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

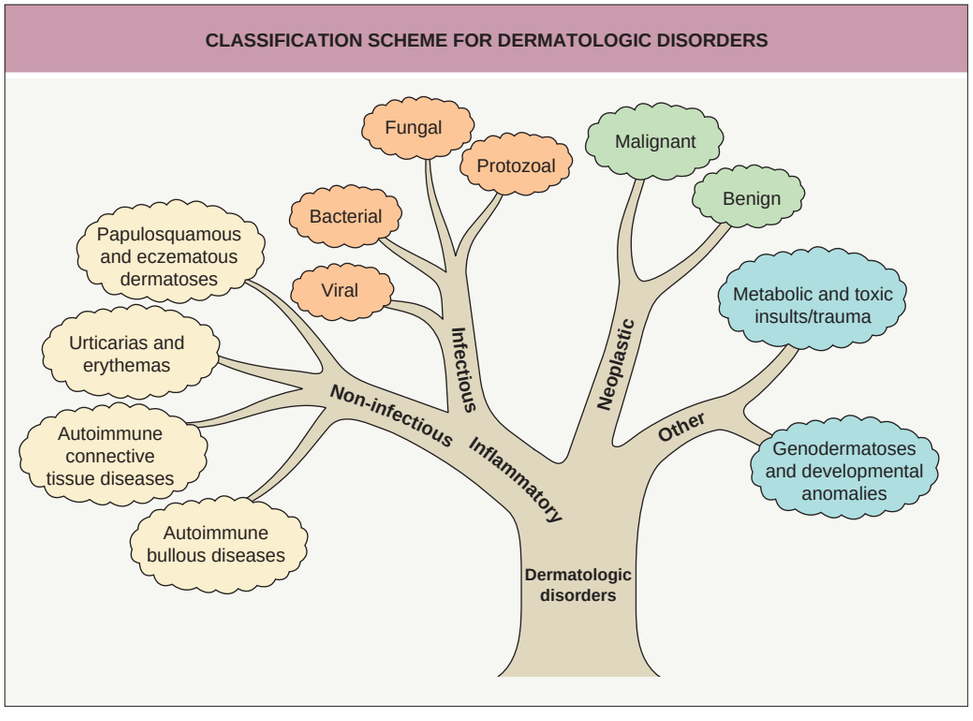


Fig. 0.1 Classification scheme for dermatologic disorders. The "trunk" of dermatology divides into the major etiologic "branches" of inflammatory, neoplastic, and other. Branches narrow and further subdivide, e.g. inflammatory into infectious and non-infectious. Branches ultimately terminate as clustered 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,
skin biopsy,
pattern analysis,
immunohistochemistry,
special stains,
inflammatory diseases,
invisible dermatoses,
clinicopathologic correlation

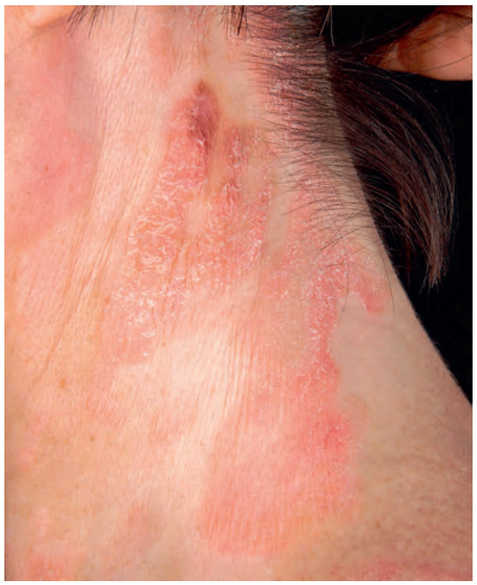


Fig. 0.2 Mycosis fungoides, the most common form of cutaneous T-cell lymphoma. Mycosis fungoides represents a neoplastic proliferation of monoclonal lymphocytes, but it presents clinically in a manner akin to that of inflammatory disorders. *Courtesy, Lorenzo Cerroni, MD.*

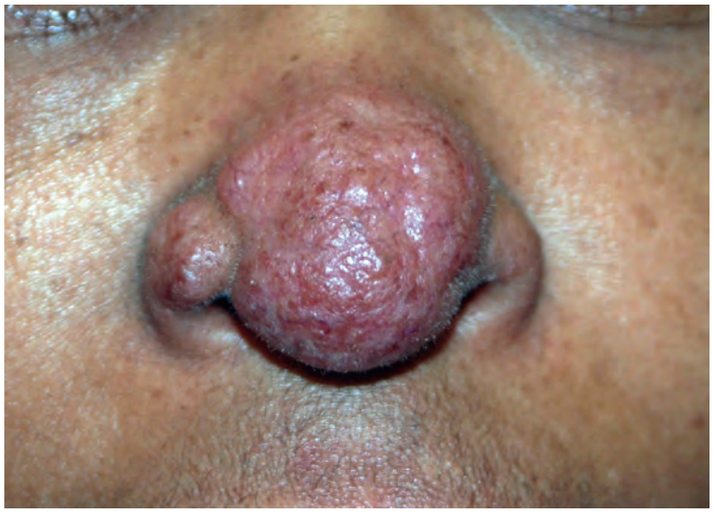
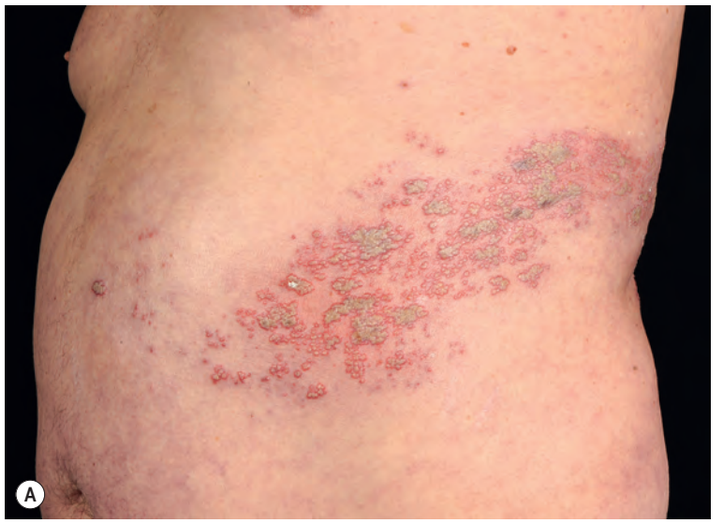


Fig. 0.3 Sarcoidosis. It is an inflammatory disorder of uncertain etiology, most prevalent in African-Americans from the southern United States, but sarcoidosis can present as a papulonodule or infiltrated plaque, mimicking a neoplastic disorder.



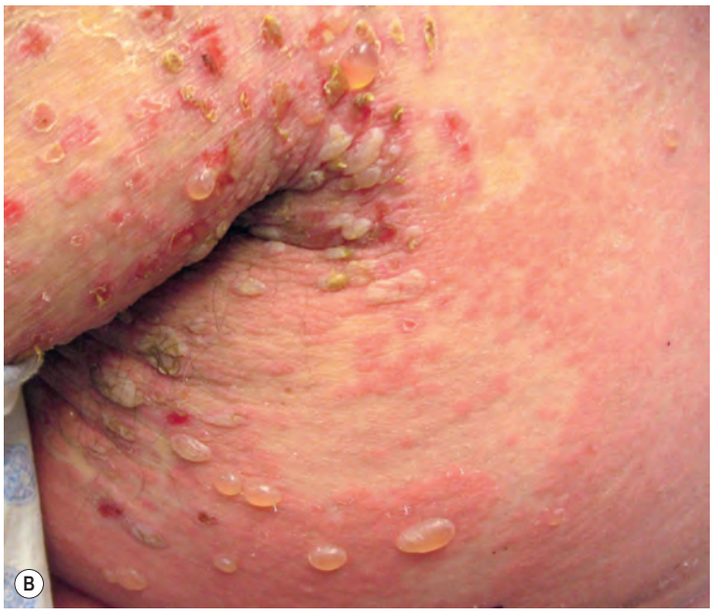


Fig. 0.4 Herpes zoster, an infectious disease, versus bullous pemphigoid, an autoimmune bullous disease. While disparate in etiology, herpes zoster (**A**) and bullous pemphigoid (**B**) result in a similar morphology – namely, cutaneous vesicles and bullae. *A, Courtesy, Lorenzo Cerroni, MD.*

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).

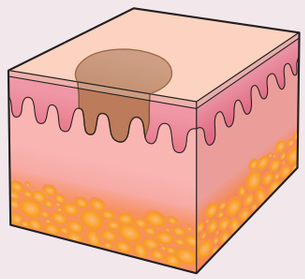
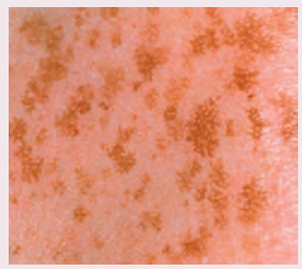
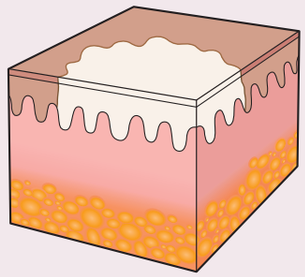
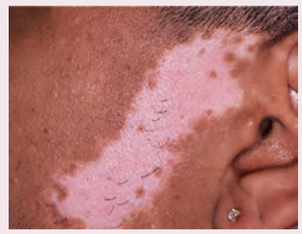
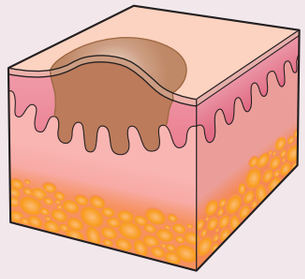
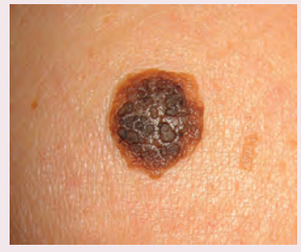
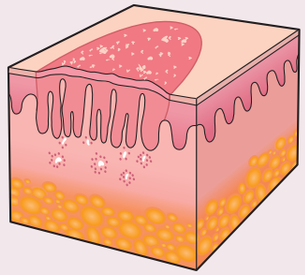
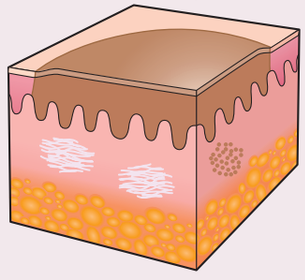
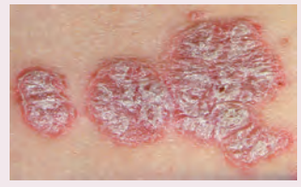
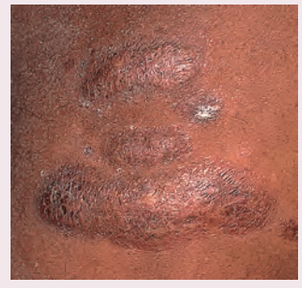
PRIMARY LESIONS – MORPHOLOGICAL TERMS				
Term	**Clinical features**		**Clinical example**	**Clinical disorders**
Macule	• Flat (non-palpable), circumscribed, differs in color from surrounding skin • <1 cm in diameter • Often hypo- or hyperpigmented, but also other colors (e.g. pink, red, violet)		 Solar 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

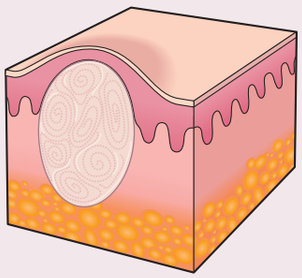
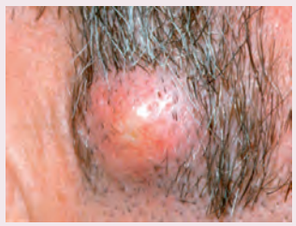
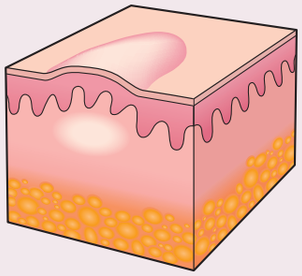
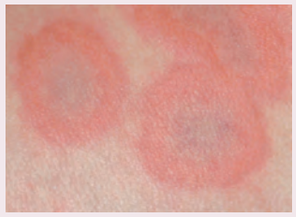
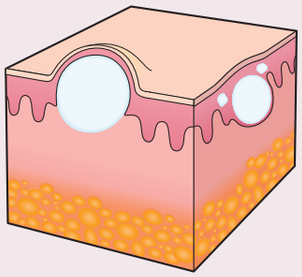
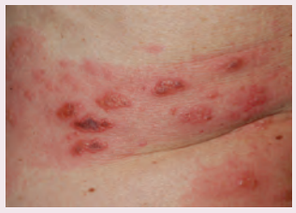
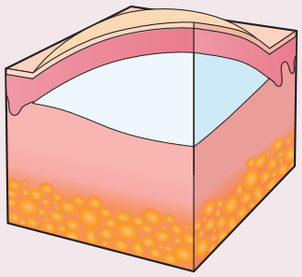
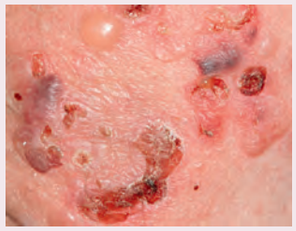
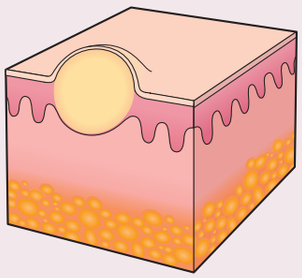
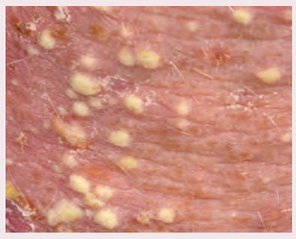
PRIMARY LESIONS – MORPHOLOGICAL TERMS				
Term	**Clinical features**		**Clinical example**	**Clinical disorders**
Nodule	• Palpable, circumscribed • Larger volume than papule, usually >1 cm in diameter • Involves the dermis and/or the subcutis • Greatest portion may be beneath the skin surface or exophytic		 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)

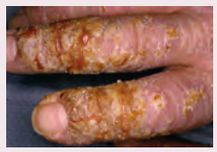
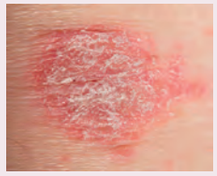
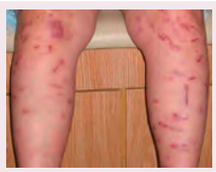
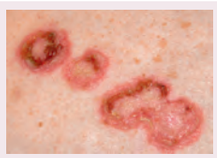
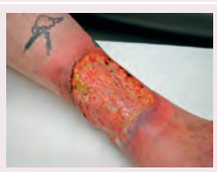
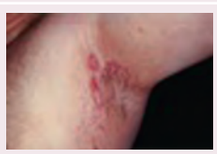
SECONDARY FEATURES – MORPHOLOGICAL TERMS			
Feature	**Description**		**Disorders**
Crust	• Dried serum, blood or pus on the surface of the skin • May include bacteria (usually *Staphylococcus*)	 Secondarily infected hand dermatitis	• Eczema/dermatitis (multiple types) • Impetigo • Later phase of herpes 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

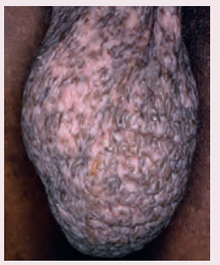
SECONDARY FEATURES – MORPHOLOGICAL TERMS			
Feature	**Description**		**Disorders**
Lichenification	• Accentuation of natural skin lines, reflecting thickening (acanthosis) of the epidermis • Often due to rubbing	 Lichen simplex chronicus	• Lichen simplex chronicus, isolated or superimposed on a pruritic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

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

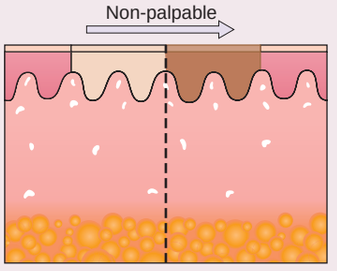
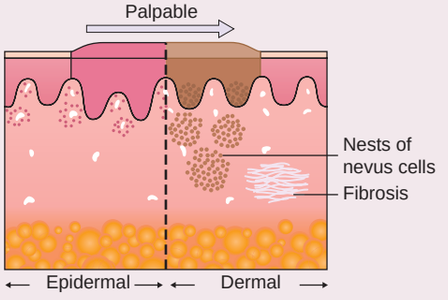
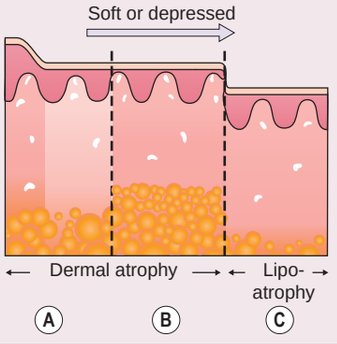
USE OF PALPATION IN DEFINING CUTANEOUS LESIONS			
Types of lesion			**Examples**
Macules & patches (non-palpable)			• Solar lentigines • Idiopathic guttate hypomelanosis • Melasma • Vitiligo • Petechiae • Dermal melanocytosis
Papules & plaques (palpable)			• Psoriasis • Lichen planus • Dermatitis • Intradermal 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

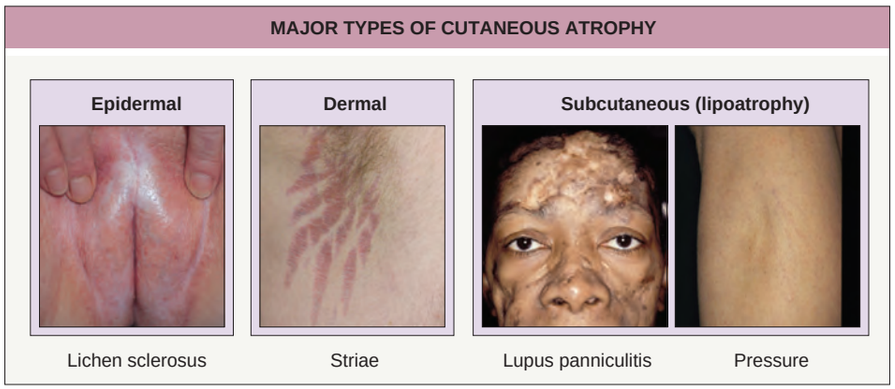


Fig. 0.5 Major types of cutaneous atrophy. *Photos courtesy, Jean L Bolognia, MD.*

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.

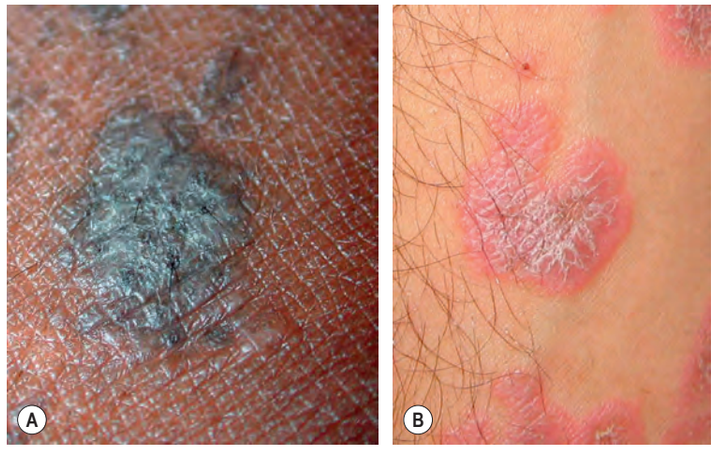


Fig. 0.6 Lichen planus presents differently in darkly pigmented versus lightly pigmented skin. A,B The erythematous to violaceous hue seen in lightly pigmented skin is more muted in darkly pigmented skin and the lesions appear brown–black in color. Wickham striae (lacy white pattern) are more easily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

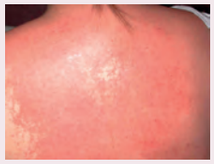
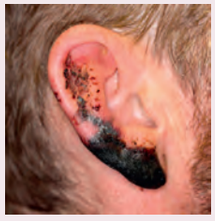
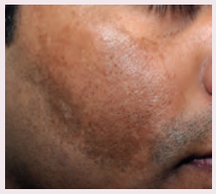
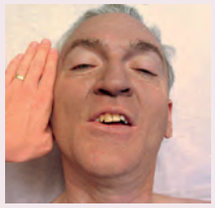
After carefully considering the morphology and color of skin lesions, the dermatologist must next analyze two closely related properties – configuration and distribution – in order to hone in on the correct diagnosis. For example, pruritic and fragile vesicles on the elbows and knees would prompt consideration 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)

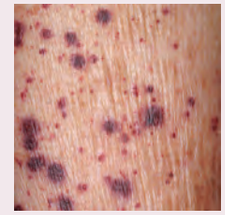
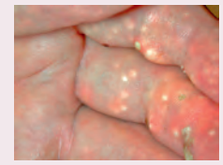
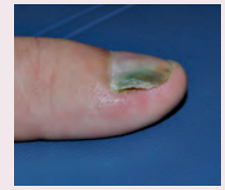
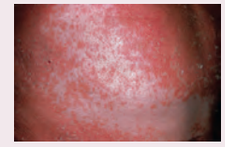
Color	Examples of diseases with this color
Purple (violaceous)  Palpable purpura of cutaneous small vessel vasculitis	• Purpura, non-palpable (e.g. solar purpura) • Purpura, palpable (e.g. small vessel vasculitis) • Vascular neoplasms (e.g. angiokeratoma, angiosarcoma) • Lichen planus • Lymphoma cutis • 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

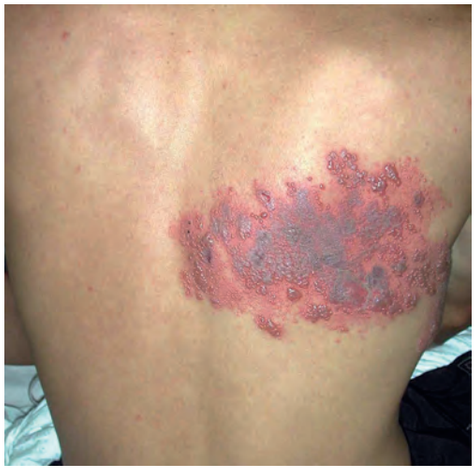


Fig. 0.7 The dermatomal pattern of herpes zoster. Note the midline demarcation.

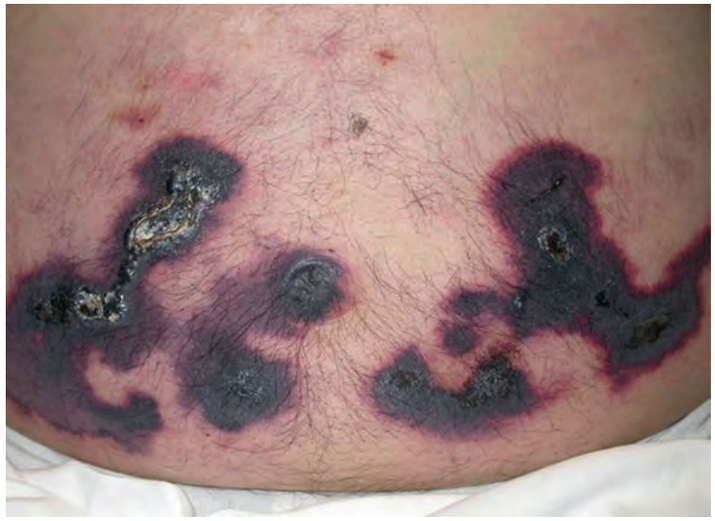


Fig. 0.8 Retiform purpura and cutaneous necrosis secondary to calciphylaxis. Note the irregular shape of the purpura. *Courtesy, Amanda Tauscher, MD.*

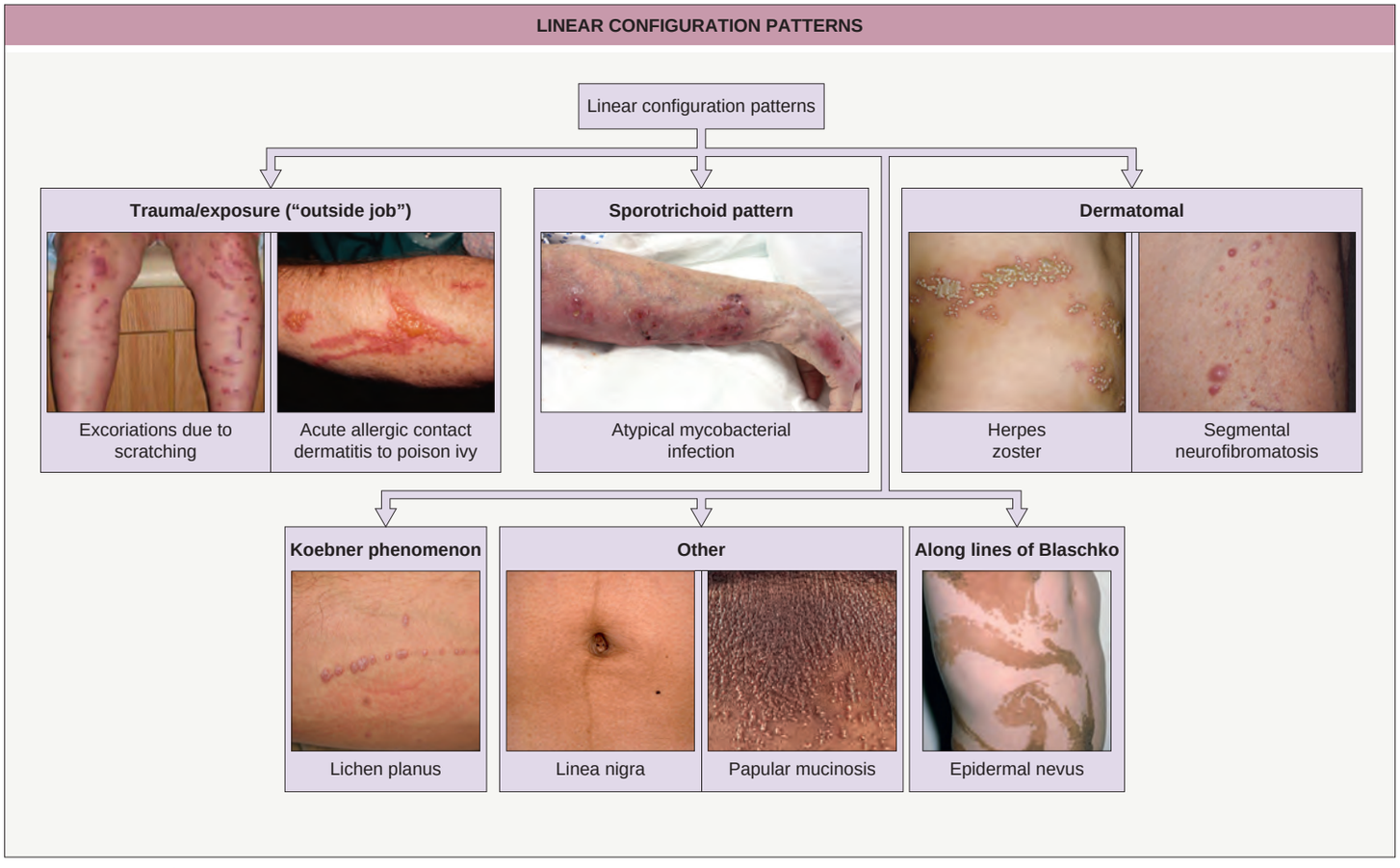


Fig. 0.9 Linear configuration patterns. *Some of the photographs courtesy, Jean L Bolognia, MD; Edward Cowen, MD; Louis A Fragola, Jr, MD; Joyce Rico, MD; Kathryn Schwarzenberger, MD.*

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).

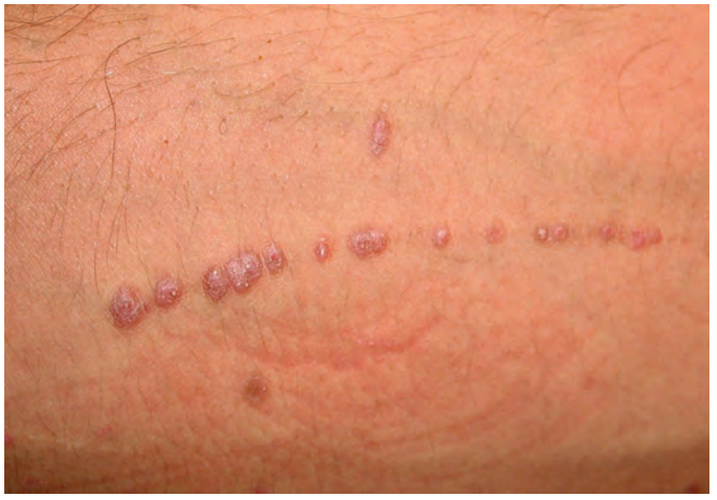


Fig. 0.10 Koebernization (isomorphic response) of lichen planus secondary to trauma. As a result, the lesions have a linear configuration.

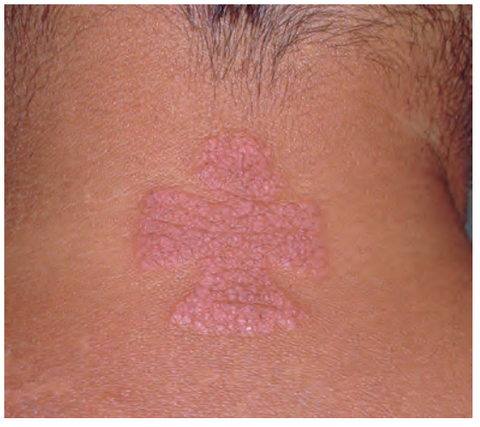


Fig. 0.11 Allergic contact dermatitis to a para-phenylenediamine-based ("black henna") temporary tattoo. The shape of the lesion clearly suggests an exogenous insult/etiology. *Courtesy, Colby Evans, MD.*

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.

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).

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.

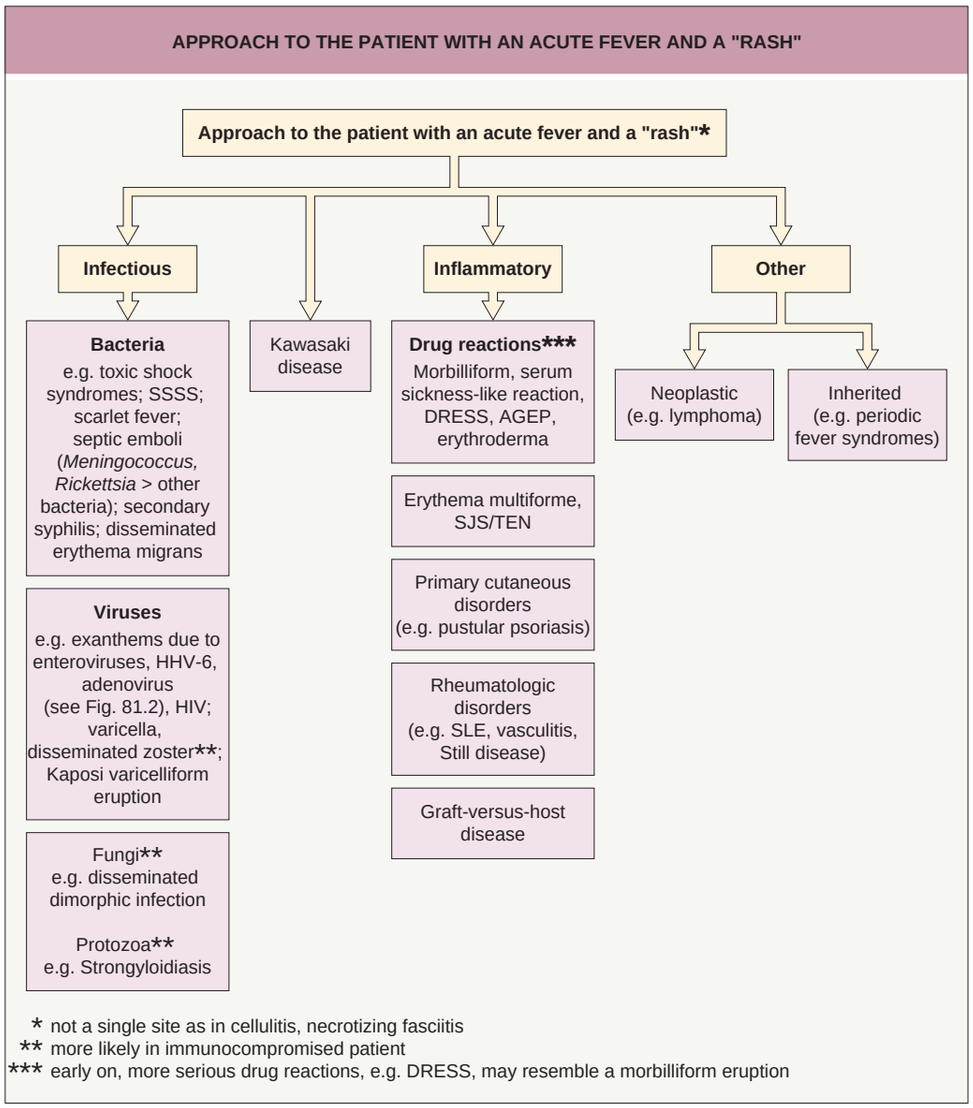


Fig. 0.12 Approach to the patient with an acute fever and a "rash". AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms (also referred to as drug-induced hypersensitivity syndrome [DIHS]); HHV, human herpes virus; HIV, human immunodeficiency 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)

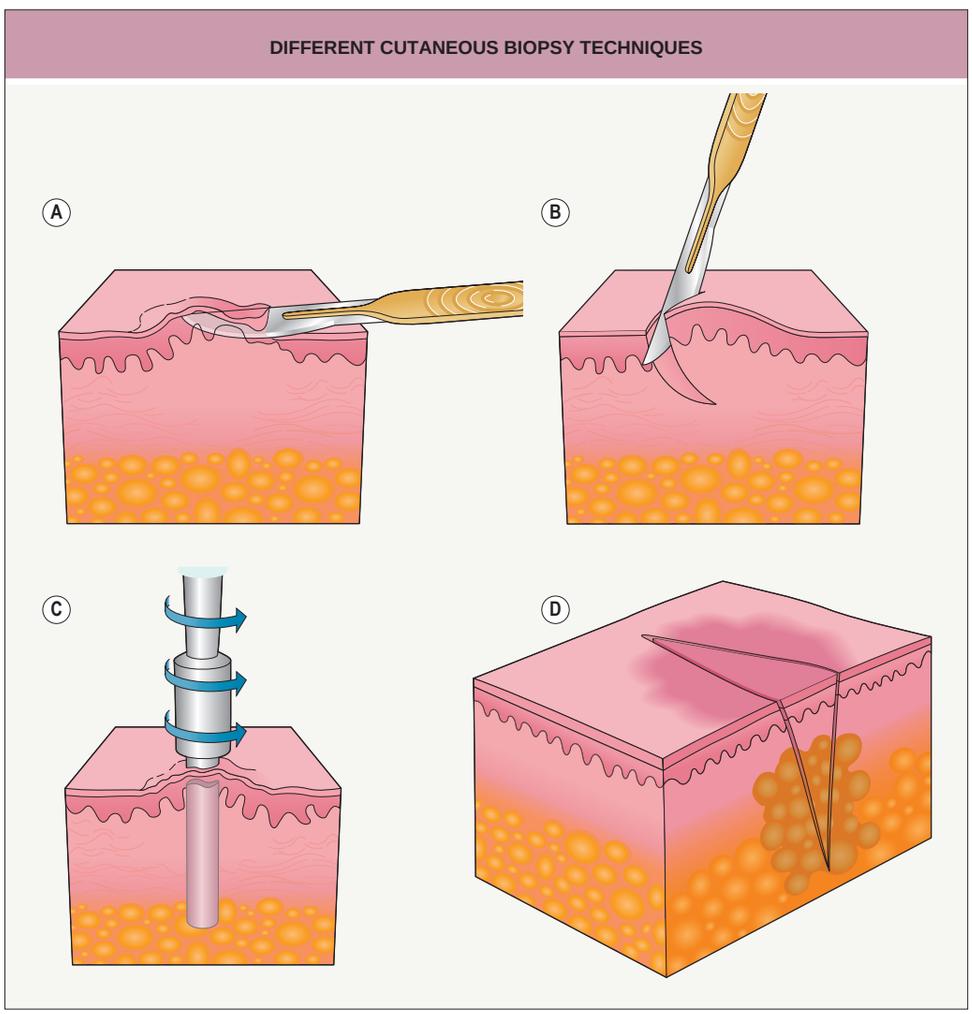


Fig. 0.13 Different cutaneous biopsy techniques. The size, topography, depth and site of the lesion, as well as the clinical differential diagnosis, influence the type of biopsy technique that is performed. **A** Superficial shave biopsy. **B** Deep shave biopsy (saucerization). **C** Punch biopsy. **D** 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