. solar purpura) • Purpura, palpable (e.g. small vessel vasculitis) • Vascular neoplasms (e.g. angiokeratoma, angiosarcoma) • Lichen planus • Lymphoma cutis • Pyoderma gangrenosum – border • Morphea – border (lilac)
White  Calcinosis cutis (systemic sclerosis)	• Absence of melanocytes or melanin production (e.g. vitiligo, piebaldism, OCA1A) • Scarring (e.g. scarring in discoid lupus erythematosus) • Vasospasm (e.g. Raynaud phenomenon, nevus anemicus) • Deposits (e.g. calcinosis cutis, gouty tophi) • Macerated stratum corneum – mucosal surfaces (e.g. leukoplakia)
Green  Onycholysis with secondary *Pseudomonas* infection	• *Pseudomonas* infection • Tattoo • Chloroma • Green hair due to copper deposits
Orange–red (salmon)  Pityriasis rubra pilaris with islands of sparing	• Pityriasis rubra pilaris • Mycosis fungoides (sometimes)
Yellow  Xanthelasma	• Solar elastosis • Carotenoderma • Xanthomas (e.g. xanthelasma, eruptive) • Xanthogranulomas • Adnexal tumors and hyperplasias with sebaceous differentiation • Necrobiosis lipoidica • Capillaritis (yellow–brown background) • Deposits/drugs (e.g. tophi, quinacrine)

Table 0.5 Color as a clue to the clinical diagnosis. AKs, actinic keratoses; DIC, disseminated intravascular coagulation; OCA1A, oculocutaneous albinism type 1A.
Some of the photos courtesy, Jean L Bolognia, MD; Ronald Rapini, MD; Julie V Schaffer, MD; Kalman Watsky, MD.

FITZPATRICK SCALE OF SKIN PHOTOTYPES		
Skin phototype	**Skin color**	**Response to UV irradiation**
I	White	Always burns, does not tan
II	White	Burns easily, tans with difficulty
III	Beige	Mild burns, tans gradually
IV	Brown	Rarely burns, tans easily
V	Dark brown	Very rarely burns, tans very easily
VI	Black	Never burns, tans very easily

Table 0.6 Fitzpatrick scale of skin phototypes.

they may be confined to a dermatome, which represents an area of skin whose innervation is from a single spinal nerve (see Fig. 80.14). Irrespective of whether the lesions are along the lines of Blaschko (e.g. epidermal nevi) or in a dermatomal pattern (e.g. herpes zoster [see Fig. 0.7]), there is often a characteristic midline demarcation. In addition to these two patterns, a linear arrangement can result from a trauma-induced Koebner phenomenon (an isomorphic response [Table 0.7]), as in vitiligo, lichen planus (Fig. 0.10), and psoriasis[15,16], or it may be due to trauma-induced autoinoculation, as in verrucae vulgares or verrucae planae. Linear lesions are frequently seen in acute allergic contact dermatitis due to plants (e.g. poison ivy), reflecting brushing of the branches and leaves against the skin. Lastly, papulonodules due to a range of

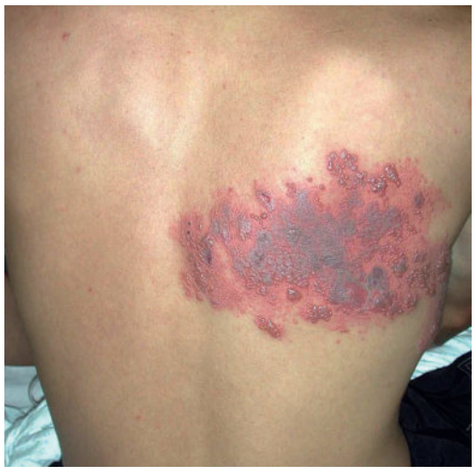


Fig. 0.7 The dermatomal pattern of herpes zoster. Note the midline demarcation.

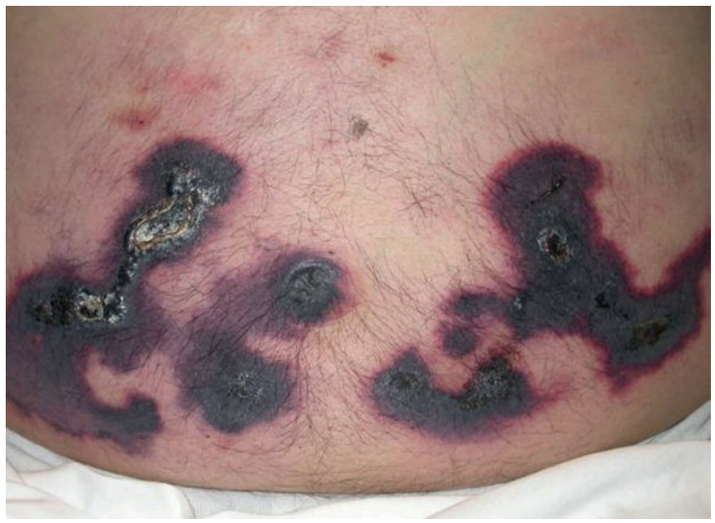


Fig. 0.8 Retiform purpura and cutaneous necrosis secondary to calciphylaxis. Note the irregular shape of the purpura. *Courtesy, Amanda Tauscher, MD.*

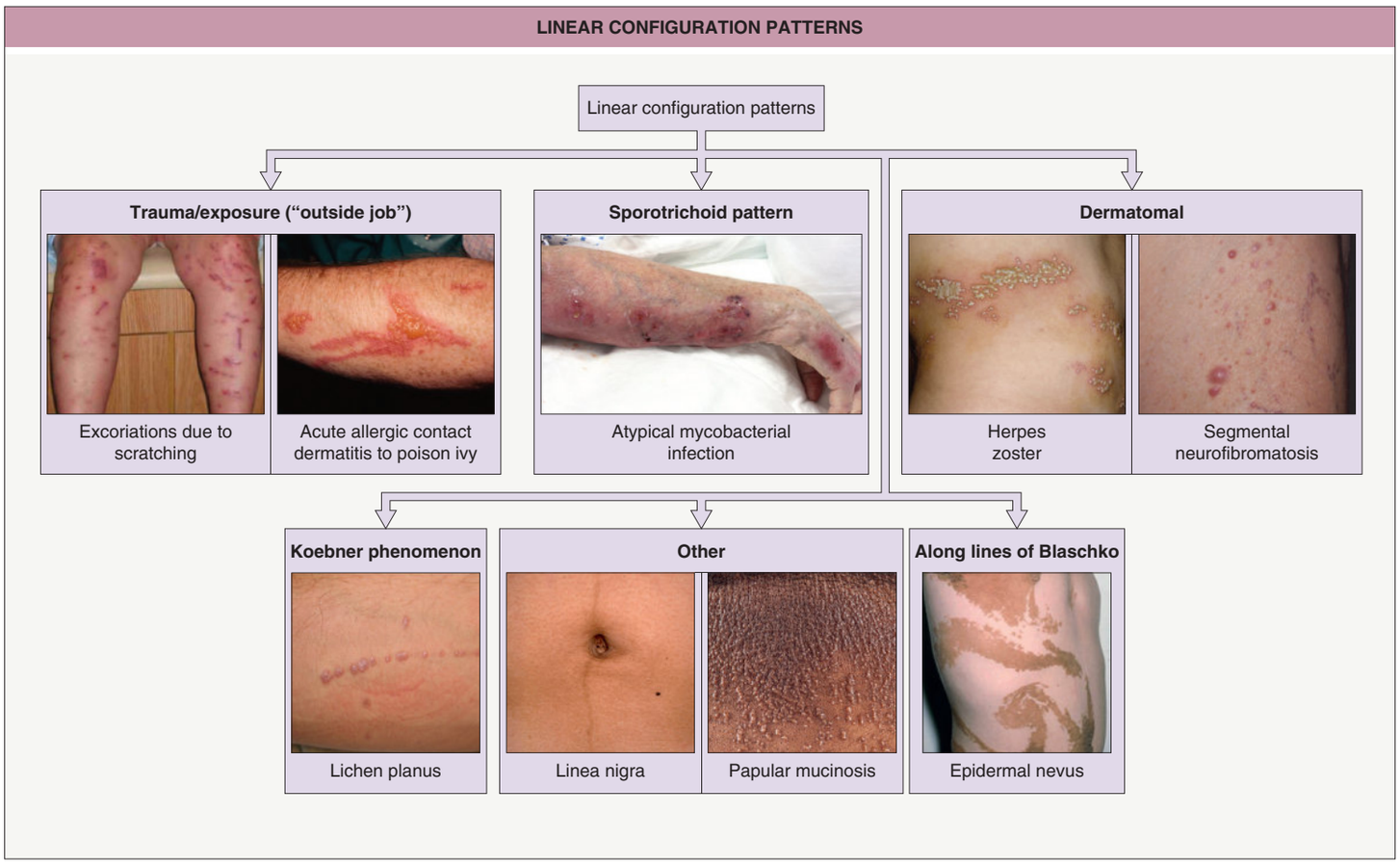


Fig. 0.9 Linear configuration patterns. *Some of the photographs courtesy, Jean L Bolognia, MD; Edward Cowen, MD; Louis A Fragola, Jr, MD; Joyce Rico, MD; Kathryn Schwarzenberger, MD.*

CLINICAL ENTITIES THAT COMMONLY DISPLAY THE KOEBNER PHENOMENON (ISOMORPHIC RESPONSE)
• Psoriasis
• Vitiligo
• Lichen planus
• Lichen niditus
• Cutaneous small vessel vasculitis
• Still disease

Table 0.7 Clinical entities that commonly display the Koebner phenomenon (isomorphic response). This is to be distinguished from both autoinoculation or pseudo-Koebner phenomenon that is seen with verrucae or mollusca as well as Wolf isotopic response where a second skin disease appears at the site of an initial unrelated and often healed skin disease (e.g. granuloma annulare at the site of healed herpes zoster).

MAJOR DISTRIBUTION PATTERNS
Disseminated vs localized vs solitary
Unilateral vs bilateral
Symmetric vs asymmetric
Sun-exposed sites vs sun-protected sites
Flexural vs extensor surfaces
Intertriginous/large body folds
Acral (hands, feet, ears, nose)
Palmoplantar
Seborrheic regions
Periorificial
Mucosal (mouth, anogenital)
"Linear" – also considered a configuration – see Fig. 0.9

Table 0.8 Major distribution patterns. Occasionally, the pattern represents a *locus minoris resistentiae* (see text).

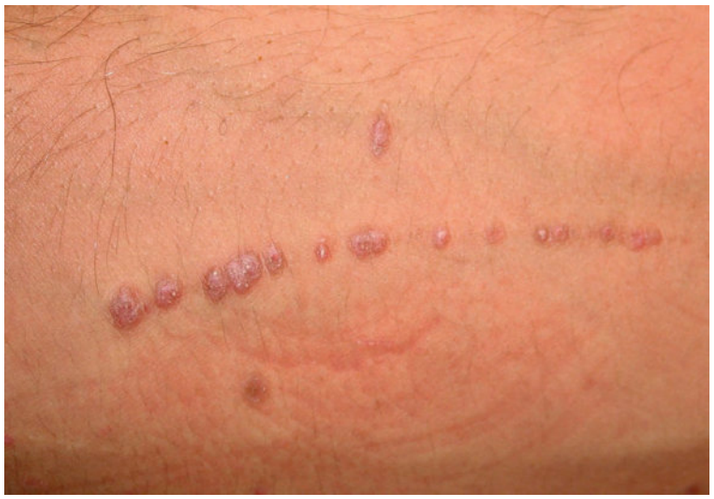


Fig. 0.10 Koebernization (isomorphic response) of lichen planus secondary to trauma. As a result, the lesions have a linear configuration.

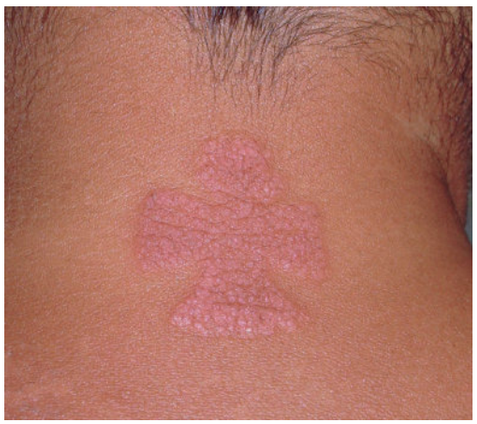


Fig. 0.11 Allergic contact dermatitis to a para-phenylenediamine-based ("black henna") temporary tattoo. The shape of the lesion clearly suggests an exogenous insult/etiology. *Courtesy, Colby Evans, MD.*

infectious agents can align along lymphatic vessels in a sporotrichoid pattern (see Ch. 77).

On occasion, cutaneous lesions have an unusual, even "unnatural", shape that corresponds to an external (exogenous) insult, such as allergic or irritant contact dermatitis (Fig. 0.11), an accidental or purposeful injury (see Ch. 90)[17], or even ritualistic medicinal practices (e.g. "cupping" or "coining"; see Ch. 133).

Distribution

Stepping back and observing the anatomic distribution pattern of skin lesions can also prove very helpful. For example, plaques of psoriasis often favor *extensor* surfaces (e.g. elbows and knees) while lichenified plaques of atopic dermatitis favor *flexural* surfaces in older children and adults (e.g. the antecubital and popliteal fossae; Table 0.8). However, to complicate matters a bit, there is an "inverse" form of psoriasis in which lesions are present in major body folds, i.e. in flexural areas (see Ch. 8). Langer cleavage lines refer to natural skin tension lines that are often used to guide the orientation of surgical excisions (see eFig. 142.3). The long axis of oval lesions of pityriasis rosea[18] and erythema dyschromicum perstans follows these cleavage lines, and this pattern is most obvious on the posterior trunk.

A *seborrheic* distribution pattern includes the head and neck as well as the upper trunk, and it reflects areas rich in sebaceous glands; seborrheic dermatitis, acne vulgaris, and pityriasis versicolor are dermatoses that favor these sites. The term "*photodistribution*" describes lesions that are accentuated in areas exposed to ultraviolet irradiation, and photodermatoses include polymorphic light eruption, phototoxic drug reactions (e.g. to doxycycline), and subacute cutaneous lupus erythematosus. Of note, sometimes a disorder will display a combination of distribution patterns; for example, in dermatomyositis, lesions can be both photodistributed and involve extensor surfaces (e.g. elbows, knees).

In addition to differences in the color of inflammatory lesions, individuals with darkly pigmented skin also have an increased frequency of several cutaneous disorders (see section on Color) and certain types of reaction and distribution patterns[19]. Examples of these reaction patterns include papular eczema and a follicular accentuation of atopic dermatitis and pityriasis versicolor, as well as an annular configuration of seborrheic dermatitis and facial secondary syphilis. An example of a favored distribution pattern is inverse pityriasis rosea in which lesions occur primarily in the axillae and groin rather than on the trunk. Although a sound explanation for these phenomena is not currently available, it is still important to be aware of their occurrence[19].

Sometimes the distribution is best explained by the phenomenon of *locus minoris resistentiae* in which certain anatomic sites are more vulnerable than others to a particular disease process[20]. Examples would be cutaneous infections within a lymphedematous limb and asteatotic eczema within a skin graft site.

Augmented Examination – Wood's Lamp and Dermoscopy

A Wood's lamp emits primarily ultraviolet A radiation with a peak wavelength of 365 nm. It is most commonly used to assist in the diagnosis of pigmentary disorders and infectious diseases (Table 0.9)[21,22]. A Wood's lamp examination is performed in a dark room, with the lamp 4–5 inches from the skin and illuminating the area of interest. After the target absorbs the UVA radiation, there is some loss of energy and therefore the emission is at a longer wavelength (with less energy) within the visible range. Dermoscopy is discussed in detail later in the chapter.

Temporal Course

Central to any medical history, including that of cutaneous disorders, is the temporal course. The patient should be queried as to duration and relative change in intensity or distribution over time. For example, there are some dermatoses that have a cephalocaudal progression over time, such as measles and pityriasis rubra pilaris. Of course, the time course is more prolonged in the latter as compared to the former.

The dermatologist is at an advantage because the skin is so accessible, and information provided by the patient can be readily compared to what is seen in the physical examination. With experience,

WOOD'S LAMP EXAMINATION OF THE SKIN	
Disorder/infection/colonization	**Fluorescent color/clinical findings**
Pigmentary disorders	
Vitiligo	Chalk-white to dull bluish-white (fluorescence of dermal collagen observed due to a marked decrease or absence of melanin within the epidermis)
Ash leaf spots	Enhancement of hypopigmentation
Hyperpigmentation due to an increase in:	
• epidermal melanin	Enhancement of brown color
• dermal melanin	Difference in color of lesional vs nonlesional skin becomes less obvious
Bacterial infections/colonizations	
Pseudomonas aeruginosa	Green
Corynebacterium minutissimum	Coral red
Propionibacterium acnes	Orange–red (in comedones)
Fungal infections	
Pityriasis (tinea) versicolor due to *Malassezia* spp.	Yellowish-white, yellow–green, golden, copper–orange
Tinea capitis due to *Microsporum* spp.	Blue–green to yellow–green
Favus due to *Trichophyton schoenleinii*	Blue–white

Table 0.9 Wood's lamp examination of the skin.

the dermatologist can usually determine by observation whether the cutaneous lesions are acute, subacute or chronic. Examples of helpful signs include scale (not to be confused with crusts), which often reflects parakeratosis that requires 2 weeks to develop, and intact tense bullae, which are rarely more than a week old. Lichenification (i.e. thickening of the skin with accentuation of normal skin markings) takes weeks to months to develop. Therefore, if lichenification is present, the lesion has not appeared acutely, despite what the patient may believe.

In an otherwise generally healthy patient, there are several diseases whose cutaneous manifestations are often acute in nature, in particular urticaria, morbilliform drug eruption, viral exanthem, acute allergic or irritant contact dermatitis, and pityriasis rosea. This is not to indicate that these diseases necessarily require immediate or emergent management, but rather that they present to the dermatologist abruptly and are distinguished, particularly from neoplasms or chronic dermatoses, by their temporal acuity. Of note, sometimes a more serious and potentially life-threatening cutaneous disease may present with skin findings that can mimic a more common and less serious disorder, especially early on.

Finally, although emergencies are unusual in dermatology, there are a few illnesses, particularly those that present with a rash and fever, which are true emergencies and must be recognized promptly and treated appropriately. Examples include Stevens–Johnson syndrome, toxic epidermal necrolysis, Kawasaki disease, meningococcemia (including purpura fulminans), Rocky Mountain spotted fever, necrotizing fasciitis, and endocarditis with cutaneous manifestations. An approach to critical dermatologic emergencies that present with a fever and rash is outlined in Fig. 0.12.

The next two sections of this introductory chapter focus on the basic principles of dermatopathology and dermoscopy, respectively, and it is important to remember that all the diagnostic techniques (unaided clinical examination, histological examination, dermatoscopic examination) discussed herein are complementary. In other words, synergistic strength and clinicopathologic correlation are achieved when the techniques are used in combination. As a corollary, using any one technique, to the exclusion of the others, may be misleading and potentially result in misdiagnosis.

THE ROLE OF DERMATOPATHOLOGY IN CLINICOPATHOLOGIC CORRELATION

Dermatopathology, the study of skin under the microscope, is uniquely related to the study of clinical dermatology, for few other medical specialties place so much emphasis on *both* the clinical and the histologic features of diseases within their realm[23]. However, this union exists not only because of overlapping subject matter, but because dermatology and dermatopathology both rely heavily upon careful observation and pattern recognition. In addition, clinical dermatology represents the "gross macroscopy" of dermatopathology, as clinical examination can be regarded akin to gross examination of biopsy specimens in other organs.

Experienced clinicians may anticipate associated histologic findings as they examine a cutaneous lesion or eruption (e.g. hyperkeratosis and/or parakeratosis when scale is present clinically, or dermal hemorrhage when there is purpura clinically). As a result, a sophisticated differential diagnosis often accompanies a skin biopsy performed by a dermatologist. Moreover, when the microscopic features are clearly delineated in a histopathology report, an experienced dermatologist can utilize clinicopathologic correlation to arrive at a final diagnosis. In a similar fashion, an experienced dermatopathologist can utilize clinical pictures to arrive at a final histopathological diagnosis.

The Skin Biopsy

In no other field of medicine is the tissue of interest so readily accessible for histologic analysis. As a result, performing a skin biopsy is an integral component of medical decision making in dermatology. A skin biopsy may be performed for a multitude of reasons, including:

- uncertainty about the clinical diagnosis
- to investigate a poor response to therapy
- to exclude or investigate the evolution of one condition into another, or
- to investigate symptoms in the absence of clinically recognizable disease.

Regardless of the rationale for performing a skin biopsy, the securing of appropriate tissue involves more than the mere mechanical procurement. Instead, a multistep process is executed, with forethought, precision and care, in order to maximize diagnostic utility[24]. Also, because a skin biopsy is often just a small sampling of a larger process, it may not always be representative of the entire disease state. Inappropriate technique or poor tissue handling may limit the diagnostic yield of a skin biopsy; accordingly, clinicians must have an appreciation of the principles of histologic examination.

Site selection

Often, the first step in performing a biopsy is to identify an unadulterated *primary lesion*. Lesions with obfuscating secondary features, such as those resulting from rubbing or traumatic injury (e.g. lichenification, excoriations) or other superimposed processes (e.g. crusting and impetiginization), should be avoided, unless the purpose of the biopsy is to prove existence of such confounders.

A well-developed, "fresh" lesion is typically chosen for biopsy. Such sampling is premised on an assumption that it will demonstrate the

Online only content

ACUTE CUTANEOUS ERUPTIONS IN OTHERWISE HEALTHY INDIVIDUALS	
Disorder	**Characteristic findings**
Urticaria (see Ch. 18)	• Pathogenesis involves degranulation of mast cells with release of histamine • Primary lesion: edematous wheal with erythematous flare • Widespread distribution • Very pruritic* • Individual lesions are transient (<24 h in duration) • May become chronic (>6 weeks)
Acute allergic contact dermatitis (see Ch. 14)	• Immune-mediated and requires prior sensitization • Primary lesion: dermatitis, with vesicles, bullae and weeping when severe • Primarily in sites of exposure; occasionally more widespread due to autosensitization • Pruritus, often marked • Spontaneously resolves over 2–3 weeks if no further exposure to allergen (e.g. poison ivy, nickel)
Acute irritant contact dermatitis (see Ch. 15)	• Direct toxic effect • Primary lesion: ranges from erythema to bullae (e.g. chemical burn) • At sites of exposure • Burning sensation • Spontaneously resolves over 2–3 weeks if no further exposure to irritant (e.g. strong acid, strong alkali)
Exanthematous (morbilliform) drug eruptions (see Ch. 21)	• Immune-mediated and requires prior sensitization • Pink to red–brown, blanching macules and papules; may become purpuric on distal lower extremities • Widespread distribution • May be pruritic • Spontaneously resolves over 7–10 days if no further exposure to inciting drug
Pityriasis rosea (see Ch. 9)	• May follow a viral illness • Primary lesion: oval-shaped, pink to salmon-colored papule or plaque with fine white scale centrally and peripheral collarette; occasionally vesicular • Initial lesion is often largest (herald patch) • Favors trunk and proximal extremities; may have inverse pattern (axillae & groin); long axis of lesions parallel to skin cleavage lines • Spontaneously resolves over 6–10 weeks; exclude secondary syphilis
Viral exanthems (see Ch. 81)	• Due to a broad range of viruses, including rubeola, rubella, enteroviruses, parvovirus, adenovirus (see Fig. 81. 2) • Often associated with fever, malaise, arthralgias, myalgias, nausea, upper respiratory symptoms • Primary lesions vary from blanching pink macules and papules to vesicles or petechiae • Distribution varies from acral to widespread; may have an enanthem • Spontaneously resolves over 3–10 days
*May have burning rather than pruritus with urticarial vasculitis, and lesions can last longer than 24 hours.	

eTable 0.1 Acute cutaneous eruptions in otherwise healthy individuals.

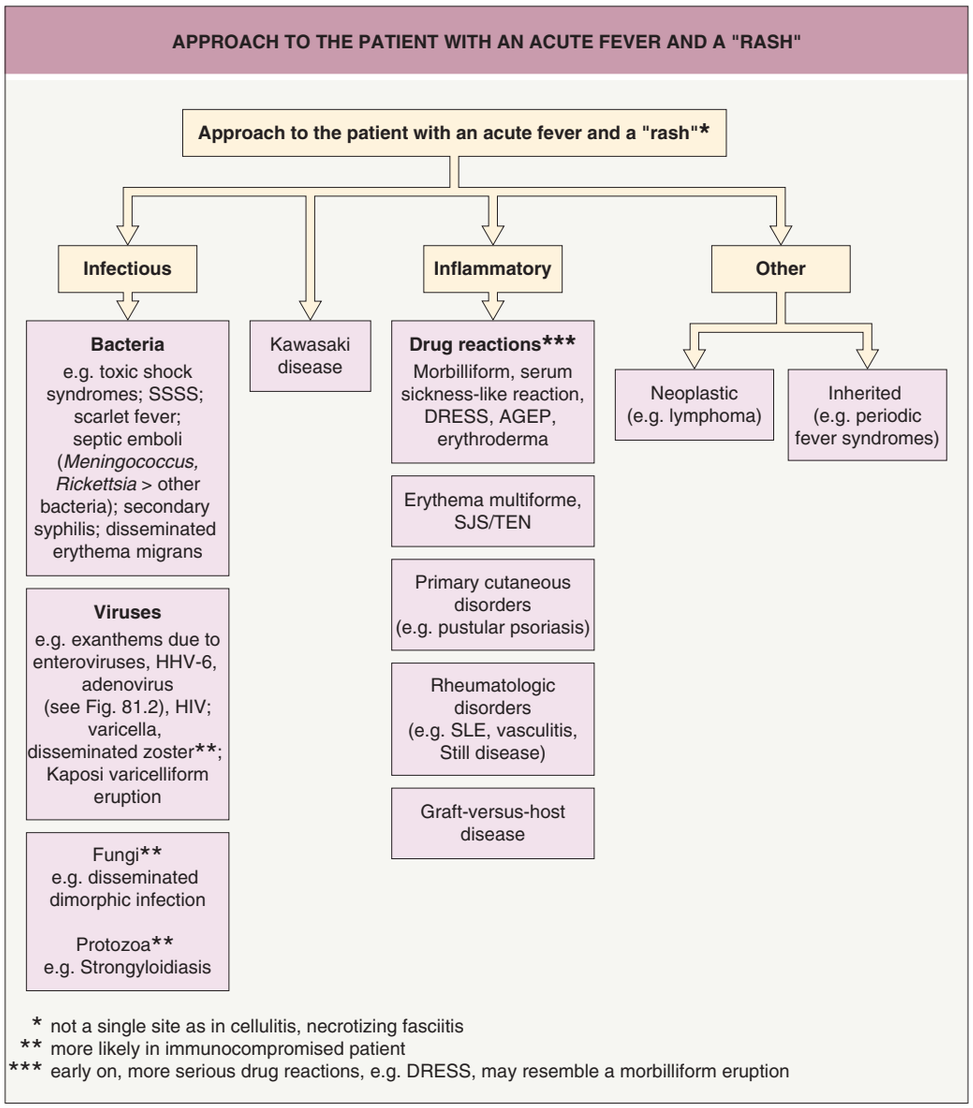


Fig. 0.12 Approach to the patient with an acute fever and a "rash". AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms (also referred to as drug-induced hypersensitivity syndrome [DIHS]); HHV, human herpes virus; HIV, human immunodeficiency virus; SJS, Stevens–Johnson syndrome; SLE, systemic lupus erythematosus; SSSS, staphylococcal scalded skin syndrome; TEN, toxic epidermal necrolysis.

most diagnostic histopathology. Immature lesions may not yet manifest characteristic histopathologic changes, and older lesions may be compromised by secondary features. Of course, there are exceptions to this general principle, such as the sampling of early lesions of cutaneous small vessel vasculitis (<24 hours old) or immunobullous diseases, especially when performing direct immunofluorescence.

While specimens are often taken from the center of a primary lesion, exceptions to this guideline exist, particularly in the case of bullae (see Fig. 29.12) and ulcers or when the histopathologic changes are subtle relative to uninvolved skin. For example, in atrophoderma an incisional biopsy should include both affected and unaffected skin and be sectioned longitudinally, so that subtle differences can be detected (see Ch. 99). In ulcers, nonspecific inflammation of vessels underneath the wound may be misinterpreted as a primary vasculitis, but in a biopsy specimen that includes the surrounding skin, the "vasculitis" disappears a few millimeters away from the ulcer. Ultimately, selection of a proper biopsy site will always be influenced by knowledge of the suspected underlying pathology.

Biopsy techniques

A wide range of biopsy techniques exist (see Ch. 146), but those most often performed include: superficial/tangential shave, deep shave ("saucerization"), curettage, punch, and incisional/excisional biopsy (Fig. 0.13). For optimal results, the technique employed must encapture tissue from the level of the skin or subcutaneous tissue where the pathologic changes are anticipated, while simultaneously balancing concerns of cosmesis and morbidity. For example, if panniculitis is suspected, a shave would not provide the appropriate tissue to establish or refute such a diagnosis (Table 0.10). Similarly, in the case of a benign exophytic lesion, such as a verruca or skin tag, it would not be expedient, economical or cosmetically savvy to remove the lesion via an excision with sutured closure. Artifactual changes due to the use of tweezers (crush) or placement of the biopsy specimen on gauze (dessication) may hinder the dermatopathologist's ability to render an accurate assessment; the cells that are most susceptible to these artifactual changes are those of cutaneous lymphoma and Merkel cell carcinoma.

- ***Superficial shave biopsy*** – this technique is employed most often when the suspected pathology is chiefly epidermal in nature (e.g. an actinic keratosis, squamous cell carcinoma *in situ*, seborrheic keratosis), or when there is a desire to remove an exophytic benign lesion (e.g. an intradermal melanocyte nevus). If the findings of interest are suspected to lie in the mid to deep dermis (e.g. discoid lupus erythematosus) then a superficial shave biopsy will not provide diagnostically useful information.
- ***Deep shave/saucerization biopsy*** – this technique is simply a deeper variant of the superficial shave, where greater angling of the blade removes more of the upper to mid-dermis (see Fig. 0.13B). Suspected non-melanoma skin cancer (e.g. basal cell carcinoma, squamous cell carcinoma) is often sampled by deep shave. Evidence suggests that when properly performed, the diagnostic value of a deep shave may rival that of an incisional/excisional procedure[25].
- ***Curettage*** – this technique is employed to remove superficial lesions that are confined to the epidermis, but it does so in a fragmented and unorientable fashion. In this regard, curettage is less desirable for diagnostic purposes, and it is not appropriate for pigmented lesions that are suspicious for melanoma or for neoplasms of uncertain etiology.

OPTIMIZING INFORMATION OBTAINED FROM A SKIN BIOPSY SPECIMEN (BASED UPON PRESUMED DIAGNOSIS)				
Inflammatory diseases				
Disorders (presumed)	**Where and when to biopsy**	**Preferred technique**	**Pitfalls**	**Ancillary techniques to consider**
Vasculitides	• Center of an early lesion • Prefer sites above the knee to avoid poor wound healing or background features due to venous hypertension	Punch or incisional biopsy (depending on the size of affected vessels)	Necrotic or ulcerated lesions may be non-diagnostic	Direct immunofluorescence (early lesions, not older than 24 h)
Livedo reticularis	• Center of the pale areas defined by the surrounding venous plexus network • Corresponds to the site of the ascending arteriole (see Fig. 106.1)	Punch or incisional biopsy	Biopsy of the venous plexus or a biopsy that is too superficial can lead to false-negative results	
Autoimmune connective tissue diseases	• Fully developed lesion • In DLE, biopsy areas of inflammation, not scarred areas	Primarily punch biopsy, unless panniculitis is suspected	• In DLE, biopsies of non-inflammatory scarred areas are often non-diagnostic • Changes of acute LE may be subtle	Direct immunofluorescence of lesional skin
Panniculitides	Early evolving lesion in lobular panniculitides (e.g. lupus panniculitis); fully developed lesion in septal panniculitides (e.g. erythema nodosum)	Large and deep incisional biopsy (must include subcutaneous fat)	• Failure to include enough fat • Late-stage lesions often have nonspecific findings	• Fresh tissue culture and/or PCR (if infectious etiology suspected) • Direct immunofluorescence (if vasculitis suspected)
Autoimmune blistering disorder	• An edematous papule/plaque or an early vesicle is preferred • If only large bullae are present, biopsy the edge of the bulla plus surrounding inflamed skin	Punch biopsy (e.g. 4 mm) or saucerization of: edematous papule/plaque, entire small vesicle, or edge of fresh, intact vesicle/bulla plus surrounding inflamed skin	• Biopsy of late-stage bullae undergoing re-epithelialization may lead to erroneous diagnosis • Late-stage, purulent, crusted or ulcerated lesions may be non-diagnostic	Direct immunofluorescence of perilesional skin (see Fig. 29.12) or nearby skin (if dermatitis herpetiformis)
Alopecias	• Active advancing edge • Areas of perifollicular inflammation	• 4–6 mm punch biopsy oriented parallel to the direction of hair • Include subcutaneous fat	Scarred areas show only end-stage fibrosis	Horizontal and vertical sectioning of biopsy Direct immunofluorescence
Infectious diseases	• Prefer mature lesions • If ulcerated, include inflammatory border	Punch biopsy or incisional biopsy (for deep-seated infections)	• Organisms may not be appreciated in histologic sections • Fresh tissue culture and/or PCR may be necessary	Immunohistochemistry, fresh tissue culture, and/or PCR
Ulcerative dermatoses	Active edge of the ulcer or early lesion if the spectrum of lesions includes a pre-ulcerative stage (e.g. pyoderma gangrenosum)	Punch or incisional biopsy	Avoid center of ulcer where nonspecific changes or possible misleading secondary changes such as underlying vasculitis	Immunohistochemistry, fresh tissue culture and/or PCR (if infectious etiology suspected)
Pigmentary disorders	Include the edge of the lesion as well as normal skin for comparison	Punch biopsy, rarely incisional biopsy	Subtle findings require clinicopathologic correlation	Special stains and/or immunohistochemistry may be necessary
Urticaria	Include the edge of the lesion as well as normal skin for comparison	Punch biopsy	Small-diameter punch biopsies may lead to false-positive results as retraction of collagen bundles may simulate interstitial edema	Direct immunofluorescence (if urticarial vasculitis is suspected)
Neoplastic processes				
Disease	**Preferred technique***		**Pitfalls**	
Melanocytic neoplasms	Excisional biopsy (preferred when melanoma is reasonably suspected) Saucerization that includes the entire lesion When major differential diagnosis is macular seborrheic keratosis vs lentigo maligna, broad shave technique as long as no underlying induration Other techniques may be appropriate depending upon the circumstances and the degree of suspicion		Partial (subtotal) punch biopsy or superficial shave biopsy may not be representative of the entire process	

*On occasion, surgical/clinical/cosmetic constraints may, in the patient's best interest, require consideration and performance of an alternative technique, or even a subtotal biopsy, with acceptance of limitations regarding the diagnostic result.

Table 0.10 Optimizing information obtained from a skin biopsy specimen (based upon presumed diagnosis). DLE, discoid lupus erythematosus; h, hour; LE, lupus erythematosus; PCR, polymerase chain reaction. *Table created with the assistance of Dr Stefano Titli.*

Continued

OPTIMIZING INFORMATION OBTAINED FROM A SKIN BIOPSY SPECIMEN (BASED UPON PRESUMED DIAGNOSIS)		
Neoplastic processes		
Disease	**Preferred technique***	**Pitfalls**
Keratinocytic neoplasms	Punch, saucerization, or excisional biopsies	Partial (subtotal) punch biopsy or superficial shave biopsy may not be representative of the entire process or allow assessment for possible dermal invasion
Dermal neoplasms	Punch or excisional biopsy	Partial (subtotal) punch biopsy or superficial shave biopsy may not be representative of the entire process
Deep dermal and/or subcutaneous neoplasms	Excisional or incisional biopsy, depending upon size	Partial (subtotal) punch biopsy or superficial shave biopsy may not be representative of the entire process
Lymphoma cutis and leukemia cutis	Punch or excisional biopsy When major differential diagnosis is patch-stage mycosis fungoides vs parapsoriasis, broad saucerization may be performed	Partial (subtotal) punch biopsy or superficial shave biopsy may not be representative of the entire process Artifactual changes, in particular crush artifact and/or dessication, are common when lymphocytic infiltrates are sampled via a small-diameter punch biopsy and then tweezers are used to remove the specimen and/or the specimen is placed on a gauze**

*On occasion, surgical/clinical/cosmetic constraints may, in the patient's best interest, require consideration and performance of an alternative technique, or even a subtotal biopsy, with acceptance of limitations regarding the diagnostic result.
**Tweezers should not be used to remove the biopsy specimen and the latter should be placed directly into a formalin solution.

Table 0.10 Optimizing information obtained from a skin biopsy specimen (based upon presumed diagnosis). (cont'd)

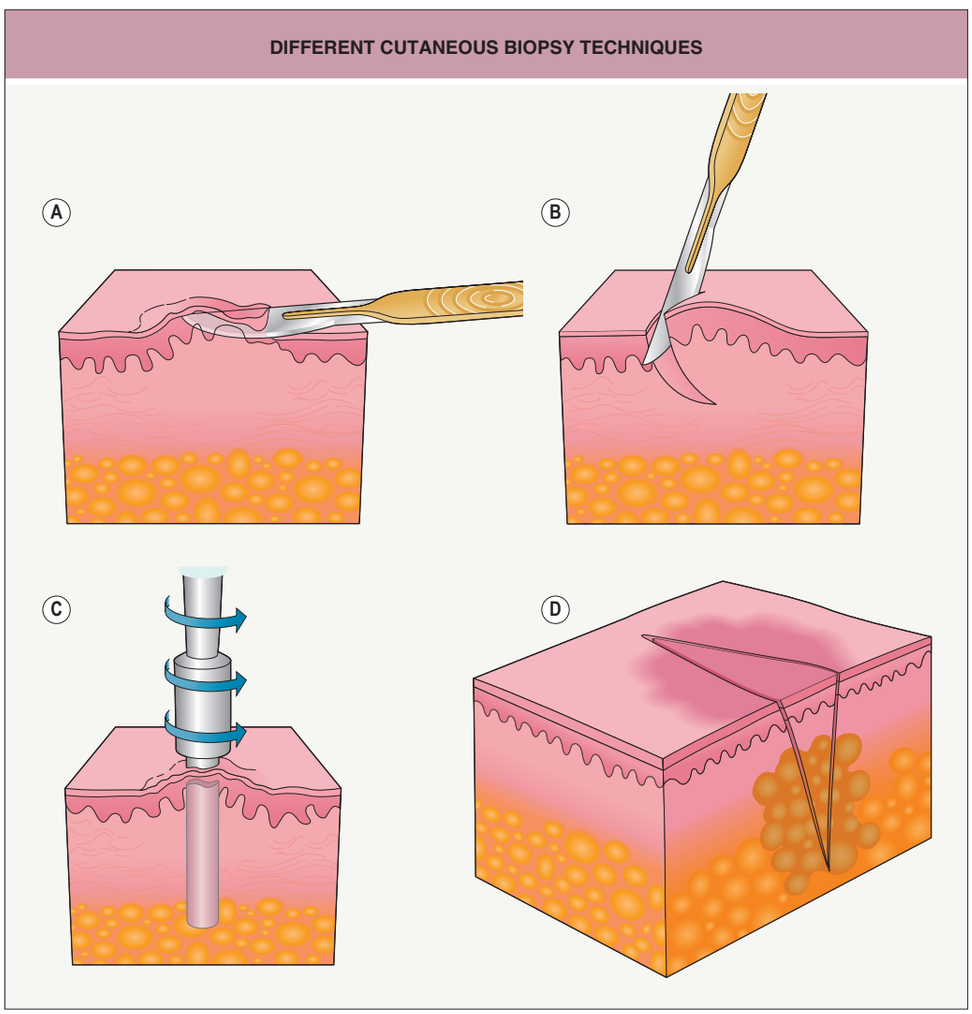


Fig. 0.13 Different cutaneous biopsy techniques. The size, topography, depth and site of the lesion, as well as the clinical differential diagnosis, influence the type of biopsy technique that is performed. **A** Superficial shave biopsy. **B** Deep shave biopsy (saucerization). **C** Punch biopsy. **D** Incisional biopsy. For more details, see text and Chapter 146. *Courtesy, Suzanne Olbricht, MD.*

- ***Punch biopsy*** – this technique is preferred when the suspected pathology lies within the dermis and when a small sampling is likely to dutifully represent the overall disease process. Common punches range from 1.5 to 8.0 mm in diameter, with 4 mm being the most commonly used size for inflammatory diseases. If the sampled lesion can be contained in the punch, then the concern regarding sampling error is rendered moot. It is controversial as to whether punch biopsies, even if performed in a "stacked" fashion, can provide adequate tissue for assessment of deeply infiltrating tumors or panniculitis. Studies suggest that *partial* punch samplings of melanocytic lesions can lead to misdiagnosis or to erroneous staging and therefore should not be performed[26].

- ***Incisional/excisional biopsy*** – this technique involves the removal of either a portion of a lesion (incisional) or the entire visible lesion (excisional) via a scalpel, using standard surgical techniques (see Ch. 146; see Fig. 0.13D). An incision is often used for examination of the subcutaneous fat (e.g. panniculitis), while an excision is often employed to inspect the entirety of a pigmented process that is reasonably suspicious for melanoma.

Optimal biopsy techniques based upon the suspected cutaneous disease are outlined in Table 0.10.

Handling of the specimen after biopsy

Skin specimens must be handled carefully upon extirpation. For example, excessive lateral pressure by forceps on small punch biopsy specimens can distort cellular infiltrates, particularly lymphomas and Merkel cell carcinoma, creating so-called "crush" artifact. This type of artifact may compromise the diagnostic utility of a biopsy. These two cell types are also subject to dessication artifact when the biopsy specimen is placed onto gauze rather than into formalin solution.

For routine histologic analysis, tissue specimens are usually fixed in 10% neutral buffered formalin (NBF) solution, with a volume 10- to 20-fold that of the tissue itself. When culturing for microorganisms, the tissue specimen cannot be placed in 10% NBF; instead it must be placed in a sterile container with a small amount of non-bacteriostatic saline. For direct immunofluorescence (DIF) studies, specimens must be flash-frozen, placed in normal saline (for no more than 24–48 hours), or placed in specialized transport medium (Michel's solution). Recently, honey was shown to be an excellent transport medium for DIF studies[26a]. Fixation in paraformaldehyde and glutaraldehyde in a cacodylate buffer is required for electron microscopy.

To obtain the most accurate histopathologic assessment, all biopsy specimens sent to a dermatopathologist should be accompanied by relevant clinical data such as: age and sex of the patient, anatomic site(s) involved, pertinent physical findings, and a suspected clinical differential diagnosis. Prior treatments that might impact upon the histologic findings should be disclosed. Any special instructions or requests should be detailed (e.g. inking of an area of special concern in a melanocytic neoplasm, longitudinal sectioning to detect subtle changes in atrophoderma). Inclusion of drawings or clinical photographs may prove useful, especially in difficult or complex cases.

Classification of Inflammatory Skin Diseases by Pattern Analysis

First conceived by Dr Hermann Pinkus, but more firmly established by Dr A Bernard Ackerman[27,28], histopathologic assessment by pattern analysis has emerged as the principal means of classifying inflammatory skin diseases (Fig. 0.14). The number of patterns and the precise descriptors assigned may vary among examiners, but the core principle remains the same – a major pattern is first identified, then additional histologic features are used to further subcategorize the disease process until a final diagnosis is rendered.

The algorithmic approach of pattern analysis is reproducible, and it minimizes subjectivity. However, the method has two important limitations, namely, it is based on artificial disease categories and it cannot include every possible pattern. Furthermore, while pattern analysis clearly narrows the differential diagnosis, a final assessment may require clinical correlation and/or ancillary laboratory testing, imaging, or genetic testing[29].

Also, the histopathologic appearance of skin disease may vary based upon the temporal course. The histologic findings may be altered by previous treatment(s) or by secondary changes such as rubbing, scratching, or infection. Lastly, pattern analysis is not only applicable to inflammatory skin diseases, but is also used for neoplastic processes.

Ten patterns defined

Over the past several decades, different classification schema based upon pattern analysis have emerged. The number of patterns in any schema has varied from 9 to 28 or more, but in this introductory chapter, 10 major patterns will be discussed.

Perivascular dermatitis

This pattern is defined and recognized by the presence of an inflammatory infiltrate that is arranged chiefly around dermal blood vessels (Fig. 0.15). Traditionally, perivascular dermatitis has been subdivided into "superficial" and "superficial and deep" variants, and while this division has some diagnostic value, considerable overlap exists. In addition, inflammatory skin diseases can exhibit a spectrum of findings, depending in part upon severity, as well as the duration of an individual lesion (acute vs chronic).

Once a perivascular pattern is identified (see Fig. 0.14A), the next step is to: (1) determine if there are associated epidermal changes; and (2) characterize the types of inflammatory cell(s) that are present in the infiltrate (e.g. lymphocytes, neutrophils, eosinophils, plasma cells). There are disorders without detectable changes within the epidermis, such as deep gyrate erythemas (see Ch. 19), and when an inflammatory process is beginning or resolving, epidermal changes may be subtle. To further refine the diagnosis, a search is performed to detect subtle *spongiosis* (intercellular edema of the epidermis), subtle *parakeratosis* (aberrant retention of nuclei in the stratum corneum), subtle *interface* and *vacuolar changes* at the dermal–epidermal junction, or extravasated erythrocytes.

Interface dermatitis

This pattern is characterized by inflammation and/or degenerative change(s) at the dermal–epidermal junction (see Fig. 0.14B). Morphologically, this pattern may be further subdivided into primarily *vacuolar* (degeneration of basilar keratinocytes with little or no inflammation; Fig. 0.16) and primarily *lichenoid* (with lymphocytes directly engaged in the destruction of basilar keratinocytes; Fig. 0.17) processes, although there is overlap between these two groups.

It is important to remember that even though an entity has lichenoid features under the microscope (e.g. fixed drug eruption), clinically, it does not have to resemble lichen planus. Also, some degree of lichenoid inflammation may be associated with a variety of benign and malignant neoplasms, such as lichenoid keratoses and melanoma, respectively. In these instances, the lichenoid inflammation represents an immunological response to the tumor.

Spongiotic dermatitis

Spongiosis (intercellular edema) is a nonspecific morphologic alteration that is observed in a variety of skin conditions. It manifests as widened spaces between keratinocytes, with elongation of intercellular bridges (see Fig. 0.14C). The degree of spongiosis may vary from microscopic foci to grossly visible vesicles or intraepidermal bullae. There is often associated *exocytosis* of inflammatory cells, with migration from the vasculature into the epidermis.

Spongiotic dermatoses may be further subdivided into acute, subacute and chronic forms. In acute spongiotic dermatitis, the spongiosis is often severe, sometimes resulting in microvesicles within the epidermis (Fig. 0.18). Parakeratosis, a histologic equivalent of scale, often overlies subacute spongiotic dermatitis. In chronic spongiotic dermatitis, the spongiosis may be more difficult to appreciate, being instead overshadowed by epidermal *acanthosis* (thickening of the epidermis). Also, a predominance of certain inflammatory cells in association with spongiosis, such as eosinophils or neutrophils, may serve as a clue to a hypersensitivity component or infectious process, respectively.

Lastly, it is important to recognize that multiple cutaneous disorders with eczematous features, such as allergic contact dermatitis, atopic dermatitis, nummular dermatitis and seborrheic dermatitis, may have histologic evidence of spongiosis, but this pattern is not exclusive to those diseases. In other words, spongiosis may also be seen as a reactive epidermal component of other disorders better classified under another pattern (see Fig. 0.14).

Psoriasiform dermatitis

The term "psoriasiform" refers to a regular pattern of *epidermal hyperplasia* (elongation of the rete ridges; see Fig. 0.14D) that is observed not just in psoriasis, but also in a number of other, generally longstanding, conditions. Clinically, this group of psoriasiform disorders is characterized by thickened, scaly papules and plaques (Fig. 0.19). Psoriasiform dermatoses can be further subdivided into those diseases that are exclusively psoriasiform and those that are associated with another pattern (e.g. psoriasiform *and* lichenoid; psoriasiform *and* spongiotic).

Pseudoepitheliomatous hyperplasia represents a related, but irregular, hyperplasia of the epidermis and/or adnexal structures. It may

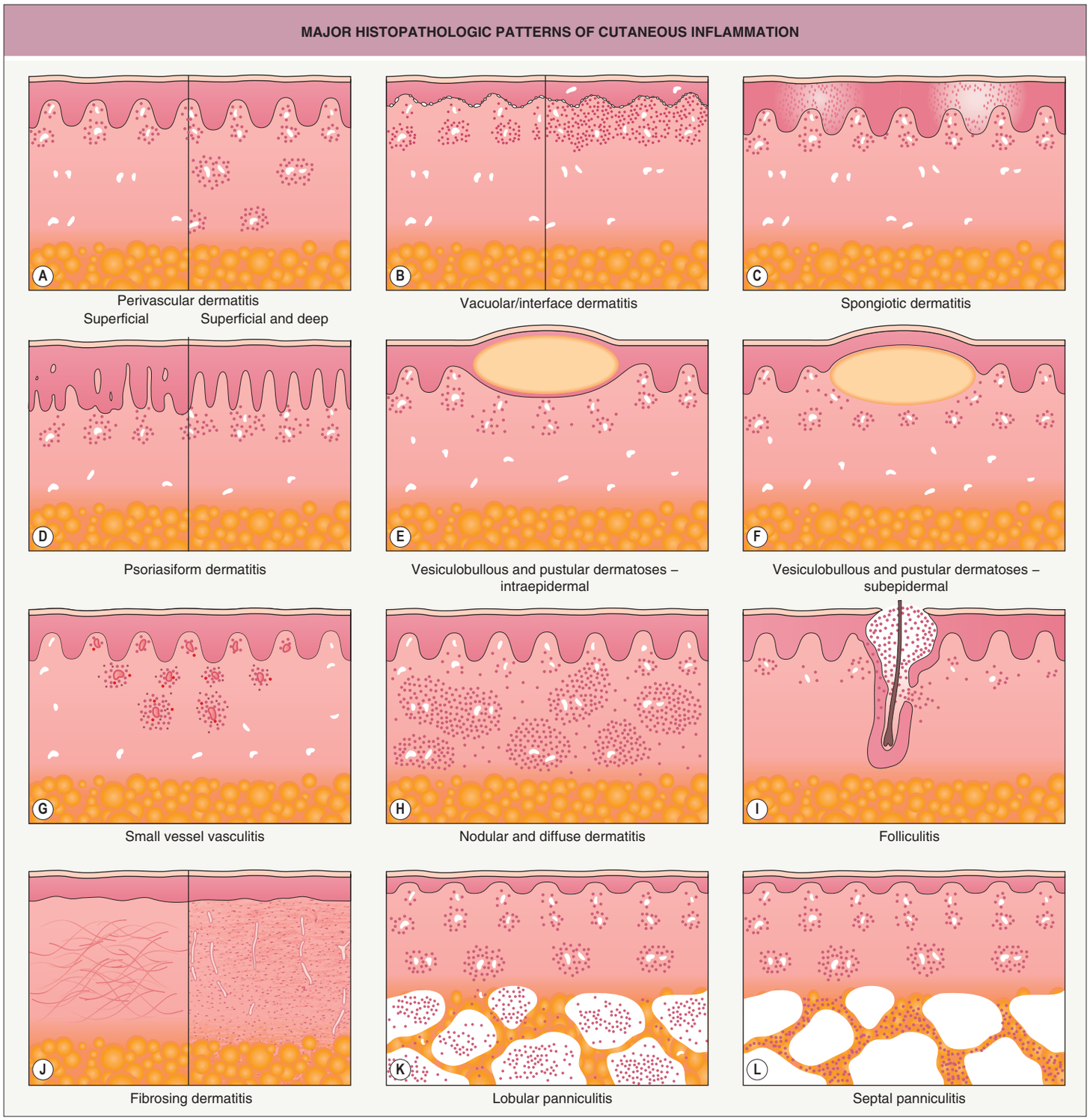


Fig. 0.14 Major histopathologic patterns of cutaneous inflammation (based upon Ackerman's classification). Basic patterns of inflammation result primarily from the distribution of the inflammatory cell infiltrate within the dermis and/or the subcutaneous fat (e.g. nodular, perivascular). It also reflects the character of the inflammatory process itself (e.g. pustular), the presence of injury to blood vessels (e.g. vasculitis), involvement of hair follicles (e.g. folliculitis), abnormal fibrous dermal and/or subcutaneous tissue, and formation of vesicles and bullae. *Adapted from Ackerman AB. Histologic Diagnosis of Inflammatory Skin Diseases: A Method by Pattern Analysis. Philadelphia: Lea & Febiger, 1978.*

occur in response to a range of insults to the skin, such as chronic rubbing or scratching (e.g. lichen simplex chronicus, prurigo nodularis), or it may appear in inflammatory, neoplastic, and infectious skin diseases (e.g. hypertrophic lupus erythematosus, halogenodermas, chromoblastomycosis).

As with spongiotic dermatitis, psoriasiform dermatitis is a histologic concept, not a specific clinical diagnosis, and its presence mandates consideration of a variety of skin diseases that share this particular constellation of histopathologic findings.

Vesiculobullous and pustular dermatoses

Intraepidermal (see Fig. 0.14E)

The concept of intraepidermal vesiculation due to spongiosis has been addressed above, but other disease mechanisms may lead to formation of intraepidermal vesicles or bullae (e.g. acantholysis, ballooning degeneration, prominent basal layer vacuolization, subepidermal edema). *Acantholysis* refers to the discohesion of keratinocytes due to disruption of *desmosomes* (intercellular connections), and this can lead to intraepidermal vesicles or bullae (Fig. 0.20).

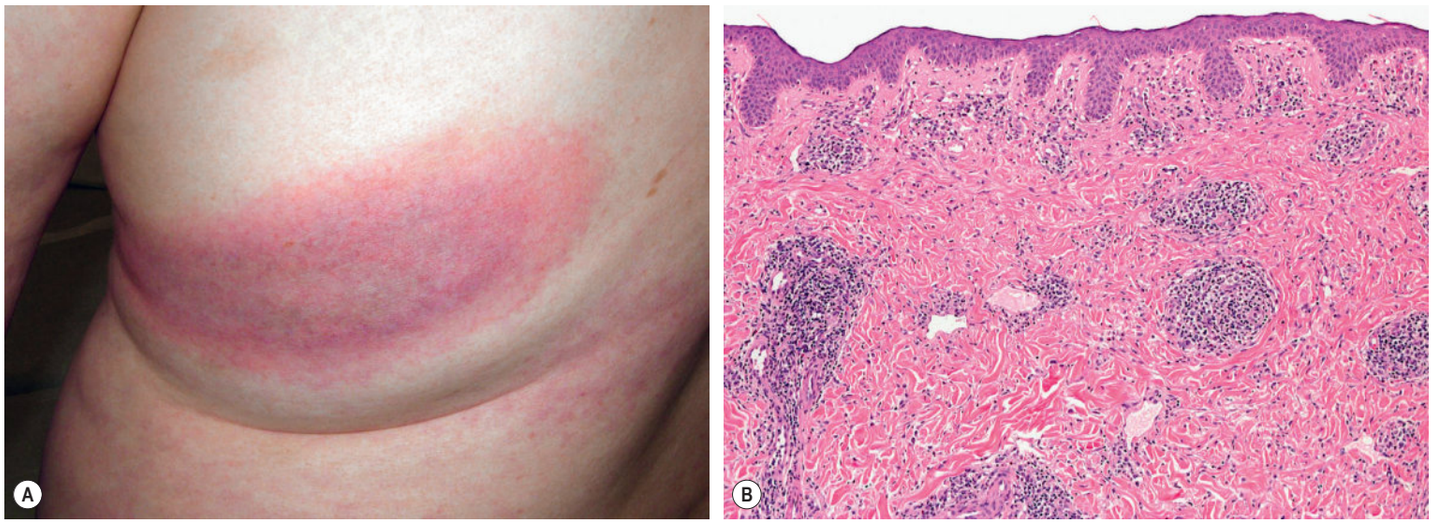


Fig. 0.15 Perivascular dermatitis. A Erythema migrans. **B** Perivascular inflammatory infiltrate composed primarily of lymphocytes. *B, Courtesy, Lorenzo Cerroni, MD.*

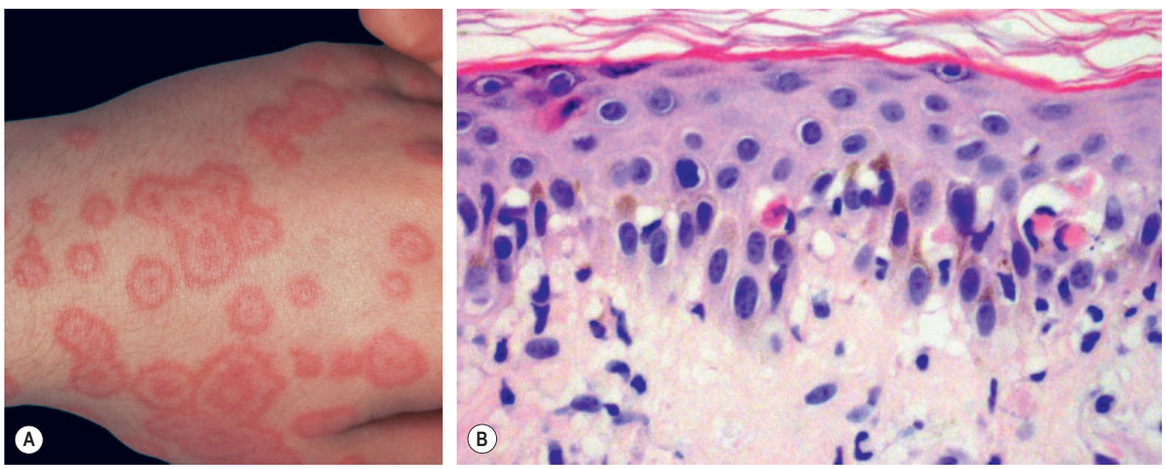


Fig. 0.16 Interface dermatitis, vacuolar type. A Erythema multiforme with target lesions. **B** Vacuolar alteration along the dermal–epidermal junction in association with exocytosis of lymphocytes and several necrotic keratinocytes.

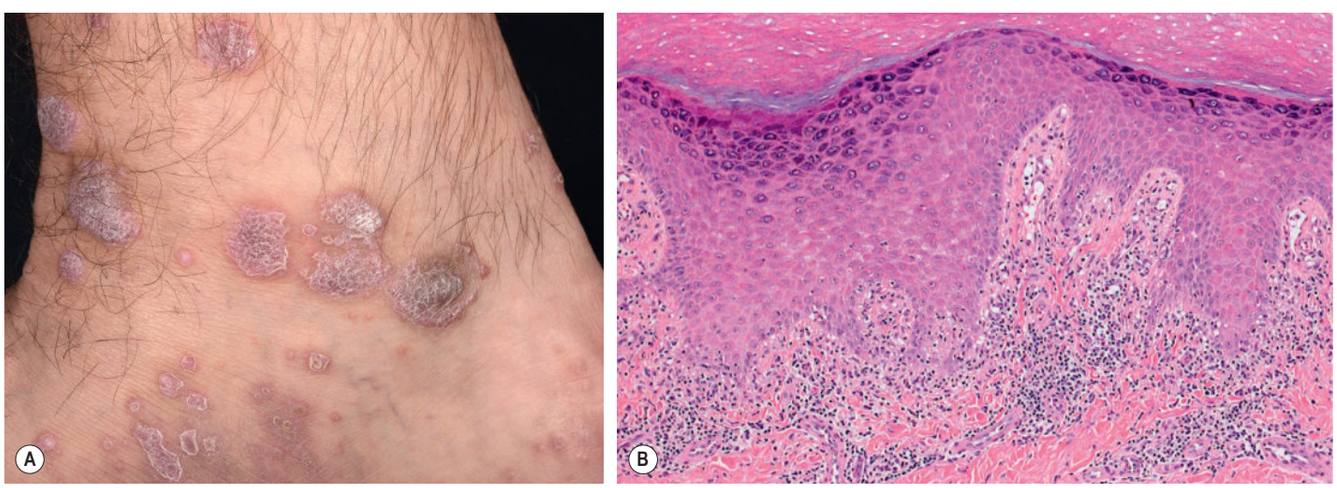


Fig. 0.17 Interface dermatitis, lichenoid type. A Lichen planus. **B** Band-like infiltrate of lymphocytes that obscures the dermal–epidermal junction in addition to jagged epidermal hyperplasia and hypergranulosis. *Courtesy, Lorenzo Cerroni, MD.*

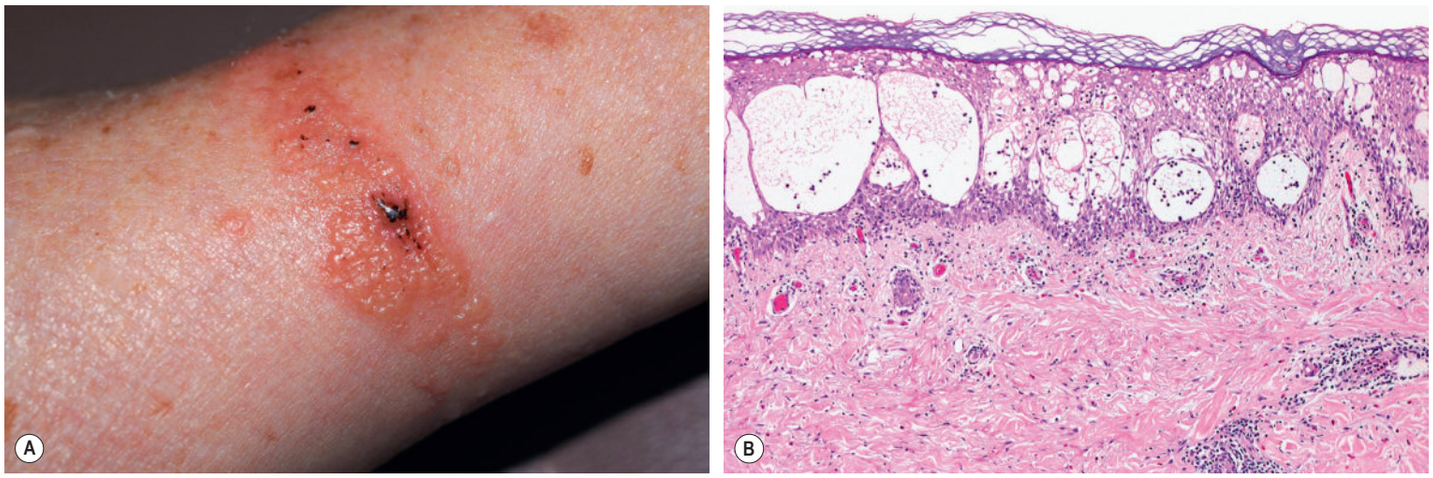


Fig. 0.18 Spongiotic dermatitis. A Acute allergic contact dermatitis from exposure to poison ivy; note the areas of oxidized resin that are black in color. **B** Intercellular edema (spongiosis) and vesicle formation within the epidermis. Lymphocytes are also seen in both the epidermis and dermis. *B, Courtesy, Lorenzo Cerroni, MD.*

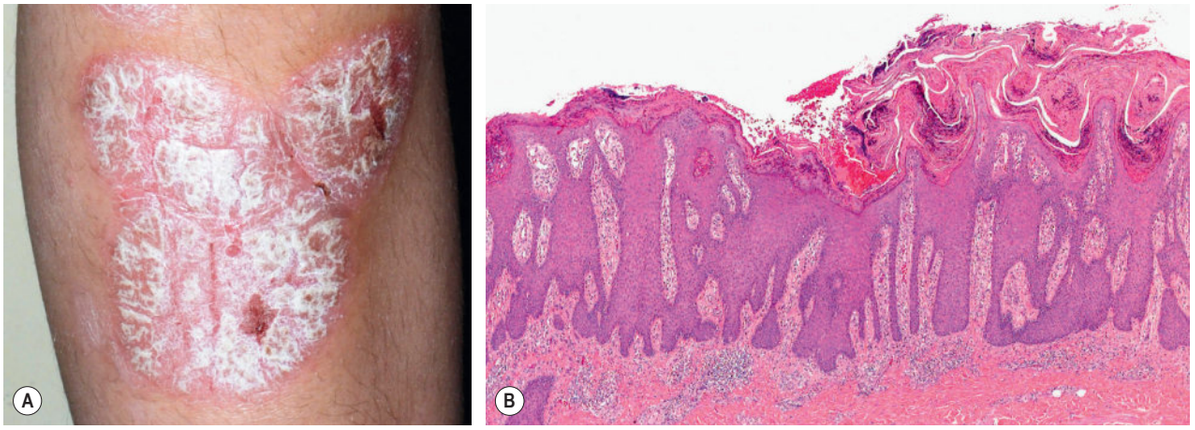


Fig. 0.19 Psoriasiform pattern. A Plaque of psoriasis vulgaris with silvery scale. **B** Regular epidermal hyperplasia and elongated dermal papillae with thin suprapapillary plates and marked confluent parakeratosis. The parakeratosis represents the histologic correlate of the visible scale. *A, Courtesy, Julie V Schaffer, MD; B, Courtesy, Lorenzo Cerroni, MD.*

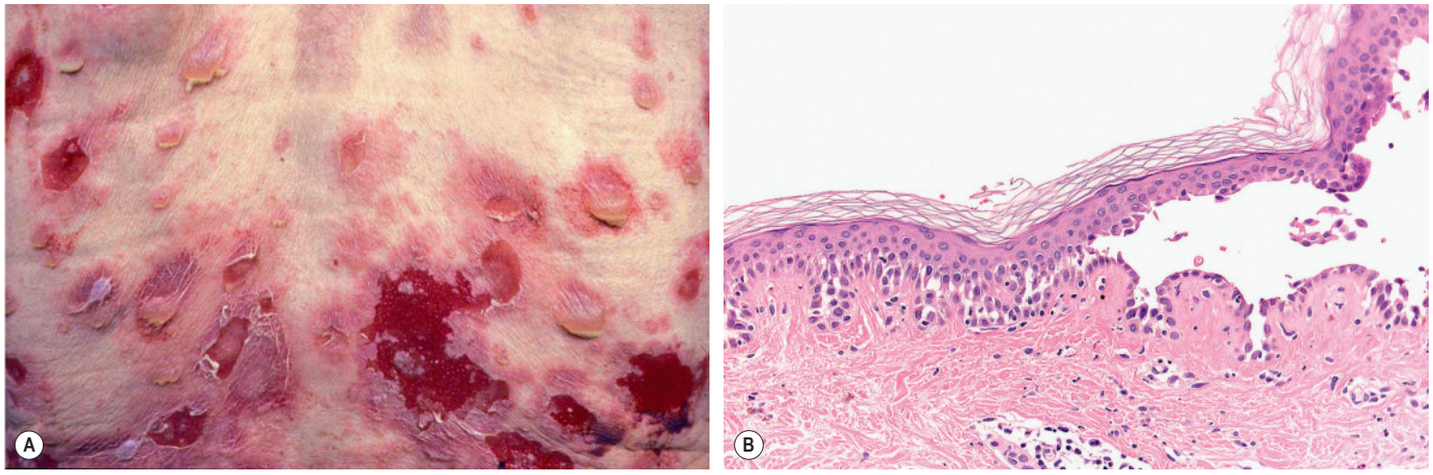


Fig. 0.20 Intraepidermal vesiculobullous dermatosis, acantholytic type. A Pemphigus vulgaris with flaccid bullae and erosions. Note the dependent location of the pustular contents of bullae. **B** The keratinocytes within the lower epidermis have lost their intercellular attachments and have separated from one another, resulting in an intraepidermal blister. *B, Courtesy, Lorenzo Cerroni, MD.*

Although acantholysis may occur at any level of the epidermis, the location of a blister cavity is often used as a clue to the underlying disorder. For example, superficial (subcorneal) acantholysis may favor pemphigus foliaceus, while acantholysis within the deeper portion of the epidermis is more characteristic of pemphigus vulgaris. *Ballooning degeneration* refers to intracellular edema in response to cytotoxic events (e.g. herpes virus infection, drug reaction), and it is identified by the presence of abundant pale cytoplasm of keratinocytes in the spinous zone. When ballooning is severe, keratinocytes rupture, resulting in reticular degeneration and epidermal necrosis.

Pustule formation (the intraepidermal accumulation of neutrophils) may be seen in a variety of infectious and non-infectious skin diseases. In early pustule formation, neutrophils are scattered within the lower portion of the epidermis, whereas later, accumulation is noted in the upper epidermis and/or beneath the stratum corneum (Fig. 0.21). In a resolving pustule, the neutrophils or their remnants may even appear within a scale-crust in the cornified layer.

In both vesiculobullous and pustular dermatoses, autoimmune and non-autoimmune mechanisms (e.g. subcorneal pustular dermatosis versus IgA pemphigus) may be indistinguishable. As a result, direct and

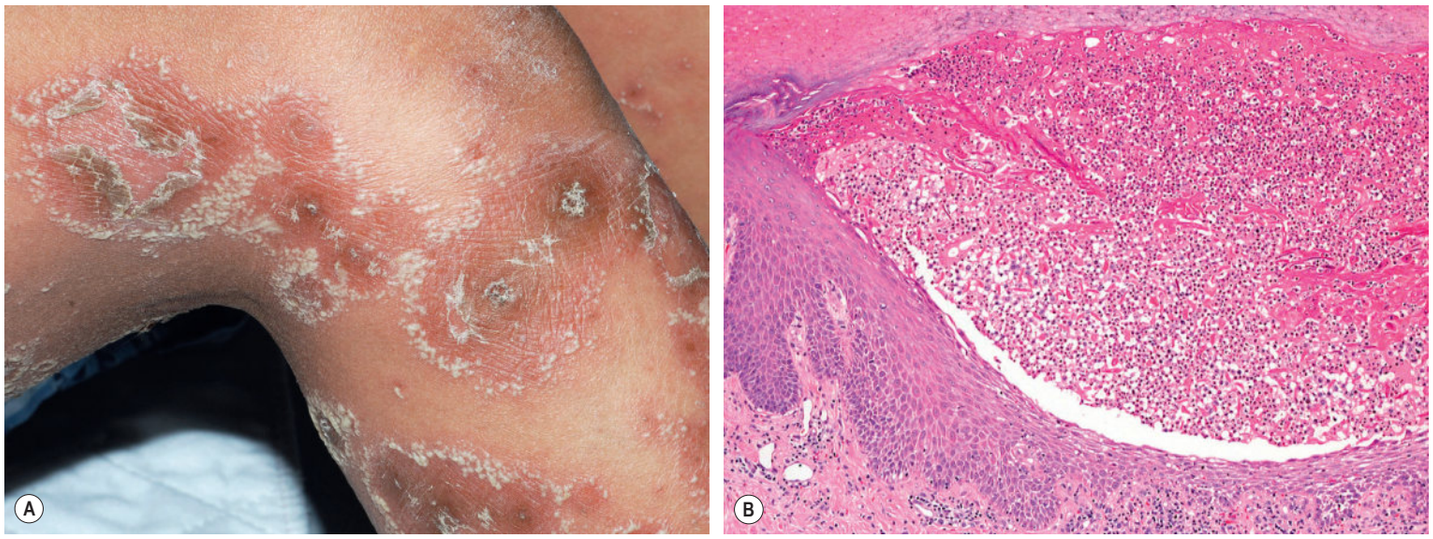


Fig. 0.21 Intraepidermal pustular dermatosis. A Annular variant of pustular psoriasis. **B** Large collection of neutrophils beneath the stratum corneum (subcorneal pustule). *A, Courtesy, Julie V Schaffer, MD; B, Courtesy, Lorenzo Cerroni, MD.*

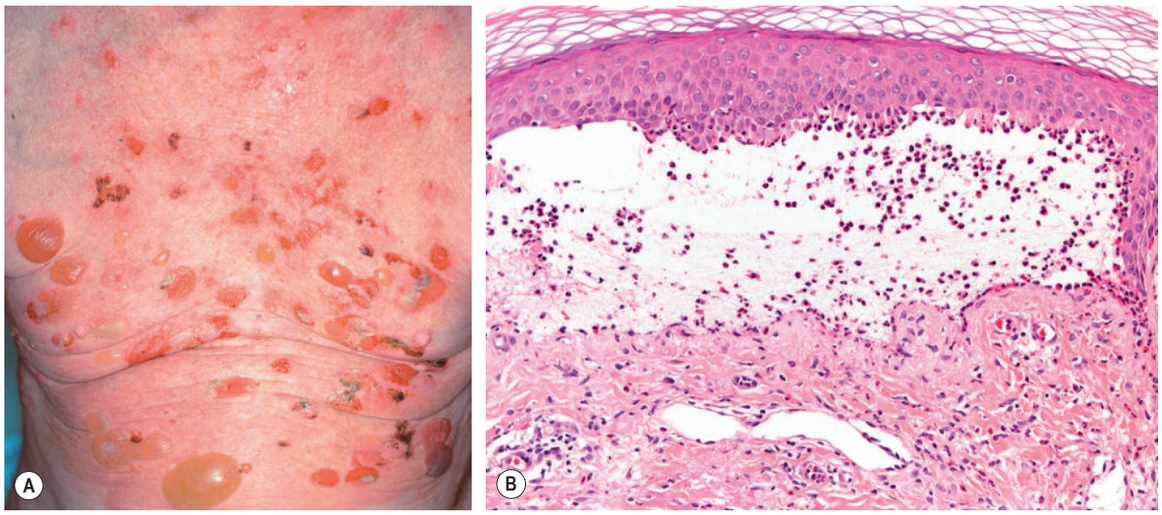


Fig. 0.22 Subepidermal vesiculobullous dermatosis. A Bullous pemphigoid with tense bullae. **B** Subepidermal blister with numerous eosinophils within the blister cavity. *B, Courtesy, Lorenzo Cerroni, MD.*

indirect immunofluorescence studies are of utility in determining the precise etiology.

Subepidermal vesiculation (see Fig. 0.14F)
In this subcategory of disease, vesicles or bullae form at the junction between the epidermis and dermis (Fig. 0.22), or between the mucosa and submucosa of mucous membranes. While such clefting can be the result of autoantibodies that target specific components of the dermal–epidermal junction (e.g. collagen XVII in bullous pemphigoid, linear IgA bullous dermatosis), it may be the result of an inflammatory or toxic/metabolic insult (e.g. bullous cellulitis or porphyria cutanea tarda, respectively).

The number of inflammatory cells varies within subepidermal blisters, and this variance impacts upon the differential diagnosis. For example, some diseases such as porphyria cutanea tarda are classically pauci-inflammatory, while the majority of cases of bullous pemphigoid contain a significant number of inflammatory cells, particularly eosinophils.

However, because there is histologic overlap among blistering disorders, the final diagnosis must depend upon cumulative information, including direct and indirect immunofluorescence microscopy, ELISA, and, of course, clinicopathologic correlation.

Vasculitis/pseudovasculitis

Vasculitis refers to inflammatory damage to and destruction of blood vessels, which leads ultimately to the deposition of fibrin and/or thrombus formation (see Fig. 0.14G). The histopathologic classification of vasculitis is based upon the size of the vessel involved (small, medium-sized or large vessel vasculitis; see Ch. 24) as well as the predominant inflammatory cell type that is mediating the damage (neutrophils, lymphocytes, eosinophils or histiocytes).

The most common form of cutaneous vasculitis is *leukocytoclastic vasculitis* (Fig. 0.23), a process that is mediated by neutrophils and affects chiefly the postcapillary venule. Leukocytoclastic vasculitis begins with deposition of circulating immune complexes in and around blood vessel walls, with neutrophils recruited to these sites of deposition; this ultimately leads to *leukocytoclasia* (nuclear fragmentation) and vessel destruction, with resultant fibrin deposition. In the few longstanding disorders that are mediated by leukocytoclastic vasculitis, such as erythema elevatum diutinum, concentric fibrosis may develop over time.

The concept of *lymphocytic vasculitis* is less well defined and is even a controversial entity among some authors. However, it is a term used to denote an inflammatory process in which there may be some fibrinoid necrosis of the vessel wall, but the mediating cell is a lymphocyte. It is postulated as a mechanism in disorders such as pernio, Sneddon syndrome, and pityriasis lichenoides et varioliformis acuta (PLEVA), although the latter lacks fibrinoid necrosis (see Table 24.2).

Granulomatous vasculitis is defined by the presence of histiocytes within and around blood vessel walls, in association with fibrin and/or degenerative and necrotic changes. Like lymphocytic vasculitis, granulomatous vasculitis is a pattern that is observed in a restricted group of diseases which includes granulomatosis with polyangiitis (formerly Wegener granulomatosis), eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome), and temporal arteritis. Occasionally, it may also represent a later evolutionary stage of another form of vasculitis, either leukocytoclastic or lymphocytic in nature.

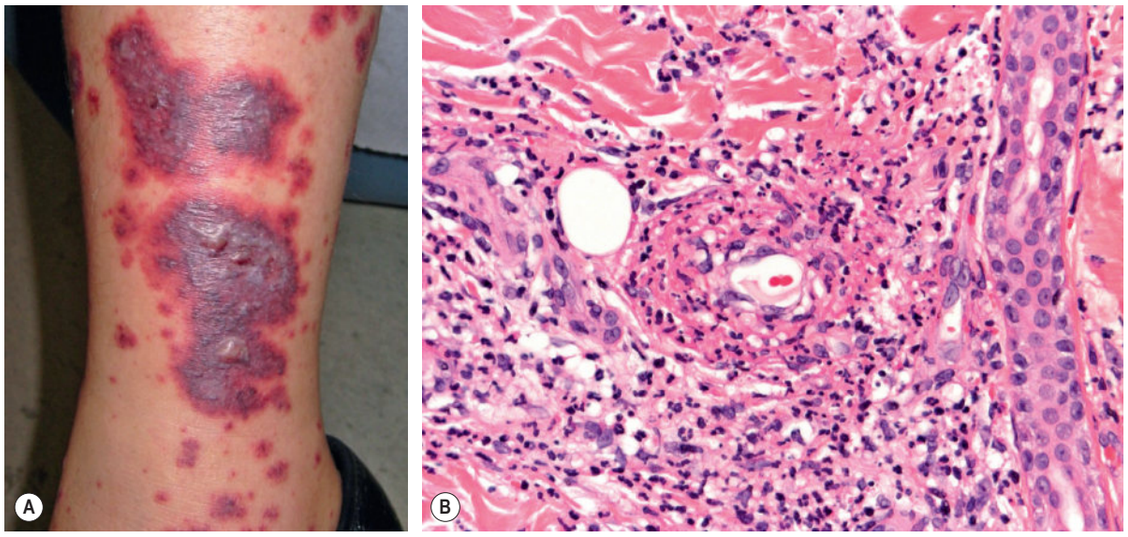


Fig. 0.23 Cutaneous small vessel vasculitis. A Inflammatory palpable purpura of the leg. **B** Perivascular and interstitial infiltrate of neutrophils with nuclear dust (leukocytoclasia). Fibrin within and around the vessel wall and extravasation of erythrocytes is also seen. *B, Courtesy, Lorenzo Cerroni, MD.*

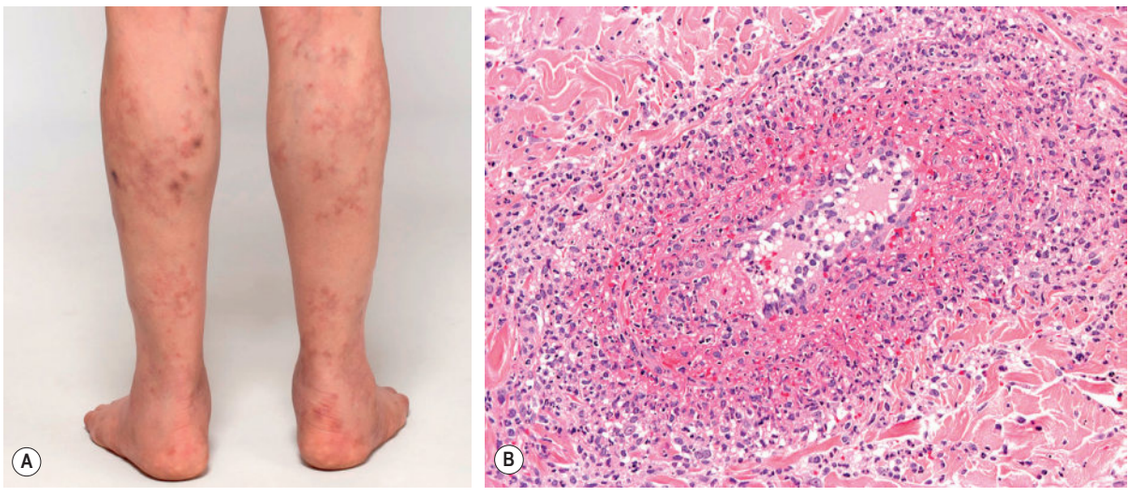


Fig. 0.24 Medium-sized vessel vasculitis. A Nodules of cutaneous periarteritis nodosa admixed with livedo reticularis. **B** Inflammation and destruction of a subcutaneous arteriole with a dense inflammatory infiltrate composed of lymphocytes, histiocytes and neutrophils admixed with hemorrhage. *A, Courtesy, David Wetter, MD; B, Courtesy, Lorenzo Cerroni, MD.*

In *medium-sized vessel cutaneous vasculitis*, there is involvement of the blood vessels at the dermal–subcutaneous junction and/or within the septa of the subcutaneous fat (Fig. 0.24). For dermatopathologists, polyarteritis nodosa is the most commonly encountered entity in this disease category. Temporal arteritis represents a form of large vessel vasculitis, but biopsies of this disorder are rarely performed by dermatologists.

Pseudovasculitis refers to a group of heterogeneous, non-inflammatory conditions that are broadly classified into *non-inflammatory purpura* (disorders that primarily cause hemorrhage) and *occlusive vasculopathies* (conditions that primarily occlude vessels) (see Chs 22 & 23). Many of these latter disorders involve occlusion of vessels due to emboli, thrombi, vasospasm, intimal–medial hyperplasia secondary to vessel trauma, or non-inflammatory vessel wall pathology. The latter includes calcification, cholesterol emboli, and amyloid deposition.

Nodular and diffuse dermatitis

Nodular dermatitis is somewhat similar to perivascular dermatitis, but the inflammatory infiltrate has enlarged and has coalesced to form one or multiple nodules within the dermis (see Fig. 0.14H). Further expansion of these nodules can fill nearly the entirety of the dermis, yielding a diffuse pattern (Fig. 0.25).

The nodular and diffuse pattern of dermatitis may be further subdivided, based upon the predominant inflammatory cell present. When *histiocytes* predominate, the pattern is considered *granulomatous*. In *foreign body granulomas*, the histiocytes form characteristic multinucleate forms, leading to so-called foreign body giant cells. Two other forms of multinucleated giant cells are observed in granulomatous entities, namely the *Langhans type* and the *Touton type*. None of these giant cells are exclusive to a singular disease, but some disorders are characterized by the conspicuous presence of one or more of these types of giant cells (e.g. Touton giant cells in juvenile xanthogranuloma).

Based on the constituent cells and other distinctive features, four major histopathologic types of granulomas can be defined (Fig. 0.26):

- ***Tuberculoid* granulomas** (see Fig. 0.26A) – comprised of epithelioid histiocytes, including multinucleate forms, surrounded by a dense infiltrate of lymphocytes and plasma cells. Central caseation may be present. The *Langhans type* of multinucleated giant cell, with a horseshoe-like arrangement of nuclei, may be observed in tuberculoid granulomas. This type of granuloma is associated with cutaneous infections (e.g. *Mycobacterium tuberculosis*) and it is also seen in lupus miliaris disseminatus faciei.
- ***Sarcoidal* granulomas** (see Fig. 0.26B) – comprised of aggregates of epithelioid histiocytes, with sparse peripheral lymphocytes or plasma cells (i.e. "naked tubercles"). While multinucleated cells may be identified, no specific type is associated exclusively with sarcoidal granulomas.
- ***Palisaded ("necrobiotic")* granulomas** (see Fig. 0.26C) – comprised of epithelioid histiocytes aligned as a rim around a central area of degenerated collagen with different tinctorial qualities. Of note, not all palisaded granulomas are markedly palisaded, and in fact, the histiocytes may also be distributed interstitially, between and amongst collagen bundles (*interstitial granuloma*).
- ***Suppurative* granulomas** (see Fig. 0.26D) – comprised of neutrophils within, and sometimes among or surrounding, aggregates of epithelioid histiocytes. Suppurative granulomas may be induced by infectious agents or foreign body material.

All granulomatous infiltrates, but particularly tuberculoid, sarcoidal and suppurative granulomas, require exclusion of infectious agents and/or foreign material by means of special stains, immunohistochemical stains, tissue culture, PCR, and/or polarization microscopy.

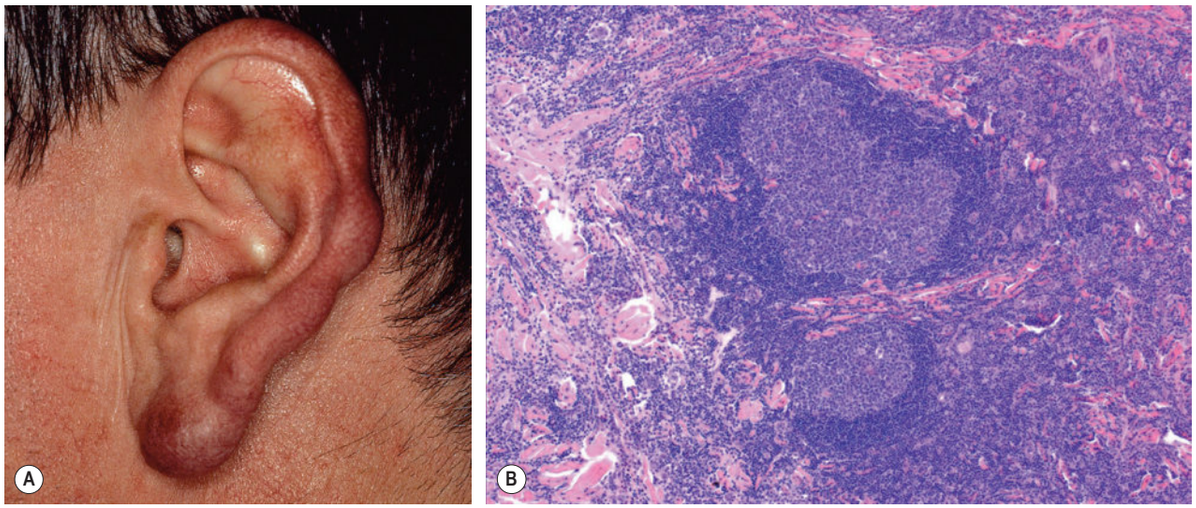


Fig. 0.25 Nodular and diffuse dermatitis, lymphocytic. A Cutaneous lymphoid hyperplasia. The earlobe is a common location. **B** Dense dermal infiltrate containing lymphoid follicles with formation of germinal centers. *B, Courtesy, James Patterson, MD.*

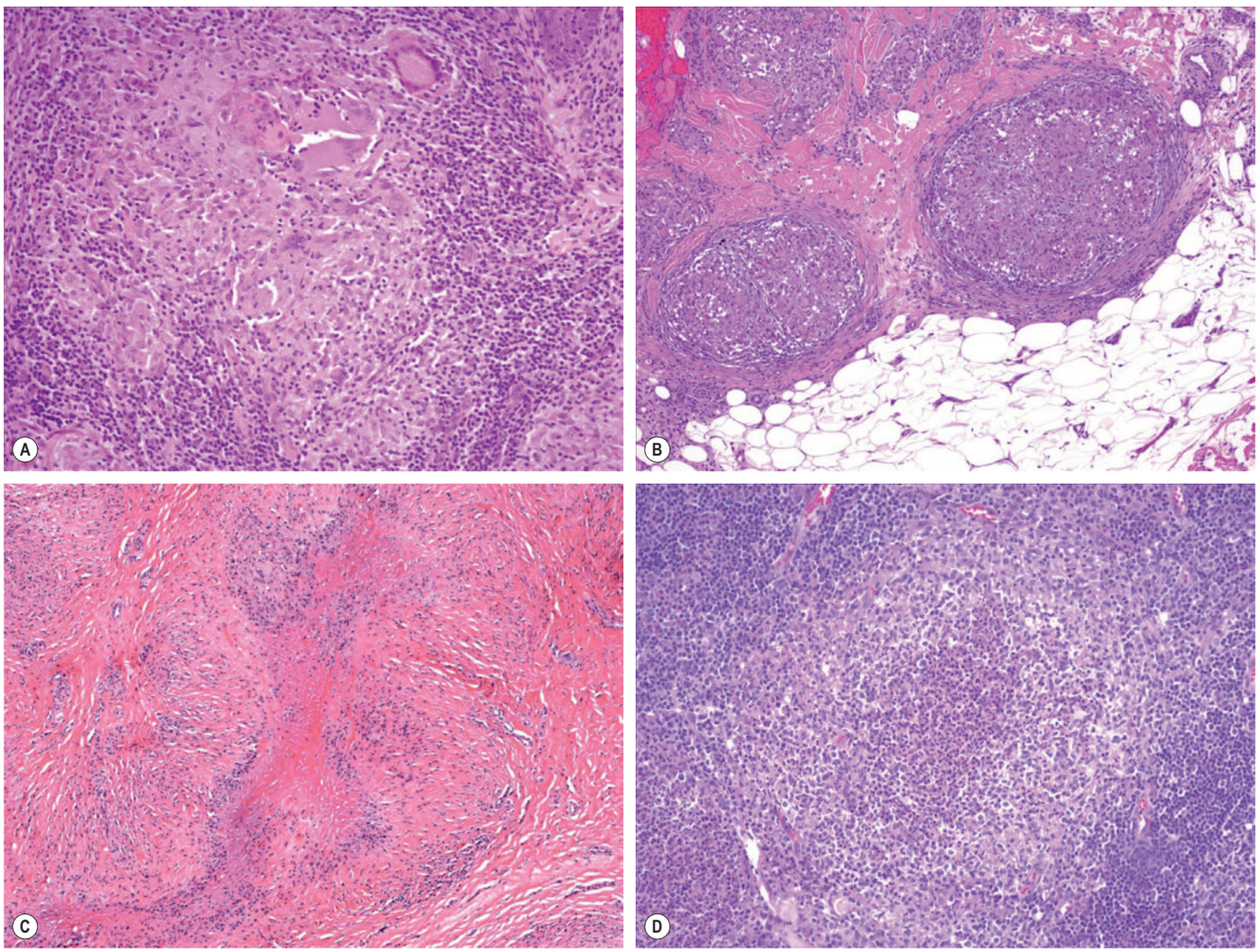


Fig. 0.26 Four major types of cutaneous granulomas. A Tuberculoid – epithelioid granuloma rimmed by lymphocytes. **B** Sarcoidal – epithelioid granulomas with minimal peripheral lymphocytic infiltrate. **C** Palisaded – granulomas surrounding areas of degenerated collagen. **D** Suppurative – granulomas with dense neutrophilic infiltrates. *A–D, Courtesy, James Patterson, MD.*

Nodular and diffuse infiltrates comprised chiefly of histiocytes may also be further subcategorized into *Langerhans cell* and *non-Langerhans cell histiocytoses* (see Ch. 91). In Langerhans cell histiocytosis, the cells of interest have reniform (kidney bean-shaped) nuclei and a characteristic immunohistochemical staining pattern (i.e. $S100^+$, $CD207^+$, and $CD1a^+$). Non-Langerhans histiocytes, on the other hand, have a range of cytologic features (vacuolated, spindle-shaped, foamy, scalloped, oncocytic) as well as multiple admixed multinucleated giant cells (Touton type, Langhans type, foreign body type). Sometimes, the histiocytes and giant cells display a homogenous "ground glass" cytoplasm. These cells are generally $S100^-$, $CD1a^-$, and $CD68^+$ (a nonspecific marker of histiocyte lineage). The varying histopathologic features of the non-Langerhans histiocytoses may possibly be related to the actual physiologic function of histiocytes within the granuloma[30].

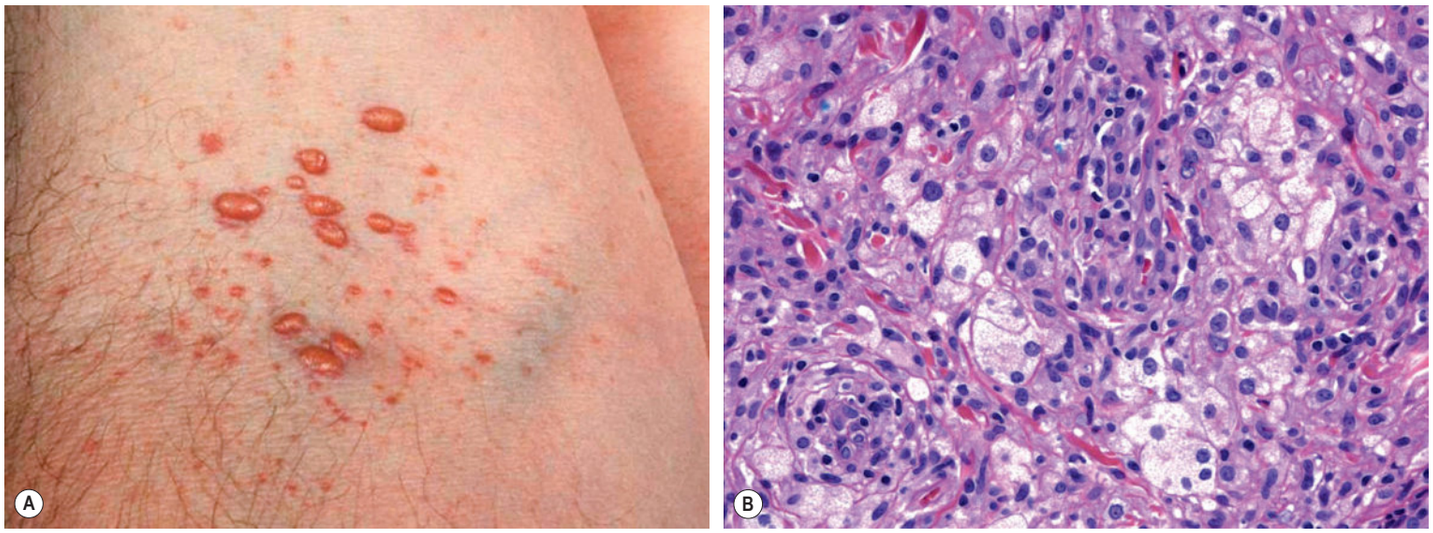


Fig. 0.27 Xanthomas. A Yellow–pink eruptive xanthomas. **B** Lipid-laden macrophages with foamy or vacuolated cytoplasm are present within the dermis. *B, Courtesy, James Patterson, MD.*

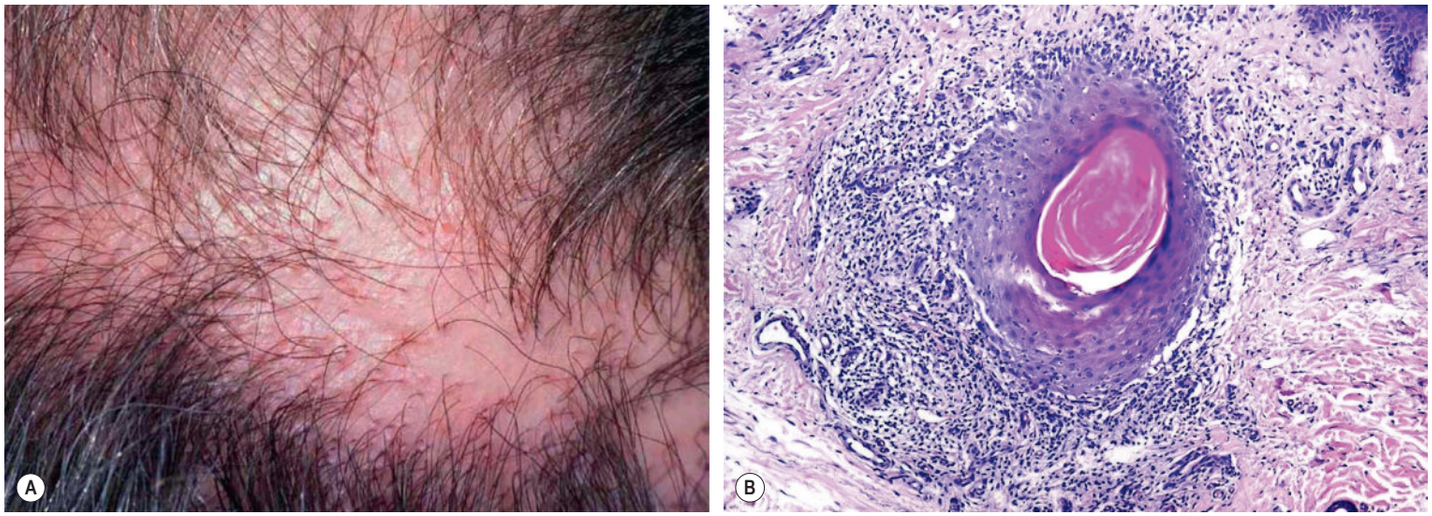


Fig. 0.28 Scarring alopecia. A Lichen planopilaris with areas of scarring alopecia and red–violet rims of inflammation around hair follicles. **B** Band-like lymphocytic infiltrate surrounding a hair follicle, with vacuolar alteration of basilar outer root sheath epithelium.

Lastly, *xanthomas* are characterized by the accumulation of *lipophages* (foamy histiocytes filled with lipid) within the dermis (see Ch. 92). The lipid content may impart a yellowish hue to the lesions (Fig. 0.27). Cutaneous xanthomas can take various forms, including widespread papules (*eruptive*), nodules (*tuberous* or *tendinous*), and plaques (*xanthelasma*, *palmar*).

Folliculitis/perifolliculitis

Folliculitis (inflammation of a hair follicle) is defined by the presence of inflammatory cells in the wall and lumen of a hair follicle (see Fig. 0.14I); perifolliculitis refers to the presence of similar cells in the adjacent dermis. Folliculitis may be due to infections (bacterial, fungal, viral, *Demodex* mites), drugs, occlusion, or unknown etiologies (e.g. eosinophilic folliculitis).

The classification of folliculitis (and perifolliculitis) can be made on the basis of the primary inflammatory cell (lymphocytes, neutrophils or eosinophils), the nature of the underlying pathologic process (e.g. dermatophyte infection), the temporal course (acute versus chronic), and the site of involvement along the length of the hair follicle. If the inflammatory process is severe and/or if it irreversibly damages epithelial stem cells, located in the bulge region of the follicle, permanent "scarring alopecia" may result (Fig. 0.28).

Fibrosing/sclerosing conditions

Fibrosing conditions include a wide spectrum of disorders that result from altered production of collagen, typically related to injury or an autoimmune connective tissue disease (see Fig. 0.14J). Histopathologically, the pattern is characterized by either: (1) abnormal fibrous dermal (and sometimes subcutaneous) tissue with an increased number of fibroblasts and increased, but rather unremarkable, collagen (*fibrosis*); or (2) homogenized, abnormally enlarged and eosinophilic collagen with a paucity of admixed fibroblasts (*sclerosis*). An example of the former is nephrogenic systemic fibrosis, while an example of the latter is morphea (Fig. 0.29) or systemic sclerosis. These two patterns represent the ends of the spectrum and overlap can occur.

Panniculitis

Panniculitis represents inflammation of the subcutis (see Fig. 0.14K,L) and it encompasses a wide range of disease processes (see Ch. 100). The diagnosis of panniculitides is difficult for clinicians and for dermatopathologists because the clinical presentation is often nonspecific and the histopathologic changes may vary over time and/or the changes may be nonspecific. Adding to the challenge, biopsy specimens are often inadequate, often due to their being too superficial in nature, too narrow in breadth or too badly crushed by forceps, to render a definitive diagnosis.

An important first step in the subdivision of panniculitides is determination of the predominant location of the cellular infiltrate (Figs 0.30 & 0.31). That is, does it chiefly affect the fat lobules or the septa between the fat lobules? Second, there should be an assessment as to whether a coexisting vasculitis is present or absent. If a coexisting vasculitis is detected, the size and type of the vessels affected must be determined.

With panniculitides, it is important to note the type and quality of the inflammatory infiltrate, as well as peculiarities in the pattern of fat

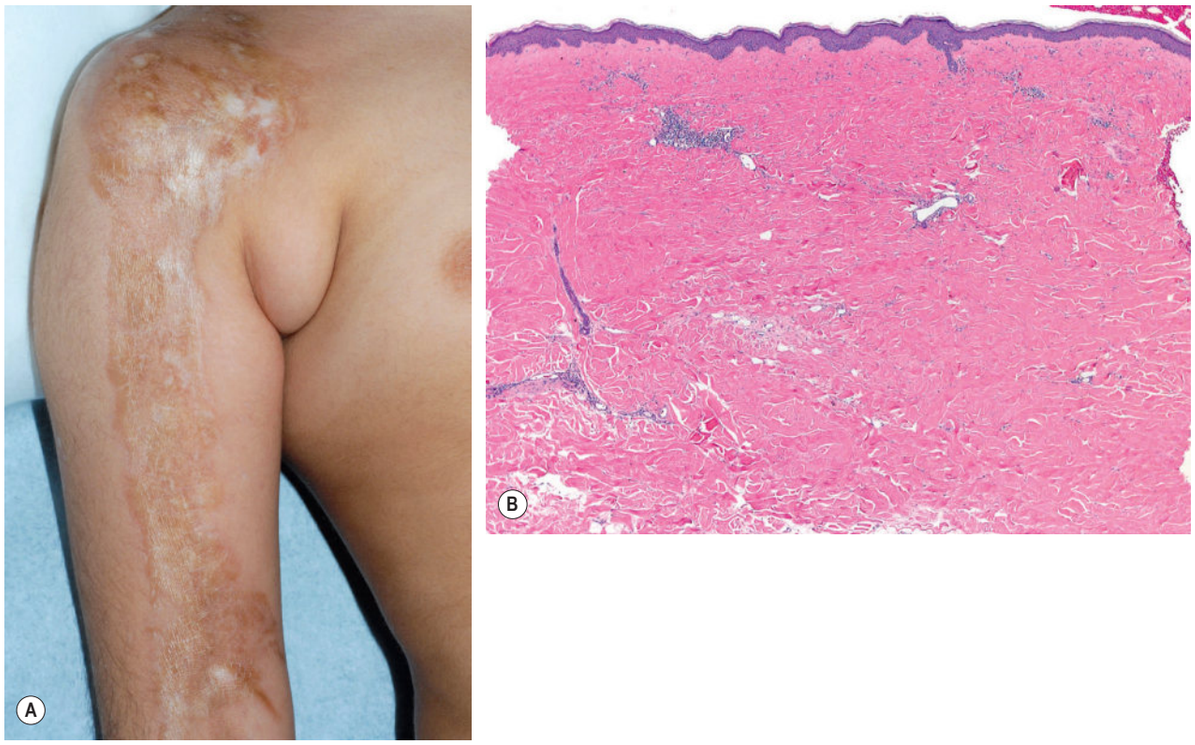


Fig. 0.29 Sclerosing disorder. A Linear morphea of the upper extremity. **B** Thickened and hyalinized collagen bundles, loss of adnexal structures and minimal inflammatory cell infiltrate. *A, Courtesy, Julie V Schaffer, MD; B, Courtesy, Lorenzo Cerroni, MD.*

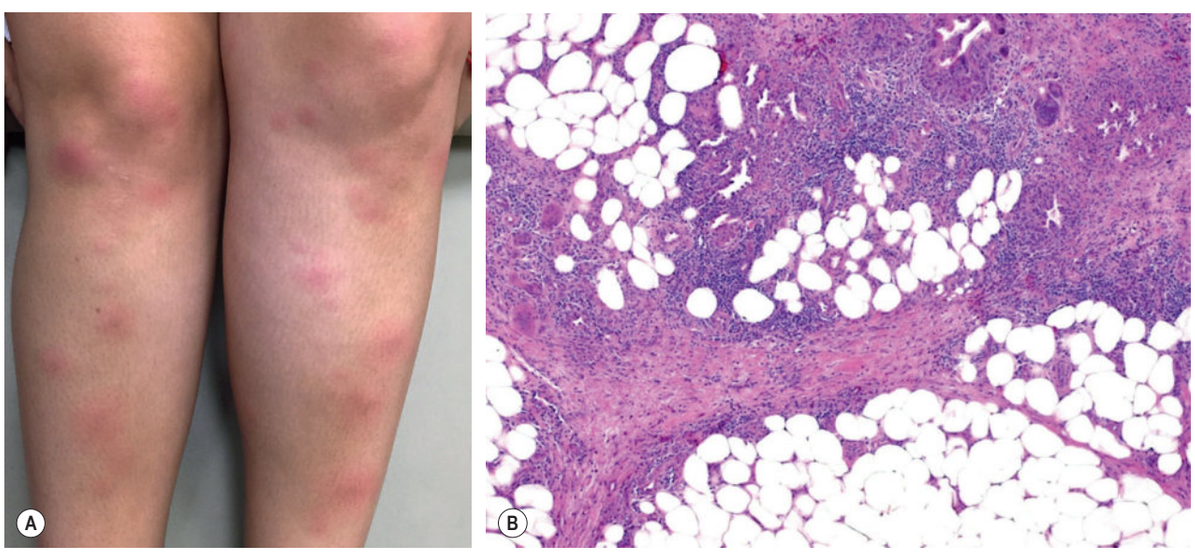


Fig. 0.30 Septal panniculitis. A Multiple pink to pink–violet nodules of erythema nodosum on the shins, admixed with healing bruise-like areas. **B** Predominantly septal granulomatous infiltrate with formation of characteristic Miescher granulomas. *A, Courtesy, Julie V Schaffer, MD; B, Courtesy, James Patterson, MD.*

necrosis. Early in the course of erythema nodosum, the most common panniculitis, the infiltrate may include acute inflammatory cells (neutrophils in particular), but in later stages, the infiltrate is composed primarily of chronic inflammatory cells (lymphocytes, histiocytes and plasma cells; see Fig. 0.30). If mononuclear cells are present, the presence or absence of cytologic atypia should be assessed, for subcutaneous panniculitis-like T-cell lymphoma may mimic an inflammatory panniculitis. Lastly, peculiarities of fat necrosis, such as the hyaline changes in lupus panniculitis, the basophilic saponification in pancreatic panniculitis (see Fig. 0.31), or the pseudomembranous degeneration in lipodermatosclerosis, should be appreciated.

As is the case for granulomatous infiltrates, panniculitis requires a low threshold for performing special stains to exclude an infectious etiology and polarized light examination to identify foreign material.

Invisible dermatoses

Occasionally, one encounters a dermatosis that lacks an immediately recognizable pattern, and these types of cases are collectively referred to as "invisible dermatoses" (Table 0.11). From the perspective of the dermatopathologist, these invisible dermatoses represent cases where disease appears to exist clinically, but the histologic examination is rather unremarkable (i.e. the microscopic findings differ minimally from those of normal skin)[31].

Among the "invisible dermatoses" are: (1) diseases with subtle pathologic changes and diseases that require special stains to visualize the diagnostic pathology (e.g. disorders of elastic and collagen tissue without significant fibrosis or sclerosis) (Fig. 0.32); (2) diseases with focal pathologic processes requiring serial tissue levels to identify diagnostic features (e.g. polyarteritis nodosa); and (3) diseases that require precise clinical information and/or strict clinical correlation to make the diagnosis (e.g. vitiligo, melasma, telangiectasia macularis eruptiva perstans).

Because the histopathologic changes in "invisible dermatoses" are subtle and vexing, careful analysis is recommended. This includes careful searching for diagnostic pathology at all levels of the skin (cornified layer, epidermis, papillary dermis, reticular dermis, hypodermis, adnexa) and the use of special stains or immunohistochemical stains. Lastly, it should be remembered that causes of a seemingly invisible dermatosis may include poor selection of the biopsy site, or mishandling or misindentification of tissue at the laboratory.

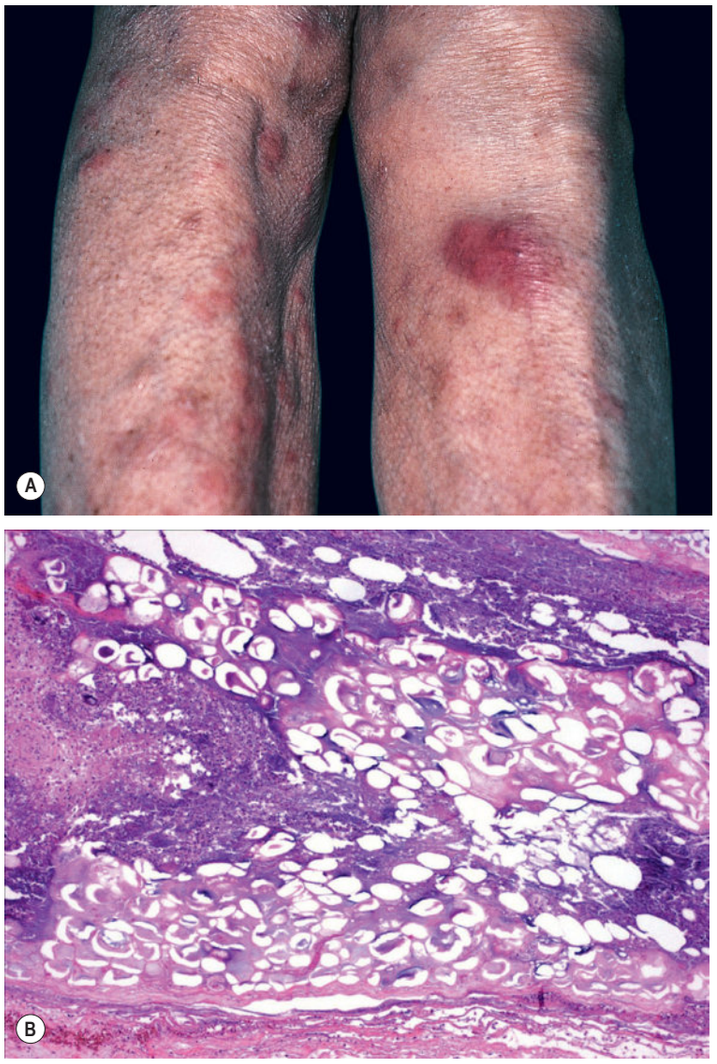


Fig. 0.31 Lobular panniculitis. A Pancreatic panniculitis. **B** Suppurative lobular panniculitis with characteristic enzyme-induced fat necrosis. *A, Courtesy, Kenneth Greer, MD; B, Courtesy, James Patterson, MD.*

Deposition of Materials Within the Skin

Occasionally, materials not normally present in the skin are deposited, either by exogenous or metabolic insult, and this can be appreciated histologically. In some patients, there is aberrant deposition of endogenously produced materials, such as uric acid in gouty tophi or light chain-derived amyloid due to an underlying plasma cell dyscrasia, whereas in others, exogenous material has been purposefully or accidentally inoculated into the skin (e.g. cosmetic filler material, tattoo pigment). These materials may accumulate within the dermis, the subcutaneous fat, or both. Deposits of some materials, such as the silver in patients with argyria, may be limited to cutaneous adnexa. Use of polarized light or darkfield microscopy (where light enters tissue at an angle that is not perpendicular to the slide) may be of use in identifying foreign material.

Some deposits engender a granulomatous inflammatory reaction (see Ch. 94), while others evoke no appreciable reaction at all. Deposited material is usually visualized during microscopic examination, but it may be removed during processing (e.g. siliconosis), leaving only characteristic "empty spaces" to suggest its clinical presence. Special stains may be helpful for precise identification, depending upon the suspected nature of the material.

Histologic Stains

The standard stain in dermatopathology is *hematoxylin and eosin*, referred to as "H&E". This stain yields a predictable pattern, with hematoxylin marking basophilic structures a blue-purple color (cellular nuclei and the granular layer of the epidermis) and eosin marking eosinophilic structures a pink–red (cytoplasm, collagen, muscle, nerve and fibrin).

INVISIBLE DERMATOSES		
Microanatomic site	**Abnormality**	**Example dermatoses**
Stratum corneum, granular cell layer	Superficial infections	• Pityriasis (tinea) versicolor • Dermatophytosis • Erythrasma • Pitted keratolysis
	Keratinization disorders	• Ichthyosis • Disseminated superficial actinic porokeratosis
Basilar layer of epidermis	Pigmentation disorders	• Vitiligo • Café-au-lait macule • Melasma
Superficial dermis	Infestations	Onchocerciasis
	Mast cell infiltration	Telangiectasia macularis eruptiva perstans
	Deposition of endogenous substances	Macular amyloidosis
Superficial and deep dermis	Deposition of exogenous substances	Argyria (basement membrane of epithelial structures)
	Deposition of endogenous substances	Systemic amyloidosis (when subtle)
	Collagen abnormalities	• Collagenoma • Atrophoderma
	Elastic tissue abnormalities	• Nevus elasticus • Anetoderma (non-inflammatory)
Absence of normal epithelial structure	Deficiency of eccrine sweat glands	Hypohidrotic ectodermal dysplasia

Table 0.11 Invisible dermatoses.

H&E staining alone enables the histopathologic diagnosis of many skin diseases, but some disorders require additional special stains to facilitate a diagnosis[32]. For example, elastic tissue, unless significantly altered by ultraviolet radiation or calcium deposits, does not stain with H&E, and special stains such as Verhoeff–van Gieson are required to identify alterations in these fibers (e.g. in anetoderma; see Fig. 0.32). Similarly, special stains exist to screen for the presence of infectious agents, such as the Brown–Brenn stain (a modified tissue Gram stain) for bacteria, the periodic acid Schiff (PAS) or Grocott methenamine silver stain for fungus, and the Ziehl–Neelsen or Fite stain for mycobacteria (see Fig. 0.32). Additional special stains may be utilized to determine the type of infiltrating cell, such as the Giemsa or chloroacetate esterase stain for mast cells. Table 0.12 lists the more commonly employed histochemical ("special") stains used in dermatopathology.

Immunohistochemical Testing

Immunohistochemistry (IHC) is the use of immunologic techniques to identify cellular antigens (proteins) that are not visible in sections stained with H&E. It exploits the principle of antibodies binding specifically to antigens in biological tissues. Visualizing this antibody–antigen interaction may be accomplished in a number of ways. Most commonly, the antibody is conjugated to an enzyme that can catalyze a color-producing reaction when the antibody–enzyme conjugate is bound to the appropriate antigen within tissue; the enzyme is often peroxidase, hence the older terminology, immunoperoxidase technique.

While IHC is most often used to characterize the cellular lineage of neoplasms, it is also helpful in assessing the biological behavior of tumors and in identifying specific infectious agents that are not discernible or are difficult to detect in routine H&E-stained sections (Fig. 0.33)[33,34]. IHC is also used as a research tool to determine the

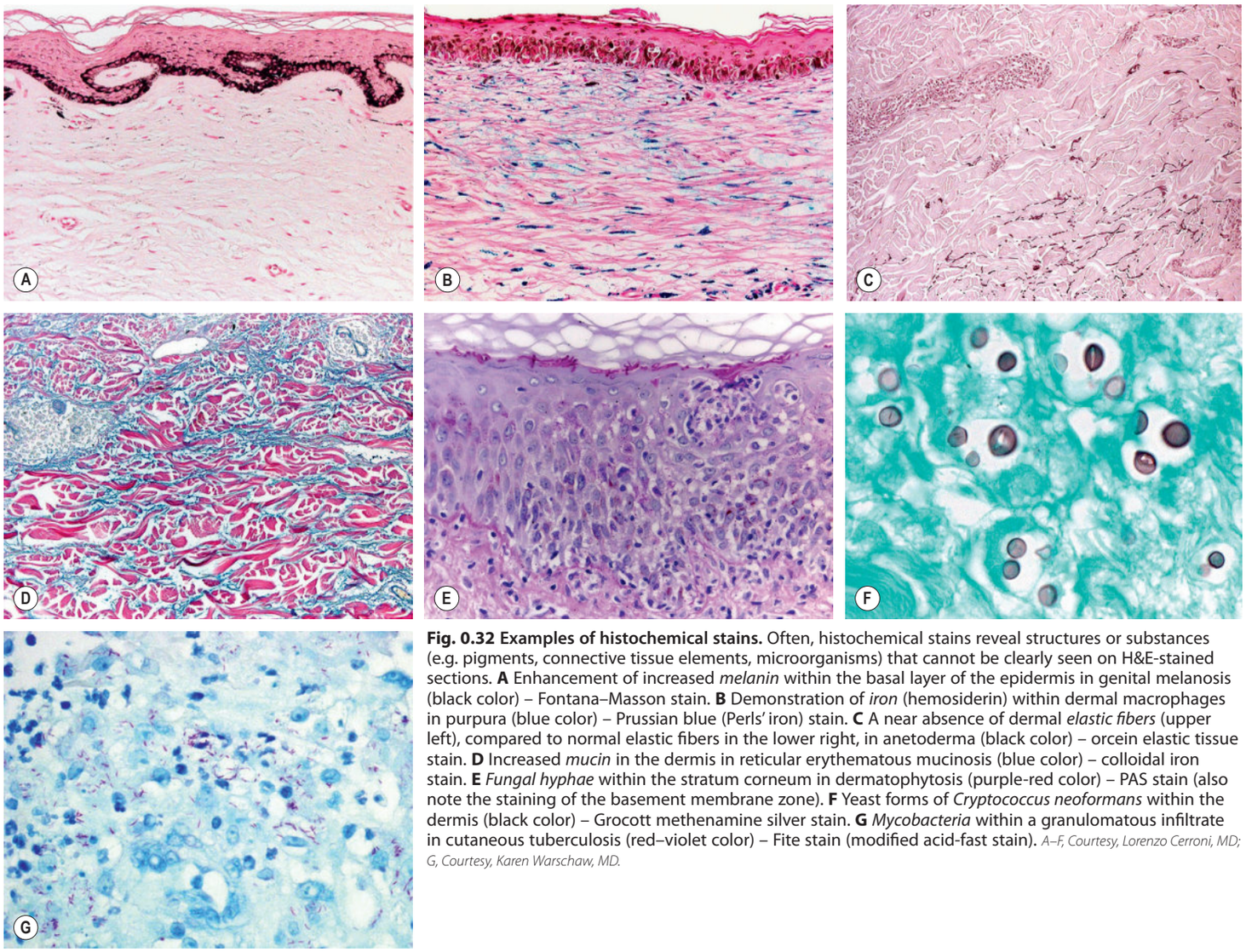


Fig. 0.32 Examples of histochemical stains. Often, histochemical stains reveal structures or substances (e.g. pigments, connective tissue elements, microorganisms) that cannot be clearly seen on H&E-stained sections. **A** Enhancement of increased *melanin* within the basal layer of the epidermis in genital melanosis (black color) – Fontana–Masson stain. **B** Demonstration of *iron* (hemosiderin) within dermal macrophages in purpura (blue color) – Prussian blue (Perls' iron) stain. **C** A near absence of dermal *elastic fibers* (upper left), compared to normal elastic fibers in the lower right, in anetoderma (black color) – orcein elastic tissue stain. **D** Increased *mucin* in the dermis in reticular erythematous mucinosis (blue color) – colloidal iron stain. **E** *Fungal hyphae* within the stratum corneum in dermatophytosis (purple-red color) – PAS stain (also note the staining of the basement membrane zone). **F** Yeast forms of *Cryptococcus neoformans* within the dermis (black color) – Grocott methenamine silver stain. **G** *Mycobacteria* within a granulomatous infiltrate in cutaneous tuberculosis (red–violet color) – Fite stain (modified acid-fast stain). *A–F, Courtesy, Lorenzo Cerroni, MD; G, Courtesy, Karen Warschaw, MD.*

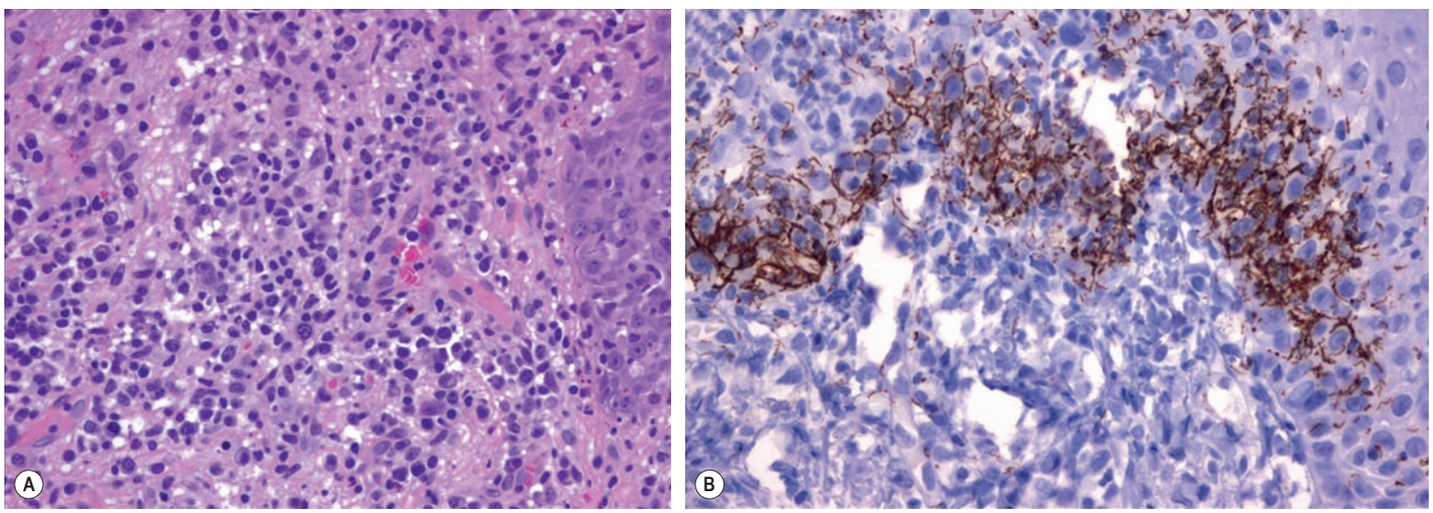


Fig. 0.33 Example of the utility of an immunohistochemical stain. A Dermal infiltrate comprised of lymphocytes and plasma cells (H&E-stained section). **B** The same area stained with antibody that recognizes a spirochetal antigen (immunoperoxidase technique) in which numerous organisms are identified (brown color), confirming the diagnosis of syphilis. *Courtesy, James Patterson, MD.*

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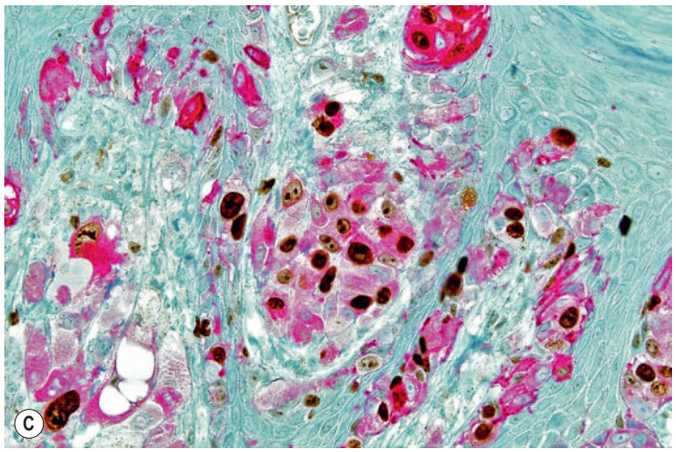


Fig. 0.33 Example of the utility of an immunohistochemical stain. (cont'd) **C** A combination of two differently colored chromogens highlights melanoma cells (Melan-A; red color) with a high relative proliferative index (Ki-67; brown color). *Courtesy, Whitney A High, MD.*

distribution and localization of specific biomarkers and proteins within biological tissue. Finally, in recent years IHC is being used in order to verify the presence of antigens targeted by specific drugs (e.g., CD52 targeted by alemtuzumab).

When used rationally and appropriately, IHC is a formidable tool in diagnostic dermatopathology, but if used without insight or used excessively, it can be misleading and economically wasteful. Important factors to consider when utilizing IHC include the following: (1) almost no antibody is specific for a certain cell type, and therefore a panel of antibodies should be employed to avoid premature, incomplete, or erroneous conclusions; (2) a differential diagnosis must be constructed prior to ordering an antibody panel so that the antibodies requested are appropriate; and (3) no antibody can differentiate irrefutably between a benign and malignant neoplasm (although, on occasion, evidence of an increased proliferative index or the aberrant expression of certain proteins may *support* such a conclusion).

A list of antibodies used most often in dermatopathology, the corresponding antigens, and the disease processes suggested by positive reactions is provided in Table 0.13. When reading about specific disease processes in other sections of this book, pay particular attention to the use of IHC techniques.

COMMONLY EMPLOYED SPECIAL STAINS IN DERMATOPATHOLOGY			
Stain	**Structures identified**	**Color**	**Application(s)**
Alcian blue (pH 2.5)	Acid mucopolysaccharides (glycosaminoglycans)	Light blue	Mucinoses (see Table 46.1) Lupus erythematosus Extramammary Paget disease Mucopolysaccharidoses
Alcian blue (pH 0.5)	Sulfated mucopolysaccharides (heparin sulfate, chondroitin sulfate)	Blue	
Chloroacetate esterase (Leder)	Myeloid cells and mast cells	Red	Neutrophilic dermatoses Malignant myeloid infiltrates Mastocytosis
Colloidal iron	Acid mucopolysaccharides	Blue	Mucinoses Lupus erythematosus Extramammary Paget disease
Congo red	Amyloid	Red; green in polarized light	Amyloidoses, cutaneous and systemic
Crystal violet	Acid mucopolysaccharides (glycosaminoglycans) and amyloid	Metachromatically purple with blue background	Mucinoses Amyloidoses
Fite–Faraco	*Mycobacterium leprae* *M. tuberculosis* MOTT (mycobacteria other than tuberculosis)	Red	Leprosy (Hansen disease) Cutaneous tuberculosis Atypical mycobacterioses
Fontana–Masson (argentaffin)	Melanin	Black	Distinction between iron and melanin Discoloration due to drugs (e.g. minocycline) Evaluation of vitiligo
Giemsa	Nuclei of cells, microorganisms	Blue	Leishmaniasis Histoplasmosis Granuloma inguinale
	Mast cell granules	Metachromatically purple	Urticaria Mastocytosis
Grocott methenamine silver	Fungal cell walls	Black	Mycotic infections
Gram (Brown–Brenn)	Gram-positive bacteria	Blue	Bacterial infections
	Gram-negative bacteria	Red	Bacterial infections
Masson's trichrome	Smooth muscle	Pink	Distinguishing leiomyomas from dermatofibromas and neural tumors
	Collagen	Blue/green	Evaluating the characteristics of dermal collagen, e.g. perforating disorders
Mucicarmine	Epithelial mucin (acid or neutral mucopolysaccharides)	Red	Usually used for sialomucin (e.g. adenocarcinoma, Paget disease) and the capsule of *Cryptococcus neoformans*
Myeloperoxidase	Immature myeloid cells	Orange	Leukemic infiltrates (myelogeneous leukemia)

Table 0.12 Commonly employed special stains in dermatopathology. In parentheses are alternative names or variations of the stain.

COMMONLY EMPLOYED SPECIAL STAINS IN DERMATOPATHOLOGY			
Stain	**Structures identified**	**Color**	**Application(s)**
Orcein (acid orcein–Giemsa)	Collagen	Pink	Elastic tissue disorders (e.g. PXE, anetoderma)
	Elastic tissue	Dark brown	
	Muscle and nerves	Yellow	
Pagoda	Amyloid	Orange	Amyloidoses
Periodic acid Schiff (PAS)	Glycogen, fungal walls, neutral mucopolysaccharides, fibrin, basement membranes, many clear cell neoplasms	Red	Mycotic infections Discoid lupus erythematosus (thickened epidermal basement membrane) Porphyria cutanea tarda (thickened vascular walls)
Perls' iron (Prussian blue)	Hemosiderin Ferric ions	Blue	Identification of iron as the source of pigment
Sudan black	Lipids (in frozen sections or formalin-fixed, unprocessed tissue)	Black	Xanthomatoses Storage diseases (e.g. Fabry disease)
Sudan orange	Lipids (in frozen sections or formalin-fixed, unprocessed tissue)	Orange	Xanthomatoses Storage diseases
Thioflavin T	Amyloid	Yellow–green by fluorescence microscopy	Amyloidoses
Truant (auramine–rhodamine)	Acid-fast organisms	Reddish-yellow by fluorescence microscopy	Mycobacterial infections
Toluidine blue	Acid mucopolysaccharides and mast cell granules	Metachromatically purple	Mastocytosis
Verhoeff–van Gieson or Weigert	Collagen	Pink to red	Elastic tissue disorders (e.g. PXE, anetoderma, mid-dermal elastolysis, acquired cutis laxa)
	Elastic tissue	Black	
	Muscle and nerves	Yellow	
Von Kossa	Calcium salts	Black	Calcium deposits PXE (oxalate salts may not stain with this method) Calciphylaxis
Warthin–Starry (modified Steiner)	Bacteria	Black	Granuloma inguinale Syphilis (and other diseases caused by spirochetes) Rhinoscleroma Bacillary angiomatosis
Ziehl–Neelsen	Acid-fast bacteria	Red	Mycobacterial infections

Table 0.12 Commonly employed special stains in dermatopathology. (cont'd) Some of these special stains are being replaced by immunohistochemical (IHC) stains, e.g. IHC for adipophilin instead of Sudan black or Sudan orange stain. PXE, pseudoxanthoma elasticum.

MOST COMMONLY EMPLOYED IMMUNOHISTOCHEMICAL (IHC) STAINS IN DERMATOPATHOLOGY		
Marker	**Definition/primary cellular expression**	**Applications/comments**
Markers for diagnosis of epithelial tumors		
Adipophilin	Marker of intracellular multilocular lipid accumulation	Diagnosis of tumors with sebaceous differentiation
Bcl2	Protein product of an oncogene which inhibits programmed cell death (apoptosis) Expressed in the basal layer of the epidermis (and lymphoid cells; see below)	Distinguishing basal cell carcinoma (diffuse staining) from trichoepithelioma (stains outermost layer)
Ber-EP4	Transmembrane glycoprotein involved in cellular adhesion Broadly distributed in epithelial cells	Distinction of basal cell carcinoma (+) from other cutaneous basaloid tumors (–)
CEA (carcinoembryonic antigen)	Expressed in a variety of epithelia, from gastrointestinal to cutaneous adnexa	Highlights tubular differentiation in epithelial tumors Diagnosis of benign and malignant adnexal neoplasms
CK5/6	Intermediate-sized basic keratins Expressed in the basal layer of stratified squamous epithelia and myoepithelial cells of eccrine and apocrine secretory tubules	Spindle cell squamous cell carcinomas Myoepithelial neoplasms

Table 0.13 Most commonly employed immunohistochemical (IHC) stains in dermatopathology. CK, cytokeratin. *Continued*

MOST COMMONLY EMPLOYED IMMUNOHISTOCHEMICAL (IHC) STAINS IN DERMATOPATHOLOGY		
Marker	**Definition/primary cellular expression**	**Applications/comments**
CK20	Low-molecular-weight cytokeratin Expressed in simple epithelia and Merkel cells	Most specific marker for Merkel cell carcinoma (especially when combined with negative TTF1 staining) Cutaneous metastases from different types of adenocarcinomas
EMA (epithelial membrane antigen)	High-molecular-weight transmembrane glycoprotein expressed in many epithelial cells	Highlights ductal differentiation in eccrine and apocrine tumors (benign and malignant) Positive staining in most sebaceous glands Perineurial cells
GCDFP-15 (gross cystic disease fluid protein-15)	Glycoprotein expressed by apocrine glands, eccrine glands (variable), minor salivary glands, bronchial glands, metaplastic epithelium of the breast, benign sweat gland tumors of the skin, and serous cells of the submandibular gland	Breast carcinoma metastases Sweat gland carcinoma with apocrine differentiation
MNF116	Epitope common to several cytokeratins (CK5, 6, 8, 17, and probably 19)	Spindle cell squamous cell carcinomas Adnexal and undifferentiated carcinomas
p63	p53 homolog that acts as a transcription factor Expressed in the basal layer of the epidermis and cutaneous adnexa as well as myoepithelial cells	Myoepithelial neoplasms Distinction of primary cutaneous adenocarcinomas (+) versus cutaneous metastasis from visceral adenocarcinomas (–)
Pancytokeratin AE1/AE3	Mixture of low- and high-molecular-weight cytokeratins	Screening tumors for an epithelial origin Useful for squamous cell carcinomas
Markers for diagnosis of melanocytic and neural tumors		
S100	Family of low-molecular-weight calcium-binding proteins Neural crest-derived cells (melanocytes, Schwann cells, glial cells), chondrocytes, fat cells, macrophages, Langerhans cells, dendritic cells Some breast epithelial cells	Melanocytic nevi and melanoma Most sensitive marker for spindle cell/desmoplastic melanoma Also stains malignant peripheral nerve sheath tumors and clear cell sarcoma (melanoma of soft parts)
Melan-A (MART-1)	Protein involved in the function of the melanosomal matrix protein pmel17/gp100 Antigen present on melanocytes (and melanoma cells) recognized by cytotoxic T cells	Melanocytic nevi and melanomas Also may stain melanosome-containing keratinocytes in sun-damaged skin Cutaneous PEComas
HMB45	Glycoprotein present in premelanosomes and melanosomes (pmel17/gp100) Expressed in melanocytes that are synthesizing melanin	Melanocytic nevi and melanomas (highly specific) Diminished staining with dermal descent more frequent in benign tumors Also may stain melanosome-containing keratinocytes Cutaneous PEComas
MITF (microphthalmia transcription factor)	Transcription factor that regulates several melanogenic enzymes, including tyrosinase, in melanocytes Plays key role in regulating melanocyte development during embryogenesis	Stains the nucleus of melanocytic nevus and melanoma cells Positive staining in most (~80–100%) of all melanoma subtypes, including desmoplastic (~50%) Lack of staining of melanin-containing keratinocytes helpful in distinguishing solar lentigo from lentigo maligna Less specificity as can also stain non-melanocytic spindle cell tumors
Tyrosinase	Enzyme involved in the initial steps of melanin biosynthesis Expressed in melanocytes	High sensitivity and specificity (97–100%) Sensitivity decreases with increased clinical stage and in metastases Positive staining in only a small percentage (~6%) of desmoplastic melanomas
SOX10	Transcription factor that is expressed in melanocytes Required for survival and proliferation of neural crest cells Controls MITF expression	High sensitivity for primary and metastatic melanomas (97%–100%) Expressed in all melanoma subtypes, including desmoplastic melanoma (~80–100%) Positive staining in clear cell sarcomas and peripheral nerve sheath tumors Useful for the detection of micrometastases in sentinel lymph nodes
BRAF V600E	BRAF = serine/threonine-protein kinase in the MAPK pathway V600E = an amino acid substitution of glutamic acid (E) for valine (V) in the BRAF protein at position 600 due to a mutation in *BRAF* BRAF V600E (less often V600K or V600D) detected in ~50% of cutaneous melanomas This missense mutation leads to activation of the kinase	Compared to PCR, IHC staining is less sensitive Detection of BRAF V600E leads to treatment with targeted inhibitors of BRAF V600E and the MAPK pathway (see Ch. 113) BRAF V600E also present in Langerhans cell histiocytosis

Table 0.13 Most commonly employed immunohistochemical (IHC) stains in dermatopathology. (cont'd) CK, cytokeratin; MAPK, mitogen-activated protein kinase; MART-1, melanoma antigen recognized by T cells; Melan-A, melanocyte antigen; PEC, perivascular epithelioid cell; PCR, polymerase chain reaction.

MOST COMMONLY EMPLOYED IMMUNOHISTOCHEMICAL (IHC) STAINS IN DERMATOPATHOLOGY		
Marker	**Definition/primary cellular expression**	**Applications/comments**
P75	Common receptor for members of the neurotrophins (NT) family Involved in programmed cell death Marker of Schwannian differentiation	Helpful for establishing the diagnosis of desmoplastic and neurotropic melanoma when S100 staining is weak or absent
PNL2	Detects fixative-resistant, uncharacterized melanocyte antigen	Highly sensitive and specific for melanocytic nevi and melanomas Positive staining of intraepidermal nevus cells (up to 100%) and primary and metastatic melanomas (~75–100%), with the exception of desmoplastic melanomas which are almost invariably negative Clear cell sarcomas, PEComas, and melanocytic schwannomas may stain positively
pHH3 (phospho-histone H3)	Core histone protein Detects mitoses and distinguishes mitoses from apoptotic cells	Precise identification of mitoses within tumors
Markers for diagnosis of neuroendocrine tumors		
Chromogranin	Granules of neuroendocrine cells and sympathetic nerves	Merkel cell carcinoma Mucin-secreting sweat gland carcinoma with neuroendocrine differentiation
CK20 (see above)	Low-molecular-weight cytokeratin Expressed in simple epithelia and Merkel cells	Most sensitive stain for Merkel cell carcinoma (especially when combined with negative TTF1 staining) Cutaneous metastases from different types of adenocarcinomas Epidermotropic metastases, e.g. secondary extramammary Paget disease
Neurofilament	Intermediate filaments in neurons and neuronal processes of central and peripheral nervous tissue	Merkel cell carcinoma Neuromas and neurofibromas
Synaptophysin	Glycoprotein of presynaptic vesicles found in neurons and neuroendocrine cells	Merkel cell carcinoma Neural tumors Mucin-secreting sweat gland carcinoma with neuroendocrine differentiation
TTF-1 (thyroid transcription factor-1)	Expressed in the epithelia of the thyroid and lung	Thyroid carcinoma Small cell lung carcinoma, visceral neuroendocrine tumors Negative in most cases of Merkel cell carcinoma
Markers for diagnosis of mesenchymal tumors		
Caldesmon	Actin and protomyosin binding protein involved in regulation of muscle and non-muscle contraction	Smooth muscle neoplasms
Calponin	Calcium-binding protein that regulates smooth muscle myosin ATPase activity Expressed in smooth muscle	Neoplasms with smooth muscle differentiation (benign and malignant)
CD99	Cell surface glycoprotein involved in leukocyte migration and T-cell adhesion Expressed on most hematopoietic cells	Ewing sarcoma, peripheral neuroectodermal tumor Atypical fibroxanthoma, dermatofibroma (strong), DFSP (weaker) Some hematopoietic neoplasms
Desmin	Intermediate filament expressed predominantly by striated and smooth muscle cells	Smooth and striated muscle cell neoplasms (benign and malignant)
Factor XIIIa	Human coagulation factor XIII Expressed in subsets of dermal dendrocytes and monocytes/macrophages	Dermatofibromas (DFs) Non-Langerhans cell histiocytoses Negative in DFSP
Smooth muscle actin	Expressed in smooth muscle around blood vessels and in arrector pili muscles Expressed in myofibroblasts	Benign and malignant smooth muscle tumors Myofibroblastic tumors and pseudotumors Myoepithelial neoplasms
Vimentin	Intermediate filaments in mesenchymal cells	All mesenchymal cells/tumors Sarcomatoid (spindle cell) carcinoma
Markers for diagnosis of vascular tumors		
CD31	Platelet-endothelial cell adhesion molecule-1 (PECAM-1) Highly sensitive for endothelial cells, but poor specificity	Benign and malignant vascular neoplasms Histiocytes also stain positively
CD34	Surface glycoprotein involved in cell–cell adhesion Highly sensitive for endothelial cells, but poor specificity	Benign and malignant vascular neoplasms DFSP (negative in DFs) Many cutaneous spindle cell neoplasms so poor specificity

Table 0.13 Most commonly employed immunohistochemical (IHC) stains in dermatopathology. (cont'd) CD, cluster of differentiation; CK, cytokeratin; DFSP, dermatofibrosarcoma protuberans; PEC, perivascular epithelioid cell.

Continued

MOST COMMONLY EMPLOYED IMMUNOHISTOCHEMICAL (IHC) STAINS IN DERMATOPATHOLOGY		
Marker	**Definition/primary cellular expression**	**Applications/comments**
Podoplanin (D2-40)	Mucin-type transmembrane glycoprotein Specifically expressed by lymphatic, but not vascular, endothelial cells	Kaposi sarcoma, lymphangiomas, angiosarcomas with lymphatic differentiation, schwannomas Distinction of primary cutaneous carcinomas (+) from cutaneous metastases from visceral carcinomas (–)
c-MYC	Proto-oncogene Detection of MYC protein expression correlates with *MYC* translocation	Angiosarcoma (particularly post-radiation) Subset of cutaneous diffuse large cell B-cell lymphomas
ERG	Proto-oncogene Transcription factor expressed in vascular endothelial cells	Benign and malignant tumors derived from endothelial cells Epithelioid sarcoma (~50% of cases)
HHV-8 (Human herpesvirus 8)	HHV-8 latent nuclear antigen	Kaposi sarcoma
Markers for diagnosis of histiocytic tumors		
CD1a	Transmembrane glycoprotein structurally related to MHC proteins that plays a role in antigen presentation Expressed in Langerhans cells and precursor T cells	Langerhans cell histiocytoses Some T-cell lymphoblastic lymphomas
CD68	Glycoprotein that binds to low-density lipoprotein (LDL) Expressed in monocytes and macrophages, as well as myeloid cells and mast cells	Blastic NK cell lymphoma (some cases), myeloid leukemias Non Langerhans cell histiocytoses Soft tissue tumors, e.g. some AFXs, dermatofibromas, giant cell tumors of the tendon sheath
CD163	Member of the scavenger receptor cysteine-rich (SRCR) superfamily that is involved in clearance and endocytosis of hemoglobin/haptoglobin complexes Exclusively expressed by monocytes and macrophages	More specific than CD68 for identifying cells of monocyte/macrophage lineage in reactive and neoplastic conditions Non Langerhans cell histiocytoses, e.g. juvenile xanthogranuloma, Rosai–Dorfman disease, reticulohistiocytoma Fibrohistiocytic tumors, e.g. dermatofibromas Chronic myelomonocytic leukemia, histiocytic sarcoma
CD207 (Langerin)	Transmembrane cell surface receptor expressed by Langerhans cells and localized within Birbeck granules Involved in internalization of antigens into Birbeck granules	Langerhans cell histiocytoses
S100 (see above)	Family of low-molecular-weight calcium-binding proteins Expressed in Langerhans cells and activated macrophages	Langerhans cell histiocytoses and Rosai–Dorfman disease Some lipomas and liposarcomas
Markers for diagnosis of mast cell tumors		
CD117 (c-KIT)	Receptor for stem cell factor Expressed on hematopoietic stem cells, mast cells, melanocytes Proto-oncogene	Mastocytosis Myeloid leukemia, some melanomas (especially acral or mucosal), melanocytic nevi The efficacy of KIT receptor inhibitors is determined by the location of amino acid substitutions
Mast cell tryptase	Serine protease within mast cell granules	Mastocytosis
Markers for diagnosis of cutaneous metastases (e.g. CK7, CK20, PSA) – see Table 122.4		
Markers for diagnosis of cutaneous lymphoproliferative disorders		
ALK (anaplastic lymphoma kinase)	Membrane-associated tyrosine kinase receptor Expressed in the nervous system, especially during development	Subgroup of anaplastic large cell lymphomas (nodal and very rarely primary cutaneous) Otherwise negative in primary cutaneous T-cell lymphomas and other specific types of anaplastic lymphoma with CD30 positivity Also positive in some spitzoid melanocytic tumors
Bcl-2	Anti-apoptosis factor for T and B cells Expressed in non-germinal center B cells and most T cells	Primary cutaneous diffuse large B-cell lymphoma, leg type Distinguishes systemic/nodal follicular lymphomas with secondary skin involvement (+) from primary cutaneous follicle center lymphomas (–)
Bcl-6	Nuclear protein expressed in mature B cells within normal germinal centers Also expressed in T follicular helper cells	Primary cutaneous follicle center lymphoma Reactive lymphoid follicles T follicular helper cells
Immunoglobulin light chains (kappa and lambda)	Small polypeptide subunits of immunoglobulin Expressed in B lymphocytes and plasma cells	Plasma cell and plasmacytoid neoplasms Monotypic expression in clonal neoplasms

Table 0.13 Most commonly employed immunohistochemical (IHC) stains in dermatopathology. (cont'd) AFX, atypical fibroxanthoma; CD, cluster of differentiation; CK, cytokeratin; MHC, major histocompatibility complex; NK, natural killer.

MOST COMMONLY EMPLOYED IMMUNOHISTOCHEMICAL (IHC) STAINS IN DERMATOPATHOLOGY		
Marker	**Definition/primary cellular expression**	**Applications/comments**
CD3	Surface glycoprotein involved in signal transduction to the T-cell interior following antigen recognition Pan T-cell marker Also expressed in NK cells (cytoplasmic staining for CD3ε)	T-cell lymphomas, including HTLV-I associated adult T-cell leukemia/lymphoma Reactive infiltrates with T lymphocytes
CD4	Transmembranous glycoprotein involved in T-cell activation (MHC class II-restricted) Expressed in T helper cells, monocytes, granulocytes, macrophages, Langerhans cells, nTreg and iTreg cells	Most T-cell lymphomas, including mycosis fungoides Blastic plasmacytoid dendritic cell neoplasm
CD5	Transmembrane glycoprotein Expressed in mature T cells, thymocytes, and a subset of mature B cells	T-cell lymphomas, B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma Reactive infiltrates with T lymphocytes
CD8	Transmembranous glycoprotein involved in T-cell activation (MHC class I-restricted) Expressed in cytotoxic T cells, NK cells, thymocytes	Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma Subcutaneous panniculitis-like T-cell lymphoma Phenotypic variants of several CTCLs (e.g. mycosis fungoides)
CD10/CALLA (common acute lymphoblastic leukemia antigen)	Membrane-associated metallo-endopeptidase Expressed in precursor B cells and germinal center cells Also expressed in follicular T helper cells	Follicle center lymphoma (both systemic and primary cutaneous) B lymphoblastic leukemia/lymphoma [Positive in most atypical fibroxanthomas but not specific]
CD15 (Lewis X)	Membrane protein that is a component of adhesion molecules that bind selectins Expressed on monocytes, granulocytes Absent on normal lymphocytes	Classic Hodgkin disease (expressed on Reed–Sternberg cells) Acute myelogenous leukemia
CD20	Unglycosylated phosphoproteins expressed only on B cells Play a role in B-cell activation and proliferation	Different types of cutaneous B-cell lymphoma (both systemic and primary cutaneous) Reactive infiltrates with B lymphocytes
CD21	Receptor for the C3d fragment of complement and EBV in B cells and epithelial cells Expressed in follicular dendritic cells and mantle and marginal zone B cells	Follicular dendritic cell neoplasms Follicular dendritic cells within both reactive and neoplastic lymphoid follicles
CD30	Member of the tumor necrosis factor (TNF) receptor family Expressed by activated T and B cells	Anaplastic large T-cell lymphoma, lymphomatoid papulosis, Hodgkin lymphoma May be expressed by a proportion of neoplastic cells in several other types of CTCL (e.g. mycosis fungoides) Expressed in activated T cells in non-neoplastic skin diseases (e.g. herpes virus infections, poxvirus infections)
CD45 (common leukocyte antigen)	Family of high-molecular-weight glycoproteins present on the surface of leukocytes (tyrosine phosphatase) Expressed by both T cells and B cells	Expressed on lymphocytes (benign and malignant, both T- and B-cell types)
CD56	Neural cell adhesion molecule Expressed on neural cells, NK cells, a subset of $CD3^+$ cytotoxic T cells, a subset of $CD4^+$ T cells, and monocytes	Extranodal NK/T-cell lymphoma, nasal type Blastic plasmacytoid dendritic cell neoplasm Myeloma, some myelogenous leukemias, neural neoplasms
CD79a	Surface glycoprotein physically associated with immunoglobulin within the B-cell membrane; involved in signal transduction after antigen binding Appears before the pre-B-cell stage Expressed on immature and mature B cells, plasma cells	B-cell lymphomas (can be positive in cases where CD20 is negative) Plasma cell neoplasms Reactive infiltrates with B lymphocytes
CD123	Marker of dendritic cells, including plasmacytoid	Blastic plasmacytoid dendritic cell neoplasm Positive staining of plasmacytoid dendritic cells in lupus erythematosus and other conditions
CD138	Surface glycoprotein involved in cell–cell and cell–matrix adhesion Expressed in plasma cells, plasmocytoid cells, activated T and B cells	Marginal zone B-cell lymphoma, plasmacytoma, myeloma, plasmablastic lymphoma Positive staining of reactive plasma cells
Cyclin D1 (PRAD1; bcl-1)	Increased expression of cyclin D1 due to translocation of the cyclin D1/bcl-1 gene locus to the IgH promoter	Mantle cell lymphoma

Table 0.13 Most commonly employed immunohistochemical (IHC) stains in dermatopathology. (cont'd) CD, cluster of differentiation; CTCLs, cutaneous T-cell lymphomas; EBV, Epstein–Barr virus; MHC, major histocompatibility complex; NK, natural killer.

Continued

MOST COMMONLY EMPLOYED IMMUNOHISTOCHEMICAL (IHC) STAINS IN DERMATOPATHOLOGY		
Marker	**Definition/primary cellular expression**	**Applications/comments**
EBER-1 (Epstein–Barr virus early ribonucleoprotein 1) [*in situ* hybridization]	EBV-infected cells	EBV-associated cutaneous lymphoproliferative disorders, e.g. hydroa vacciniforme, post-transplant lymphomas, extranodal NK/T-cell lymphoma (nasal type), Hodgkin disease
Granzyme B	Serine protease expressed specifically by activated cytotoxic T lymphocytes	Cytotoxic lymphocytes in benign and malignant lymphoid infiltrates
MUM1 (multiple myeloma oncogene-1)	Member of the interferon regulatory factor family of transcription factors Plasma cells, late B cells, and activated T cells	$CD30^+$ lymphoproliferative disorders, anaplastic $CD30^+$ lymphoma Strong expression in cutaneous diffuse large B-cell lymphoma, leg type
Myeloperoxidase	Lysosomal protein most abundant in neutrophils and monocytes	Myeloid leukemias
PD-1 (programmed cell death protein 1)	Member of the CD28 family This receptor, along with its two ligands, comprises a checkpoint that downregulates immune responses Expressed primarily in activated T cells	Positive staining of T follicular helper lymphocytes Angioimmunoblastic T-cell lymphoma Primary cutaneous CD4-positive small/medium T-cell lymphoproliferative disorder Mycosis fungoides, Sézary syndrome Adult T-cell leukemia/lymphoma
Perforin	Cytolytic protein stored in cytoplasmic granules and then released from cytotoxic T cells	Cytotoxic lymphocytes in benign and malignant lymphoid infiltrates
TCR-beta (βF1)	Beta chain of the T-cell receptor	CTCLs with alpha/beta phenotype Positive staining of most reactive T lymphocytes
TCR-gamma	Gamma chain of the T-cell receptor	CTCLs with gamma/delta phenotype Positive staining of only a few reactive T lymphocytes
TdT (terminal deoxyribonucleotidyl transferase)	Expressed in immature, pre-B and pre-T cells	Lymphoblastic lymphoma/leukemia Variably positive in blastic plasmacytoid dendritic cell neoplasm
TIA-1	Granule-associated RNA-binding protein that defines a subset of $CD8^+$ lymphocytes with cytotoxic potential	Cytotoxic lymphocytes in benign and malignant lymphoid infiltrates
Microorganisms		
Herpes simplex virus (HSV)	Glycoproteins present within the viral envelope and core	HSV-1 or -2 infection
Varicella–zoster virus (VZV)	Glycoprotein I of VZV	Varicella or herpes zoster
Epstein–Barr virus (EBV)	EBV membrane protein encoded by *BNLF*	See EBER-1 under lymphoproliferative disorders
Cytomegalovirus (CMV)	Glycoproteins expressed during the immediate–early and early stages of CMV replication within infected cells	CMV infection
Human herpesvirus 8 (HHV-8)	HHV-8 latency-associated nuclear antigen	Kaposi sarcoma, primary effusion lymphoma, Castleman disease
BCG	Anti-Bacillus Calmette–Guérin	Mycobacterial infections
Treponema pallidum	Specific for all *Treponema pallidum* antigens	Syphilis
Bartonella spp.	*Bartonella henselae, Bartonella quintana*	Bacillary angiomatosis, cat scratch disease, verruga peruana
Proliferation markers and markers for mitoses		
Ki-67	Prototypic antigen for cell cycle-related nuclear proteins, expressed by proliferating cells during the active phases of the cell cycle, but not during the resting phase (G0)	Assessment of proliferative activity
MIB-1	Peptides from recombinant fragments of the gene for Ki-67 antigen	

Table 0.13 Most commonly employed immunohistochemical (IHC) stains in dermatopathology. (cont'd) CD, cluster of differentiation; CTCLs, cutaneous T-cell lymphomas; EBV, Epstein–Barr virus; NK, natural killer.

INTRODUCTION TO THE USE OF DERMOSCOPY (DERMATOSCOPY)

In the prior two sections, we reviewed the basic principles of clinical dermatology and then dermatopathology, with particular emphasis on clinicopathologic correlations. We now turn to an increasingly utilized ancillary examination technique known as dermoscopy (dermatoscopy). It is a non-invasive diagnostic technique that allows for the observation of morphologic features that are not visible to the naked eye, thus forming a link between macroscopic clinical dermatology and microscopic dermatopathology. This "sub-macroscopic" observation of colors and structures (Figs 0.34–0.39) enhances clinical assessment by providing new diagnostic criteria for the differentiation of melanoma from other benign and malignant neoplasms, both melanocytic and non-melanocytic[35–37].

The technique of dermoscopy classically involves applying a liquid or gel to the skin surface and then inspecting the lesion using a hand-held, illuminated microscope (also called a dermatoscope), a

Orange	keratin	epidermis
Yellow	keratin – cholesterol	epidermis – dermis
Black	melanin	stratum corneum
Brown	melanin	basal layer
Gray	melanin	papillary dermis
White	fibrosis	dermis
Blue	melanin	papillary and reticular dermis
Red	hemoglobin	papillary dermis
Purple	hemoglobin	reticular dermis

Fig. 0.34 Dermoscopy colors of keratinizing, melanocytic, and vascular tumors.

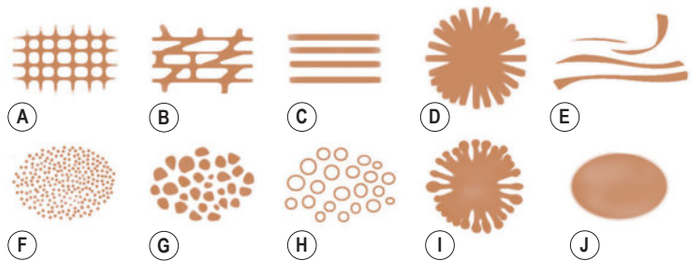


Fig. 0.35 Patterns of dermoscopy. Patterns formed by lines (upper row): **A** Reticular. **B** Branched. **C** Parallel. **D** Radial. **E** Curved lines. Patterns formed by other basic elements (lower row): **F** Pattern of dots. **G** Pattern of clods. **H** Pattern of circles. **I** Pattern of pseudopods. **J** Structureless (absence of discernible basic elements). Combinations of patterns may occur. If multiple patterns are present, they may be arranged symmetrically or asymmetrically.

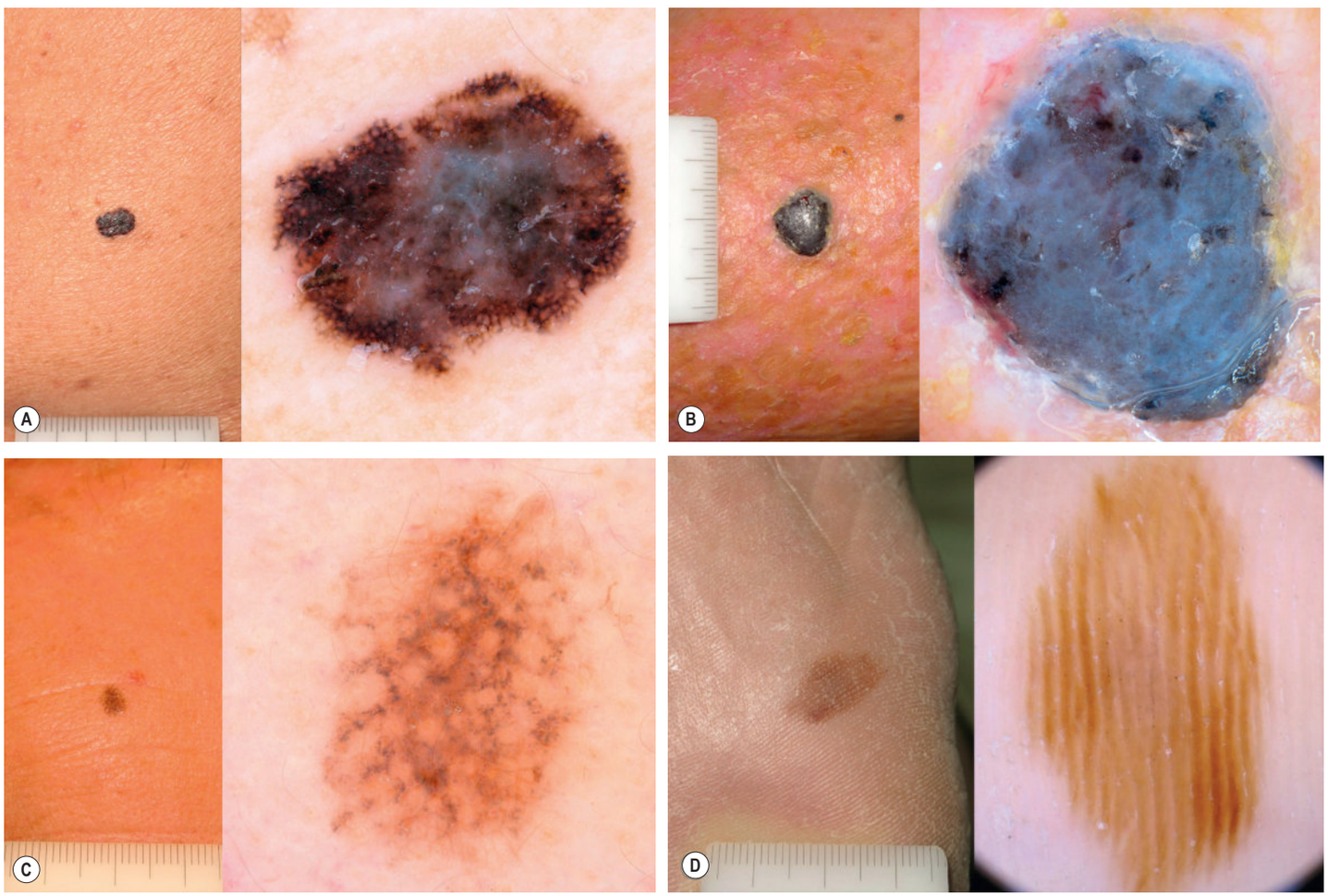


Fig. 0.36 The four most common types of melanoma. A Small superficial melanoma typified dermoscopically by asymmetry of color and structure, atypical network, and blue–white structures. **B** Larger thick melanoma with predominant blue–white veil and a few irregular black globules/areas. The combination of blue and black colors (as seen here) is highly specific for the diagnosis of nodular melanoma. **C** Small facial melanoma *in situ* (lentigo maligna) typified by gray granules around the hair follicles. **D** Acral melanoma *in situ* typified by the characteristic parallel-ridge pattern.

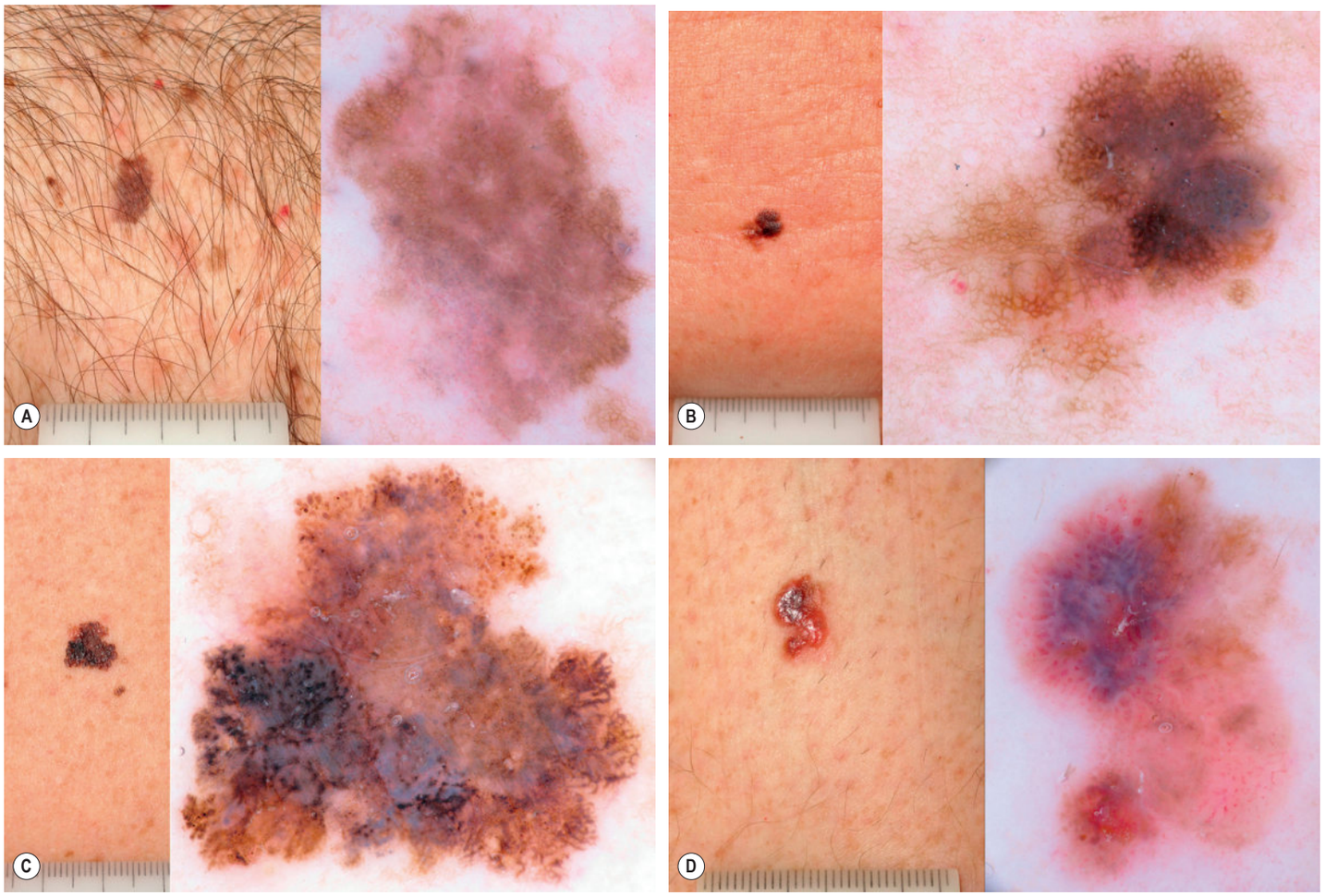


Fig. 0.37 Four examples of superficial melanomas of increasing tumor thickness. A Melanoma *in situ* typified dermoscopically by asymmetry of color and structure, atypical network, and blue–white structures intermingled with dotted vessels. **B** Melanoma 0.5 mm in depth typified predominantly by an atypical pigment network and blue–white structures. **C** Melanoma 0.8 mm in depth typified by multiple melanoma-specific criteria including asymmetry of color and structure, irregular dots and globules, blue–white structures, and peripheral irregular streaks. **D** Melanoma 1.3 mm in depth typified predominantly by blue–white veil and atypical vascular pattern, both signs of increased tumor thickness. Remnants of an atypical pigment network and irregular brown globules are also observed.

stereomicroscope, a camera, or a digital imaging system. The magnification of these instruments ranges from 6× to 40× and even up to 100×.

The widely used dermatoscope has a 10-fold magnification, sufficient for routine assessment of skin tumors. The fluid placed on the lesion eliminates surface reflection and renders the cornified layer translucent, thus allowing a better visualization of pigmented structures within the epidermis, the dermal–epidermal junction, and the superficial dermis. Moreover, the size and shape of vessels within the superficial vascular plexus are better visualized with this procedure (Figs 0.40–0.42)[38]. More recently, hand-held devices have been introduced that utilize polarized light which renders the epidermis translucent. With these latter devices, use of a liquid medium is no longer required in order to visualize sub-surface structures.

Nowadays, the dermatoscope is increasingly being used by dermatologists as a stethoscope equivalent. This is because it not only facilitates the diagnosis of pigmented and non-pigmented skin tumors, but it also improves recognition of a growing number of non-pigmented skin conditions. For example, dermoscopy can facilitate the diagnosis of scabies due to the presence of the pathognomonic "jet with contrail" sign[39] (Fig. 0.43A). Additional skin infections and infestations that may be differentiated with increased confidence include pediculosis, phthiriasis, tungiasis, tinea nigra, and molluscum contagiosum (see Fig. 0.42D). For two of the more common inflammatory skin disorders – psoriasis and lichen planus – the use of dermoscopy allows for the visualization of specific sub-macroscopic features, including the "red dots" pattern in psoriasis and the "whitish striae" pattern in lichen planus (Fig. 0.43B,C). Scalp psoriasis and seborrheic dermatitis may also be differentiated via dermoscopy. The most notable scalp psoriasis features are red dots and globules, twisted red loops, and glomerular vessels, whereas seborrheic dermatitis is characterized by the presence of arborizing vessels and atypical red vessels, as well as featureless areas with no particular vascular pattern and no red dots or globules. In a recent review of the indications for dermoscopy, more than 35 different inflammatory and infectious skin diseases were listed[40]. One of the newest applications of this technique is trichoscopy, namely the dermoscopic observation of the scalp, which may prove helpful in the differential diagnosis of hair and scalp diseases[41] (Fig. 0.43D; see Fig. 69.7).

With regard to melanoma screening, the aim of dermoscopy is to maximize early detection while minimizing the unnecessary excision of benign skin tumors. Over the past several years, three meta-analyses and two randomized studies have proven definitively that dermoscopy improves the sensitivity for melanoma detection as compared to just the naked eye[42–46]. In a meta-analysis of dermoscopic studies performed in a clinical setting, the relative odds ratio for dermoscopic diagnosis of cutaneous melanoma (compared to naked eye examination) was 15.6 (p=0.016). The average sensitivities for melanoma detection by naked eye versus dermoscopic examinations were 74% and 90%, respectively. Furthermore, this improved sensitivity came about without a decrease in specificity, suggesting that better melanoma detection (16% improvement) occurred without increasing the number of unnecessary excisions of benign lesions[46]. A randomized study found

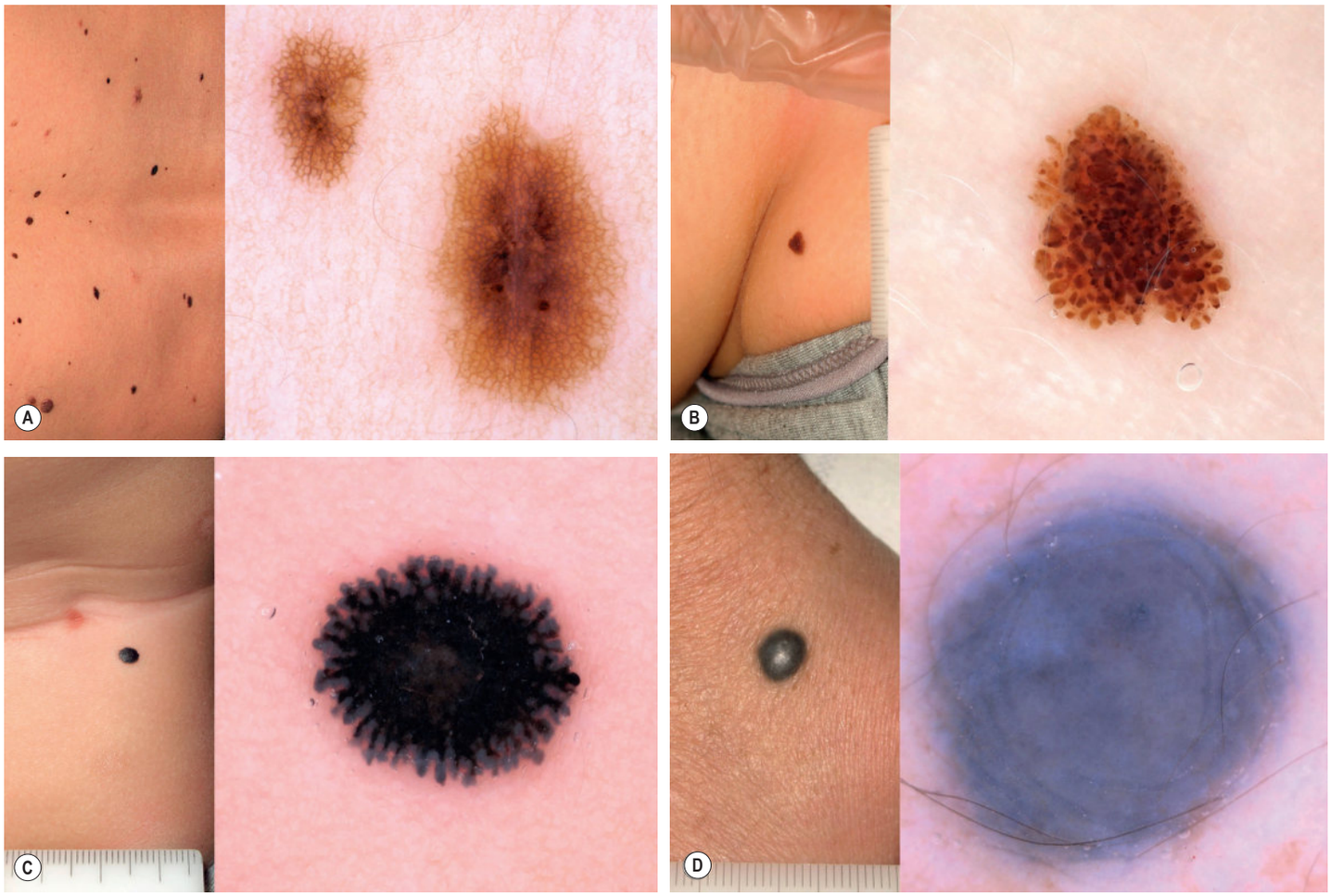


Fig. 0.38 The four most common types of melanocytic nevi – clinical and dermoscopic findings. A Two typical acquired nevi with a reticular pattern by dermoscopy. **B** Small congenital nevus with a globular pattern. **C** Reed nevus (pigmented spindle cell nevus) typified dermoscopically by the classic starburst pattern (regular streaks at the periphery of a heavily pigmented and symmetric small macule). **D** Classic homogenous blue color typically found in blue nevi.

that combining eye and dermoscopic examinations led to a significant reduction in the percentage of patients referred for biopsy (9% vs 15.6%; p=0.013)[44]. In summary, the use of dermoscopy is associated with a significant increase in the number of excised melanomas, as well as a significant reduction in the number of excised benign pigmented skin lesions[47,48].

Pattern analysis is the most well-known and reliable method for differentiating pigmented skin tumors. This is based on a two-step algorithm, where first there is recognition of basic criteria for melanocytic and non-melanocytic tumors (first step; Table 0.14) and then benign and malignant features of melanocytic nevi and melanoma, respectively (second step; Tables 0.15 & 0.16)[35]. Recent attempts to simplify the dermoscopic approach to diagnosing melanocytic nevi and melanoma include the ABCD rule, the Menzies method, and the 7-point checklist[35] (Tables 0.17–0.19).

In a virtual "Consensus Net Meeting on Dermoscopy"[35], 40 experts were able to correctly classify more than 95% of melanocytic lesions and more than 90% of non-melanocytic lesions, with pattern analysis producing the best diagnostic performance. The alternative algorithms (ABCD rule, Menzies method, and 7-point checklist) revealed similar sensitivities as compared to pattern analysis but ~10% less specificity. The favorable results of pattern analysis were not unexpected, as this method probably best reflects the workings of the human brain when categorizing morphologic images and is similar to the pattern analysis utilized in general clinical dermatology and dermatopathology (see above). That is, there is a subjective perception of the "gestalt" of a given lesion and its integration into an internalized knowledge base, which is the result of expertise on the subject; in contrast, "simplified" algorithms were designed to keep non-experts from failing to detect melanomas, even at the cost of decreased specificity.

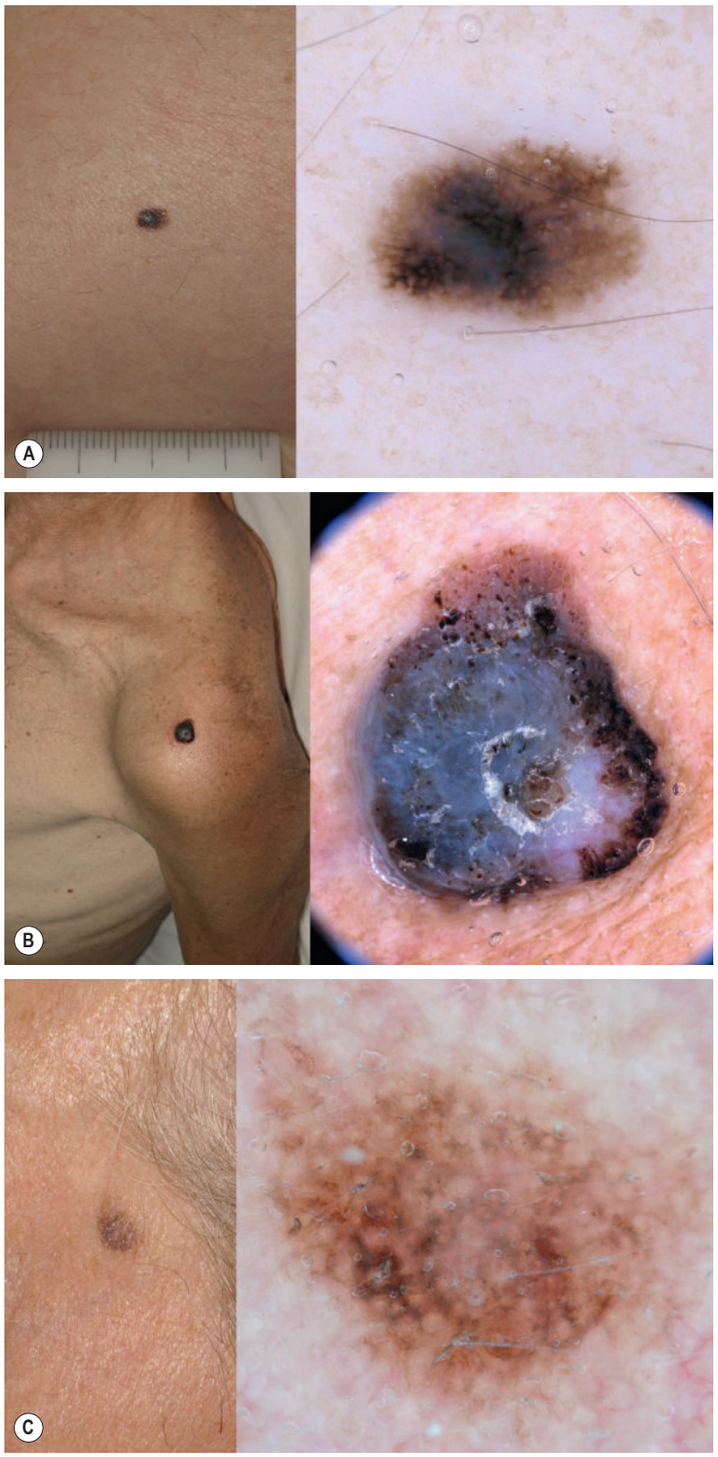
Results of the virtual consensus study showed that three criteria (asymmetry, atypical network, and blue–white structures) were especially important in distinguishing malignant from benign pigmented skin tumors (Table 0.20). Using this 3-point dermoscopy rule as a screening test, general physicians previously inexperienced in the use of dermoscopy were able to perform a better triage of skin lesions suggestive of skin cancer as compared to examination with the naked eye (referral sensitivity of 79% and 54%, respectively), without increasing the number of unnecessary expert consultations[45].

While the continued, skilled use of dermoscopy will undoubtedly aid in the early recognition of melanoma as well as the diagnosis of inflammatory disorders and other cutaneous neoplasms, there are additional technologies that may also have a significant impact on our specialty over the next decade, including confocal microscopy (see Ch. 113)[49].

CONCLUSION

In conclusion, this chapter has sought to provide an introduction and basic structural framework to the study of dermatology by addressing terminology, morphology, pattern recognition, and a number of techniques that will all serve to enhance the practice of clinicopathologic correlation. The desired end results are more accurate diagnoses and better care of patients.

For table on acute cutaneous eruptions in otherwise healthy individuals plus additional online figures visit www.expertconsult.com



eFig. 0.1 The three most common types of melanoma. A Small superficial melanoma typified dermoscopically by asymmetry of color and structure, atypical network, blue–white structures, and irregular streaks at the periphery. **B** Large thick melanoma with predominant blue–white veil. The combination of blue color with irregular black to brown dots, globules, and blotches (as seen here) is highly specific for the diagnosis of thick melanoma. **C** Small facial melanoma *in situ* (lentigo maligna) typified by gray color and rhomboidal structures in dermoscopy.

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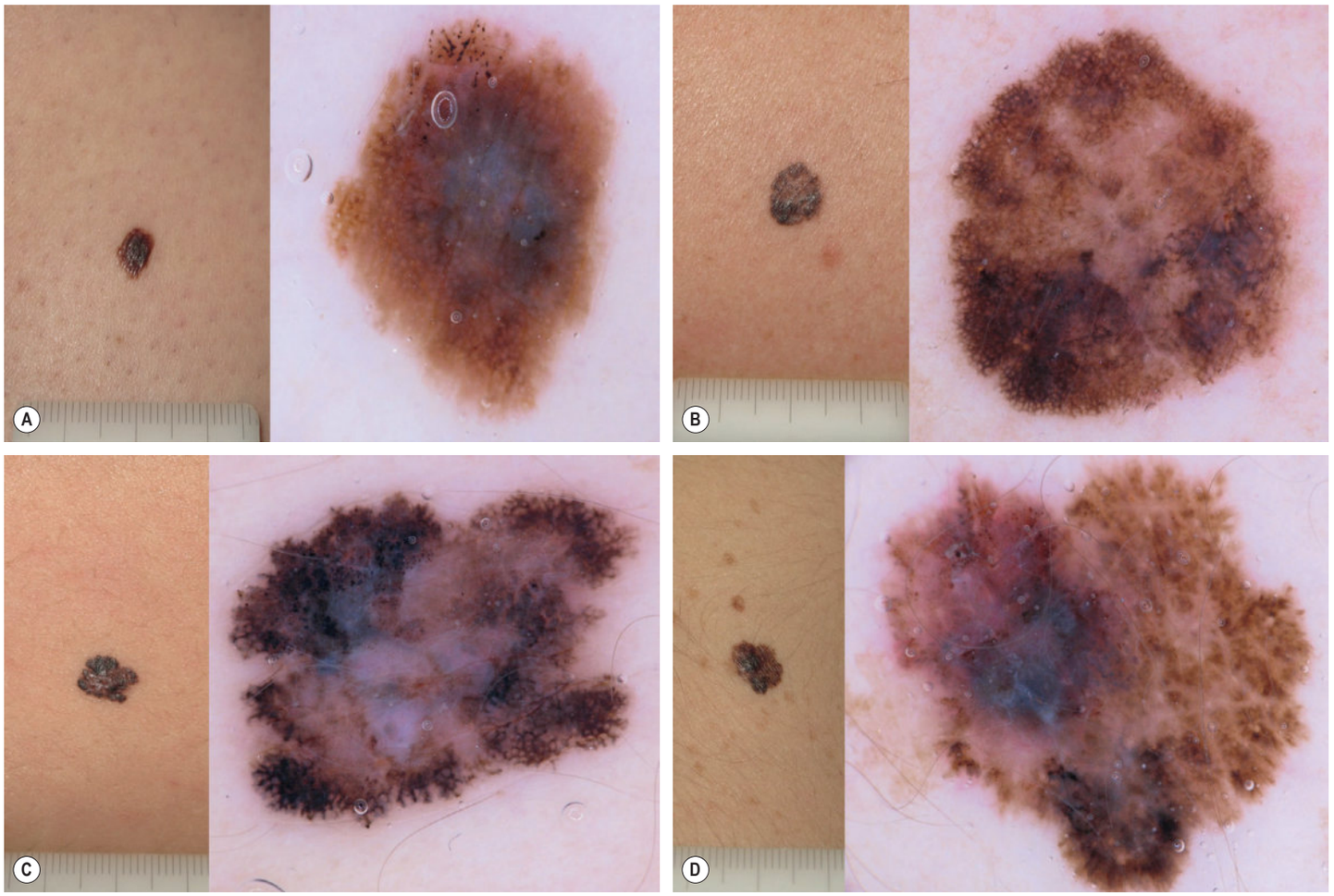
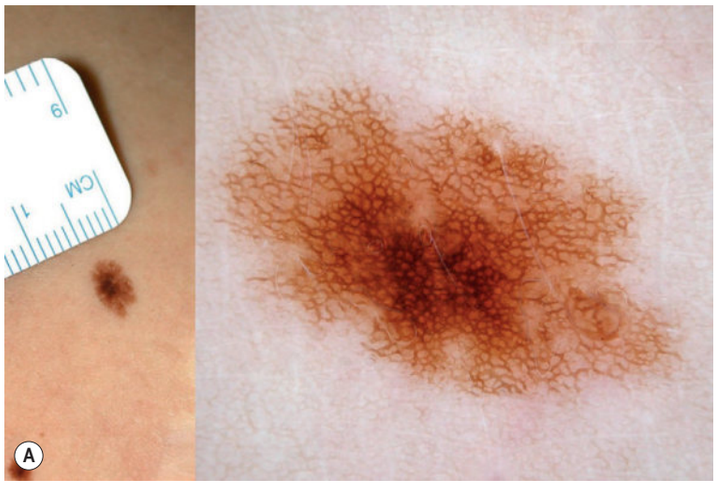
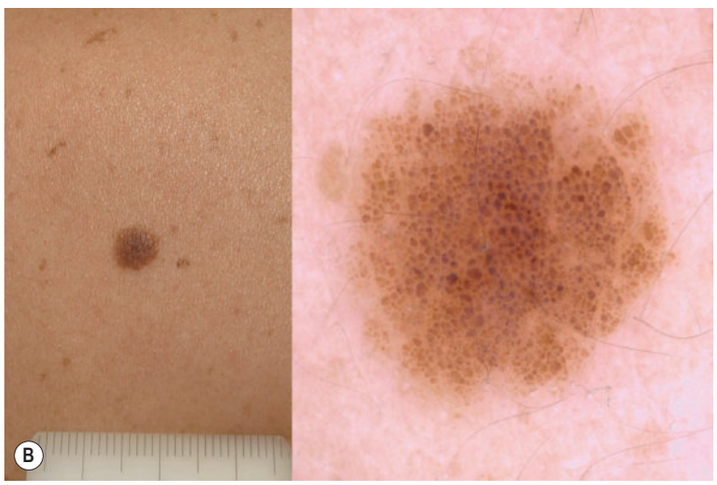
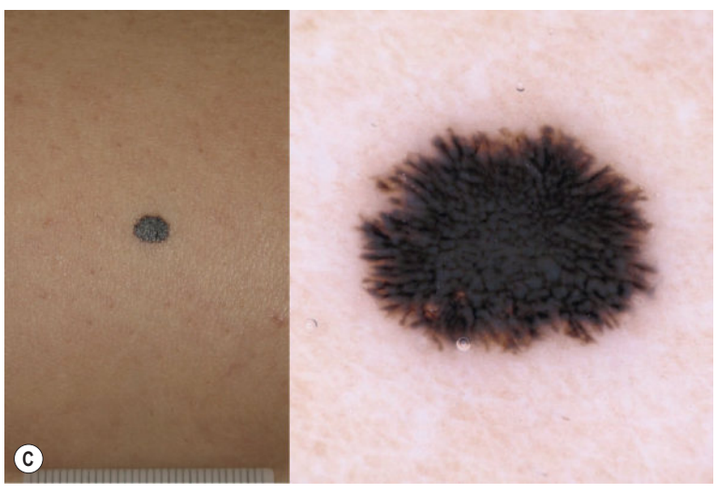


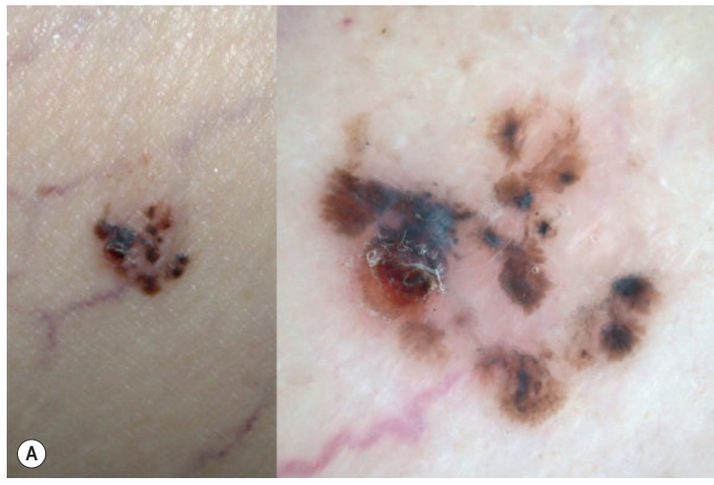
eFig. 0.2 Four examples of superficial melanomas of increasing tumor thickness. A Melanoma *in situ* typified dermoscopically by asymmetry of color and structure, atypical network, blue–white structures, and irregular black dots and globules (at the upper side of the lesion). **B** Melanoma 0.5 mm thick typified predominantly by atypical pigment network and regression structures. The latter are composed by areas of pigment loss (in the center of the lesion) and bluish pepper-like granules corresponding to melanophages. **C** Melanoma 0.75 mm thick typified by multiple melanoma-specific criteria including asymmetry of color and structure, atypical network, irregular streaks at the periphery, irregular dots and globules (upper side of the lesion), and blue–white structures especially in the center. **D** Melanoma 0.9 mm thick. Clinically, a palpable area is visible, corresponding dermoscopically to the presence of blue–white veil, a sign of increased tumor thickness. Irregular dots and globules (at the upper side), irregular streaks at the periphery, and uneven brown to black pigmented areas (blotches) are also observed.

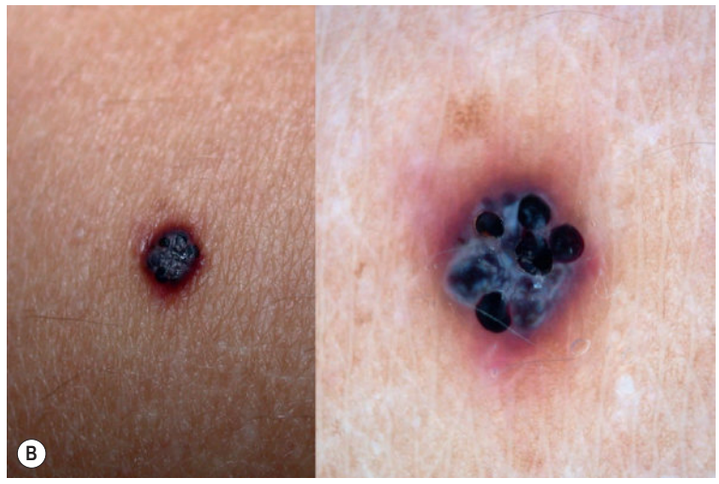


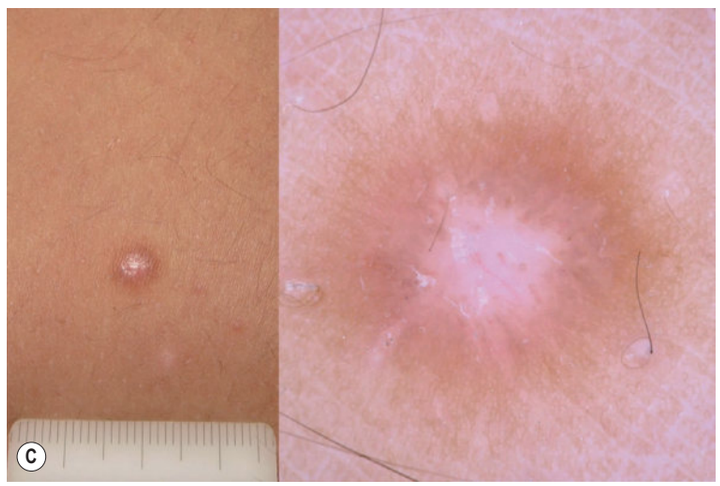




eFig. 0.3 The three most common types of melanocytic nevi – clinical and dermoscopic findings. A Typical acquired nevus with reticular pattern in dermoscopy. **B** Small congenital nevus with globular pattern. **C** Reed nevus typified dermoscopically by the classic starburst pattern (regular streaks at the periphery of a heavily pigmented and symmetric small macule).







eFig. 0.4 Three non-melanocytic pigmented tumors – clinical and dermoscopic findings. A Pigmented basal cell carcinoma with leaf-like areas (islands of blue–gray color) at the periphery and a small erosion of reddish color at the left side of the lesion. **B** Angiokeratoma with red–black lacunas clearly visible as well-demarcated roundish structures. **C** A dermatofibroma with characteristic central white patch and peripheral delicate pseudo-network.

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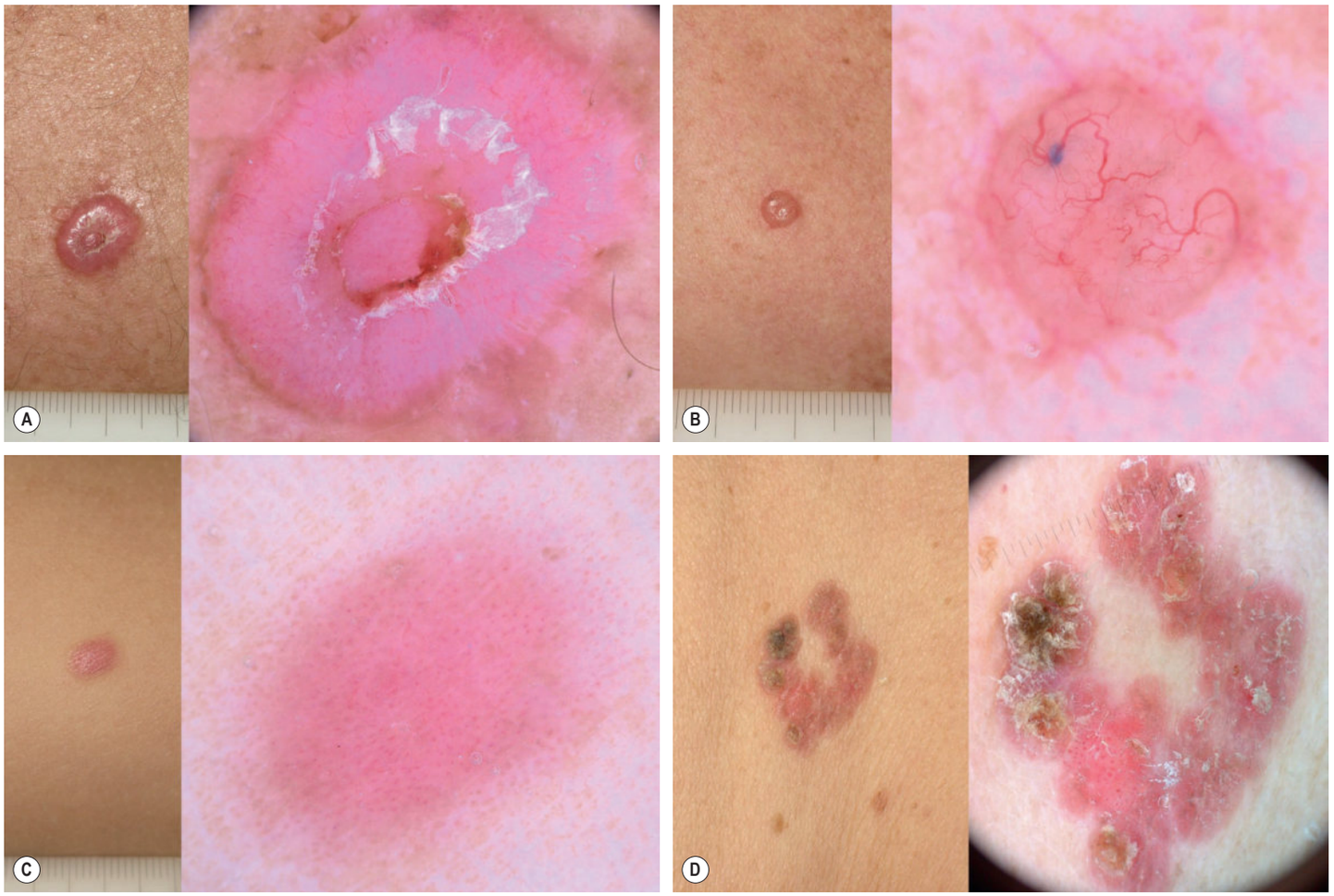

eFig. 0.5 Four non-pigmented skin tumors – clinical and dermoscopic findings. A This amelanotic melanoma is typified by a central ulceration, polymorphic vascular structures (combination of dotted and linear-irregular vessels), and milky-red color in the background. **B** Nodular basal cell carcinoma with striking arborizing vessels. **C** A Spitz nevus with dotted vessels and typical negative pigment network (reticular depigmentation) at the periphery. **D** An example of Bowen disease with clusters of glomerular vessels that in combination with superficial scales are highly specific for the diagnosis.

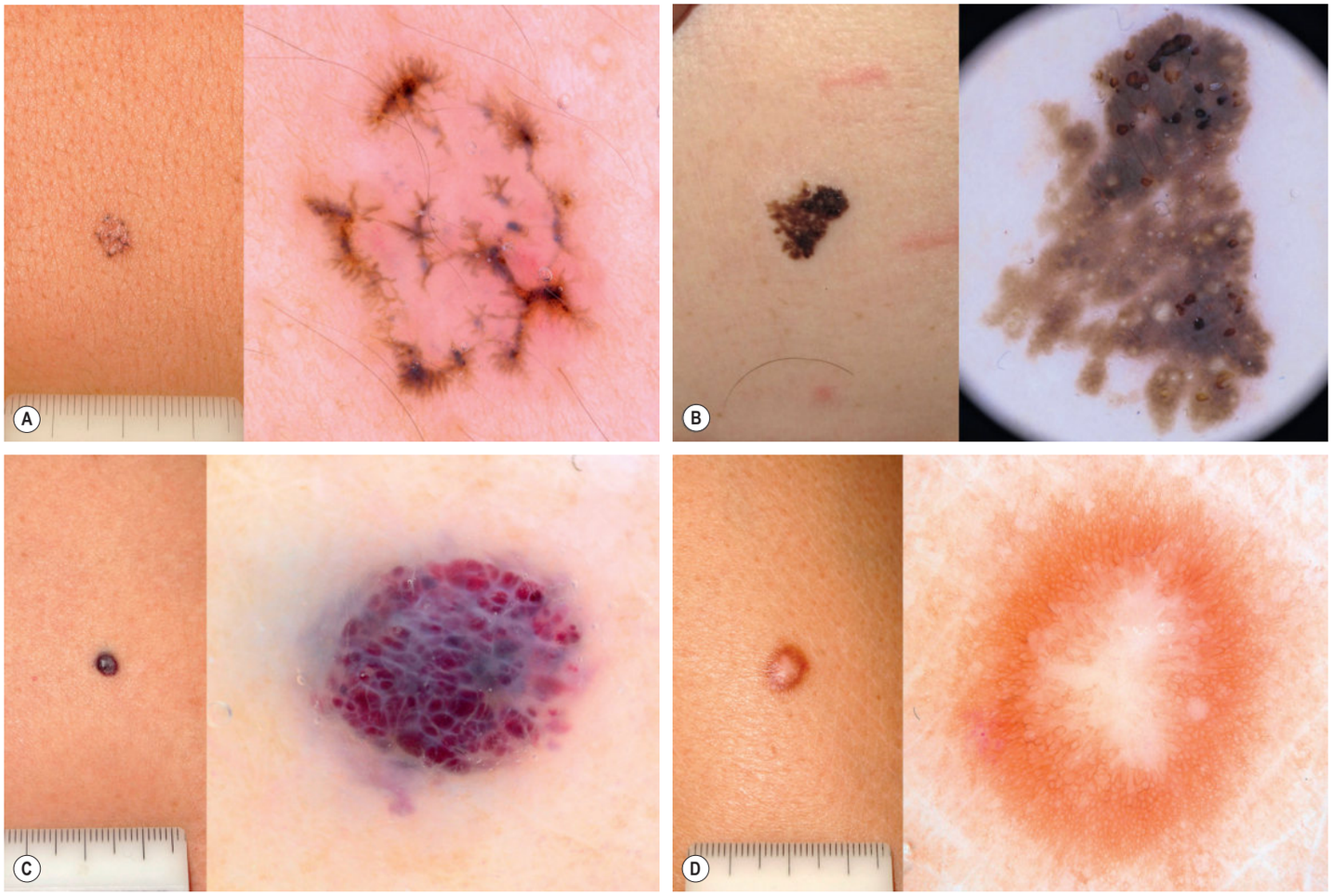

Fig. 0.39 Four non-melanocytic pigmented tumors – clinical and dermoscopic findings. A Pigmented basal cell carcinoma with typical leaf-like areas (islands of brown–gray color) and blue-gray globules. **B** Seborrheic keratosis with typical milia-like cysts (white shining dots/globules) and comedo-like openings (black targetoid globules). **C** Angiokeratoma with red–blue lacunas clearly visible as well-demarcated roundish structures. **D** A dermatofibroma with characteristic central white patch and peripheral delicate network.

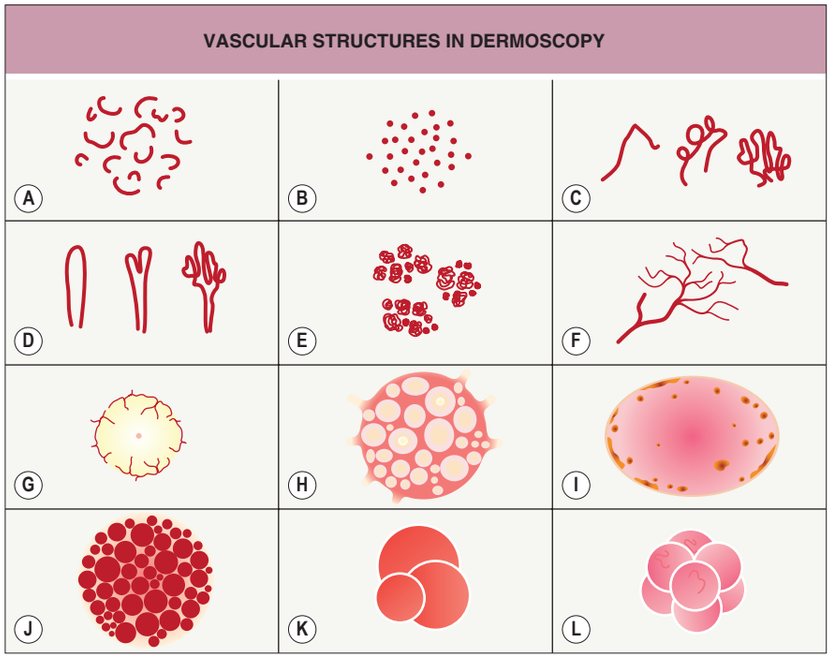

Fig. 0.40 Vascular structures in dermoscopy. (See also Table 0.16 for definitions and diagnostic significance). **A** Comma vessels – typical of dermal and congenital nevi. **B** Dotted vessels – often found in melanoma and Spitz nevi. **C** Linear-irregular vessels – typical of melanoma. **D** Hairpin vessels – most common in keratinizing tumors, such as seborrheic keratosis and squamous cell carcinoma. **E** Glomerular vessels – found in Bowen disease. **F** Arborizing vessels – typical of basal cell carcinoma. **G** Crown vessels – common finding in sebaceous hyperplasia. **H** Strawberry pattern – typical of facial actinic keratosis. **I** Multiple blood crusts over a red background – typical finding in superficial basal cell carcinoma. **J** Red lacunas – typical finding in hemangiomas. **K** Red homogenous areas intersected by whitish lines – most common in pyogenic granuloma. **L** Milky-red areas – typical of melanoma.

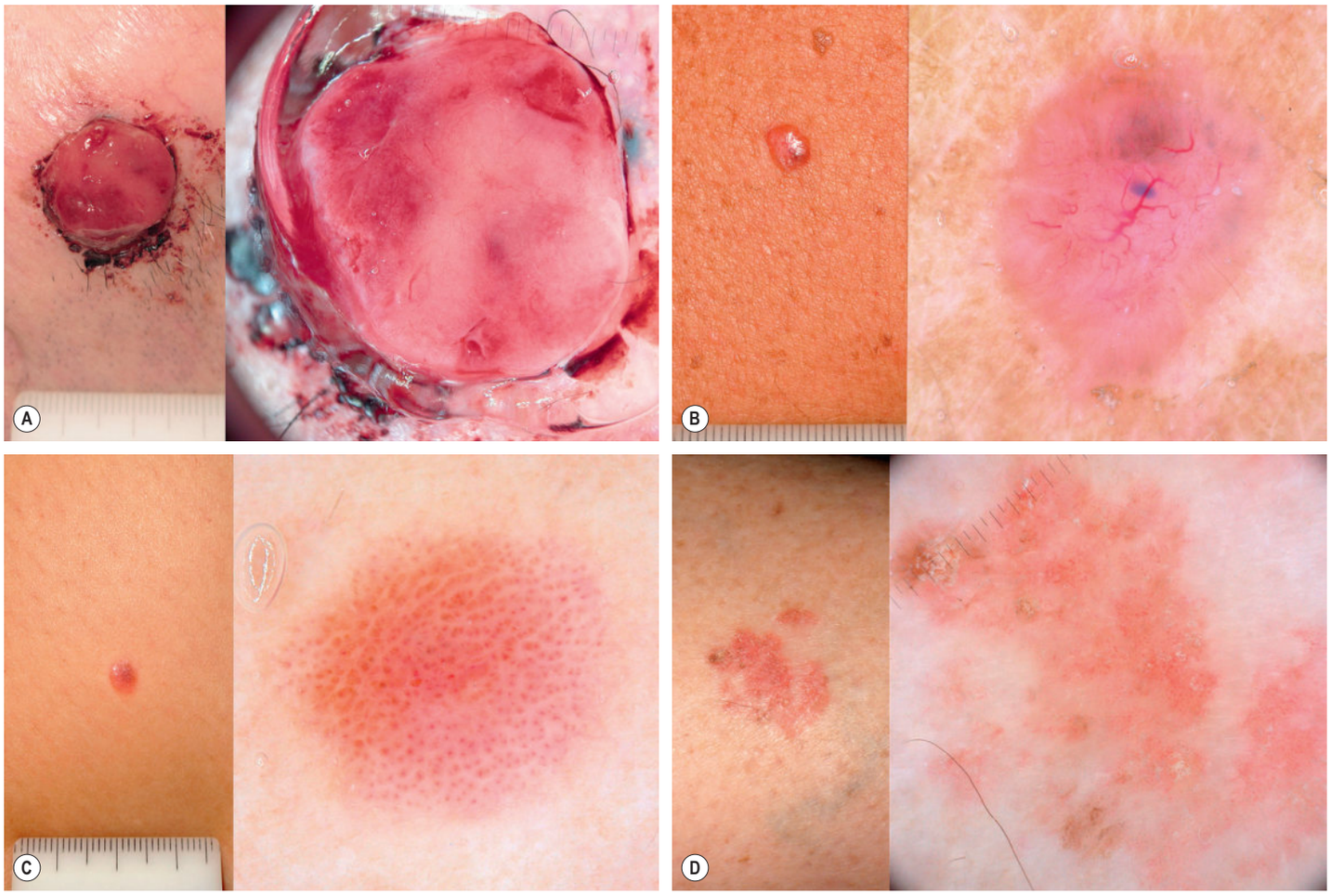

Fig. 0.41 Four non-pigmented skin tumors – clinical and dermoscopic findings. A An amelanotic melanoma typified by polymorphic vascular structures and a milky-red color in the background. **B** Nodular basal cell carcinoma with obvious arborizing vessels and blue-gray globules. **C** Spitz nevus with dotted vessels and typical reticular depigmentation. **D** An example of Bowen disease with clusters of dotted/glomerular vessels; these findings in combination with superficial scales are highly specific for the diagnosis.

PATTERN ANALYSIS: FIRST-STEP ALGORITHM FOR DIFFERENTIATION BETWEEN MELANOCYTIC AND NON-MELANOCYTIC LESIONS		
Dermoscopic criterion	**Definition**	**Diagnostic significance**
Pigment network – pseudo-network†	Network of brownish interconnected lines over a background of tan diffuse pigmentation. In facial skin, a peculiar pigment network, also called a pseudo-network, is typified by round, equally sized network holes corresponding to the pre-existing follicular ostia	Melanocytic lesion
Aggregated globules	Numerous, variously sized, more or less clustered, round to oval structures with various shades of brown and gray–black. They should be differentiated from multiple blue–gray globules	Melanocytic lesion
Streaks	These have been previously described separately as pseudopods and radial streaming, but are now combined into the one term. They are bulbous and often kinked or finger-like projections seen at the edge of a lesion. They may arise from network structures but more commonly do not. They range in color from tan to black	Melanocytic lesion
Homogeneous blue pigmentation‡	Structureless blue pigmentation in the absence of pigment network or other distinctive local features	Melanocytic lesion
Parallel pattern	Seen in melanocytic lesions of palms/soles and mucosal areas. On palms/soles, the pigmentation may follow the sulci or the cristae (i.e. furrows or ridges) of the dermatoglyphics. Rarely arranged at right angles to these structures	Melanocytic lesion
Multiple milia-like cysts	Numerous, variously sized, white or yellowish, roundish structures	Seborrheic keratosis
Comedo-like openings	Brown–yellowish to brown–black, round to oval, sharply circumscribed keratotic plugs in the ostia of hair follicles. When irregularly shaped, comedo-like openings are also called irregular crypts	Seborrheic keratosis

Table 0.14 Pattern analysis: first-step algorithm for differentiation between melanocytic and non-melanocytic lesions. *Adapted from Argenziano G, Soyer HP, Chimenti S, et al. Dermoscopy of pigmented skin lesions: results of a consensus meeting via the Internet. J Am Acad Dermatol. 2003;48:679–93.*

Continued

PATTERN ANALYSIS: FIRST-STEP ALGORITHM FOR DIFFERENTIATION BETWEEN MELANOCYTIC AND NON-MELANOCYTIC LESIONS		
Dermoscopic criterion	**Definition**	**Diagnostic significance**
Light-brown fingerprint-like structures	Light-brown, delicate, network-like structures with the pattern of a fingerprint	Seborrheic keratosis
Cerebriform pattern	Dark-brown furrows between ridges typifying a brain-like appearance	Seborrheic keratosis
Arborizing vessels	Tree-like branching telangiectasias	Basal cell carcinoma*
Leaf-like structures	Brown to gray/blue discrete bulbous structures forming leaf-like patterns. They are discrete pigmented nests (islands) never arising from a pigment network and usually not arising from adjacent confluent pigmented areas	Basal cell carcinoma*
Large blue–gray ovoid nests	Well-circumscribed, confluent or near confluent, pigmented, ovoid or elongated areas that are larger than globules and not intimately connected to a pigmented tumor body	Basal cell carcinoma*
Multiple blue–gray globules	Multiple globules (not dots) that should be differentiated from multiple blue–gray dots (melanophages)	Basal cell carcinoma*
Spoke-wheel areas	Well-circumscribed radial projections, usually tan in color but sometimes blue or gray, meeting at an often darker (dark brown, black or blue) central axis	Basal cell carcinoma*
Ulceration§	Absence of the epidermis, often associated with congealed blood, not due to a well-described recent history of trauma	Basal cell carcinoma*
Red–blue lacunas	More or less sharply demarcated, roundish or oval areas with a reddish, red–bluish, or dark-red to black coloration	Vascular lesion
Red–bluish to reddish-black homogeneous areas	Structureless homogeneous areas of red–bluish to red–black coloration	Vascular lesion
None of the listed criteria	Absence of the above-mentioned criteria	Melanocytic lesion

†Exception 1: Pigment network or pseudo-network is also present in solar lentigo and rarely in seborrheic keratosis and pigmented actinic keratosis. A delicate, annular pigment network is also commonly seen in dermatofibroma and accessory nipple (clue for diagnosis of dermatofibroma and accessory nipple: central white patch).
‡Exception 2: Homogeneous blue pigmentation (dermoscopic hallmark of blue nevus) is also seen (uncommonly) in some hemangiomas and basal cell carcinomas and (commonly) in intradermal melanoma metastases.
§Exception 3: Ulceration is also seen less commonly in invasive melanoma.
*To diagnose a basal cell carcinoma, the negative feature of pigment network must be absent and one or more of the positive features listed here must be present.

Table 0.14 Pattern analysis: first-step algorithm for differentiation between melanocytic and non-melanocytic lesions. (cont'd)

PATTERN ANALYSIS: SECOND-STEP ALGORITHM FOR DIFFERENTIATION BETWEEN MELANOCYTIC NEVI AND MELANOMA		
Dermoscopic criterion	**Definition**	**Diagnostic significance**
Global features		
Reticular pattern	Pigment network covering most parts of the lesion	Melanocytic nevus
Globular pattern	Numerous, variously sized, round to oval structures with various shades of brown and gray–black	Melanocytic nevus
Cobblestone pattern	Large, closely aggregated, somehow angulated globule-like structures resembling a cobblestone	Intradermal melanocytic nevus
Homogeneous pattern	Diffuse, brown, gray–blue to gray–black pigmentation in the absence of other distinctive local features	Melanocytic (blue) nevus
Starburst pattern	Pigmented streaks in a radial arrangement at the edge of the lesion	Spitz/Reed nevus
Parallel pattern	Pigmentation on palms/soles that follows the sulci or the cristae (furrows or ridges), rarely arranged at right angles to these structures	Acral nevus/melanoma (see below)
Multicomponent pattern	Combination of three or more of the above patterns	Melanoma
Nonspecific pattern	Pigmented lesion lacking above patterns	Possible melanoma
Local features		
Pigment network	Typical pigment network: light- to dark-brown network with small, uniformly spaced network holes and thin network lines distributed more or less regularly throughout the lesion and usually thinning out at the periphery	Benign melanocytic lesion
	Atypical pigment network: black, brown or gray network with irregular holes and thick lines	Melanoma
Dots/globules	Black, brown, round to oval, variously sized structures regularly or irregularly distributed within the lesion	If regular, benign melanocytic lesion If irregular, melanoma

Table 0.15 Pattern analysis: second-step algorithm for differentiation between melanocytic nevi and melanoma. *Adapted from Argenziano G, Soyer HP, Chimenti S, et al. Dermoscopy of pigmented skin lesions: results of a consensus meeting via the Internet. J Am Acad Dermatol. 2003;48:679–93.*

PATTERN ANALYSIS: SECOND-STEP ALGORITHM FOR DIFFERENTIATION BETWEEN MELANOCYTIC NEVI AND MELANOMA		
Dermoscopic criterion	**Definition**	**Diagnostic significance**
Local features		
Streaks	These have been previously described separately as pseudopods and radial streaming. Streaks are bulbous and often kinked or finger-like projections seen at the edge of a lesion. They may arise from network structures but more commonly do not. They range in color from tan to black	If regular, benign melanocytic lesion (Spitz/Reed nevus) If irregular, melanoma
Blue–whitish veil	Irregular, structureless area of confluent blue pigmentation with an overlying white "ground-glass" film. The pigmentation cannot occupy the entire lesion and usually corresponds to a clinically elevated part of the lesion	Melanoma
Regression structures	White scar-like depigmentation and/or blue pepper-like granules usually corresponding to a clinically flat part of the lesion	Melanoma
Hypopigmentation	Areas with less pigmentation than the overall pigmentation of the lesion	Nonspecific
Blotches	Black, brown, and/or gray structureless areas with symmetrical or asymmetrical distribution within the lesion	If symmetrical, benign melanocytic lesion If asymmetrical, melanoma
Site-related features		
Face	Typical pseudo-network (round, equally sized network holes corresponding to the pre-existing follicular ostia)	Benign melanocytic lesion
	Annular-granular structures (multiple blue–gray dots surrounding the follicular ostia with an annular-granular appearance)	Melanoma
	Gray pseudo-network (gray pigmentation surrounding the follicular ostia, formed by the confluence of annular-granular structures)	Melanoma
	Rhomboidal structures (gray–brown pigmentation surrounding the follicular ostia with a rhomboidal appearance)	Melanoma
	Asymmetric pigmented follicles (eccentric annular pigmentation around follicular ostia)	Melanoma
Palms/soles	Parallel-furrow pattern (pigmentation following the sulci superficiales)	Acral nevus
	Lattice-like pattern (pigmentation following and crossing the furrows)	Acral nevus
	Fibrillar pattern (numerous, finely pigmented filaments perpendicular to the furrows and ridges)	Acral nevus
	Parallel-ridge pattern (pigmentation aligned along the cristae superficiales)	Melanoma

Table 0.15 Pattern analysis: second-step algorithm for differentiation between melanocytic nevi and melanoma. (cont'd)

VASCULAR STRUCTURES SEEN IN VARIOUS SKIN TUMORS		
Pattern	**Definition**	**Diagnostic significance**
Comma	Coarse vessels that are slightly curved and barely branching	Congenital and intradermal melanocytic nevi
Dotted	Tiny red dots densely aligned next to each other	Melanocytic lesion (often Spitz nevus and melanoma)
Linear-irregular	Linear, irregularly shaped, sized and distributed red structures	Melanoma
Hairpin	Vascular loops sometimes twisted and bending. They can be surrounded by a whitish halo	With white halo: keratinizing proliferation (seborrheic keratosis, squamous cell carcinoma, keratoacanthoma, verruca) Without white halo: melanoma
Glomerular	Variation on the theme of dotted vessels. They are tortuous capillaries often distributed in clusters mimicking the glomerular apparatus of the kidney	Bowen disease
Arborizing	Stem vessels of large diameter branching irregularly into fine terminal capillaries. The color is bright red, being sharply focused in dermoscopic images due to their location immediately beneath the surface of the tumor	Basal cell carcinoma
Crown	Groups of orderly bending, scarcely branching vessels located along the border of the lesion	Sebaceous hyperplasia
Strawberry	Pink-to-red "pseudo-network" around hair follicles of the face, frequently intermingled with fine, linear-wavy vessels. Often hair follicles are filled with yellowish keratotic plugs	Actinic keratosis
Corkscrew	Linear vessels twisted along a central axis	Thick melanoma or melanoma metastasis
Milky-red color	Globules and/or larger areas of fuzzy or unfocused milky-red color often corresponding to an elevated part of the lesion	Melanoma
Polymorphous	Any combination of two or more different types of vascular structures. The most frequent is linear-irregular and dotted vessels	Malignant tumor, including melanoma, basal cell carcinoma, squamous cell carcinoma

Table 0.16 Vascular structures seen in various skin tumors. See also Figs 0.40–0.42.

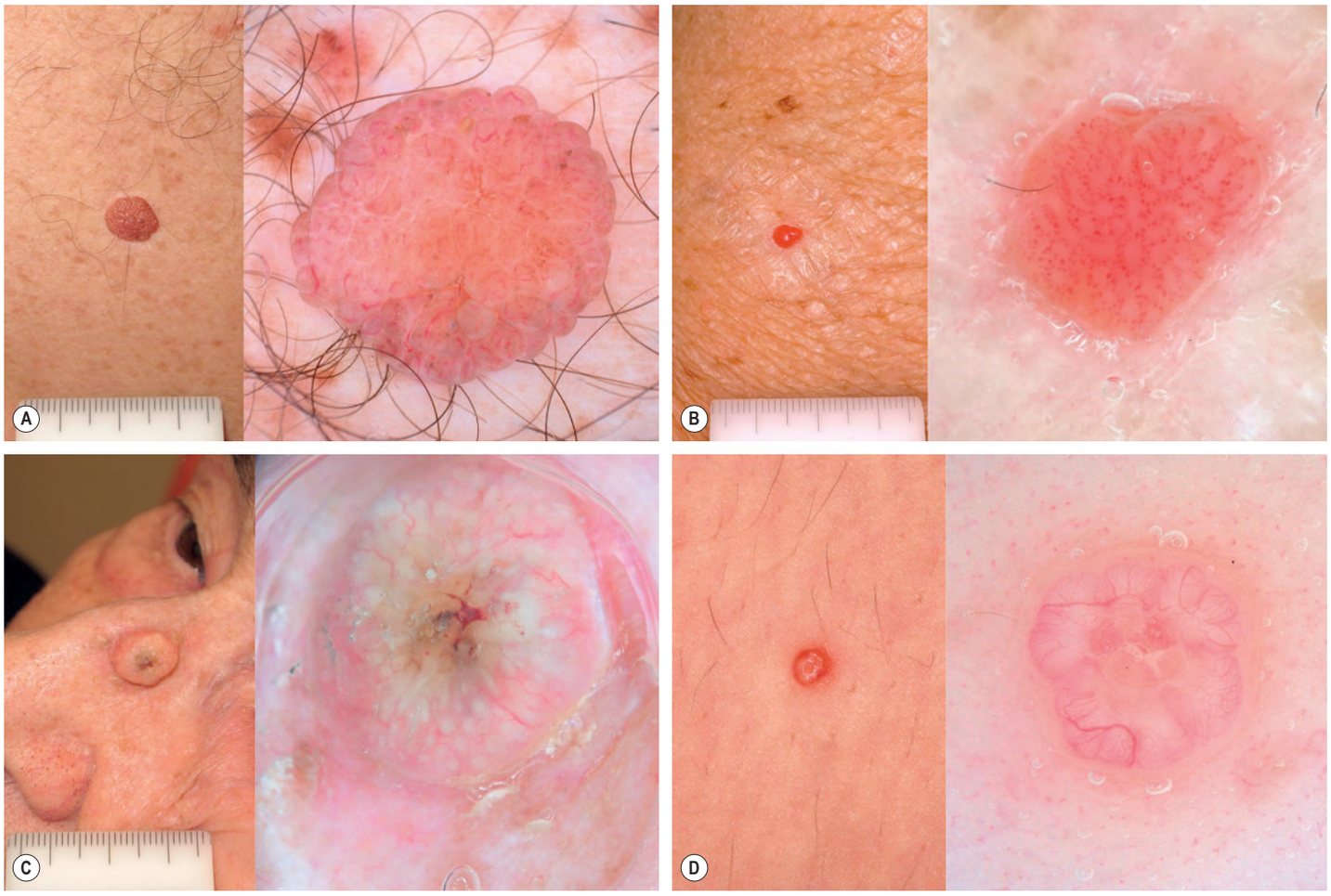

Fig. 0.42 Four non-pigmented skin lesions – clinical and dermoscopic findings. A An intradermal melanocytic nevus with typical comma-shaped vessels. **B** Clear cell acanthoma with dotted vessels linearly arranged as strings of pearls. **C** Well-differentiated squamous cell carcinoma with white keratin masses, white circles and clods, and polymorphic vessels. **D** Molluscum contagiosum with peripheral arborizing vessels superimposed on a white background. Amorphous yellow clods are typically seen in the center.

ABCD RULE FOR THE DERMOSCOPIC DIFFERENTIATION BETWEEN BENIGN MELANOCYTIC LESIONS AND MELANOMA			
Dermoscopic criterion	**Definition**	**Score**	**Weight factor**
Asymmetry	In 0, 1, or 2 perpendicular axes; assess not only contour, but also colors and structures	0–2	×1.3
Border	Abrupt ending of pigment pattern at the periphery in 0–8 segments	0–8	×0.1
Color	Presence of up to six colors (white, red, light brown, dark brown, blue–gray, black)	1–6	×0.5
Dermoscopic structures	Presence of network, structureless (homogeneous) areas, branched streaks, dots, and globules	1–5	×0.5

Table 0.17 ABCD rule for the dermoscopic differentiation between benign melanocytic lesions and melanoma. Formula for calculating total score: (A score×1.3) + (B score×0.1) + (C score×0.5) + (D score×0.5). Interpretation of total score: <4.75, benign melanocytic lesion; 4.75–5.45, suspicious lesion (close follow-up or excision recommended); >5.45, lesion highly suspicious for melanoma. *Adapted from Argenziano G, Soyer HP, Chimenti S, et al. Dermoscopy of pigmented skin lesions: results of a consensus meeting via the Internet. J Am Acad Dermatol. 2003;48:679–93.*

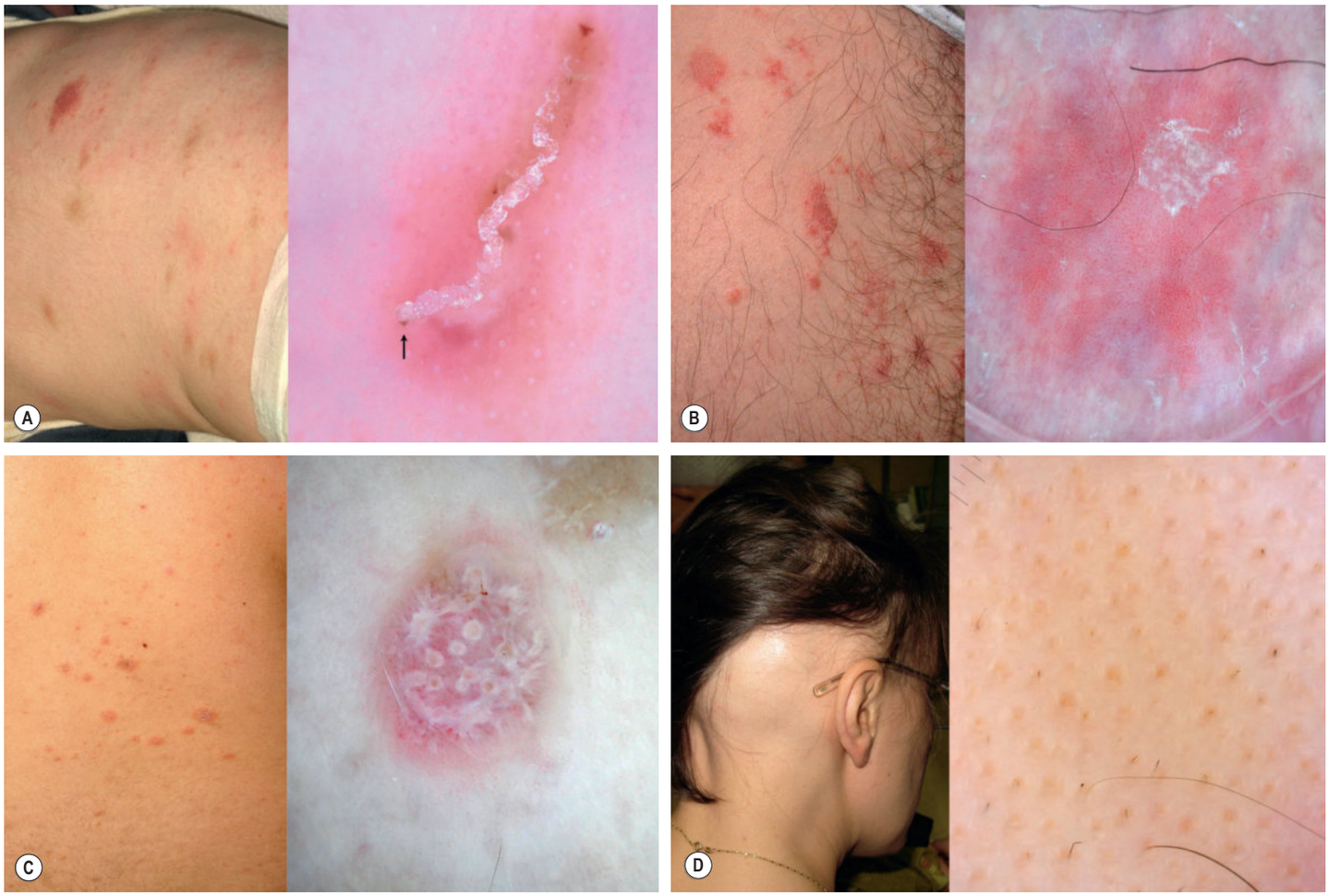

Fig. 0.43 Four non-neoplastic skin disorders – clinical and dermoscopic findings. A A 6-month-old boy with scabies. By dermoscopy, a characteristic "jet with contrail" structure can be identified corresponding to the anterior part of the mite (arrow) and the burrow behind it. **B** By dermoscopy, classic psoriasis plaques exhibit regular dotted vessels. **C** The dermoscopic pattern of lichen planus is definitely different from that of psoriasis. In the former, dotted vessels are seen at the border of typical whitish lines and clods, which closely resemble the Wickham striae found in lichen planus of the oral mucosa. **D** Typical follicular yellow dots seen dermoscopically in patches of alopecia on the scalp in alopecia areata.

MENZIES SCORING METHOD FOR THE DERMOSCOPIC DIFFERENTIATION BETWEEN BENIGN MELANOCYTIC LESIONS AND MELANOMA	
Dermoscopic criterion	**Definition**
Negative features	
Symmetry of pattern	Symmetry of pattern is required across all axes through the lesion's center of gravity (center of the lesion). Symmetry of pattern does not require shape symmetry
Presence of a single color	The colors scored are black, gray, blue, dark brown, tan and red. White is not scored as a color
Positive features	
Blue–white veil	An area of irregular, structureless confluent blue pigmentation with an overlying white "ground-glass" haze. It cannot occupy the entire lesion and cannot be associated with red–blue lacunas
Multiple brown dots	Focal areas of multiple brown (usually dark brown) dots (not globules)
Pseudopods	Bulbous and often kinked projections that are found at the edge of a lesion, connected either directly to the tumor body or to the pigmented network. They can never be seen distributed regularly or symmetrically around the lesion. When connected directly to the tumor body, they must have an acute angle to the tumor edge or arise from linear or curvilinear extensions. When connected to the network, the width of the bulbous ending must be greater than the width of any part of the surrounding network and at least double that of its directly connected network projection
Radial streaming	Finger-like extensions at the edge of a lesion which are never distributed regularly or symmetrically around the lesion
Scar-like depigmentation	Areas of white distinct irregular extensions (true scarring), which should not be confused with hypo- or depigmentation due to simple loss of melanin
Peripheral black dots/ globules	Black dots/globules found at or near the edge of the lesion
Multiple (5–6) colors	The colors scored are black, gray, blue, dark brown, tan and red. White is not scored as a color
Multiple blue/gray dots	Foci of multiple blue or gray dots (not globules) often described as "pepper-like" granules in pattern
Broadened network	A network made up of irregular thicker "cords" of the net, often seen focally thicker

Table 0.18 Menzies scoring method for the dermoscopic differentiation between benign melanocytic lesions and melanoma. For melanoma to be diagnosed, a lesion must have neither of both negative features and one or more of the nine positive features. *Adapted from Argenziano G, Soyer HP, Chimenti S, et al. Dermoscopy of pigmented skin lesions: results of a consensus meeting via the Internet. J Am Acad Dermatol. 2003;48:679–93.*

SEVEN-POINT CHECKLIST FOR THE DERMOSCOPIC DIFFERENTIATION BETWEEN BENIGN MELANOCYTIC LESIONS AND MELANOMA		
Dermoscopic criterion	**Definition**	**Score**
1. Atypical pigment network	More than one type of network (in terms of color and thickness of the meshes) irregularly distributed within the lesion	2
2. Blue–whitish veil	Irregular, structureless area of confluent blue pigmentation with an overlying white "ground-glass" film. The pigmentation cannot occupy the entire lesion and usually corresponds to a clinically elevated part of the lesion	2
3. Atypical vascular pattern	Linear-irregular or dotted vessels not clearly seen within regression structures	2
4. Irregular streaks	Brown to black, bulbous or finger-like projections irregularly distributed at the edge of a lesion. They may arise from network structures but more commonly do not	1
5. Irregular dots/globules	Black, brown, round to oval, variously sized structures irregularly distributed within the lesion	1
6. Irregular blotches	Black, brown, and/or gray structureless areas asymmetrically distributed within the lesion	1
7. Regression structures	White scar-like depigmentation and/or blue pepper-like granules usually corresponding to a clinically flat part of the lesion	1

Table 0.19 Seven-point checklist for the dermoscopic differentiation between benign melanocytic lesions and melanoma. By simple addition of the individual scores, a minimum total score of 3 is required for the diagnosis of melanoma, whereas a total score of less than 3 is indicative of non-melanoma. *Adapted from Argenziano G, Soyer HP, Chimenti S, et al. Dermoscopy of pigmented skin lesions: results of a consensus meeting via the Internet. J Am Acad Dermatol. 2003;48:679–93.*

DEFINITIONS OF DERMOSCOPIC CRITERIA FOR THE 3-POINT CHECKLIST	
Criterion	**Definition**
Asymmetry	Asymmetrical distribution of colors and dermoscopic structures
Atypical network*	More than one type of network (in terms of color and thickness of the meshes) irregularly distributed within the lesion
Blue–white structures†	Presence of any type of blue and/or white color
*Usually found in early melanoma. †Usually found in both melanoma and pigmented basal cell carcinoma.	

Table 0.20 Definitions of dermoscopic criteria for the 3-point checklist. The presence of more than one criterion suggests a suspicious lesion. *Adapted from Argenziano G, Puig S, Zalaudek I, et al. Dermoscopy improves accuracy of primary care physicians to triage lesions suggestive of skin cancer. J Clin Oncol. 2006;24:1877–82.*

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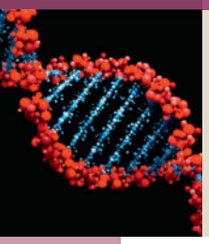


1 Anatomy and Physiology

Travis W. Vandergriff

Key features

- The relationship between function and structure of the skin is best demonstrated by presenting diseases that illustrate how skin can fail. Thus, disease reveals function, and function illustrates structure
- The most obvious function of skin is to maintain an internal environment that allows an organism to protect DNA and to reproduce it relatively faithfully
- Cutaneous structures include an *epidermis* that serves as a barrier (preventing loss from within as well as damage from external insults) and a *dermis* that provides circulation and nutrition. Other functions provided by the cells that reside within the skin include immune recognition and memory, a capacity to repair damage, thermoregulation, and communication
- Evidence that skin has failed may be found in barrier disruption, infection, autoimmunity, cancer, and an undesirable appearance

INTRODUCTION

Most reviews of the anatomy and physiology of skin begin with detailed descriptions of cellular composition, structural proteins, and extracellular matrix ("ground substance"). Because each of these subjects, with relevant documentation, is presented in subsequent sections of the textbook, these aspects of cutaneous function will be introduced only briefly, using references to appropriate chapters. Following this, the conventional approach is reversed by examining diseases that illustrate cutaneous function in the context of the cells and structures that sustain it. This method is derived from the assertion that the structure and function of skin is revealed best through disease. The validity of this alternative methodology may be seen in clinical vignettes easily recognized by those who care for patients with skin disease:

- a young man with oculocutaneous albinism from Central Africa develops multiple squamous cell carcinomas (SCCs) before the age of 25
- a 16-year-old boy with hypohidrotic ectodermal dysplasia suffers heat stroke while competing in outdoor athletics in Texas
- toxic epidermal necrolysis due to phenytoin develops in a 40-year-old woman, leading to dehydration and sepsis
- numerous SCCs arise on the face and extensor forearms of a renal transplant recipient who continues to work outdoors
- linear eruption of grouped vesicles due to varicella–zoster virus develops on the left flank of an otherwise healthy young man

These patients and their diseases illustrate at least four of the functions of skin: photoprotection, thermoregulation, barrier formation, and immunologic protection. Each function is supported by the cells and structural elements that reside there.

STRUCTURE AND FUNCTION

Conventional Concepts of the Structure of Skin

Epidermis

Consistent with conventional introductory chapters on cutaneous structure and function, we begin with a schematic representation of a section through normal skin (Fig. 1.1). The anatomic structures observed by light microscopy are fairly similar in most regions of the body (Fig. 1.2). However, specialized regions of skin, including the palms, soles, genitalia and scalp, have modified forms that address regional functional requirements (Fig. 1.3).

As seen in Fig. 1.2, the outer layer of skin (epidermis) consists of a thin matrix of cells. In humans, the epidermis contains four major resident populations: keratinocytes (Ch. 56), melanocytes (Ch. 65), Langerhans cells (Ch. 4), and Merkel cells (Chs 2 & 115)[1]. *Keratinocytes*, the major population, originate in a stem-cell pool situated in the basal layer; cells that leave this pool then undergo maturation as they migrate upward, ultimately forming the laminated stratum corneum (Fig. 1.4). The human epidermis averages 50 microns in thickness, with a surface density of approximately 50 000 nucleated cells/mm^2. Under basal conditions, differentiated keratinocytes require about two weeks to exit the nucleated compartment and an additional two weeks to move through the stratum corneum[2]. It should be noted that keratinocytes have the capacity to increase rates of proliferation and maturation to levels far greater than this, when stimulated to do so by injury, inflammation or disease (Ch. 8).

Melanocytes, as noted in a DOPA-stained whole mount of epidermis (see Fig. 65.6), have the capacity to elaborate the light-absorbing pigment melanin, which plays a major role in protecting the skin from UV radiation[3] (Ch. 86). Melanosomes, with their complement of melanin, are produced by melanocytes and then transferred by excretion and phagocytosis into nearby keratinocytes, where they assume their preferred location above the nucleus (see Fig. 65.5)[4].

Members of the third major resident epidermal population, *Langerhans cells*, have the capacity to metabolize complex antigenic materials into peptides, some of which are immunogenic (see Fig. 4.4). After activation, these cells traffic out of the epidermis toward regional lymph

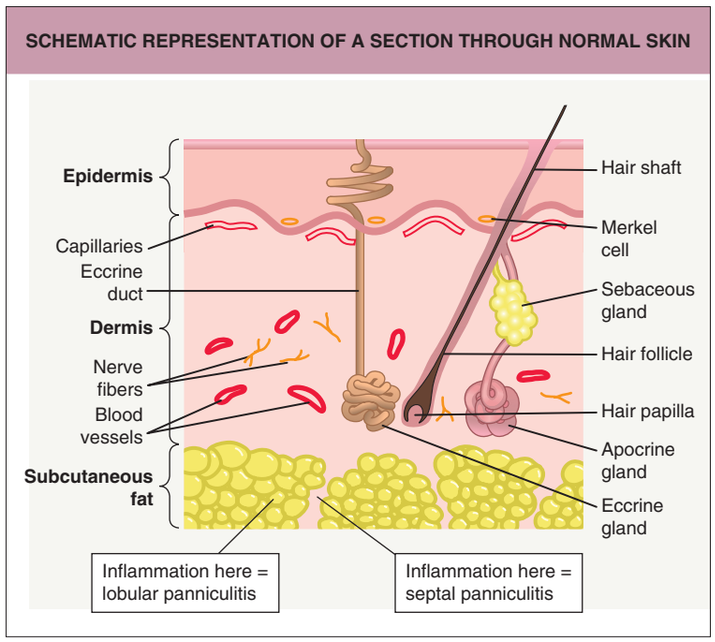


Fig. 1.1 Schematic representation of a section through normal skin. The skin is divided into 3 major layers: (1) the epidermis, which serves as a barrier to prevent loss of fluid and electrolytes and to protect against external insults such as chemicals and microbes (see Fig. 1.4); (2) the dermis, which provides structural and nutritional support (see Fig. 1.5); and (3) the subcutaneous fat. Adnexal structures, including hair follicles, sebaceous glands, eccrine glands and apocrine glands, are found within the dermis.

ABSTRACT

Most reviews of the anatomy and physiology of skin begin with detailed descriptions of cellular composition, structural proteins, and extracellular matrix ("ground substance"). Because each of these subjects, with relevant documentation, is presented in subsequent sections of this textbook, these aspects of cutaneous structure will be introduced only briefly, using references to appropriate chapters. Following this, the conventional approach is reversed by examining diseases that illustrate cutaneous function in the context of the cells and structures that sustain it. This method is derived from the assertion that the structure and function of skin is revealed best through disease. The validity of this alternative methodology may be seen in the diseases with which patients present daily to dermatologists around the world. Thus, disease reveals function, and function illustrates structure. Cutaneous structures include an *epidermis* that serves as a barrier to prevent loss from within and damage from external insults and a *dermis* that provides circulation and nutrition. Other functions provided by the cells that reside in the skin include immune recognition and memory, a capacity to repair damage, thermoregulation and communication. Evidence that skin has failed may be found in barrier disruption, infection, autoimmunity, cancer and an undesirable appearance. These are the subjects of this introductory chapter. Ultimately, however, the most obvious function of skin is to maintain an internal environment that allows an organism to protect its DNA and to reproduce it relatively faithfully.

KEYWORDS:

structure and function,
epidermis,
dermis,
DNA,
skin barrier,
cutaneous infection,
skin cancer,
skin immunity,
cutaneous circulation

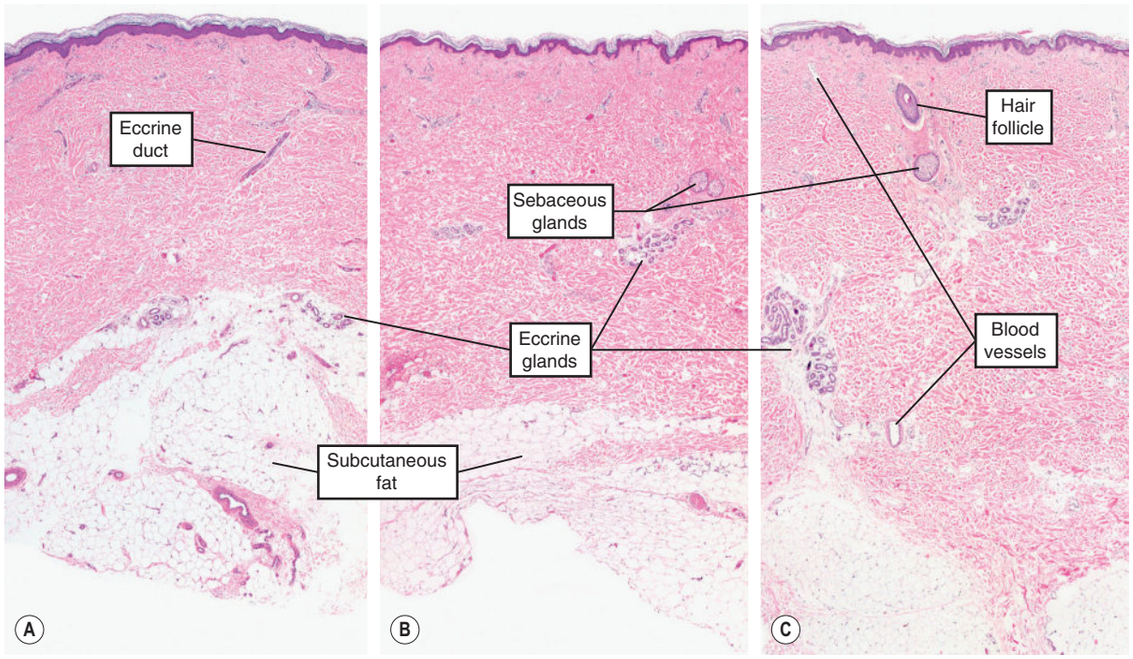


Fig. 1.2 Histopathologic features of normal skin from three different anatomic sites. A comparison of biopsy specimens from the arm (**A**), flank (**B**), and back (**C**) demonstrates the increasing thickness of the dermis. However, there is a similarity with regard to the presence of blood vessels and adnexal structures including eccrine glands. *Courtesy, Lorenzo Cerroni, MD.*

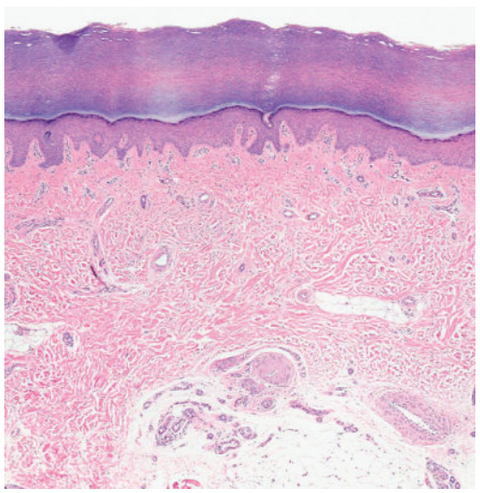


Fig. 1.3 Histopathologic features of normal plantar skin. Note the markedly thickened stratum corneum, compared to the photomicrographs in Fig. 1.2. The thickened stratum corneum protects against mechanical stress. *Courtesy, Lorenzo Cerroni, MD.*

nodes, where they play a critical role in antigen presentation during the induction and regulation of immunity (see Fig. 4.14).

Merkel cells, which contain neuroendocrine peptides within intracytoplasmic granules, are also found in the basal layer of the epidermis, although they may not be apparent in routine histologic sections. Over the past decade, there have been advances regarding their origin and pathology (Chs 2 & 115)[1].

The most obvious function of epidermis lies in the stratum corneum (see Fig. 1.4), the semipermeable laminated surface aggregate of differentiated (keratinized) squamous epithelial cells, which serve as a physiologic barrier to chemical penetration and microbiologic invasion from the environment, as well as a barrier to fluid and solute loss from within[5] (Ch. 124).

Dermis

Beneath the epidermis, a vascularized dermis provides structural and nutritional support. It is composed of a glycosaminoglycan gel held together by a collagen- and elastin-containing fibrous matrix (Fig. 1.5) (Ch. 95). Vascular structures, accompanied by nerves and mast cells (Ch. 118), course through the dermis to provide nutrition, recirculating cells, and cutaneous sensation. Three additional cells, fibroblasts, macrophages and dermal dendritic cells, complete the list of dermal residents. In pathologic conditions such as acute inflammation, the functions and types of dermal cells change substantially, with a variety of infiltrating leukocytes arriving via vascular routes. In fact, the composition of cutaneous infiltrates differs depending on the disease entity, which provides students of dermatopathology useful diagnostic clues (Fig. 1.6).

Dermal–epidermal interface

The boundary between epidermis and dermis consists of a specialized aggregation of attachment molecules, collectively known as the basement membrane[6] (Ch. 28). This structure is of considerable interest, because a variety of diseases originate from genetic defects in its composition; it also may serve as a target of autoimmune attack.

Knowledge of the Function and Structure of Skin Begins With Skin Disease

We have chosen to present in the remainder of this chapter a conceptual framework into which the other chapters of this textbook may be placed. This framework is derived from the assertion that knowledge of cutaneous function begins with disease. One corollary of this assertion is that there may be unrecognized functions of skin, either because there is no corresponding disease or because the disease is fatal. For example, no one would have guessed that incontinentia pigmenti was lethal in males had it not been for the survival of heterozygous females with this X chromosome-linked disease[7,8]. Overwhelming apoptosis is thought to explain the death of male fetuses *in utero*.

Two other prejudices color the picture we choose to paint. First, we deviate from the concept that physicians should invariably attempt to develop a single diagnosis for an illness. Rather, we believe that it is possible and even likely that two or more disease processes and/or predispositions may underlie an illness and that such simultaneous occurrences may alter the clinical presentation. In fact, practicing dermatologists are quite aware of the unusual morphologic features of pityriasis rosea when it occurs in a patient with underlying psoriasis or when a patient with atopic dermatitis improves substantially following treatment with an antibiotic, even in the absence of obvious infection. A growing array of genetic factors and infectious agents are known to modulate the course of otherwise conventional skin diseases. Witness the presence of numerous viral warts or tumors of molluscum contagiosum in patients with immunodeficiency from occult HIV infection or from iatrogenic immunosuppression. Thus, dermatologists have an extra assignment: to find otherwise hidden genetic, infectious and environmental factors that modify the appearance and severity of cutaneous disease.

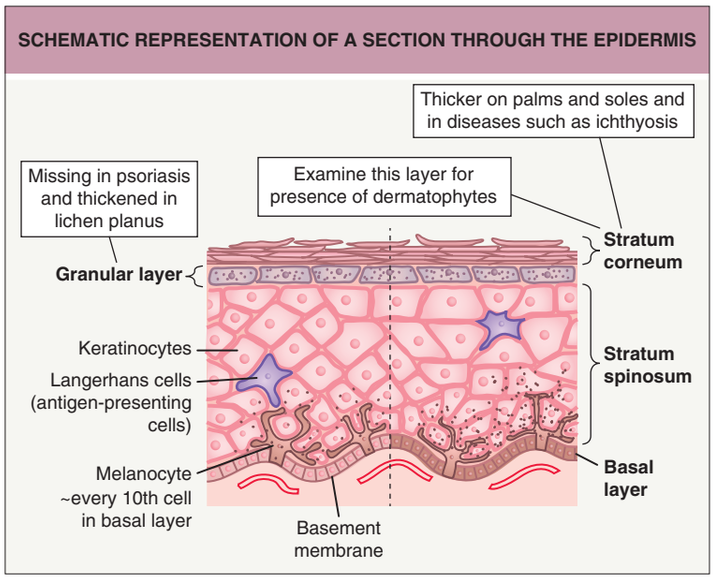


Fig. 1.4 Schematic representation of a section through the epidermis. The epidermal layers from the surface are: (1) the stratum corneum; (2) the granular layer (stratum granulosum); (3) the stratum spinosum; and (4) the basal layer (stratum basale). Under basal conditions, differentiated keratinocytes require about two weeks to exit the nucleated compartment and an additional two weeks to move through the stratum corneum. The basement membrane zone represents the junction between the epidermis and the dermis. Additional cell populations that reside within the epidermis include melanocytes along the basal layer, which supply melanin to the surrounding keratinocytes via melanosomes, and Langerhans cells, which serve as antigen-presenting cells. On the left is lightly pigmented skin and on the right is darkly pigmented skin.

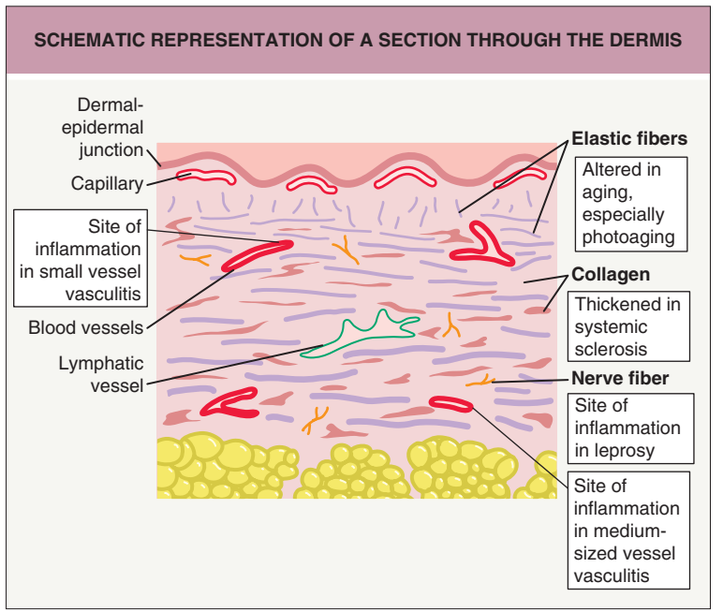


Fig. 1.5 Schematic representation of a section through the dermis. The extracellular matrix of the dermis is composed of structural proteins (collagen, elastin) and a gel-like ground substance (glycosaminoglycans). There are also blood vessels that supply nutrition and recirculating cells, lymphatic vessels, and nerve fibers. Adnexal structures seen in Fig. 1.1 are also present, with variations depending upon body site. Other cell types present in the dermis include mast cells, fibroblasts, macrophages, and dermal dendritic cells.

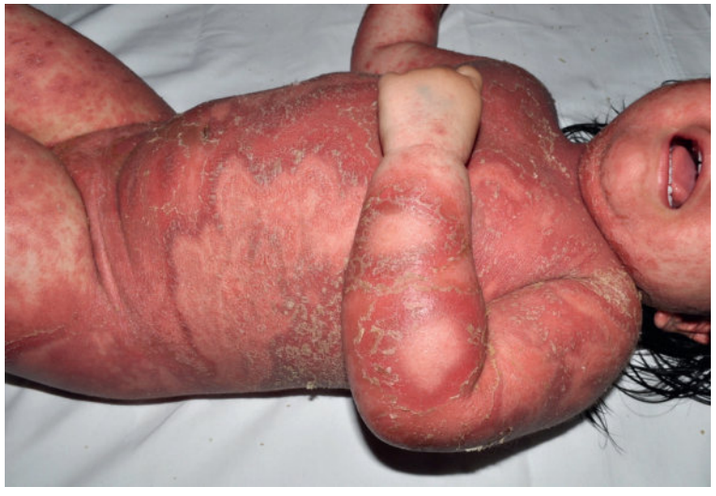


Fig. 1.6 Severe pustular psoriasis in an infant. The pustules represent sterile collections of neutrophils. Sterile infiltrates of neutrophils within the skin are seen most commonly in pustular psoriasis, pustular drug reactions (acute generalized exanthematous pustulosis), and neutrophilic dermatoses (Ch. 26).
Courtesy, Antonio Torrelo, MD.

All plants and animals possess limiting membranes that define an internal space and at the same time protect against insults. In mammals, these membranes, which may be described functionally as "barriers", occur primarily in three organs: the lung, gastrointestinal tract, and skin (Ch. 124). Although similar in concept, the barrier properties of these organs are fundamentally different. Pulmonary and gastrointestinal barriers, by virtue of their internal location, are protected from many environmental influences, and at the same time they promote rather than retard the transfer of gases, nutrients, and wastes. By contrast, and with the possible exception of UV radiation-facilitated vitamin D_3 production[9], there is no obvious benefit to skin penetration, or, at least, there are as yet no recognized diseases attributed to the failure of any material or form of energy to penetrate the skin. It should be noted, however, that biomedical scientists now try to subvert the cutaneous barrier, as skin has become a target of novel therapies based upon percutaneous penetration[5] (Chs 124–129). In addition to serving as a useful portal of entry for pharmaceutical agents, there is the possibility of the skin serving as a site for immunization with gene-based materials and as a gene-driven cutaneous factory[10].

The Central Role of Protecting DNA as a Function of Skin

Although we begin with the common rhetorical question: "What are the functions of skin?", it is followed by a more complicated question: "What are the requirements of skin that allow it to serve those functions?". We propose that the primary function of skin is to maintain an internal environment that allows an organism to protect DNA and to reproduce it relatively faithfully. In short, preservation and reproduction of DNA sustains the species. A second and highly related process in a changing world is the generation of useful changes in DNA that accommodate new environmental circumstances. Evolution of the species subsequently ensues as an adaptation. For example, skin pigmentation improves reproductive success in tropical climes by protecting folate from UV-mediated degradation, while lightly pigmented skin is advantageous for vitamin D biosynthesis in areas where UV radiation is scarce[11].

Although the permanent repository of DNA lies in the gonads, the protection of DNA in all sites, including the skin, is also essential for biologic success. This concept of the centrality of DNA has been developed by Reg Morrison in his monograph *The Spirit in the Gene: Humanity's Proud Illusion and the Laws of Nature*, which reviews how life-form competition may be modeled as a method of protecting DNA[12]. Morrison makes the striking observation that human DNA has in the last 300 years come to dominate all life on earth.

The requirements of skin are identified in its failings

So, what are the requirements of skin in order to protect and replicate DNA? In fact, these requirements have not been identified through logical considerations; rather, as noted above, they have been identified through the various failures that eventuate in skin disease. For this reason, we begin our survey with a listing of failures of skin (Table 1.1).

SELECTED REQUIREMENTS AND FAILINGS OF SKIN	
Requirement	**Selected failings**
Prevent infection via innate and adaptive immunity	Fungal, bacterial and viral infections; autoimmunity, cancer
Maintain a barrier	Infection, dehydration
Repair injury	Cancer, leg ulcers
Provide circulation	Infarction (due to embolization, vasculitis, or other forms of occlusion)
Communicate	Sensory neuropathy, pruritus
Provide nutrition	Vitamin D deficiency
Regulate temperature	Hypothermia, hyperthermia
Attract attention	Photoaging, vitiligo, alopecia

Table 1.1 Selected requirements and failings of skin.

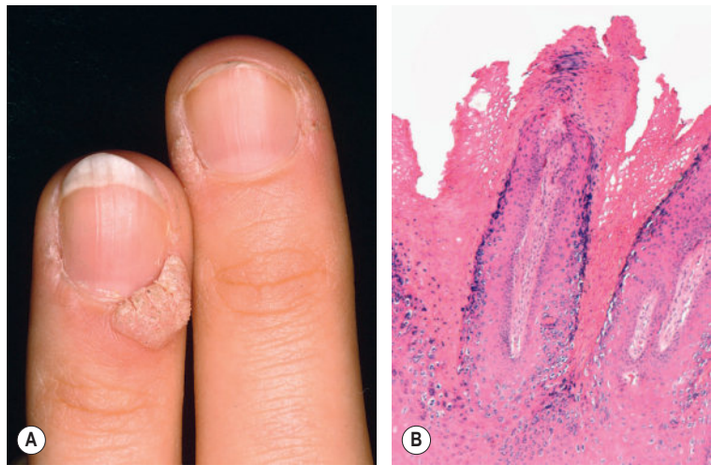


Fig. 1.7 Verrucae vulgares. A Multiple periungual warts. **B** Papillomatosis, hyperkeratosis, mounds of parakeratosis at the tips of the verrucous epidermal projections, and vacuolated keratinocytes (koilocytes) within the upper layers of the epidermis. The latter are due to a halo surrounding a shrunken nucleus.
A, Courtesy, Louis A Fragola, Jr, MD; B, Courtesy, Lorenzo Cerroni, MD.

Preventing Infection: Skin as an Immunologic Organ

An intricate system of immunologic recognition, both innate and adaptive, protects skin (and underlying tissues) from infection[13] (Ch. 4). The cornerstone of adaptive immunity lies in recirculating lymphocytes and antibodies that are specifically recruited and "tuned" to recognize "foreign" materials, primarily peptides derived from infectious agents. Initial recognition occurs when sentinel dendritic cells in the epidermis (Langerhans cells) and dermis (dermal dendritic cells) are activated. Prior to activation, these cells acquire the capacity to engulf particles of many sizes and to metabolize complex proteins into small immunogenic fragments. Once activated, motility is induced, allowing these cells to travel out of their cutaneous residence, and, via draining lymphatics, move to regional lymph nodes. Thus, these residents of normal skin have the capacity to travel to a distant location where reactive lymphocytes are selected and then expanded greatly in number. Within a lymph node, activated T helper lymphocytes assist B lymphocytes to generate antibodies, while T helper lymphocytes and cytotoxic T lymphocytes begin to recirculate preferentially to and from skin. A population of effector memory T lymphocytes resident within the skin has also been identified, and these cells play a critical role in immune responses[14].

Failure of immunity: infection

The diagnosis and treatment of infection constitutes a substantial portion of dermatology (Chs 74–83). Examples of chronic and recurrent infectious skin diseases illustrate the extent to which mechanisms of resistance to infection are lost or defective in some patients. In examples that follow, initial resistance depends upon the structural integrity of the stratum corneum.

Warts

Trauma to the stratum corneum interrupts a physical barrier that is ordinarily not susceptible to viral infection (Ch. 79). In addition, trauma allows implantation of infectious particles among the underlying keratinocytes, which are viable and less resistant. Following this structural failure, immunologic recognition of infected keratinocytes is ordinarily followed by a cytotoxic cellular response, destruction, and cure. When this fails, chronic infection may ensue (Fig. 1.7). It is of interest that many therapies for warts, other than physical destruction, rely on modulating the immune response. On the other hand, few problems are more vexing than chronic and recurrent warts, particularly in patients who are immunosuppressed. Especially important are the viral serotypes associated with SCC and the genetic disorder epidermodysplasia verruciformis[15] (Ch. 79). It is instructive that protective immunity against warts often appears to be balanced precariously, so that minor shifts in responsiveness may lead to their elimination in many sites simultaneously. This has been attempted therapeutically by the use of oral cimetidine, topical applications of imiquimod, elicitation of contact sensitivity reactions, and intralesional injection of recall antigens such as *Candida* or mumps[16].

Dermatophytosis

The diagnosis and treatment of infections with dermatophytes remain largely the responsibility of dermatologists (Ch. 77). Perhaps this is because dermatophyte infections are almost invariably limited to the skin, hair and nails, inasmuch as one or more serum factors (e.g. transferrin) may prevent growth where serum can reach[17]. As yet unidentified genetic factors protect some individuals from infection, because it is not uncommon to encounter families in which several individuals are chronically infected, whereas other family members, in the face of obvious exposure, are seemingly never infected. On the other hand, experience from tropical climates indicates that individuals who are relatively resistant in a dry environment may lose that resistance as the ambient humidity increases or when occlusive military shoes are worn[18]. Obviously, dermatophyte infection and resistance include a complicated interplay among genetic susceptibilities, immune responsiveness, and environmental circumstances.

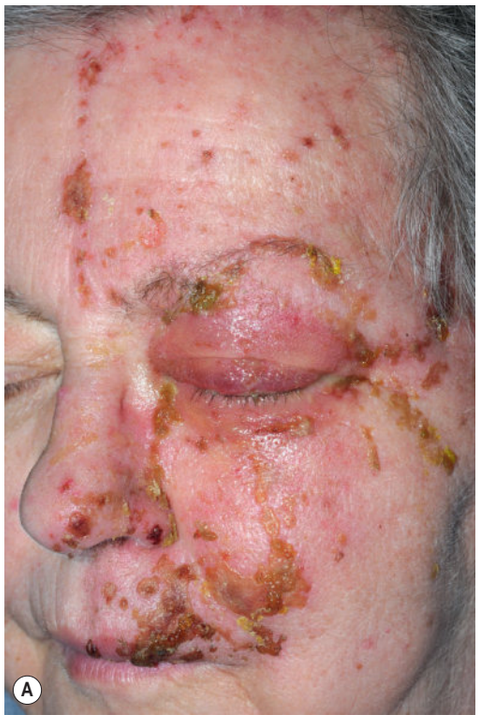
Opportunistic infections in the setting of human immunodeficiency virus infection

An enormous body of biomedical knowledge has accrued during the 35-year epidemic of HIV infection (Ch. 78). As a beginning, it appears that HIV penetrates through small tears in genital and rectal mucosae. Once infection has occurred, the virus has been impossible to completely delete, despite a panoply of relatively effective therapies. With loss of immunologic integrity, patients develop AIDS and thereby demonstrate the relevance of effective cellular immunity to protection against infections with a wide variety of agents, including *Mycobacterium tuberculosis, Pneumocystis jirovecii*, varicella–zoster (Fig. 1.8), and herpes simplex viruses. What more evidence would one want to demonstrate the relevance of cellular immune protection of skin than the diseases that are described in Chapter 78?

Leprosy (Hansen disease)

Leprosy is instructive in that the majority of humans exposed to its causative organism, *Mycobacterium leprae*, develop an effective immune response that is seemingly curative (Ch. 75). On the other hand, a small percentage of exposed individuals develop chronic infection that may take any one of several forms, based on immunologic resistance. In fact, observations made in patients with leprosy have been important in formulating the Th1/Th2 paradigm (Ch. 4), with each patient's clinical response falling along a spectrum from tuberculoid to lepromatous[19]. Importantly, leprosy also illustrates the relevance of cutaneous sensation to protection against traumatic injury, as will be presented later.

Warts, dermatophytosis, opportunistic infections in the setting of HIV infection, and leprosy all illustrate important aspects of cutaneous function, ranging from a structural barrier provided by the stratum corneum to immunologic recognition and protective immunity.



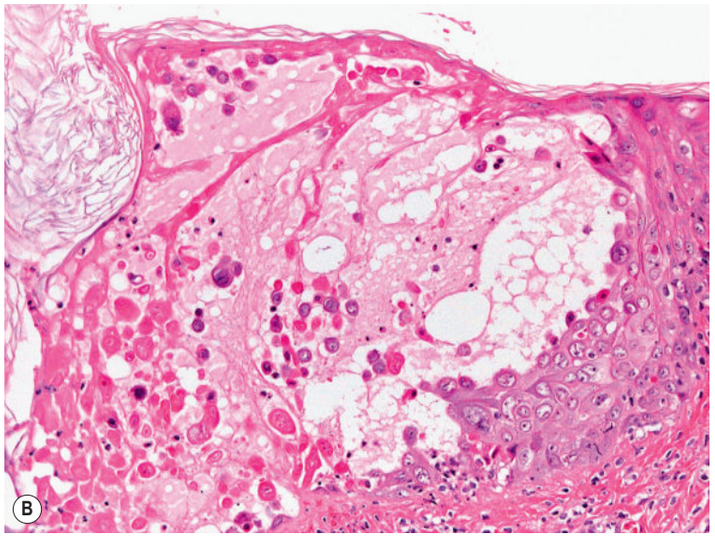


Fig. 1.8 Herpes zoster involving the ophthalmic (V1) and maxillary (V2) branches of the trigeminal nerve. A Erythema, especially of the eyelids, plus serous and hemorrhagic crusts of the left side of the forehead, nose, cheek, and upper cutaneous lip. Note the sharp midline demarcation on the forehead. **B** An intraepidermal vesicle forms as a consequence of ballooning degeneration, acantholysis, and necrosis of infected keratinocytes. Note the keratinocytes with enlarged, partly dyskeratotic nuclei or multiple nuclei in the side wall of the blister cavity, in addition to acantholytic, necrotic keratinocytes and fibrin within the blister. *A, Courtesy, Kalman Watsky, MD; B, Courtesy, Lorenzo Cerroni, MD.*

Faulty immunity: autoimmunity

We have made a case for the concept that the primary task of immunity is to recognize and destroy infectious organisms. Having stated this, autoimmunity may then be modeled as a failure in distinguishing "self" from infection, i.e. autoimmunity is a misidentification and destruction of portions of the host, as if it were dangerous or "foreign". Autoimmune diseases are legion, with components of the epidermal basement membrane and desmosomes serving as important targets (Fig. 1.9). Moreover, cutaneous cellular elements serve as both regulators and targets of autoimmune injury. Table 1.2 lists several common autoimmune diseases that affect the skin, each with a different target. These diseases have different sets of genetic factors and environmental insults that promote their development. Subsequent chapters detail their relevant elements.

COMMON AUTOIMMUNE SKIN DISEASES		
	Target antigen	**Chapter**
Diseases with identified autoantigens		
Pemphigus foliaceus	Desmoglein 1	29
Pemphigus vulgaris (Fig. 1.9A)	Desmoglein 3 and 1	29
Bullous pemphigoid (Fig. 1.9D)	Collagen XVII (BPAG2), BPAG1*	30
Epidermolysis bullosa acquisita	Collagen VII	30
Dermatitis herpetiformis	Transglutaminase-3	31
Diseases with unknown or multiple autoantigens		
Subacute cutaneous lupus erythematosus	Unknown, possibly SSA/Ro	41
Chronic cutaneous lupus erythematosus	Unknown	41
Psoriasis	Unknown	8
*Neural isoforms are referred to as dystonin.		

Table 1.2 Common autoimmune skin diseases.

We know a substantial amount about molecular targets in these diseases, and we also know much about how immunity works in protecting against infectious diseases. However, we continue to learn about skin structure by observing disease states in which errors in recognition lead to immune responses that target "self" antigens inappropriately and damage residential structures. For example, in pemphigus vulgaris, autoantibodies directed against desmogleins compromise intercellular adhesion, leading to intraepithelial acantholysis and widespread erosions (see Fig. 1.9). It has also become apparent that autoimmunity directed against cutaneous antigens may impact other organ systems. For example, in patients with bullous pemphigoid and concomitant neurologic disease, circulating anti-basement membrane antibodies were found to recognize antigens in both the skin and brain[20].

Failure of immunity: cancer

Data to support the concept that immune responses also protect against malignancy are strongest for those malignancies that arise in skin and lymphatic tissues[21], especially cutaneous SCC, Merkel cell carcinoma, and melanoma. Cutaneous SCC is a well-known and relatively common complication of immunosuppression in solid organ transplant recipients[22,22a]. Many recent developments in melanoma therapy are based on attempts to enhance immune responsiveness (Ch. 113).

Maintaining a Barrier: Skin as a Protective Organ

From the outset, the most obvious function of skin is to maintain a barrier that prevents the loss of fluids, electrolytes, and other molecules from within the body and, at the same time, prevents penetration by microorganisms, toxic materials, and UV radiation[23,24] (Ch. 86). For all but UV radiation, the stratum corneum is the central element in that function. By contrast, protection against UV radiation occurs through several independent phenomena, including photon scattering in the stratum corneum and photon absorption by underlying melanin.

Failure of protection against toxic chemicals

The analysis of barrier failure begins with the observation that the stratum corneum is defective in disorders of keratinization[25] as it is less resistant to chemical penetration. Two diseases typify this defect: epidermolytic ichthyosis (formerly epidermolytic hyperkeratosis; Fig. 1.10) and Darier disease (keratosis follicularis)[25,26]. An instructive set of circumstances arose with the problem that patients with these diseases commonly have recurrent bacterial infections. In an attempt to treat and to prevent such infections, dermatologists and other physicians had recommended for decades the prophylactic use of topical antibacterial agents to decrease bacterial carriage and, at the same time, the associated odor.

In an article published in 1960, Medansky and Woloshin[27] described an extraordinarily high frequency of neuropsychiatric disorders in

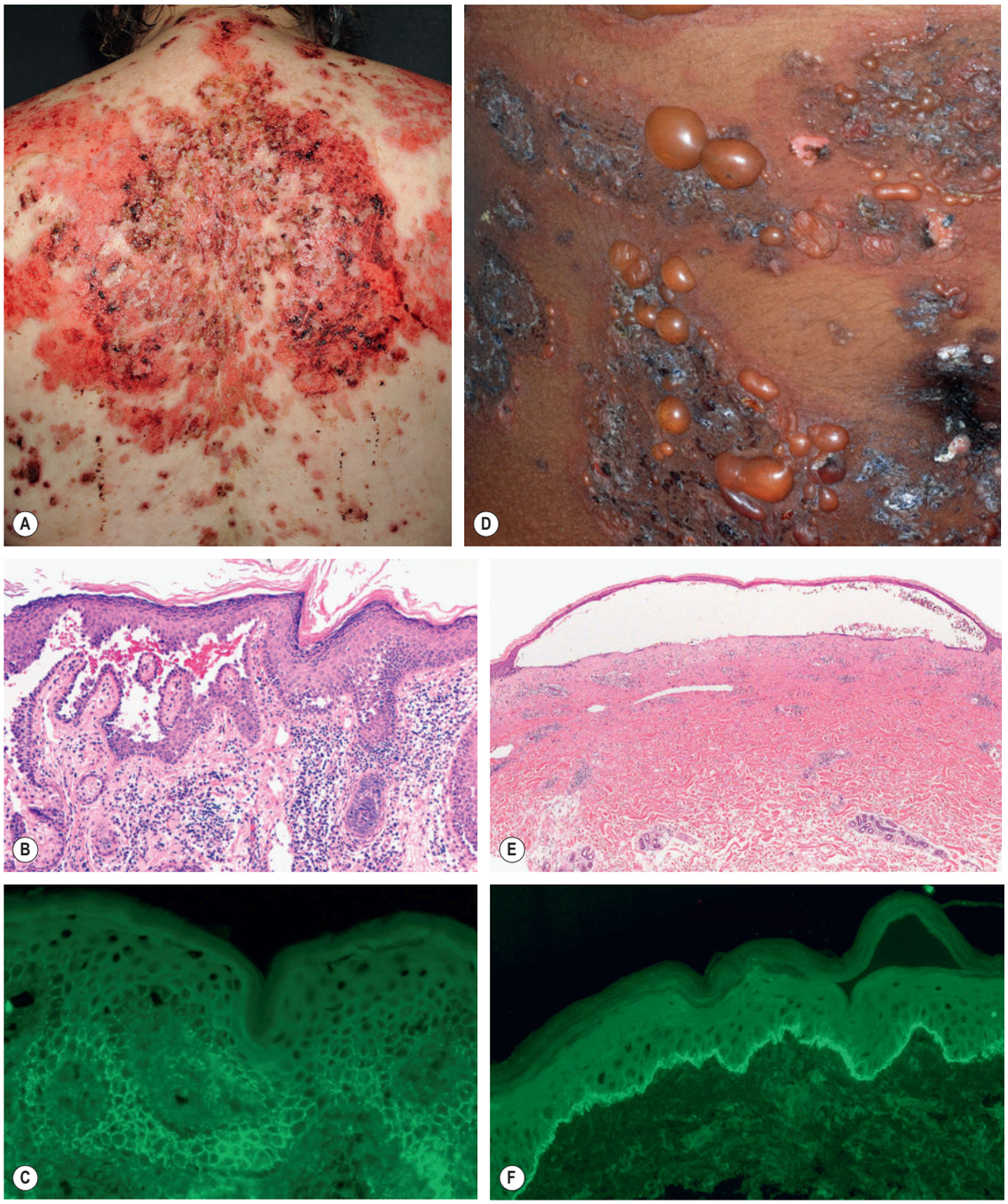


Fig. 1.9 Pemphigus vulgaris versus bullous pemphigoid. A In pemphigus vulgaris, fragile blisters are short-lived and rupture easily, leading to crusting and erosions that can become extensive. **B** Acantholysis due to loss of desmosomal function from anti-desmoglein autoantibodies produces an intraepidermal split. Note the retention of hemidesmosomes between the basal cells of the epidermis and the basement membrane leads to a resemblance to tombstones. **C** Direct immunofluorescence (DIF) microscopy (see Fig. 29.17) demonstrates *in vivo* intercellular deposits of IgG within the lower epidermis in a "chicken wire" pattern. **D** In bullous pemphigoid, multiple tense bullae are seen; the contents of the bullae are usually serous, as in this patient. The bullae are longer-lasting than in pemphigus, but do eventually rupture, leading to erosions and crusts. **E** A subepidermal separation is seen. The cells within the blister cavity are often eosinophils. **F** DIF microscopy demonstrates linear deposits of C3 at the basement membrane zone.
A,B,E, Courtesy, Lorenzo Cerroni, MD; C,F, Courtesy, Christine Ko, MD; D, Courtesy, Julie V Schaffer, MD.

patients with keratosis follicularis, even though no mechanism was known that would link keratin function with CNS function. In retrospect, however, hexachlorophene had been recommended as a useful antibacterial agent soon after its introduction in 1944. Several decades later, it was recognized that hexachlorophene was potentially neurotoxic, with its use eventually curtailed in the 1970s[28]. Since that time, there have been fewer reports of neuropsychiatric findings in keratosis follicularis. Our conclusion is that hexachlorophene penetrates a defective barrier in toxic amounts. However, an alternative explanation proposed by others is that dysfunction of SERCA2 within the brain may potentially lead to neuropsychiatric findings[28]. In sum, the barrier for chemical penetration is invested in the stratum corneum (Ch. 124), and this barrier is defective in diseases of keratinization.

Failure to protect against dehydration and infection: toxic epidermal necrolysis

The most dramatic form of epidermal failure occurs in patients with toxic epidermal necrolysis (TEN; Ch. 20). In this drug-induced disease, rapidly progressive keratinocyte death leads to detachment of the epidermis over large areas of the body. There is a complete loss of barrier function (Fig. 1.11). TEN is most often associated with sulfonamides, aromatic anticonvulsants, and nonsteroidal anti-inflammatory drugs. It has a mortality rate that depends upon the area of skin involved, but death is not uncommon. There is as yet no specific treatment for TEN. However, there is evidence that drug-induced triggering of massive keratinocyte apoptosis may underlie the disease[29], and inhibition of the apoptosis signaling pathway (e.g. by administration of immunomodulators such as cyclosporine) may improve survival[29a]. However, the point of this discussion is that the complications that accompany loss of the epidermis reveal all of its functions. Despite intensive treatment with similar techniques as those employed for burns, complications are common and can include enormous fluid and electrolyte losses leading to dehydration as well as infections with bacteria and yeast.

Failure to protect against UV radiation: albinism

UV radiation induces a myriad of changes in the skin, ranging from acute toxicity and immunosuppression to carcinogenesis and premature

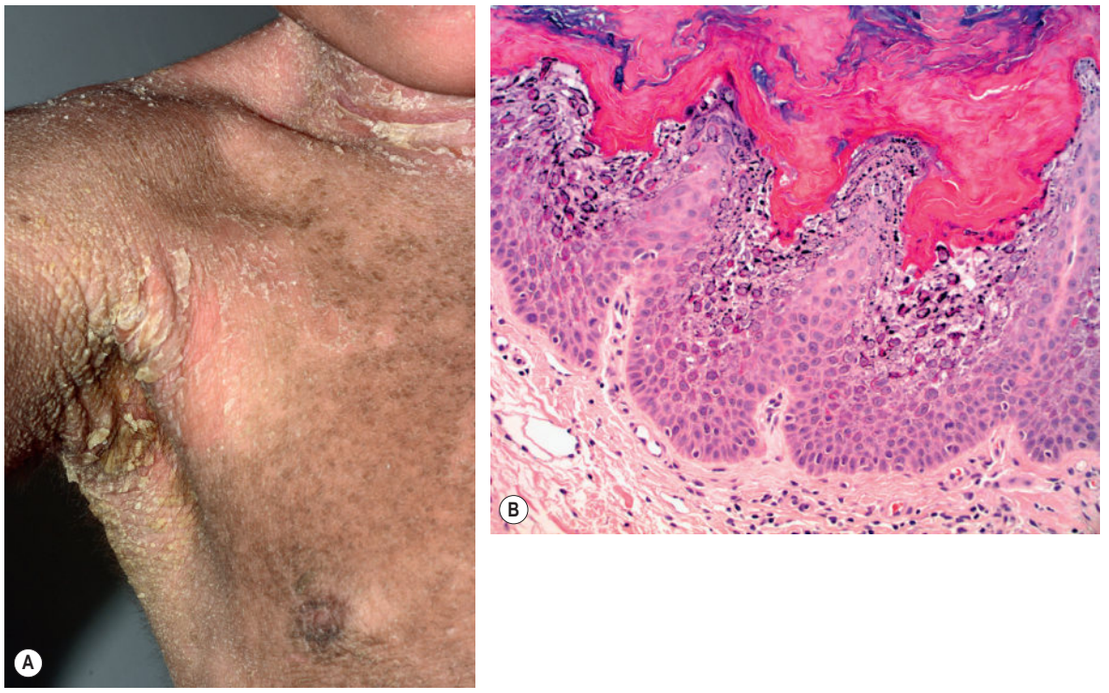


Fig. 1.10 Epidermolytic ichthyosis (formerly epidermolytic hyperkeratosis). A Mild background erythema with markedly thickened scale, especially near the axilla. Note the corrugated pattern of the scale. The fragility of the upper epidermis leads to peeling and erosions. **B** Marked compact orthokeratosis overlies a hyperplastic epidermis showing epidermolytic change with dyskeratotic cells in its upper layers. *A, Courtesy, Julie V Schaffer, MD; B, Courtesy, Lorenzo Cerroni, MD.*

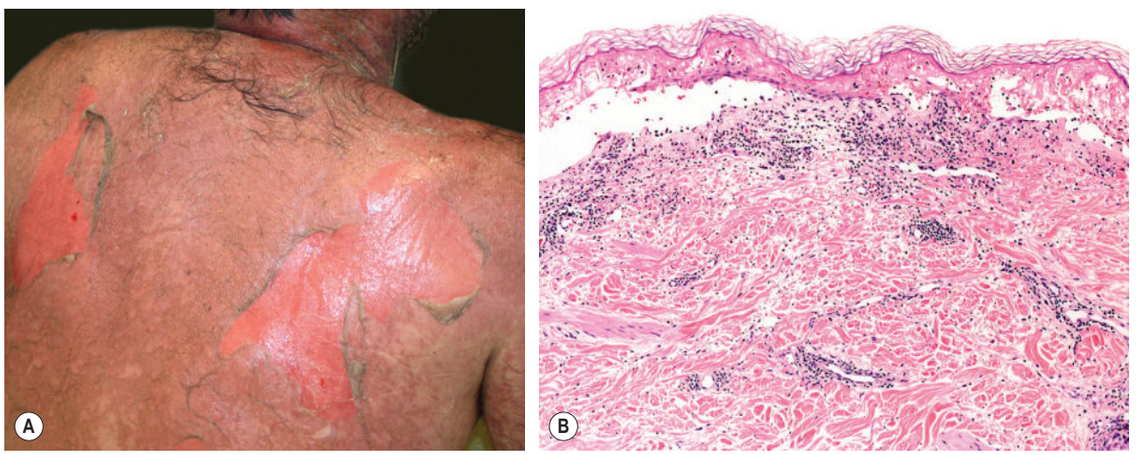


Fig. 1.11 Toxic epidermal necrolysis. A Detachment of necrolytic epidermis, leading to large areas of denuded skin. In the glistening areas, one is looking at dermis. **B** Full-thickness epidermal cell death results in a subepidermal separation. The normal stratum corneum points to the acute nature of the disease process. In the dermis, there is a lymphohistiocytic inflammatory infiltrate admixed with a few eosinophils.

aging (Chs 86, 87, 107 & 108). However, there is an apparent contradiction in the recommendations of dermatologists: effective therapies for a number of skin diseases are based on the use of UV radiation of various wavelengths (Ch. 134), while protection from the sun's rays is in general recommended to prevent adverse effects from UV radiation (Ch. 132). In addition to wearing clothing and using topical preparations that include UV-absorbing or UV-blocking molecules, several characteristics of the skin itself limit UV radiation-induced damage. Due to its optical characteristics, the stratum corneum tends to reflect and scatter photons, and those that penetrate the stratum corneum are usually absorbed by molecules such as melanin. Additional mechanisms are the scavenging of reactive oxygen species by antioxidants and repair of damage with DNA repair enzymes.

The importance of cutaneous pigment in protecting the skin against UV damage is demonstrated in patients with oculocutaneous albinism (OCA)[3]. The impact of melanin in limiting UV penetration may be seen unequivocally in patients who have type 1 OCA due to a reduction or absence of tyrosinase activity and, as a result, melanin production (Fig. 1.12). Striking amongst the evidence is the experience of individuals with OCA who live in sub-Saharan Africa. Because of little relief from sunlight exposure, compounded by the absence or paucity of cutaneous melanin, there is an extraordinarily high frequency of cutaneous actinic keratoses and SCCs[30]. Likewise, acute toxicity, photosensitivity diseases, and premature photoaging (Ch. 87) are known complications for these patients.

Maintaining the Integrity of Skin: Repair Mechanisms

Physical injury occurs commonly in the skin, including many small breaks from blunt and sharp objects that are repaired almost without notice. A special type of injury is caused by the penetration of UV radiation. This includes a variety of effects that range from sunburn to immune suppression, accelerated aging, and carcinogenesis. Thermal injury occurs upon exposure to a hot object or radiant energy, e.g. from fire, that heats the skin excessively (see below, thermoregulation). Injury also occurs when there is interruption of the underlying vascular supply. Each episode of injury is followed by a sequence of repair processes that eliminate foreign objects and cover defects. This "wound healing" response has been studied in considerable detail (Ch. 141), because delays in wound healing are both incapacitating and expensive.

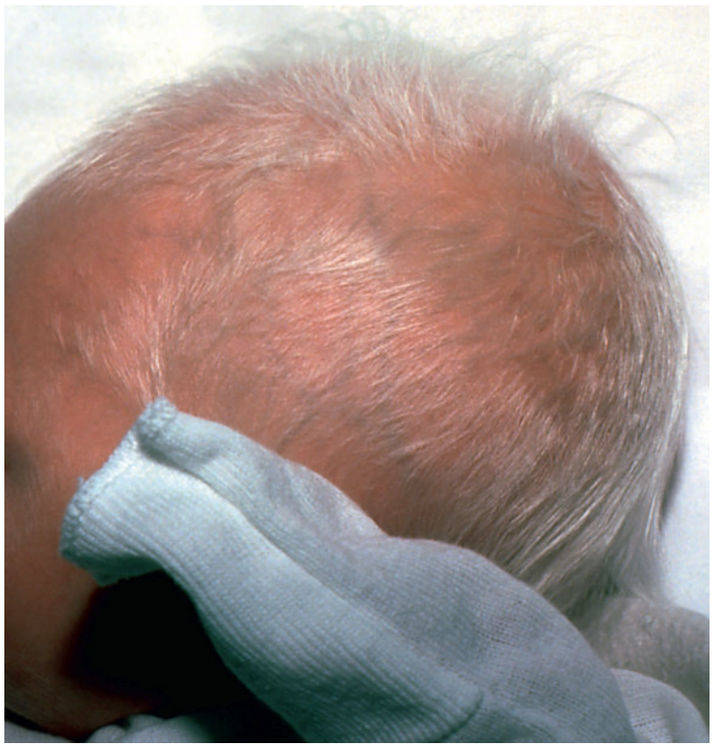


Fig. 1.12 An infant with oculocutaneous albinism (OCA). The scalp hairs are strikingly white. Patients with OCA are at higher risk for UV radiation-induced carcinogenesis, in particular cutaneous squamous cell carcinoma, as well as ocular abnormalities, e.g. decreased visual acuity, nystagmus.

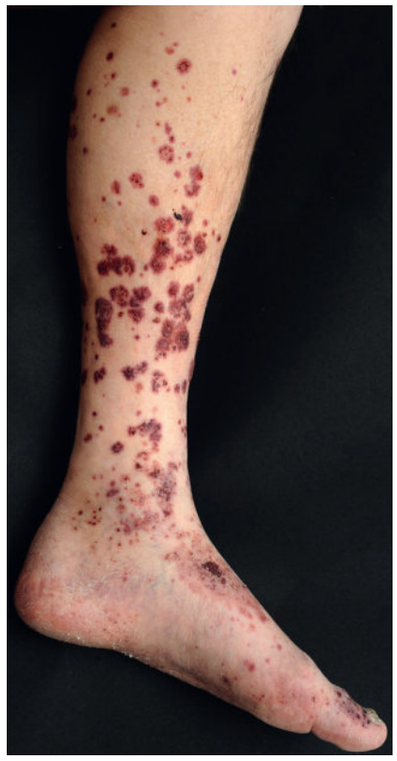


Fig. 1.13 Palpable purpura of the lower extremity due to cutaneous small vessel vasculitis. Immune complex deposition within postcapillary venules leads to circular purpuric macules and papules. *Courtesy, Lorenzo Cerrroni, MD.*

Failure to effectively repair injury

Delayed wound healing

Delayed and incomplete wound healing have been associated with diabetes mellitus, peripheral artery disease, and aging. The treatment of chronic leg ulcers, especially in the elderly, is an important part of dermatology and rehabilitation medicine (Ch. 105). The need to address issues of chronic cutaneous ulceration led to the formation of the Wound Healing Society (www.woundheal.org), a consortium composed of clinical and basic science investigators along with representatives from industry and government.

Keloids

The formation of hypertrophic scars and keloids may be seen as an exuberant response to injury. It combines a unique mix of genetic and environmental factors. The most reasonable explanation of pathogenesis may be seen in studies showing that transforming growth factor-β (TGF-β) activity is excessively high in fibroblasts derived from keloids[31]. Despite preliminary evidence that TGF-β may play a role in the establishment of an environment that favors overgrowth of dermal elements to form hypertrophic scars and keloids, the discipline of wound healing remains in its infancy.

Xeroderma pigmentosum

An important failure occurs when UV radiation-induced DNA damage is not repaired effectively. The prototype for this deficiency is the disease xeroderma pigmentosum[32]. The high incidence of several types of skin cancer in these patients supports the assertion that UV radiation-induced injury is an important cause of skin cancer in humans. Thus, it is necessary for the skin to protect itself against the detrimental effects of UV radiation. This illustrates two points: first, UV radiation is dangerous; and second, when DNA repair mechanisms are defective, cancers arise much more quickly.

Providing Circulation: Skin as a Nutritive Organ

The movement of cells and soluble elements to and from skin is mediated by two circulatory systems: (1) a two-way hematologic system that conducts blood flow; and (2) a one-way lymphatic system that returns leukocytes and interstitial fluids, first to draining lymph nodes and then, via the thoracic duct, into the central venous system. Hematologic circulation, the most obvious because of the red and blue colors of blood, serves three major functions: nutritional support, the delivery of leukocytes, and thermoregulation. Although the movement of oxygen and solutes from blood into interstitial tissues occurs largely by passive diffusion, the emigration of cellular elements from the vascular space occurs by a highly ordered sequence of signaling, attachment, and migratory processes that are described in Chapter 102.

The hematologic system includes two types of vessels: (1) nutritive vessels (arteries, capillaries and veins); and (2) anastomosing arteries and veins that participate in heat regulation. This latter system includes an extensive subcutaneous venous plexus, which can hold large quantities of blood (to dissipate heat from the surface of the skin), and arteriovenous anastomoses, which are direct connections between arterial and venous plexuses. These anastomoses are prominent in areas often exposed to maximal cooling, such as the volar surfaces of the hands and feet, lips, nose, and ears.

Cutaneous lymphatic drainage begins in microscopic, blind-ended, dermal vessels called lymphatic capillaries. These collect both cells and interstitial substances that are then directed toward regional lymph nodes. Lymphocytes, macrophages, and dendritic cells all have the capacity to exit the skin via lymphatic drainage. Stoitzner and colleagues[33] have provided an exquisite photographic description of Langerhans cells in their travels from epidermis to draining lymphatic vessels.

Failure of circulation: arteries and veins

Embolic occlusion of arteries

The most dramatic form of blood vessel occlusion occurs with embolimediated blockage, which can produce changes within hours. This is followed rapidly by necrosis of all cutaneous structures distal to that blockage. The extent of necrosis depends on the size of the vessel occluded, and occlusion due to non-infectious cholesterol emboli is usually associated with generalized arteriosclerotic cardiovascular disease. Occlusion followed by cutaneous necrosis demonstrates in vivid fashion the complete dependence of skin on arterial circulation.

Vasculitis

Cutaneous inflammation centered in the blood vessel wall is responsible for a spectrum of cutaneous findings that vary depending upon the size of vessel affected (Fig. 1.13). Vasculitis is commonly associated

with autoimmune connective tissue diseases, especially Sjögren syndrome, rheumatoid arthritis, and lupus erythematosus (Chs 24, 41 & 45). The critical element in terms of cutaneous structure is that, once again, the survival of skin is highly dependent upon an intact circulation.

Occlusive vasculopathy

Other disorders characterized by vascular occlusion result from aberrant coagulation or cold-related "gelling" (Ch. 23). Examples of hypercoaguable disorders include antiphospholipid antibody syndrome and factor V Leiden mutation leading to activated protein C resistance (Ch. 105).

Venous insufficiency

Although listed last, venous insufficiency through partial occlusion and valvular incompetence contributes to the most common vascular problem, the development of venous stasis ulcers of the legs (Ch. 105).

Failure of circulation: lymphatic blockage

Blockage of lymphatic drainage may also occur in certain inflammatory skin conditions. The inflammation associated with recurrent streptococcal and staphylococcal infections may lead to scarring and loss of lymphatic drainage, resulting in distal edema. With chronic infection, permanent edema may develop, associated with widespread verrucous change at the skin surface, a condition described as elephantiasis nostras verrucosa (Ch. 105). Likewise, blockage of lymphatic drainage in parasitic infections is known to cause deforming patterns of lymphedema (Ch. 83). It is also relevant that, many years ago, Frey and Wenk[34] demonstrated that ligation of lymphatic drainage caused a back-up of leukocytes unable to return from tissue sites as well as a failure to immunize against antigens that penetrated skin affected in this way.

Interfacing With External and Internal Environments: Skin as a Communicating Organ

Communication in skin occurs by three mechanisms: conventional nerve conduction via cutaneous fibers; intercellular signaling mediated by cytokines and hormones (endocrine, paracrine and autocrine effects); and the physical movement of "message-carrying" cells from one site to another. The roles and importance of these mechanisms have been revealed through various defects in their execution.

Skin is "wired" with afferent and efferent nerve fibers that accompany vascular structures, forming an intricate network within the dermis. They envelop the pilosebaceous apparatus (Ch. 68), blood vessels, and sweat glands. Although the head and distal extremities are innervated most densely, all skin contains nerves. Within the dermis, larger fibers are surrounded by a myelin sheath, but as diameters diminish, many fibers run free. In fact, most nerve fibers appear to end in the dermis, although there is clear evidence that some small endings penetrate the basement membrane and travel into the epidermis, where they have the capacity to modulate immune responsiveness[35]. Diminished or functionally impaired intraepidermal nerve fibers lead to neuropathic symptoms, including burning and pruritus[36].

Nerves control vascular tone, as demonstrated in blushing responses, and they mediate the sensations of heat, cold, itch, touch and pain (Chs 5 & 6). Defects in sensation and neurologic function occur commonly, and they may be seen in patients with postherpetic neuralgia, uncontrolled itching, neurologic syndromes (e.g. trigeminal trophic syndrome), and excessive sweating. A highly useful therapeutic development has been the intradermal injection of botulinum toxin to uncouple cholinergic nerve fibers. This technique has at least two dermatologic applications: (1) to decrease muscle tone, leading to a loss of facial lines for cosmetic purposes; and (2) to inhibit the excessive sweating that characterizes disabling axillary and palmar hyperhidrosis[37] (Ch. 159).

Abnormality of neurologic communication: excessive sensitivity

Itch is a major problem for patients with skin disease (Chs 5 & 6). We presume that modest levels of itching confer some beneficial effect, but, most certainly, excessive itching can be devastating to both personal and social activities. On the other hand, there is at present little evidence for structural abnormalities that predispose to excessive itching. Postherpetic neuralgia is similarly important (Ch. 80), although, once again, there is no obvious structural defect in this exquisitely painful disorder[38].

Abnormality of neurologic communication: excessive sweating

Hyperhidrosis is a potentially debilitating disorder of sweating, which commonly involves the axillae as well as the palms and soles. Accumulated evidence favors a neurologic abnormality rather than a structural abnormality[37]. Moreover, injection of botulinum toxin now offers considerable potential for relief (Ch. 159).

Abnormality of neurologic communication: decreased sensitivity

The most obvious and devastating effects of altered touch and pain sensation may be found in patients with the peripheral neuropathies that accompany leprosy[39] (Ch. 75) and diabetes mellitus[40] (Ch. 105). Similar problems may occur in patients under the influence of narcotic anesthesia. In each of these settings, the loss of sensory function leads to the failure of patients to recognize, and therefore avoid, cutaneous trauma. For patients with leprosy, numerous injuries over months and years lead to a gradual loss of tissue. In a similar fashion, a loss of cutaneous sensory function in patients with longstanding diabetes mellitus leads to unappreciated pressure ulcers in weight-bearing areas of the feet. In both of these conditions, a profound loss of sensation leads to unrecognized trauma to the skin, with consequent ulcer formation and loss of tissue. What we can learn from patients with these diseases is the exquisite vulnerability of skin to traumatic injury in the absence of appropriate sensation.

Communication via hormones and cytokines

Hormones

A relevant model for indirect hormonal influences on skin is adrenocorticotropic hormone (ACTH), which was recognized in classic studies as having systemic effects through the induced secretion of adrenal corticosteroids. This, in turn, had temporarily beneficial effects on inflammatory skin disorders such as psoriasis (Ch. 8) and atopic dermatitis (Ch. 12). On the other hand, a model for pathologic changes induced by inappropriate secretion of hormones is seen in the effects of the catecholamine hormones and their precursors (norepinephrine, epinephrine or dopamine) in patients with vascular instability caused by pheochromocytomas. Likewise, several of the clinical signs of Cushing disease (altered fat distribution, vascular dilation, and striae) result from excessive secretion of corticosteroids (Ch. 53). In contrast, diminished production of adrenocortical hormones causes excessive secretion of ACTH, which, in turn, gives rise to the hyperpigmentation seen in patients with Addison disease (Ch. 67).

Skin also plays a unique hormonal role in calcium metabolism. Vitamin D_3 (cholecalciferol) is produced in the epidermis by the action of UV radiation on 7-dehydrocholesterol[9]. It then leaves the skin and is hydroxylated in the liver and kidneys to the active form of vitamin D (1,25-dihydroxycholecalciferol; see Fig. 51.11).

Cytokines

Over the past 30–40 years, a new field of cutaneous knowledge has evolved, beginning with the recognition that keratinocytes contain large amounts of the biologically active cytokine interleukin-1 (IL-1)[41]. This was followed in rapid succession by the recognition that cells within skin are able to produce an array of biological response modifiers. Most prominently, keratinocytes produce IL-1, IL-8, and TGF-β[42]. The capacity of these substances to exert important physiologic functions is demonstrated by the beneficial effect TGF-β has on wound healing[43]. Looking at other cutaneous cells, Langerhans cells produce a unique spectrum of cytokines and chemotactic factors related to their immunologic properties[44]. Vascular endothelial cells produce IL-1β, IL-6, and IL-8[45]. In fact, cytokine-mediated communication within the skin is an active area of research[42, 46–49], and the interplay between cytokines and cells is often reciprocal[50,51]. For example, mast cells produce tumor necrosis factor (TNF), which affects cutaneous immunity[52], but, at the same time, mast cell function is regulated by other cytokines[53]. Unraveling the complex relationships among cutaneous cells, their own hormones (autocrine), hormones from adjacent cells (paracrine), and hormones from distant cells (endocrine) will occupy the attention of skin biologists and skin pharmacologists for the next generation.

Cellular communication

We have only recently begun to appreciate that certain resident cutaneous cells, in the course of their normal function, depart from the skin while in possession of information that ultimately has direct impact on the function of the skin. Chief among these cells are dendritic cells, which, after activation, leave the skin and traffic to regional lymph nodes. In this location, they select and prime naive and resting T lymphocytes (Ch. 4). The processes of activation, outward migration, and repopulation have been areas of intense investigation, with the prospect of developing methods by which immunity may be modulated.

Failure of cytokine and cellular communication

Knowledge about the roles of cytokines and cell traffic in cutaneous communication is as yet in its infancy, meaning that defects are only now being recognized. Stemming from an improved understanding of the role of cytokines in keratinocyte biology, major developments in dermatologic therapy have been achieved over the past 15 years in the management of inflammatory skin diseases, most notably psoriasis. Aberrant levels of TNF-α, IL-17, and IL-23 have emerged as critical targets of immunobiologic agents used to treat psoriasis. As our understanding of cytokine biology increases, new developments in targeted therapy will continue to expand our therapeutic armamentarium.

Regulating Temperature: Skin as a Thermoregulatory Organ

Regulation of core temperature is a characteristic of all mammals, which, by definition, are euthermic. For humans, core temperature is maintained at approximately 37°C (98–99°F). Because environmental influences tend to change that temperature, there exists an intricate system of regulation in which skin plays a decisive role as both radiator and insulator. Temperature regulation by the skin is effected primarily through evaporative cooling after eccrine sweating (Ch. 39) and through vasodilation and vasoconstriction.

Human skin includes several million eccrine sweat glands distributed over most of its surface, with the total mass of eccrine glands approximately that of one kidney. Under neurologic control, the secretory activity of eccrine sweat glands consists of two major activities: (1) secretion of an ultrafiltrate of a plasma-like fluid; and (2) reabsorption of sodium by the duct to produce hypotonic sweat.

Failure of thermoregulation: effects of excessive heat

Excessive heating may be local or systemic, and, when this occurs, skin plays a cooling role to prevent injury. Cooling may be required under two non-exclusive circumstances: (1) in response to central heating, which occurs when heat enters skin from an external source or when energy is generated through muscular exertion in amounts sufficient to increase core temperature; and (2) in response to sustained local heating, which occurs when a portion of skin is heated to a temperature at which critical proteins begin to denature, i.e. in the neighborhood of 45–50°C (113–122°F; Ch. 88). The subsequent physiologic responses that lower temperature to prevent injury require innervation, circulation, and successful sweating. Dispersion of local heat takes place by direct radiation into the environment and by heat transfer to other body locations via circulating blood. In contrast, the elimination of central heat occurs through radiation from the skin surface and from the evaporative cooling that follows sweating.

The relevance of sweating to the elimination of heat, and, ultimately, to survival may be found in the vignette of hyperthermia found at the beginning of this chapter. In this patient with the X-linked genetic disorder hypohidrotic ectodermal dysplasia, the defining defect is a nearly complete absence of sweat glands, in association with other features such as hypotrichosis and abnormal teeth (Ch. 63)[54]. This disease demonstrates the importance of sweating, as death from overheating during exercise is known to occur, especially when the environmental temperature is high. It is of interest that since evaporative cooling normally plays no role in these patients, there is virtually no effect of environmental humidity on core temperature, because all heat loss occurs through radiation. On the other hand, heat loss may be increased substantially by a relatively simple measure that allows patients with this disease to engage in vigorous outdoor activities in hot climates. Exogenous "sweat" may be created by spraying water over the body repeatedly throughout an exercise or event[54].

Heat injury as therapy

The production of local heat injury may also have a beneficial side, as electrocautery is a time-honored method of therapy in cutaneous medicine (Ch. 140). Additionally, heat therapy has been used in the management of cutaneous infections, including sporotrichosis and leishmaniasis.

Failure of thermoregulation: effects of excessive cold

In contrast to heat injury, individuals exposed to cold temperatures require heating to prevent injury. This also occurs under two related circumstances: (1) in response to heat loss to the environment in amounts that cool the body centrally (hypothermia); and (2) in response to exposure locally to sustained temperatures below freezing, which otherwise would lead to direct freezing injury ("frostbite"). With extreme exposure, of course, both may occur together.

Extreme examples of excessive core and surface cooling in association with limited central heat generation were described vividly by Jon Krakauer in his report of the Mount Everest climbing disasters of 1996[55]. Unfortunately, aside from vascular constriction to reduce radiation of heat from the skin surface and shivering (or exercise) to increase central heating, there are no intrinsic cutaneous mechanisms to protect against excessive cooling. However, humans have become quite adept at creating artificial methods to prevent cold or heat injury through clothing and shelter. These have enabled humans, and consequently human DNA, to survive successfully in geographic areas of extreme temperature. Perhaps the most obvious are the mountain climbers who scale the Himalayan mountains and the firefighters who wear insulated clothing as they enter burning buildings.

Cold injury as therapy

When properly applied, local cold injury (e.g. cryosurgery) has been used successfully as a therapeutic tool for decades (Ch. 138).

Interpersonal Communication: the Skin Conveys Beauty, Attracts Attention and Contributes to Self-Identity

An important function of skin begins with the need for humans to communicate with each other so that personal and societal goals can be met. The skin plays an important role in interpersonal communication by conveying beauty to others, attracting attention, and contributing to the development and expression of self-identity.

The presence of beauty, as seen in photographs or paintings, tends to attract attention, which is sometimes intense. It is easy to imagine that these responses are coded genetically, because high attractiveness would seem to increase the likelihood that DNA survives and also, therefore, that the species survives. In sum, without any confirming data, we assert that the desire to be attractive helps to insure the selective survival of human DNA.

Virtually all attraction that occurs at a distance beyond that of touch and smell is mediated by vision, and, thus, the skin assumes overwhelming importance as a visual target for humans. Having said this, it should not be surprising that in every society, the physical appearance and condition of the skin seems to have assumed fundamental importance. There is not sufficient space to list the physical features that are considered beautiful, but let us assert that the loss of these features has much to do with the anxiety that often characterizes patients with acne, vitiligo, alopecia, aging and photoaging, as well as virtually all other skin diseases. Over the past two decades, increasing attention has been given by both researchers and clinicians to the effect of skin disease on quality of life. Myriad reports have been published defining the extent to which chronic skin diseases, including psoriasis, eczema and pigmentary disorders, affect the way in which patients perceive themselves. As dermatologists become more aware of the psychosocial impact of chronic skin disease, we are better able to treat patients with these conditions.

Finally, the skin represents a "canvas" onto which individuals may make modifications in order to communicate with each other and to display aspects of self-identity. Tattoos, ritual scarification, and piercings have long been seen as expressions of self-identity. Dermatologists can participate in skin modification by interventions meant to improve

the attractiveness of the patient. Many dermatologists now practice cosmetic surgery and procedures, repairing a variety of defects and moving fat from one site to another. During the last 25 years, increasing amounts of discretionary money have been diverted into procedures that improve appearance (Chs 152–159). Dermatologists and their patients have played major roles in this transition.

Failures to present an attractive appearance

Appropriately proportioned, symmetric, unblemished skin seems to be preferred in the majority of societies. Our question at this point concerns the types of changes that are considered to be "defective". The defects that are most disagreeable do vary from culture to culture, so that one cannot assume that what is unattractive in one culture is necessarily unattractive elsewhere.

Pigmentary turmoil

Pigmentary disorders tend to be more pronounced, and thus more important, in populations with greater amounts of constitutive pigmentation. For this reason, Western cultures, which until recently have been derived primarily from European immigrants, may underestimate the critical role of pigmentation throughout the world. Although dermatologists care for patients who have many different disorders of pigmentation, two diseases predominate: vitiligo (Fig. 1.14) (Ch. 66)[56] and melasma (Ch. 67).

The preference for unblemished skin is exceedingly important in cultures in which altered pigmentation may be confused with leprosy (Ch. 75) or viewed as hereditary. In Indian culture, for example, it is not uncommon for the discovery of vitiligo to invalidate a marriage contract[57]. The defect in vitiligo is the absence of epidermal melanocytes after physical destruction guided by autoimmune influences. Not only is vitiligo an important disease in its own right, the associated autoimmune phenomena have profound implications for melanoma therapy (Ch. 113).

Likewise, melasma has a high frequency in Hispanic individuals in the Americas, and it is often extraordinarily distressing[58] (Ch. 67). It is not uncommon to observe that money for necessities may be diverted to this seemingly inconsequential problem.

Inappropriate hair distribution

Hair performs no vital function for humans in the twenty-first century, as body hair can be removed without any physiologic disadvantage. By contrast, the psychologic contributions of hair for many humans cannot be underestimated. Scalp hair is a major social and sexual display feature for humans. The biology of hair and hair growth is detailed in Chapter 68, and additional information may be found in other useful references[59,60]. A discussion regarding excessive hair may be found in Chapter 70 and elsewhere[61]. Two phenomena predominate in concerns about hair: (1) too much hair in the wrong place; and (2) not enough hair in the right place. Too much hair in the wrong place occurs in congenital and acquired forms of hypertrichosis, in response to therapy with minoxidil and cyclosporine, and as a manifestation of androgen excess (Ch. 70). However, the vast majority of patients who seek help for excessive hair do so primarily for cultural reasons.

In terms of insufficient hair (Ch. 69), three diseases predominate: (1) androgenetic alopecia in men; (2) female pattern alopecia in women[62]; and (3) alopecia areata (Fig. 1.15). Hair transplantation has become a popular procedure performed by dermatologists (Ch. 157).

Undesirable fat distribution

With the possible exception of hemifacial atrophy and lipodystrophy syndromes, indications for the absolute removal and for the movement of fat are based on psychologic needs rather than on abnormalities in the structure of the skin and subcutaneous tissues. Nevertheless, the movement of fat is becoming a fairly common procedure and, once again, dermatologists are playing increasingly important roles in this arena[63] (Ch. 156).

The next steps

We could go on at length about dermabrasion for acne scars, rejuvenation protocols, blepharoplasties, and other techniques to reverse the effects of aging. However, the point has been made. What we propose is that anxiety about appearance is genetically programmed. The discipline of cosmetic dermatology has arisen to address that anxiety, with the important goals of alleviating scars, hiding defects, and preventing photoaging.

An Important Corollary, With an Eye to the Future

In this introductory chapter, we have asserted that the structure and function of skin is revealed through careful study of skin disease. An important corollary to this statement becomes apparent when we apply our knowledge of skin disease to patient care: the structure and function of skin is also revealed by observing the outcomes of our specific interventions. For example, study of signaling pathways involved in tumorigenesis, including the RAS/RAF/MEK/ERK pathway, led to the discovery of BRAF V600E (due to activating mutations) in 40–60% of cutaneous melanomas. Selective inhibitors of BRAF V600E lead to rapid clinical responses in patients with metastatic melanoma, but paradoxical activation of downstream signaling in cells with wild-type BRAF leads to enhanced proliferation. In the case of keratinocytes, keratoacanthomas and SCCs develop[64,65]. Because of the development of resistance within months with the sole use of BRAF V600E inhibitors[66], patients are now treated with a combination of BRAF and MEK inhibitors and the incidence of keratoacanthomas and SCCs has been

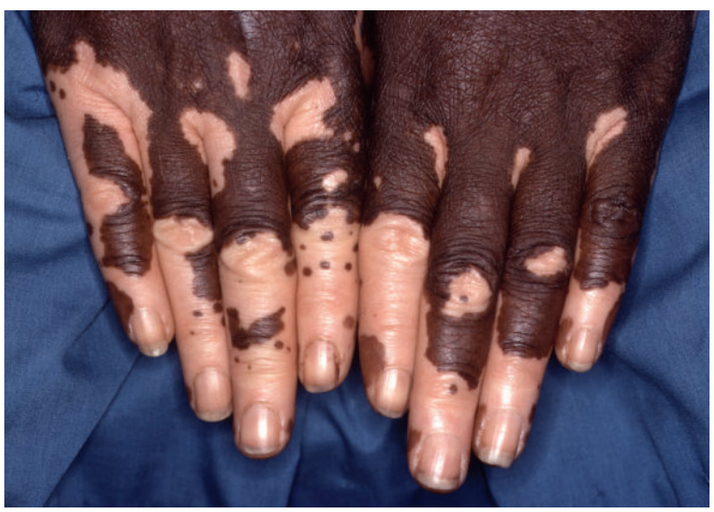


Fig. 1.14 Vitiligo in an African-American man. The digits are a common site of involvement and repigmentation of the distal fingers can prove challenging due to the lack of hair follicles. Vitiligo and other pigmentary disorders are much more obvious in patients with darker skin phototypes.

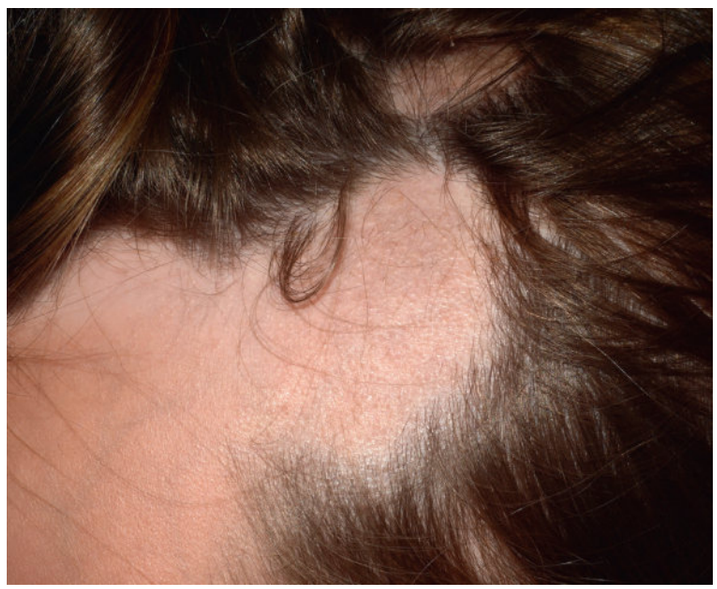


Fig. 1.15 Circumscribed area of hair loss due to alopecia areata. The detrimental social impact of hair loss in patients with diseases such as alopecia areata cannot be underestimated.

markedly reduced. Many more such observations are bound to follow as we continue to develop new ways of treating skin disease. Furthermore, the acuity of our power to observe changes in the skin will be aided by advances in technology, including artificial intelligence. If we remain curious about the diseases we treat, the potential for additional discoveries regarding the structure and function of skin is endless.

Acknowledgment

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For additional online figures visit www.expertconsult.com

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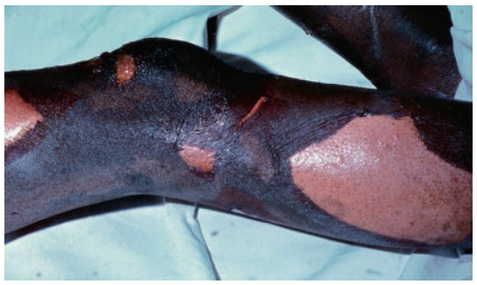
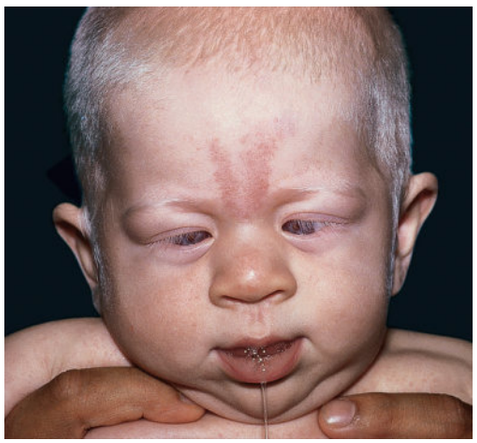
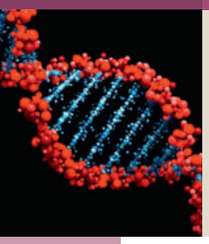


eFig. 1.1 Toxic epidermal necrolysis. Full-thickness epidermal cell death leads to stripping off of the epidermis. In this African patient, it becomes apparent that melanin is located predominantly in the epidermis.



eFig. 1.2 Albinism in an infant. Note the normally pigmented fingers of the child's mother. Patients with albinism are at substantially higher risk for UV radiation-induced carcinogenesis.



2 Skin Development and Maintenance

Isaac Brownell, Cynthia A. Loomis and Tamara Koss

Chapter Contents

INTRODUCTION

Development of the human embryo is a complex process involving highly orchestrated cell movements, proliferation, death, and differentiation. This chapter focuses on key events and regulatory mechanisms that result in skin morphogenesis, maintenance, and regeneration. The spectrum of cutaneous abnormalities that can result from mutations in genes with critical roles in skin development is discussed. Ultimately, improved understanding of the pathways and signaling cascades that are disrupted in genetic skin disorders will aid in the development of therapeutic approaches for patients with acquired as well as inherited skin disorders.

EMBRYONIC ORIGIN OF THE SKIN

The skin is composed of diverse cell types of both ectodermal (e.g. keratinocytes, melanocytes, Merkel cells, neurons) and mesodermal (e.g. fibroblasts, hematopoietic cells such as Langerhans cells, endothelial cells) lineages. To understand the origins of these cells, it is important to review the early stages of embryogenesis. Immediately after fertilization, cells divide rapidly, and by the end of the first week, the embryo begins to implant into the uterine wall. During the third week, the embryo undergoes gastrulation, a complex process resulting in the formation of the three embryonic germ layers: endoderm, mesoderm, and ectoderm.

During the next stage of embryogenesis, ectodermal cells commit to either a surface ectodermal or neuroectodermal fate. The surface ectodermal cells eventually differentiate into the keratinocytes of the embryonic epidermis, whereas the neuroectodermal cells invaginate to create the neural tube in a process called neurulation. As the neural tube forms, cells in its dorsal portion separate to form the neural crest. An important neural crest-derived cell in the skin is the melanocyte. Although Merkel cells were once believed to be neural crest derivatives, it has now been established that they descend from the epidermal lineage. The lineage of the dermis depends on the body site. The dermis (and other mesenchymal structures) of the face and frontal scalp are derived from the neural crest, whereas the dermis elsewhere is derived from the mesoderm. Knowing from which germ layer and lineage different cell types in the skin derive helps one to understand the pathophysiology of cutaneous disorders such as Waardenburg syndrome in which craniofacial dysmorphism and hearing impairment as well as pigmentary abnormalities reflect disrupted migration and survival of neural crest-derived cells.

An overview of key events in the development of skin and its specialized structures is shown in Fig. 2.1.

EPIDERMAL DEVELOPMENT

The ectoderm that covers the developing embryo after gastrulation is a single-layered epithelium (Fig. 2.2A). The first step in epidermal development occurs when cells of the surface ectoderm adopt an epidermal fate[1]. Although this process does not result in major morphologic changes, it is marked by dramatic alterations in gene expression that result in the formation of the embryonic epidermis, which initially consists of a simple epithelium (Fig. 2.2B). Primitive keratinocytes subsequently generate cells of the periderm, a single cell layer that covers the developing epidermis until the cornified cell layer is formed (Figs 2.2C–F & 2.3A,B). The periderm is believed to exchange substances across fetal skin and to protect the developing epidermis from forming interepithelial adhesions.

The embryonic epidermis begins to stratify at approximately 8 weeks' estimated gestational age (EGA)[2]. At this time, basic organogenesis is complete and bone marrow hematopoiesis commences, marking the transition from embryo to fetus. Of note, expression of *TP63* is required for epidermal stratification. During the first stage of stratification, an intermediate cell layer is formed between the basal layer and periderm (see Figs 2.2D & 2.3B). Unlike suprabasal keratinocytes in the postnatal epidermis, the intermediate layer consists of actively proliferating cells. As a consequence, it is able to expand to accommodate the rapid growth of the embryo as well as create additional layers of intermediate cells over the next several weeks (see Fig. 2.2E). However, the intermediate cell layer is ultimately replaced by post-mitotic keratinocytes undergoing terminal differentiation.

Terminal differentiation, the process resulting in the formation of mature keratinizing epidermal cells, begins during the second trimester. Early cornification can be observed within the hair canal at approximately 15 weeks' EGA[3], but it does not commence in the interfollicular epidermis until 22–24 weeks' EGA, occurring first in the skin on the head, palms, and soles. The process begins when cells in the intermediate layer permanently withdraw from the cell cycle and differentiate into spinous and granular cells (see Fig. 2.2F). The cornified cell layer, which is composed of "dead" keratinocytes (corneocytes) held together by a matrix of proteins and lipids (see Chs 56 & 124), subsequently starts to form and is several cells thick by 24–26 weeks' EGA. The corneocytes are a reflection of the closely regulated process of terminal differentiation that is required for normal functioning of the skin. At the time of keratinization, the periderm detaches from the underlying epidermis and is sloughed off into the amniotic fluid, with remnants contributing to the vernix caseosa that coats newborns. During the third trimester, the number of keratohyalin and lamellar granules as well as stratum corneum layers increases. By the mid third trimester, the epidermis is morphologically similar to adult skin (Figs 2.2G & 2.3C), although it does not acquire full barrier function until a few weeks after birth.

Clinical Relevance

Genetic abnormalities affecting various stages of epidermal morphogenesis have been found to underlie inherited skin disorders in humans. However, generalized abnormalities in epidermal specification, the process through which the surface ectoderm adopts an epidermal fate, have not been identified. It is likely that generalized epidermal defects would be incompatible with survival past the first trimester. Mosaic skin conditions that result in abnormalities of the epidermis and/or its appendages often have a distribution pattern that follows the lines of

ABSTRACT

This chapter focuses on key events and regulatory mechanisms that result in the morphogenesis, maintenance, and regeneration of the skin and its appendages. Understanding skin development provides essential insights into genetic skin diseases and facilitates the development of therapeutic approaches to acquired as well as inherited disorders. Maintenance and repair of the skin are dependent on skin stem cells with multiple independent progenitor pools that have diverse biological potential and regulatory mechanisms. Harnessing stem cells for therapy, either directly or by reprogramming them into pluripotent stem cells, holds great promise.

KEYWORDS:

skin development,
skin differentiation,
ectoderm,
neural crest,
mesoderm,
hair development,
skin maintenance,
skin repair,
epidermal stem cells,
bulge stem cells

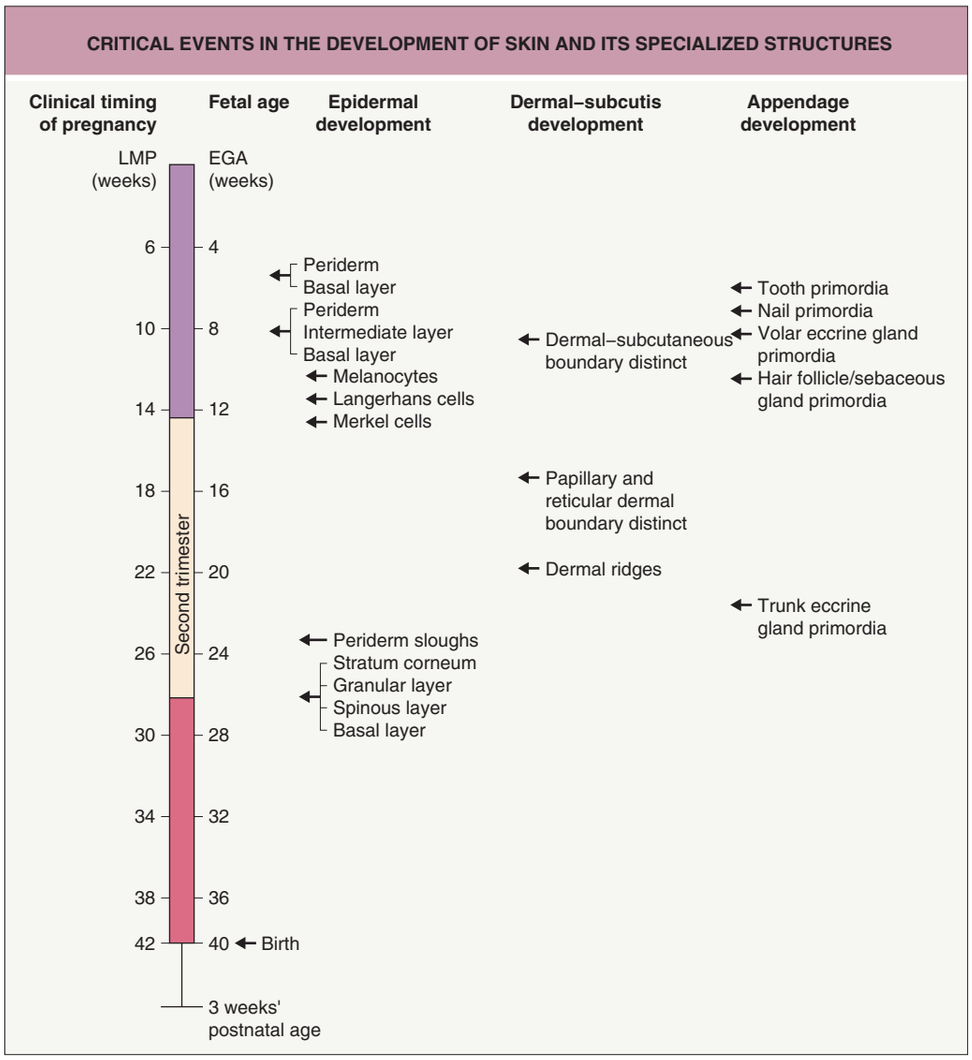


Fig. 2.1 Critical events in the development of the skin and its specialized structures. The timeline indicates the time of initiation defined by estimated gestational age (EGA) and duration of pregnancy (by last menstrual period [LMP]). Refers to skin on the back unless otherwise noted.

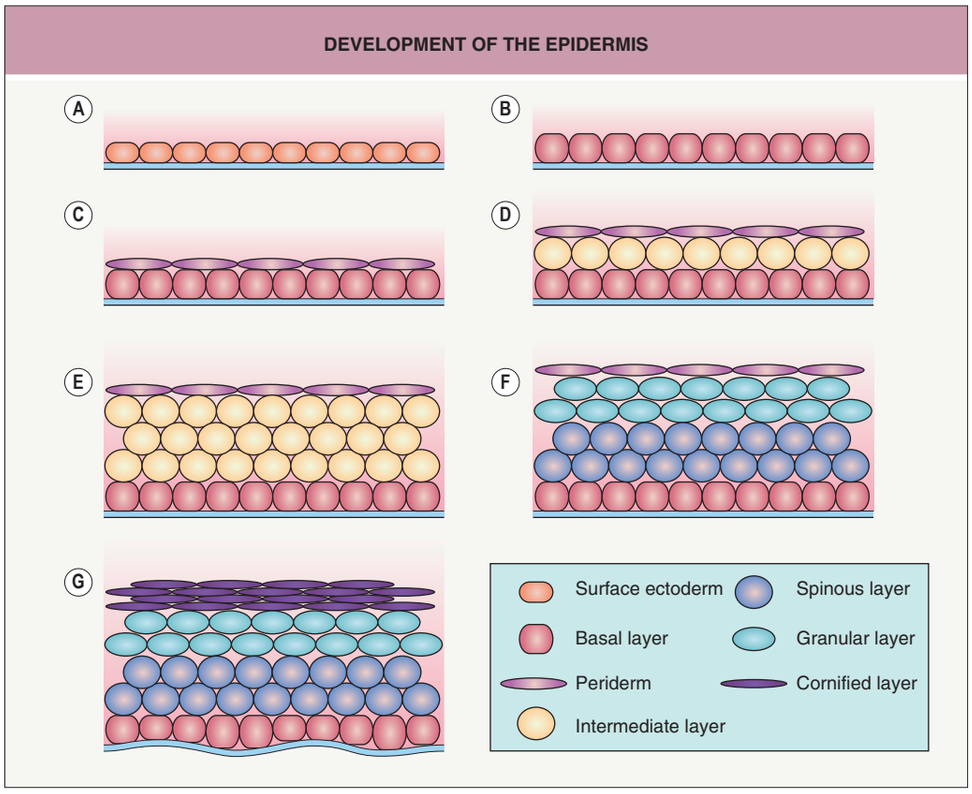


Fig. 2.2 Development of the epidermis. A The epidermis develops from the surface ectoderm, a single-layered epithelium that initially covers the developing embryo. **B** Through changes in gene expression, cells of the surface ectoderm adopt an epidermal fate. **C** Epidermal cells subsequently give rise to the periderm, a cell layer that covers the developing epidermis until cornification occurs. **D** Epidermal stratification begins with the formation of a highly proliferative intermediate layer between the basal layer and the periderm. **E** The intermediate layer becomes several cells thick over the next few weeks. **F** Intermediate cells ultimately withdraw from the cell cycle and differentiate into spinous and granular keratinocytes. **G** The periderm is replaced by the cornified cell layer.