THIRD EDITION

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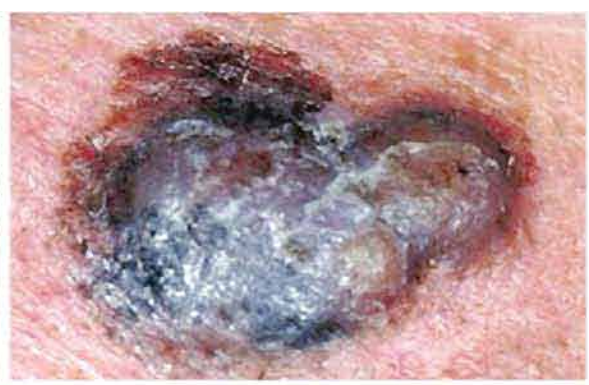
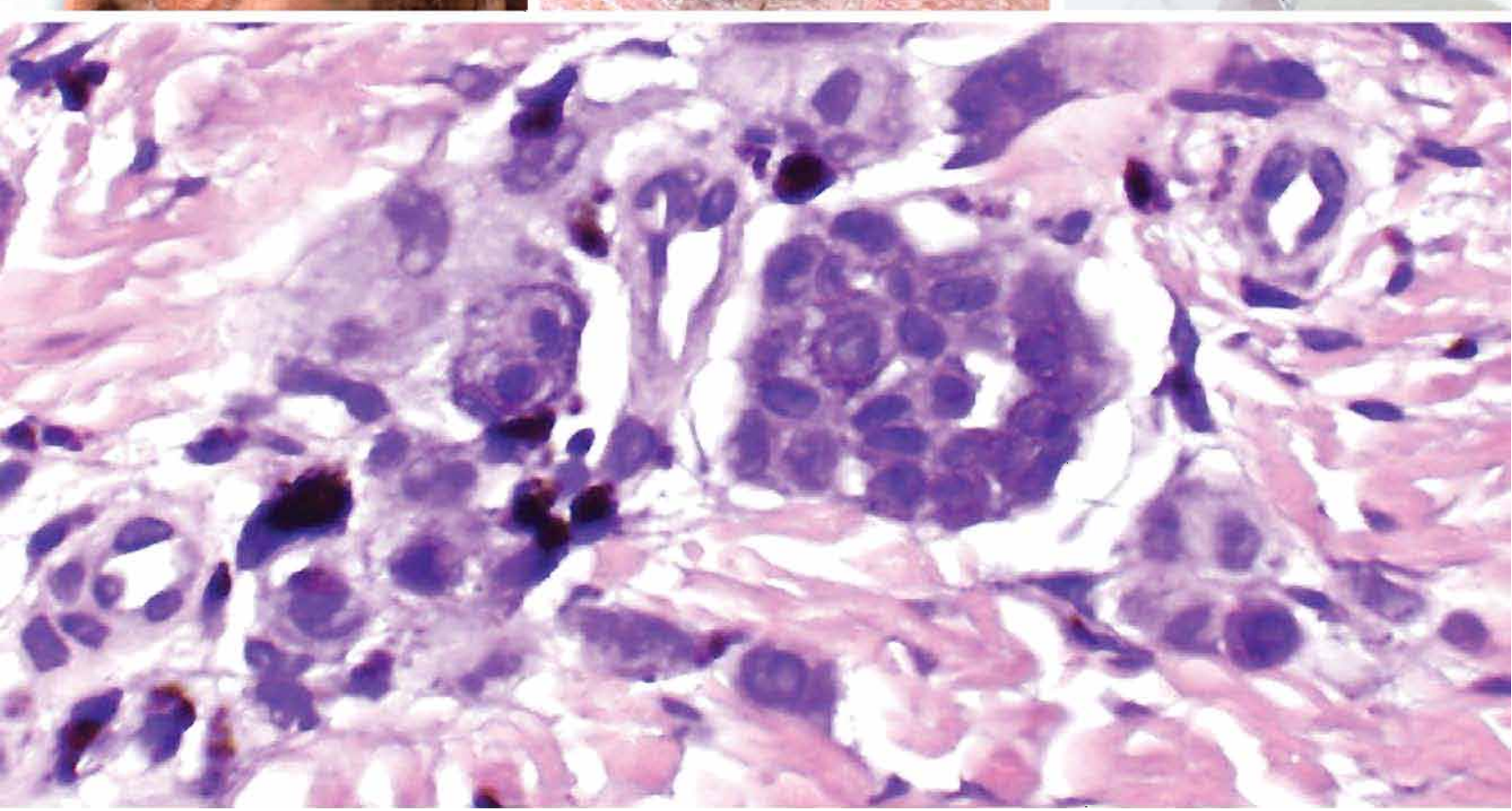
Dermatopathology



Dermatopathology

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To Claire

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FOREWORD

As senior editor of this new *Textbook of Dermatopathology*, Dr. Raymond Barnhill brings to the task years of experience as a dermatopathologist, clinical dermatologist, clinical investigator, and author. This has given him an unparalleled understanding of inflammatory and neoplastic diseases of the skin and the ability to teach others. As director of dermatopathology at the Brigham and Women's Hospital and the Children's Hospital in Boston, he has had contact with both pediatric and adult dermatologic conditions, and as a member of the Combined Harvard Dermatopathology Training Program, he has developed the knowledge and skills to interact with pathologists, dermatologists, trainees, and students. The success of his monograph on melanocytic lesions of the skin speaks to the effectiveness of his writing and teaching approaches.

For this book, Dr. Barnhill has assembled a stellar roster of authors from various disciplines and has appropriately included both established leaders in the field as well as the cream of our younger generation of dermatopathologists. He himself has coauthored one-third of the chapters of the book, and I know first hand that he has spent a great deal of effort meticulously editing all chapters for consistency, style, and accuracy. His associate editor, Dr. Neil Crowson, has been instrumental in providing the high-quality micrographs for many of the entities in the book, and two young, energetic assistant editors, Drs Klaus Busam and Scott Granter, contributed heavily to the book.

I look forward to the publication of this text and wish it the success it truly deserves.

Ramzi S. Cotran, MD, 1998

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PREFACE TO THE THIRD EDITION

The editor and publisher are extremely enthusiastic to offer a third edition of this book to physicians and others in the fields of dermatopathology, dermatology, and allied specialties. It is the express wish of the editors, contributors, and the publisher that the information compiled in this work greatly aides physicians and other health care workers in facilitating the best patient care possible. The editor is deeply appreciative of the prodigious work of the new coeditors Neil Crowson, Cynthia Magro, and Michael Piepkorn and the many eminent contributors in producing an accessible and scholarly book.

The third edition has been revised with the same goals as the first and second editions, that is, to provide "descriptive histopathology and differential diagnosis, critical analysis, balanced perspectives on what is known and what is not, clarity of writing, the use of tables to summarize the key features of major entities, and color photomicrographs" and also to maintain a rather uniform style.

In the course of revising the book, a significant effort has been made to improve the overall quality of photographs in the book. The latter has been accomplished by replacing the existing black and white with color images, improving the quality of many existing color images, increasing the overall number of photographs, and finally including new clinical images. All chapters have been superbly revised, and much new information has been included with respect to various inflammatory conditions, infections, melanocytic, vascular, lymphoid and other neoplastic conditions. Newly described entities have been added to the book where appropriate, and approximately one hundred new color photomicrographs have been incorporated into the third edition.

As before, I acknowledge the tremendous efforts of the many people involved in this third edition, without which it would not have been possible. I am especially indebted to all the contributors and to the staff at McGraw-Hill who have made the third edition a reality. I sincerely hope that the information contained in this book may contribute to improved and more enlightened patient care.

Raymond L. Barnhill, MD

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PREFACE TO THE FIRST EDITION

The question might be posed, "Why another textbook of dermatopathology?" since a number of books are currently available and would seem to do justice to the subject. Quite simply, I have perceived the need for another book. Following on the success of a monograph on melanocytic lesions of the skin, *The Pathology of Melanocytic Nevi and Malignant Melanoma*, I believe that there is indeed a need for a general text on dermatopathology emphasizing the same format as the aforementioned monograph: descriptive histopathology and differential diagnosis, critical analysis, balanced perspectives on what is known and what is not, clarity of writing, the use of tables to summarize the key features of major entities, and color photomicrographs.

At the same time it must be acknowledged that the scope of such a book goes well beyond that of a monograph on melanocytic lesions. As a result, I have engaged a scholarly group of individuals to help in writing such a book in a timely fashion. Nonetheless, one of my major goals has been to maintain a uniform style in keeping with the philosophy of the book.

In recent years I have been impressed with the need to provide some orientation for beginning the process of learning dermatopathology. Thus, the first chapter of this book is devoted to the approach to diagnosis at the microscope. Daniel Jones, MD, PhD, also discusses succinctly the scientific basis of pattern recognition as a prologue to algorithms and the description of the major patterns of inflammation of the skin. Christopher French, MD, has, in addition, designed schematic color figures that enhance the recognition of patterns of inflammation of the skin. Another major feature is that associate editor Neil Crowson, MD, has taken high-quality photomicrographs for most of the entities in the book. This is another characteristic that provides a uniform style to the book. I am deeply grateful to Dr. Crowson for this enormous undertaking.

Although all major entities have been covered in an erudite fashion in the book, a number of unique features must be mentioned. The chapter on disorders of the skin appendages provides new quantitative information on the alopecias and describes the use of transverse sections in the diagnosis of alopecia. Dr Crowson has written a comprehensive chapter on drug eruptions and included lists of medications implicated in these eruptions. Critical chapters on controversial and difficult topics such as vasculitis, panniculitis, disorders of pigmentation, and melanocytic lesions will provide greater insight and aid to the pathologist dealing with these conditions. Finally, there are more detailed chapters on disorders of the nails and the oral mucosa than are currently available in most other texts. Another modification has been the inclusion of a scholarly section on normal skin histology, laboratory methods, immunohistochemistry, and the molecular biology of cutaneous lymphoid infiltrates in an appendix rather than in the text itself.

It will become evident to the reader that there is occasionally some overlap or duplication of some conditions among the various chapters, since no method of classification is entirely consistent. My intention has been to allow some duplication since this provides different perspectives on a disease process.

Finally and most importantly, I would like to acknowledge the tremendous efforts of many friends and colleagues without whose advice, encouragement, and help this book would not have been possible. First of all, I would like to thank Neil Crowson for his enormous contributions in photography, writing, and for his unflagging encouragement and support throughout the project. I am also indebted to my former fellows Klaus Busam and Scott Granter for their commitment and hard work on the book, and I am most appreciative of my secretaries Robin McCarthy (who has since departed for an undoubtedly easier job!) and Maria Palaima, and the staff at McGraw-Hill for their dedication and efforts in bringing the book to closure. Lastly, I am most grateful to all the contributors who have sacrificed so much of their time and energy to make the book not only possible but a learned work that will have an impact on the field.

Raymond L. Barnhill, MD

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PART 1

Inflammatory Reactions In the Skin

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CHAPTER 1

Introduction to Microscopic Interpretation

Raymond L. Barnhill
Daniel M. Jones

INTRODUCTION

Perhaps in no other area of pathology does one encounter such diverse disease processes and bewildering terminology as in dermatopathology. The classic approach to learning dermatopathology, as in many other areas of medicine, has been disease oriented, a style not easily mastered by beginners or even more advanced students. However, in recent years there has been greater emphasis on using a systematic and logical approach of pattern recognition for diagnosis, particularly for inflammatory conditions in the skin.[1-5]

The objectives of this chapter are (1) to present an outline of the perceptual principles and pitfalls underlying pathologic diagnoses and (2) to outline a practical step-by-step method for interpreting a microslide and formulating a differential diagnosis using techniques of pattern recognition and algorithms.

Interpretation of the Slide

The diagnostic approach of this textbook is to bring a systematic approach to diagnosis of skin lesions. The chapter organization reflects this explicit algorithmic approach, with an emphasis in the chapter on a step-by-step approach to microslide review (see Fig. 1-1).

Although the correct diagnosis of common skin tumors often can be made by inspection of the microslide with the naked eye or at the lowest scanning magnification, the perceptual processes involved in diagnosis are quite complex. They can be schematized by the simplified algorithm that follows.

1. "Reading" the slide (ie, visual perception/attention)
2. Processing the acquired visual information
3. Arriving at a tentative diagnosis (ie, model building)
4. Testing the preliminary diagnosis with further examination
5. Confirming the diagnosis
6. Attending to secondary features (eg, status of margins, tumor grade)
7. Correlating available clinical information
8. Finalizing the diagnosis

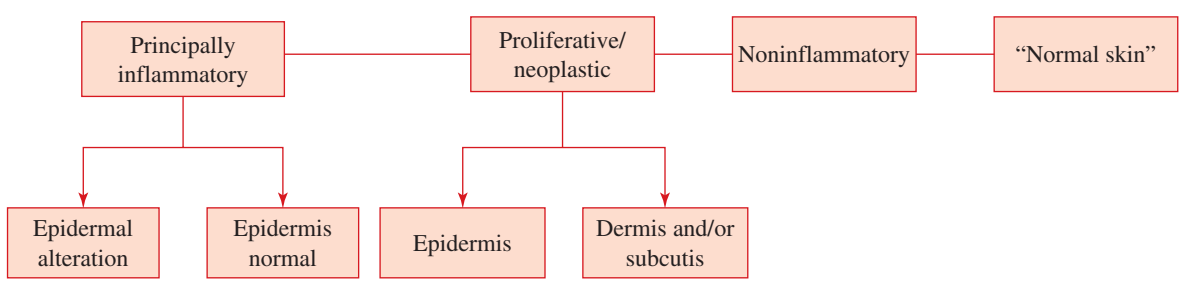
Initial Examination of the Slide with the Naked Eye

The histopathologist should first inspect the microslide with the naked eye in order to gain some appreciation of the size, number, and nature of the histologic sections on the slide. Often one can make certain deductions from this gross examination alone. For example, a small specimen is either a curetting, a shave, or a punch biopsy and connotes particular pathologic processes (In contrast, a large specimen generally indicates an excision. Often it is possible to establish the process as epidermal, dermal, or subcutaneous by this examination. The tinctorial properties (histochemical staining) also may provide clues to diagnosis; for example, bluish cellular aggregates or nodules suggest high nuclear-to-cytoplasmic ratios because of basophilic staining of nuclei and, as a result, processes such as basal cell carcinoma, small cell carcinoma, and infiltrates of small lymphocytes or calcium deposition.

Examination of the Microslide at Scanning (2× or 4×) Magnification

The microslide next should be viewed at scanning magnification, that is, with a 2× or 4× objective. Although a 2× objective may prove optimal for the initial examination of many specimens, particularly large specimens, many microscopes are equipped only with 4× objectives. However, the 4× objective is a reasonable alternative, and additional information generally can be obtained at this magnification. If possible, the specimen always should be studied initially without knowledge of age, gender, or other clinical information in order to gather information objectively and formulate a differential diagnosis. Although the experienced pathologist often does not need to resort to such a method unless a diagnosis is not immediately apparent, the beginner should systematically study a slide with specific goals in mind.

1. First of all, the pathologist should attempt to identify the *type of specimen* submitted; that is, is it a curettage, punch, shave, or excisional specimen? Determination of the type of specimen is important because it often provides some clue to the type of disease process suspected by the submitting clinician. For example, curettage specimens often are taken for neoplastic processes such as actinic or seborrheic keratoses or basal cell carcinoma. Shave biopsies usually are obtained for diagnosis of keratoses



▲ **FIGURE 1-1** Algorithmic approach to diagnosis.

or basal or squamous cell carcinoma. In general, punch biopsies are submitted for diagnosis of either neoplastic or inflammatory conditions. In some instances they are used to "excise" a proliferation or tumor, and thus margins may need to be assessed. By and large, skin ellipses (excisions) are submitted for suspected tumors but also on occasion for inflammatory processes such as vasculitis or panniculitis.

2. Next, the pathologist should inspect the specimen with the idea of determining in general terms from what *anatomic site* the tissue was taken. In general, based on characteristics such as prominence of sebaceous follicles, relative paucity of hair follicles, thickness of the reticular dermis, and thickness of the stratum corneum, one can recognize the following general regions of the integument: (a) head and neck, (b) trunk and proximal extremities, and (c) acral (including frictional) surfaces. It is evident that many diseases have characteristic site distributions, and knowledge of the particular localization of the lesion or eruption is useful in formulating one's differential diagnosis.
3. The entire specimen (ie, epidermis, dermis, or subcutis) should be scanned for the principal site of involvement by a disease process, if any, and the nature of the process, whether inflammatory, proliferative, inflammatory *and* proliferative, or noninflammatory. Although in most instances the site of involvement is obvious, it is important that the specimen is examined systematically when the process is not so obvious. In general, the specimen should be scrutinized in a sequential fashion, for example, beginning with the stratum corneum and then proceeding to the epidermis, dermis, subcutis, and fascia. At scanning magnification, one should be able to appreciate many aspects of the disease process without going to greater magnification. If an inflammatory process is present, one should attempt to recognize the nature of epidermal involvement, for example, spongiosis, interface vacuolopathy, psoriasiform epidermal hyperplasia, or vesicle, blister, or pustule formation; the pattern of the inflammatory infiltrate, whether bandlike (cell-poor or cell-rich/lichenoid), perivascular, interstitial, periadnexal, nodular, or diffuse (pandermal); the depth of the infiltrate, for example, superficial only or superficial and deep; possibly the presence of vascular damage; the cellular composition of an infiltrate, that is, whether it is comprised of mononuclear cells, suggesting small lymphocytes or larger cells; and alterations of the dermis, for example, by fibrosis or sclerosis resulting in a "square" punch biopsy versus the typical inverted cone configuration, thickening, or atrophy of the dermis or deposition of material such as calcium. A primary proliferative or neoplastic condition also should be obvious in most instances at scanning magnification.

After the completion of this exercise, the pathologist is often able to establish the basic nature and localization of the disease process and possibly to develop a preliminary differential diagnosis if he or she has not already arrived at a specific diagnosis. In many instances, this may not be possible at scanning magnification because the changes are too subtle for diagnosis at this or perhaps any magnification or there has been a sampling error. At this point, the pathologist must go to greater magnification in order to confirm an impression or to gain more information that is only possible at increased magnification.

Examination at Intermediate Magnification

It cannot be overemphasized that, in general, most information about a pathologic process is obtained at scanning magnification. The tendency to go to higher magnification too soon should be resisted because one often will overlook a crucial feature, and thus, in effect, one "cannot see the forest for the trees." The reasons for closer inspection of the specimen (with 10× and 20× objectives) are to confirm particular features of pathologic processes, for example, parakeratosis, spongiosis, fibrinoid necrosis, or mucin deposition, and for identification of specific cell types, such as lymphocytes or granulocytes. However, in some instances, greater magnification may be needed in order to identify a morphologic feature not recognizable at low magnification, such as, hyphal elements in the cornified layer, epidermal basal layer vacuolopathy, amyloid deposits in the papillary dermis, or mucinosis in the reticular dermis.

Examination at High Magnification

As mentioned for intermediate magnification, use of the high-power objective also should be reserved for specific indications. Such examination is necessary in order to study the cytologic details of cells, such as, the nuclear contours of lymphocytes or nuclear atypia in general; to confirm the nature of infectious organisms; and to confirm other findings.

Integration of All Information

During the preceding exercise of examining the microslide, the histopathologist should take the perspective that he or she is objectively gathering information that can be integrated with other (clinical and laboratory) information to arrive at some conclusion about the disease process and not necessarily to arrive at a single diagnosis. One should, at all times, try to avoid reaching a conclusion too quickly and failing to observe other pertinent findings in the specimen. The pathologist always should try to think expansively of every potential pathologic process that might explain the histologic findings. One should continuously weigh the various points that argue for or against a particular pathologic condition.

After completing the preceding examination and reaching some tentative impression (or lack of conclusion) about the specimen without knowledge of clinical parameters, it is then necessary to consider the clinical context of the specimen. Even if the histopathologic diagnosis appears straightforward, such as, for example, basal cell carcinoma, the pathologist always should have certain clinical information before finalizing the case: age, gender, anatomic site, and clinical diagnosis. Without such information, the pathologist is much more prone to blatant errors, such as mislabeled specimens or misdiagnosis.

On the other hand, for many conditions, particularly inflammatory processes, detailed clinical information concerning the onset, evolution, distribution, and specific character of the skin lesions is essential in order to arrive at a diagnosis or to formulate a differential diagnosis. Many inflammatory reaction patterns are not specific and may be secondary to several processes. Thus an accurate clinical history is needed to establish the most likely condition or group of conditions that might explain the histologic findings.

Finally the histopathologist must recognize the limitations of histopathological interpretation: in some instances specific diagnosis is not possible since either the histological findings are nonspecific and diagnosis rests in the clinical domain, current knowledge about the disease process is inadequate, the biopsy specimen is inadequate, or sampling error has occurred.

PATTERN RECOGNITION IN DERMATOPATHOLOGY

Accurate perception of the findings on a microslide is obviously the initial step in accurate diagnosis. Many, perhaps most, serious errors in diagnosis are related to a failure to attend to or notice critical histologic findings rather than a misinterpretation of these features. A trivial but common reason for misdiagnosis is simply a failure to examine a relevant tissue fragment or level. Poor tissue preservation and histologic detail or substandard tissue sectioning also can contribute greatly to problems in accurate perception. The visual fatigue and information overload that occur after examining many cases also contributes to perceptual mistakes.

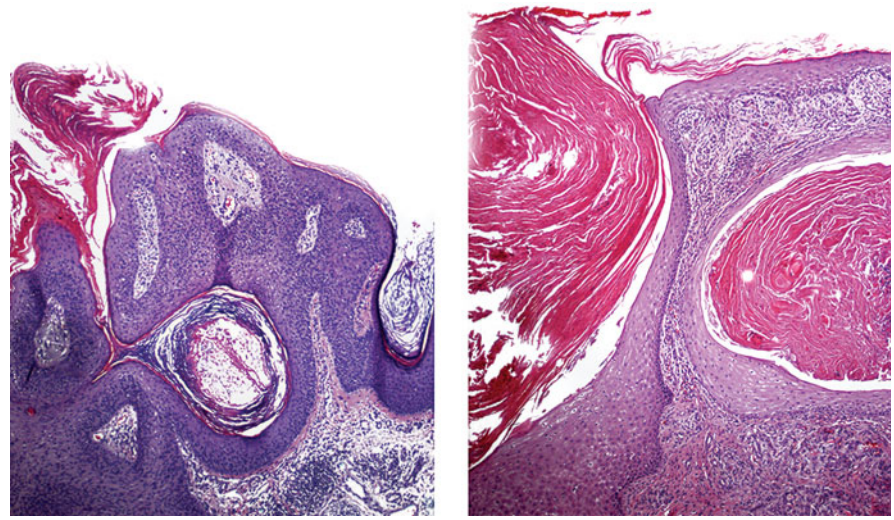
As outlined in Fig. 1-1, the initial decision one must make is whether a process is predominantly inflammatory, predominantly proliferative/neoplastic, both inflammatory and proliferative, or noninflammatory/nonproliferative. This is not always possible, but, in general, the vast majority of pathologic processes can be categorized into one of these groups. Thus one is able to proceed along one of the decision trees.

Features of Benign versus Malignant Tumors

Although it may appear intuitive and instantaneous, recognition of cutaneous tumors is a highly complex perceptual process that involves more than simple "wallpaper matching." However, in the diagnosis of cutaneous tumors, the low-power pattern (*tumor silhouette*) often can be at least as important if not definitive for diagnosis as high-power cytologic findings.[3]

Certain tumor growth patterns appear to be intrinsically more readily recognizable and often are the first to be mastered by the student of dermatopathology. This is supported by a large body of perceptual research demonstrating that some visual targets (termed *good patterns*) are consistently recognized more rapidly than others. Conversely, there is impaired performance of visual tasks that involve recall of "poor" visual targets. Easy recognition of some benign skin tumors (Fig. 1-2, eg, seborreic keratosis, keratoacanthoma, or cylindroma) in contrast to others (eg, a sclerosing melanocytic nevus or desmoplastic melanoma) is due to the visual impact of their particular growth patterns evident at low magnification.

Similarly, the presence of ancillary features such as inflammatory infiltrate can be an instantly recognizable clue to search for evidence of tumor invasion (Fig. 1-3). As a pathologist gains experience with dematopathology tumors, the distinction of the range of benign versus malignant growth patterns becomes easier.

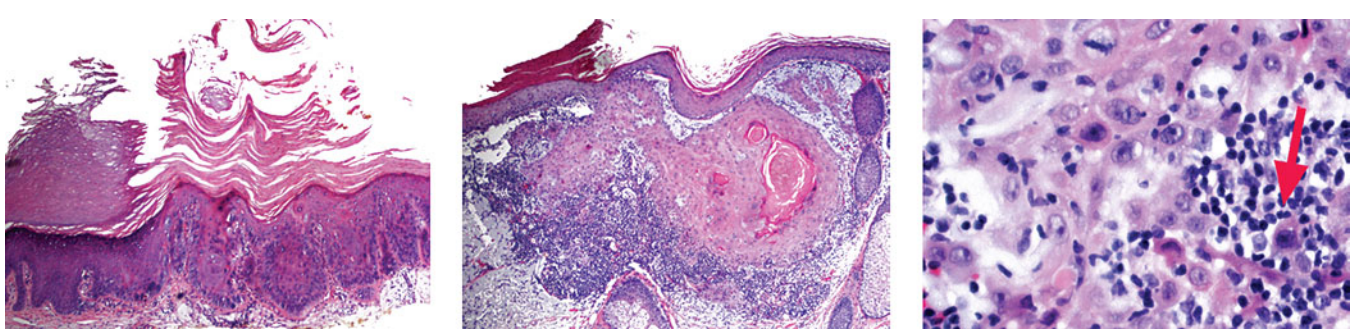


▲ **FIGURE 1-2** Distinguishing benign from malignant neoplasms by low-power microscopic features. Characteristic acanthosis, hyperkeratosis, and keratin pseudocyst formation in seborrheic keratosis are easy to detect (left). Similar features are evident in a benign keratosis due to chronic irritation (right).

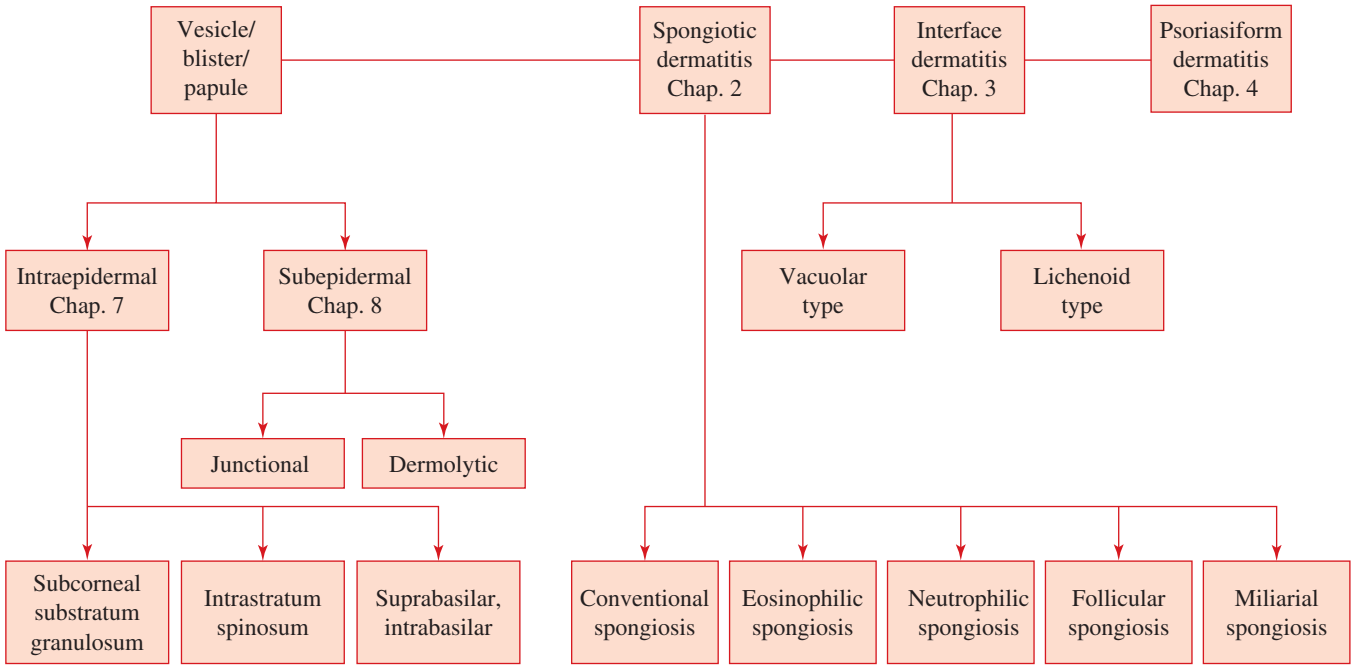
Features of Inflammatory and Reactive Lesions

Although it also involves pattern recognition, the diagnosis of inflammatory lesions presents a much different challenge. Instead of rendering a definitive diagnosis, the usual approach is descriptive (ie, what kinds of epidermal alterations and inflammatory cells are present and where they are located). In the absence of adequate clinical information, a range of possible diagnoses usually is provided. This is a different perceptual task where the goal is simply not to match a precise stored visual image but to compare the features of a lesion with the clinical entity to which it is (statistically) most similar.

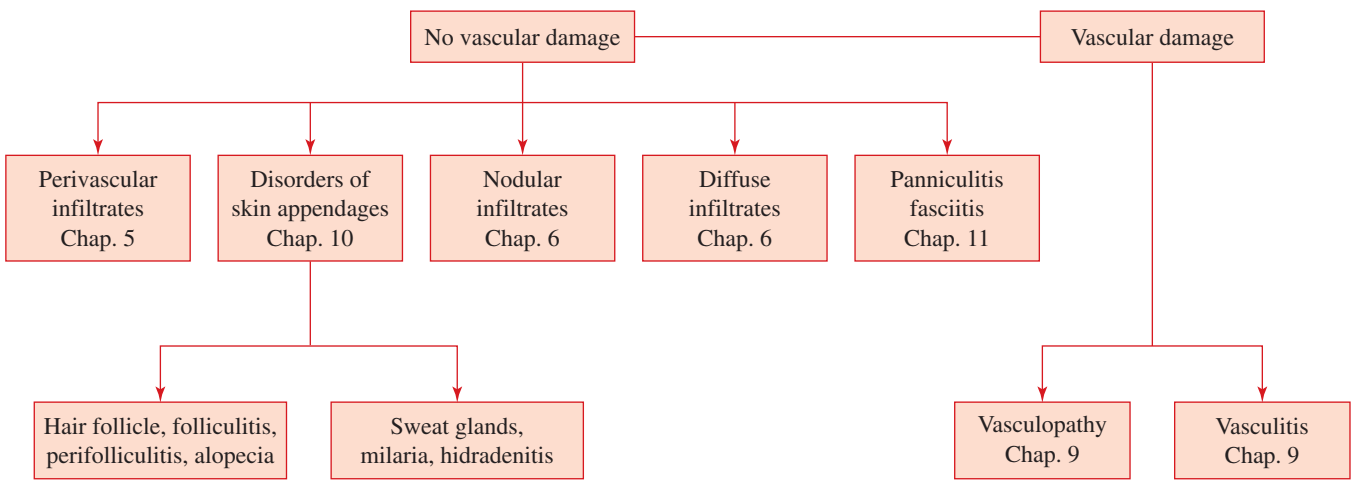
Inflammatory lesions are grouped initially into general categories (see Figs. 1-4 to 1-8), and then specific features are sought to narrow (or prioritize) the diagnoses. For instance, once the pattern of



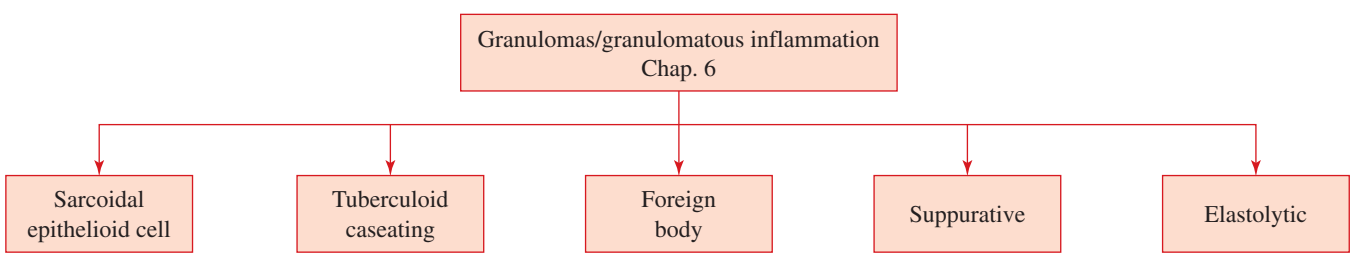
▲ **FIGURE 1-3** Combining epidermal changes and reaction patterns in diagnosis. Even at low magnification, the regular pattern of acanthosis and hyperkeratosis seen in squamous cell carcinoma in situ (right) is contrasted with the irregular squamous proliferation, abnormal maturation, and robust inflammatory infiltrate associated with invasive squamous cell carcinoma (middle). Examination at higher magnification reveals infiltrating tumor cells (right panel, arrow).



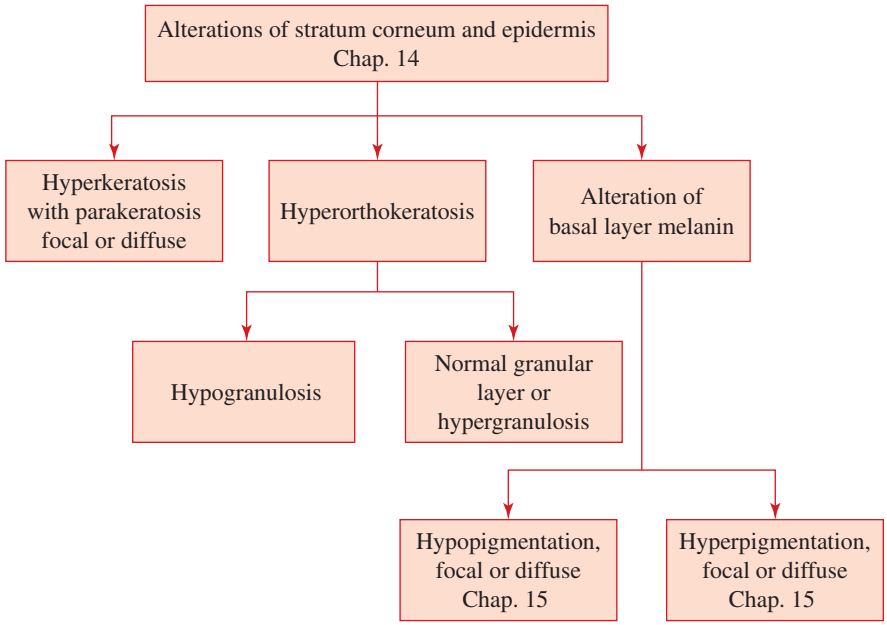
▲ **FIGURE 1-4** Inflammatory conditions with epidermal alteration.



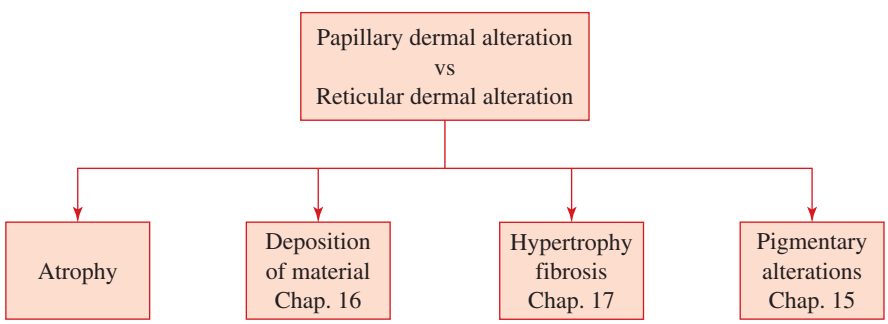
▲ **FIGURE 1-5** Inflammatory conditions of the dermis and/or subcutis without epidermal alterations and with and without vascular injury.



▲ **FIGURE 1-6** Inflammatory infiltrates with granulomas/granulomatous inflammation.



▲ **FIGURE 1-7** Noninflammatory disorders with alterations of stratum corneum and epidermis.



▲ **FIGURE 1-8** Noninflammatory disorders with dermal alteration.

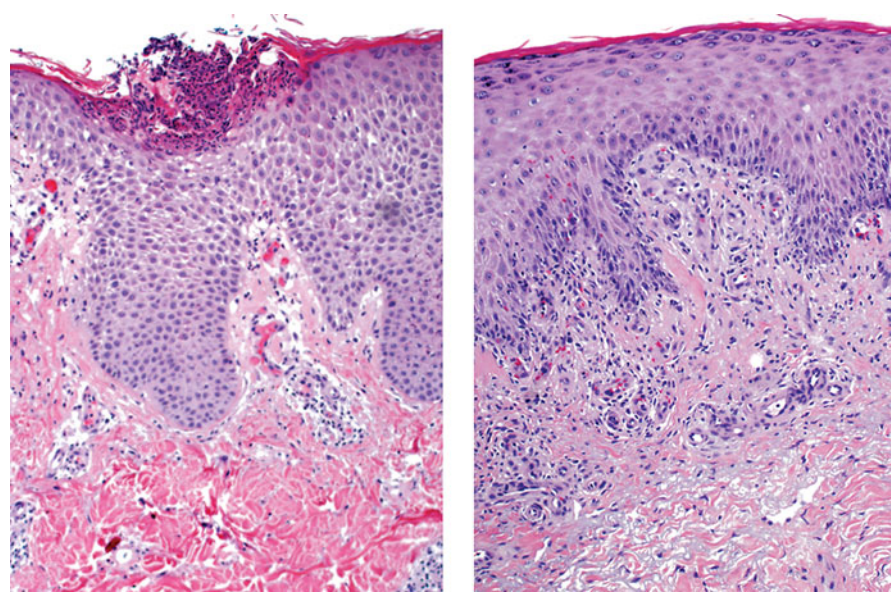
vacuolar interface dermatitis has been identified, visual search for viral inclusions or apoptotic bodies could support the diagnoses of a viral exanthem or erythema multiforme.

Combining the available information on the gross appearance and the clinical differential diagnosis with the histologic diagnosis is the vitally important penultimate stage prior to rendering a final diagnosis. The close linkage in training and expertise between dermatologist and dermatopathologist often makes this process easier because the histopathologist becomes more familiar with the clinical appearance of the lesions in the differential diagnosis. This synergistic effect is most obvious in the rare cases where the biopsy specimen is being diagnosed by the person who has actually examined the patient. However, in all cases, the differential diagnosis provided by the submitting dermatologist may force a reexamination of the microscopic features, and as a result, this book provides detailed descriptions of both the histologic features and clinical appearance of each entity.

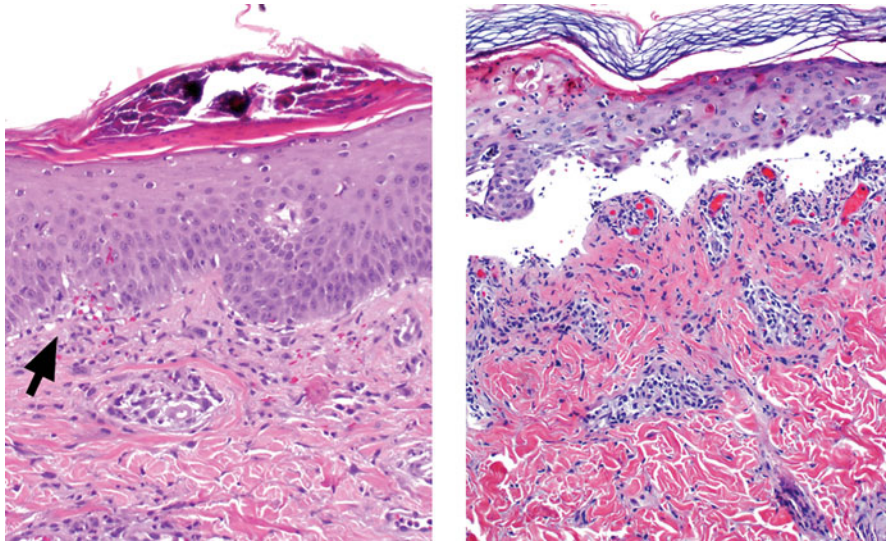
There are also added complexities to diagnosis of inflammatory lesions in the skin that are related to the nature of the immune responses producing these lesions. These include:

1. The temporal phase of a lesion. Many dermatitis reactions have acute, subacute, and chronic phases with fairly specific histologic correlates (Fig. 1-9). Therefore, it is important to consider the varying histologic appearances that can occur over the life span of a skin lesion.
2. The severity of the reaction. For inflammatory lesions incited by external or internal antigenic reaction, there is a spectrum of responses ranging from mild to severe (Fig. 1-10).
3. The overlap of benign dermatoses and cutaneous T-cell lymphomas. There are a limited number of epidermal reaction patterns seen in response to infiltration by immune cells or neoplastic lymphocytes. Furthermore, cutaneous T-cell lymphomas (CTCL) often evolve from preceding dermatitis. Therefore, there can be overlap in the histologic features seen in CTCL and reactive inflammatory conditions requiring careful attention to lymphocyte atypia at high magnification (Fig. 1-11).

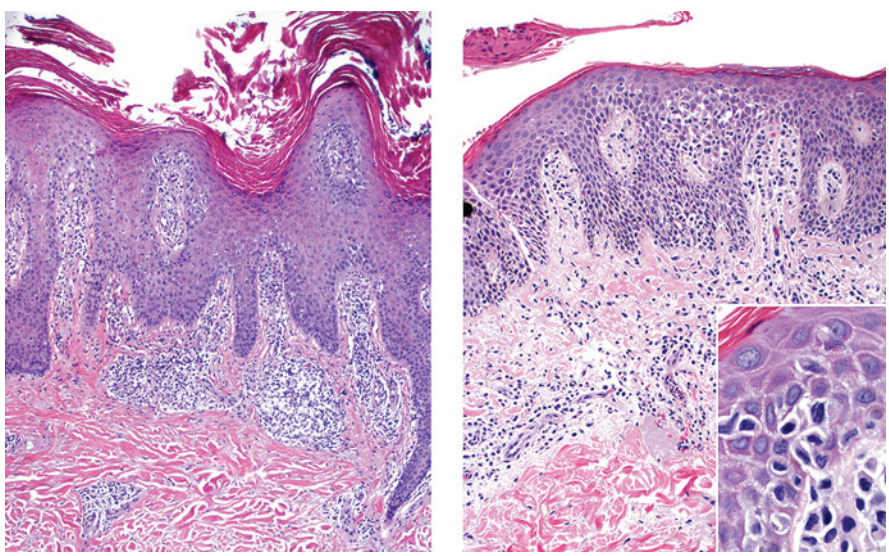
Full maturation of expertise in dermatopathology thus requires not only a



▲ **FIGURE 1-9** Spongiotic dermatitis, acute versus chronic changes. Spongiosis and neutrophilic crust are characteristic of a self-limited contact dermatitis (left). In contrast, chronic spongiotic dermatitis results in dermal fibrosis and vascular proliferation (right).



▲ **FIGURE 1-10** Interface dermatitis, mild to severe. Mild graft-versus-host (GVH) disease shows minimal interface lymphoid infiltrate (left panel, arrow). In comparison, severe GVH shows numerous necrotic keratinocytes and subepidermal cleft formation (right).



▲ **FIGURE 1-11** Psoriasiform reaction pattern. Psoriasis shows hyperkeratosis with thinned granular layers and elongation of the rete ridges (left). A case of mycosis fungoides shows similar psoriasiform epidermal hyperplasia, with cytologic atypia of the lymphocytes only appreciated on high magnification (inset).

"library" of stored visual images of inflammatory skin lesions that correlate with clinical syndromes but also knowledge of the time-course and spectrum of changes seen for each particular entity. As discussed below, the stepwise approach to learning to diagnose inflammatory lesions in skin emphasizes the importance of mastering the diagnostic differential for each inflammatory pattern.

Major Inflammatory Reaction Patterns in the Skin

Since the pathogenesis of most inflammatory dermatitides is unknown, one must, of necessity, use morphologic criteria for classification at present. Although most inflammatory conditions can be categorized into one of the major reaction patterns, there are inevitable dermatitides that show overlapping features and some that defy classification. Some inflammatory conditions may be sampled either too early or too late in their evolution to be diagnostic. Inflammatory diseases are dynamic, and knowledge of the point in time when the dermatitis is sampled is critical to optimal microscopic interpretation. The histopathologist should strive to assess specimens with the "fourth dimension" of time always kept in mind.

As mentioned previously, one initially attempts to ascertain whether the epidermis shows one of the following major reaction patterns or is uninvolved by the inflammatory process.

INFLAMMATORY REACTION PATTERNS OF THE EPIDERMIS

Spongiotic dermatitis *Spongiotic dermatitis* refers specifically to the presence of spongiosis or intercellular edema that stretches apart keratinocytes and sometimes results in the formation of intraepidermal vesicles. Spongiosis is often variable, multifocal, and accompanied by intracellular edema and exocytosis of inflammatory cells. The disease process is dynamic and in general has been categorized according to morphologic features correlating with the stages of its life history (1) acute, (2) subacute, and (3) chronic (Fig. 1-9). Other alterations such as granulocyte infiltration of the epidermis (eg, eosinophilic or neutrophilic spongiosis) or involvement of skin appendages (eg, follicular spongiosis) may be observed.

Spongiosis is a relatively nonspecific morphologic alteration observed in a wide variety of conditions (see Table 1-1). It is

Table 1-1
Spongiotic Dermatitis

Conventional spongiotic dermatitis
- Allergic contact dermatitis
- Irritant contact dermatitis
- Atopic (endogenous) dermatitis
- Nummular dermatitis
- Dyshidrotic eczema (pompholyx)
- Id reaction
- Seborrheic dermatitis
- Stasis dermatitis
- Spongiotic drug eruption
- Erythroderma
- Pityriasis rosea
- Pityriasis alba
- Photoallergic contact dermatitis
- Polymorphous light eruption
- Arthropod bites
- Gyrate/figurate erythemas
- Dermatophyte infection
- Transient acantholytic dermatosis
- Pigmented purpuric dermatitis
- Papular and urticarial eruptions of pregnancy

Eosinophilic spongiosis
- Pemphigus group
- Bullous pemphigoid
- Allergic contact dermatitis
- Spongiotic drug eruptions
- Infestations
- Cutaneous larva migrans
- Arthropod bites
- Incontinentia pigmenti
- Eosinophilic folliculitis

Neutrophilic spongiosis
- Psoriasis
- Reiter syndrome
- Seborrheic dermatitis
- Irritant contact dermatitis
- Phototoxic dermatitis
- Pemphigus variants (particularly IgA pemphigus)

Follicular spongiosis
- Atopic dermatitis
- Pityriasis alba
- Contact dermatitis
- Infundibulofolliculitis
- Eosinophilic folliculitis
- Follicular mucinosis
- Fox-Fordyce disease

Miliarial spongiosis
- Miliaria

perhaps most characteristic of the group of conditions referred to as *eczematous dermatitis.* These disorders include endogenous or atopic dermatitis, contact allergic and irritant dermatitis, and nummular dermatitis. Other common dermatitides showing spongiosis include seborrheic dermatitis, spongiotic drug eruptions, and some primary bullous conditions.

Interface dermatitis *Interface dermatitis* refers to a morphologic alteration at the junction or interface between the epidermis (or epithelium) and dermis. Specifically, one observes vacuolization (vacuoles or discrete clear spaces) either within basilar keratinocytes or within the basement membrane zone. This reaction pattern is often accompanied by a number of other alterations present to variable extent: individually dyskeratotic keratinocytes (which are probably apoptotic cells), disruption of orderly keratinocytic maturation to the surface, and clefts resulting from coalescence of vacuoles.

Interface dermatitides may be further subclassified according to the density and pattern of the inflammatory cell infiltrate in the papillary dermis as (1) the vacuolar or cell-poor type, based on perivascular or patchy infiltrates in the papillary dermis or (2) the lichenoid or cell-rich type, which shows a dense bandlike infiltrate that fills the papillary dermis (Table 1-2). As with all inflammatory processes, interface dermatitides also may be characterized according to their severity (Fig. 1-10, illustrating graft-versus-host reaction) or their stage of evolution as acute or early stage, subacute or developed, or chronic or late stage. Certain diseases are prototypic of the two patterns of interface dermatitis

Table 1-2
Interface Dermatitis

Vacuolar interface dermatitis
- Erythema multiforme
- Fixed drug eruption
- Drug eruptions
- Viral xanthems
- HIV interface dermatitis
- Connective tissue disease
  - Lupus erythematosus
  - Dermatomyositis
- Graft-versus-host reaction
- Pityriasis lichenoides
- Poikiloderma congenitale
- Bloom syndrome
- Vitiligo
- Pigmented purpuric dermatitis

Lichenoid interface dermatitis
- Lichen planus and variants
- Lichenoid drug eruption
- Lichenoid keratosis
- Lichen striatus
- Lichen nitidus
- Lichenoid purpura
- Porokeratosis
- Histologic regression of many tumors

mentioned earlier. Erythema multiforme, many drug eruptions, viral exanthems, and connective tissue diseases result in a vacuolar pattern of interface dermatitis. On the other hand, lichen planus, lichenoid drug eruptions, lichen planus-like keratosis, and "halo" nevus are associated with lichenoid patterns of inflammation.

Psoriasiform dermatitis *Psoriasiform dermatitis* refers to a characteristic pattern of epidermal hyperplasia typified by elongation of the epidermal rete ridges (Fig. 1-11). In general, the topography of the epidermal surface is unaffected, that is, remains essentially flat-topped. This pattern of epidermal alteration may be further described as either regular or irregular. Regular psoriasiform hyperplasia, as the name suggests, indicates elongated epidermal rete ridges of fairly uniform length and thickness and is typical of psoriasis in a well-developed stage. This morphologic feature is accompanied by a number of other histologic alterations notable in psoriasis: broad zones of parakeratosis, absence of the granular layer, exocytosis of neutrophils, pallor of keratinocytes (intracellular edema), thinning of the epidermis above the dermal papillae, prominent dilated and tortuous papillary dermal microvessels, and papillary dermal edema. Irregular psoriasiform epidermal hyperplasia may

Table 1-3
Psoriasiform Dermatitis

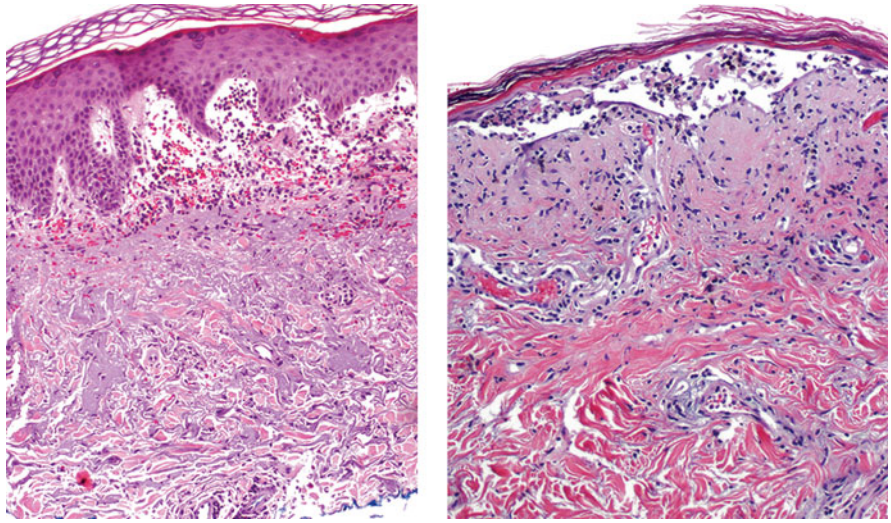
- Psoriasis
- Reiter syndrome
- Subacute to chronic eczematous dermatitis
- Seborrheic dermatitis
- Lichen simplex chronicus
- Pityriasis rubra pilaris
- Parapsoriasis
- Mycosis fungoides
- Psoriasiform drug eruption
- Erythroderma
- Candidiasis
- Secondary syphilis
- Inflammatory linear verrucous epidermal nevus (ILVEN)
- Scabies
- Lamellar ichthyosis
- Clear cell acanthoma
- Pellagra
- Acrodermatitis enteropathica
- Migratory necrolytic erythema
- Bazex syndrome

be observed in psoriasis but typifies other processes more commonly, such as chronic eczematous dermatitis, lichen simplex chronicus, or mycosis fungoides (Table 1-3, Fig. 1-11).

Other conditions that exhibit this reaction in addition to those already mentioned are psoriasiform drug eruptions, lamellar ichthyosis, and secondary syphilis.

Vesicular and bullous dermatitis This reaction pattern refers to the formation of tissue clefts or spaces that may or may not be accompanied by cellular infiltrates such as eosinophils, neutrophils, or lymphocytes. In general, these disorders are classified according to whether the level of cleavage is (1) intraepidermal or (2) subepidermal (Figs. 1-4, 1-12; see also Tables 1-4 and 1-5). Intraepidermal blisters may include, for example, subcorneal or intragranular layer cleavage or cleavage through the superficial layer or suprabasal layer of the epidermis. Subepidermal blisters may be further delineated as cleavage through the lamina lucida of the basement membrane zone or through the superficial dermis.

Blistering dermatitides may then be characterized as predominantly inflammatory or noninflammatory. If inflammatory, the composition of the infiltrate and possibly immunofluorescence and serological studies will further aid classification. Finally, one may be able to recognize the mechanism of vesicle/blister formation as spongiotic, acantholytic,



▲ **FIGURE 1-12** Subepidermal bullous dermatitis. Bullous pemphigoid shows numerous lymphocytes and eosinophils with no necrosis of overlying epithelium (left). Erythema multiforme shows nearly full-thickness epidermal necrosis and mild lymphocytic infiltrate in association with the subepidermal blister.

Table 1-4
Intraepidermal Vesicular and Pustular Dermatitis

Intracorneal and subcorneal vesicles and pustules
- Impetigo
- Staphylococcal "scalded skin" syndrome
- Superficial fungal infection
- Pemphigus foliaceus
- Pemphigus erythematosus
- Subcorneal pustular dermatosis
- Infantile acropustulosis
- Erythema toxicum
- Transient neonatal pustular melanosis
- Miliaria crystallina

Intraepidermal vesicles and pustules
- Spongiotic vesicles
- Viral vesicles
- Palmoplantar pustulosis
- Friction blister
- Epidermolysis bullosa

Table 1-5
Subepidermal Vesicular Dermatitis

Subepidermal blisters with little inflammation
- Epidermolysis bullosa
- Porphyria
- Pseudoporphyria
- Bullous pemphigoid (cell-poor type)
- Burns
- Toxic epidermal necrolysis
- Bullae associated with diabetes
- Blisters overlying scars
- Bullous amyloidosis

Subepidermal blisters with lymphocytes
- Erythema multiforme
- Fixed drug eruption
- Lichen planus pemphigoides
- Polymorphous light eruption
- Bullous mycosis fungoides
- Bullous fungal infections

Subepidermal blisters with eosinophils
- Bullous pemphigoid
- Epidermolysis bullosa acquisita
- Pemphigoid gestationis
- Arthropod bites
- Drug reactions

Subepidermal blisters with neutrophils
- Dermatitis herpetiformis
- Linear IgA bullous dermatosis
- Cicatricial pemphigoid and localized cicatricial pemphigoid
- Pustular vasculitis
- Bullous lupus erythematosus
- Sweet syndrome
- Epidermolysis bullosa acquisita
- Erysipelas
- Bullous urticaria

Subepidermal blisters with mast cells
- Bullous mastocytosis

Miscellaneous blistering diseases
- Drug-overdose-related bullae
- PUVA-induced bulla
- Etretinate-induced bullae

ballooning degeneration, or resulting from prominent basal layer vacuolization or subepidermal edema.

Other epidermal reactions and overlapping patterns Inevitably the procedure of classification is somewhat artificial, and there are always exceptions and entities that defy categorization. Many inflammatory conditions in the skin show two or more of the patterns of epidermal alteration just discussed. The predominant reaction pattern generally should be used as the basis for categorization, if possible. The following morphologic reactions represent additional subsets:

Pityriasiform dermatitis A small but important group of inflammatory dermatitides shows a constellation of epidermal changes that include focal or spotty parakeratosis, slight epidermal hyperplasia, and variable spongiotic and interface alteration. Depending on which of these features might predominate, various dermatitides in this group also might be classified as a subacute spongiotic, psoriasiform, or interface dermatitis (see Overlapping Patterns below).

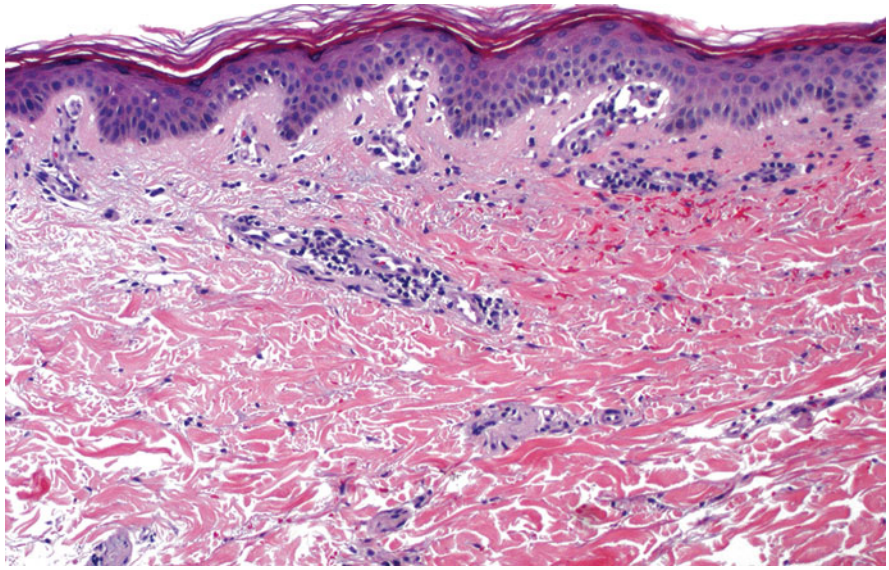
These conditions generally include pityriasis rosea, pityriasis lichenoides, seborrheic dermatitis, eruptive or guttate psoriasis, pre- or early mycosis fungoides lesions (parapsoriasis), some drug eruptions, subacute eczematous dermatitis, pityriasis rubra pilaris, and superficial fungal infections.

Overlapping reaction patterns The four patterns listed below emphasize the prominence of two or more morphologic alterations. Particular patterns often correlate with particular disease processes. For example, spongiotic psoriasiform dermatitis is a typical pattern associated with chronic-active eczematous dermatitis.

1. Spongiotic psoriasiform dermatitis
2. Spongiotic interface dermatitis
3. Spongiotic psoriasiform interface dermatitis
4. Psoriasiform interface dermatitis

CHARACTERIZATION OF THE INFLAMMATORY PROCESS IN THE DERMIS After one has examined the epidermis for morphologic alteration, one proceeds to evaluate the inflammatory process in the dermis (and subcutis and fascia, as the case may be). An immediate concern is whether recognizable vascular injury is present or absent.

Absence of vascular injury At this point, one proceeds with the assessment of the pattern, depth, density, and composition of the inflammatory cell infiltrate, as well as whether it is granulomatous or not. The patterns of inflammatory infiltrates in the dermis generally are described as lichenoid, perivascular (Fig. 1-13), periadnexal, interstitial (infiltrating collagen bundles), nodular (Fig. 1-14), or diffuse (occupying the entire dermis) (Fig. 1-15 and Table 1-6). The depth of involvement is important to recognize because many dermatitides correlate with depth. For example, drug eruptions and viral exanthems often show superficial perivascular involvement only, whereas conditions such as lupus erythematosus,



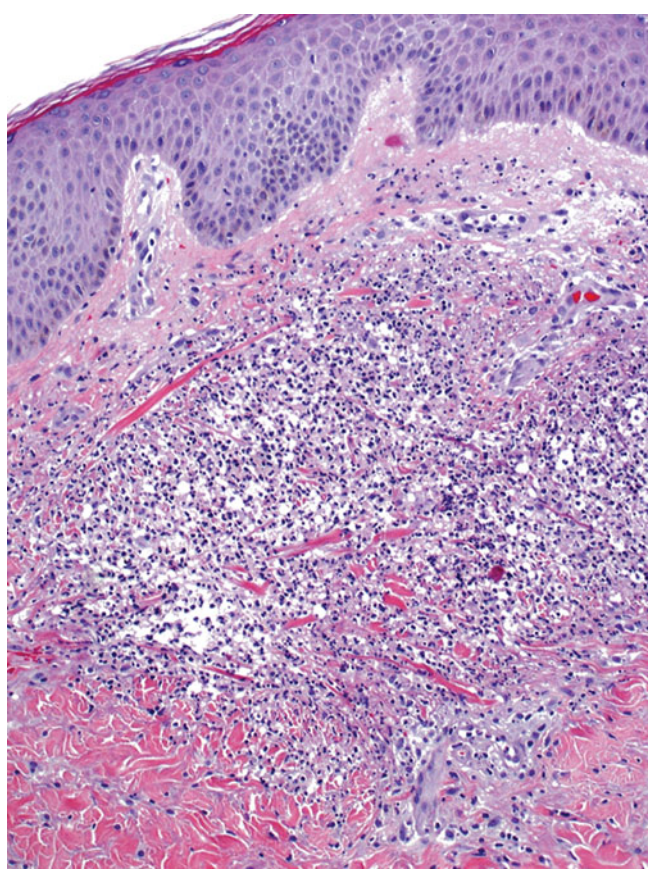
▲ **FIGURE 1-13** Superficial perivascular dermatitis. Nonspecific features of mild lymphocytic infiltrate with no atypia and perivascular edema are seen in this case of self-limited drug rash.

polymorphous light eruption, and secondary syphilis are prone to involvement of the deep dermal vascular plexus (ie, so-called superficial and deep perivascular pattern). Deep infiltrates also may be indicative of a systemic disease process, as in lupus or secondary syphilis. Density of an infiltrate is difficult to assess except in rather subjective terms, such as sparse, moderate, or dense. However, recognizing the density of an infiltrate has relevance for particular disease processes, such as acute urticaria (which is sparse), figurate erythema (which is moderately dense), and cutaneous lymphoid hyperplasia or lymphoma (which tends to be dense).

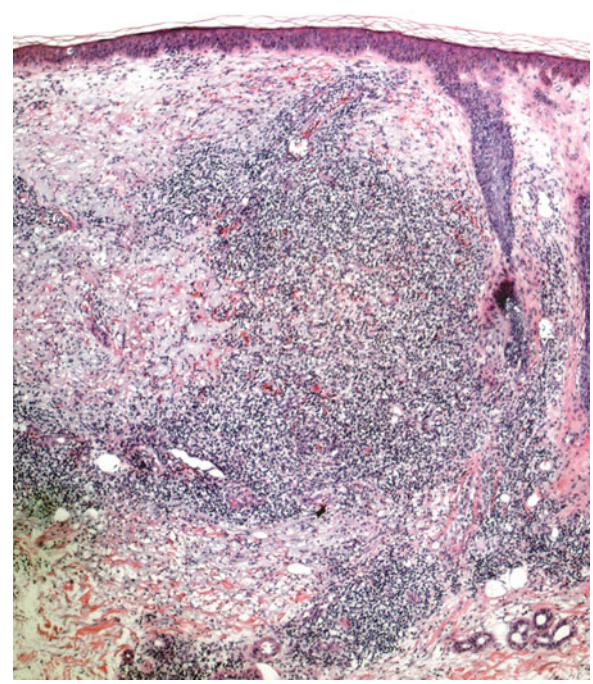
Table 1-6
Dermal Inflammatory Infiltrates without Vascular Injury

*Superficial or superficial and deep perivascular infiltrates**
Urticaria
Urticarial reactions
Viral exanthems
Drug eruptions
Gyrate/figurate erythemas
Lupus erythematosus
Polymorphous light eruption
Photosensitive eruptions
Chilblains/perniosis
Leprosy (indeterminate)
Syphilis
Borreliosis
Leukemia
Urticaria pigmentosa
Nodular infiltrates
Arthropod bite reactions
Cutaneous lymphoid hyperplasia
Histiocytic infiltrates
Neutrophilic dermatoses
Lymphoma
Diffuse infiltrates[a]
Reactive infiltrates
Leukemia
Lymphoma
Histiocytic infiltrates
Mast cell infiltrates

[a]Further classified according to cell types present, such as lymphocytes, eosinophils, neutrophils, and so on.



▲ **FIGURE 1-14** Nodular dermal infiltrates. Multifocal neutrophil-rich dermal infiltrates centered on destroyed follicles likely representing pustular folliculitis.



▲ **FIGURE 1-15** Diffuse dermal infiltrate. Loose lymphoid infiltrate representing cutaneous infiltration by chronic lymphocytic leukemia (CLL).

The cellular infiltrates in the dermis commonly are composed of lymphocytes, possibly with varying admixtures of other cell types, including monocytes/macrophages (histiocytes), eosinophils, neutrophils, plasma cells, and mast cells. The particular cellular composition often has diagnostic significance, particularly when integrated with the other features mentioned earlier, such as pattern, depth, and density. Thus a sparse superficial perivascular infiltrate containing lymphocytes and eosinophils (and often neutrophils) would suggest urticaria. Infiltrates with the same cell types but of greater density (moderate) would suggest the broad category of allergic hypersensitivity reactions, and finally, circumscribed superficial and deep perivascular aggregates of epithelioid macrophages would suggest the sarcoidal granulomatous reaction pattern (see Granulomatous Reaction Patterns).

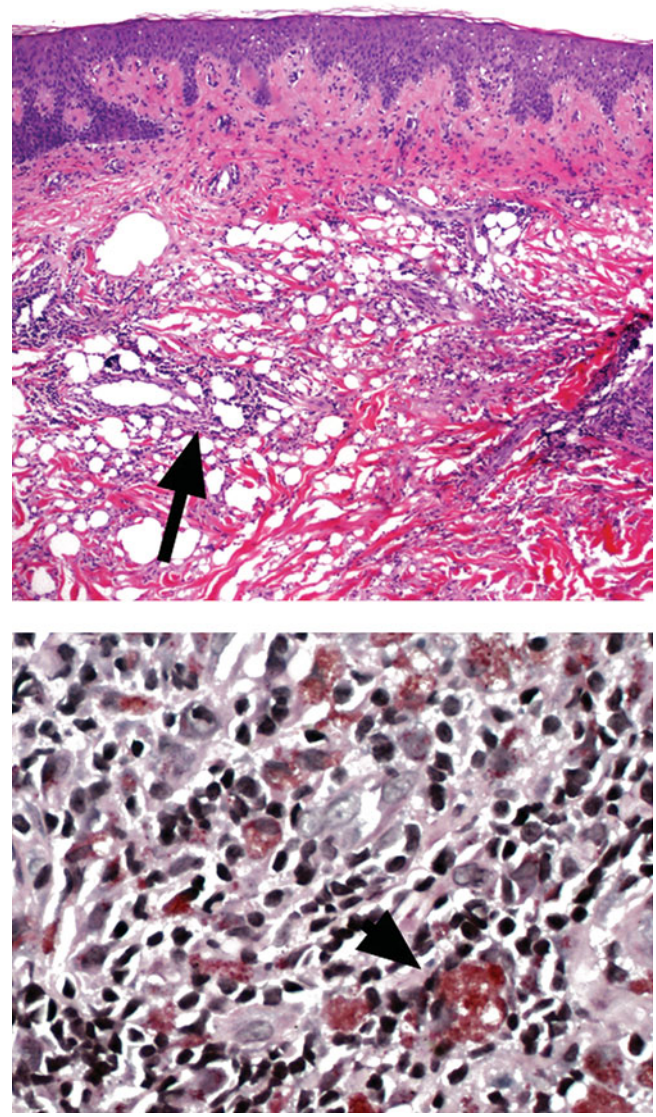
Presence of vascular injury *Vascular injury* refers to a spectrum of morphologic alterations ranging from endothelial perturbation or activation to frank fibrinoid necrosis and the presence of inflammation for an interpretation of vasculitis (Table 1-7). These changes may be primary or secondary (a distinction not always easily made). In assessing vascular injury, a number of parameters must be considered, and these include caliber and type of vessels involved, degree of vascular injury (as already mentioned), the composition and density of the cellular infiltrate, and the presence or absence of such factors as antineutrophil cytoplasmic antibodies (ANCA).

Granulomatous reaction patterns The essential definition of a granuloma is a circumscribed aggregate of macrophages. The cytologic characteristics of such cells vary from mononuclear cells with abundant pale, vacuolated, or lipidized cytoplasm to cells with plentiful pink cytoplasm, resembling epithelial cells and hence the term *epithelioid* cells (Fig. 1-6). Multinucleated giant cells are commonly present and are generally one of two types: foreign-body and Langhans giant cells. Granulomas often contain a variable admixture of other cell types, such as lymphocytes, plasma cells, neutrophils, and mast cells. Poorly defined granulomatous infiltrates often are referred to as *granulomatous inflammation.* Granulomas may be classified in a number of ways, such as infectious (Fig. 1-16) or noninfectious or by morphologic features, acknowledging that there is considerable overlap among many of these entities. A generally accepted scheme is as follows: (1) sarcoidal or epithelioid cell granulomas, (2) tuberculoid or caseating granulomas, (3) foreign-body granulomas, (4) suppurative granulomas, (5) palisading/necrobiotic granulomas, and (6) elastolytic granulomas. In general, these reaction patterns are nonspecific and should prompt a differential diagnosis and systematic evaluation, as discussed in more detail in Chap. 6 (see Fig. 1-6).

Table 1-7
Vasculitis and Related Disorders

Vasculopathy
Small-vessel vasculitis
- Neutrophilic/leukocytoclastic vasculitis
- Lymphocytic vasculitis
- Granulomatous vasculitis

Medium-Sized vessel Vasculitis



▲ **FIGURE 1-16** Granulomatous reaction pattern. Multifocal histiocytic infiltrates in dermis (arrow) and subcutis caused by bacterial infection (bottom panel shows organisms detected by Fite stain, arrow).

Disorders of skin appendages The skin appendages, principally the hair follicle and the eccrine sweat apparatus, may show primary inflammatory involvement.

Disorders of the hair follicle In general, folliculitis is categorized as to whether it is infectious or noninfectious and according to its depth: superficial only or superficial and deep. Acne is an extremely common form of folliculitis that has a multifactorial basis, for example. The hair follicle also may show a peculiar reaction—follicular mucinosis—which may be associated with a number of processes, including mycosis fungoides and inflammatory

conditions such as arthropod bites and lupus erythematosus.

Alopecia histologically refers to an overall reduction in the number of terminal anagen hair follicles, which may be reversible or irreversible. Operationally (and perhaps simplistically), alopecia may be classified as nonscarring or scarring. Nonscarring alopecias may result from any number of factors interrupting the hair growth cycle, whether inflammatory, as in the case of alopecia areata, or noninflammatory, as in androgenetic alopecia or telogen effluvium. Scarring alopecia follows a wide variety of processes such as infective folliculitis, lupus erythematosus, lichen planus, or traumatic injury.

Disorders of the sweat apparatus The eccrine duct may be involved primarily in an inflammatory reaction termed miliaria and categorized according to depth of involvement as (superficial) miliaria crystallina, miliaria rubra, and miliaria profunda. Hidradenitis refers to an inflammatory disorder involving the sweat coil as in neutrophilic eccrine hidradenitis, which may be infectious or noninfectious.

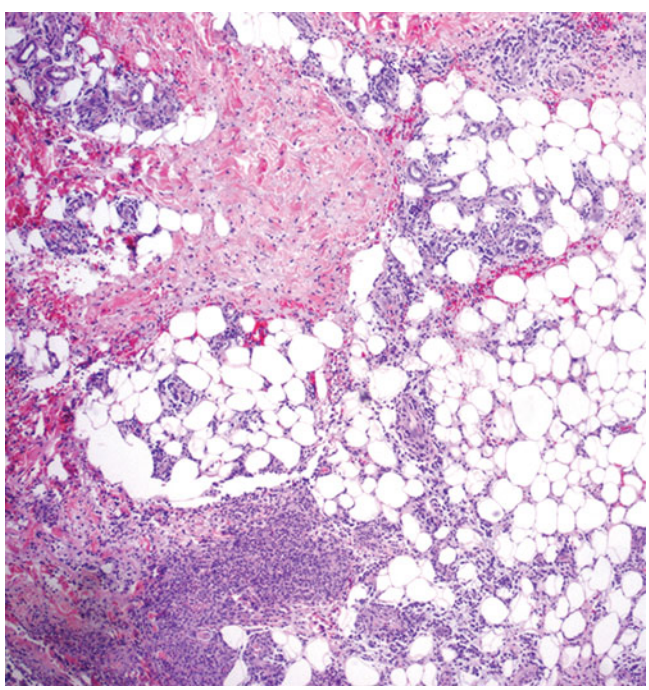
Panniculitis The primary focus of inflammation may be in the subcutaneous fat, fascia, or both. Although traditionally panniculitis has been classified as septal or lobular, in fact, in most instances the inflammatory process is both septal and lobular, often spreading from the septae. Particular factors that should be considered when evaluating panniculitis include presence or absence of infection, vascular injury, cold-related injury, factitial disease, or physical injury. Adequate sampling and the stage of disease when the biopsy is taken will influence the morphologic findings observed. The reaction pattern of adipose tissue to injury is rather limited. Initially one observes an influx of neutrophils (erythema nodosum pattern, Fig. 1-17), followed by mononuclear cells (lymphocytes and macrophages), and finally, reparative fibrosis (Fig. 1-18), depending on the nature and severity of the insult.

Proliferative or Neoplastic Conditions

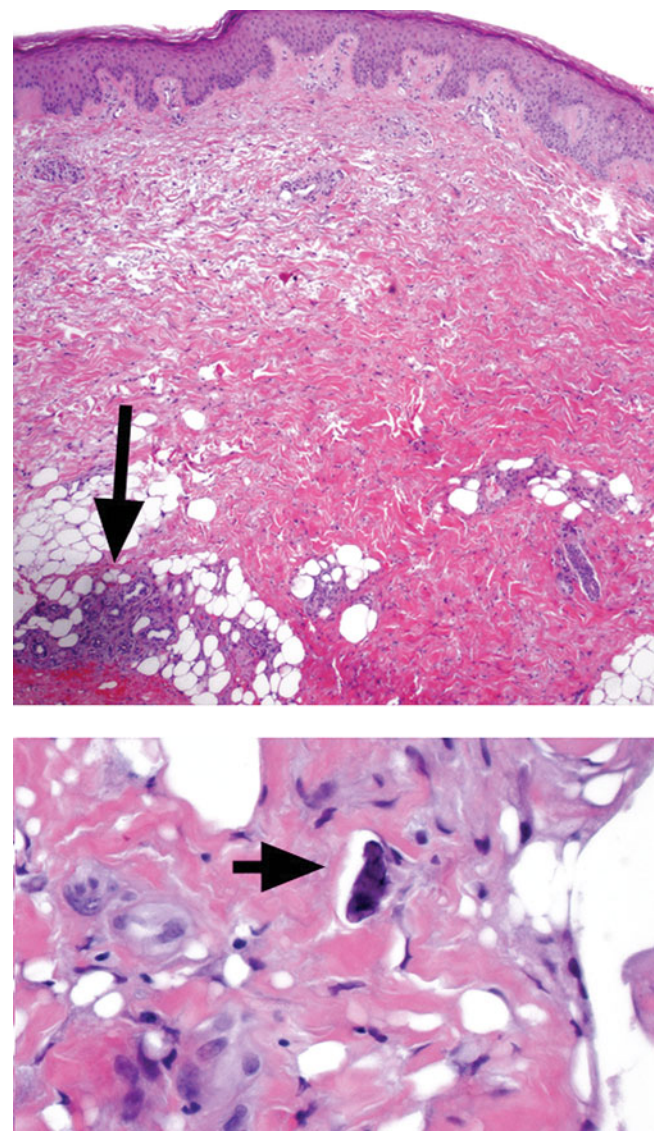
A large category of conditions encompasses hyperplasias, hamartomas, and benign and malignant neoplasms involving the epidermis, melanocytes, skin appendages, dermis, subcutis, and hematopoietic cells in the skin.

Noninflammatory Conditions

In the absence of an obvious inflammatory dermatitis or proliferative/neoplastic process, one must proceed along the



▲ **FIGURE 1-17** Panniculitis (erythema nodosum reaction pattern). Dense neutrophil-rich inflammatory infiltrates extending out from the fibrous septae into the fat lobules in a patient undergoing treatment for Hodgkin lymphoma.



▲ **FIGURE 1-18** Panniculitis with fibrous replacement. Histiocyte-rich lobular and septal panniculitis with ischemic fat necrosis and progressive fibrosis and calcification (bottom panel arrow) caused by lipodermatosclerosis (venous insufficiency).

Table 1-8
Differential Diagnosis of "Normal Skin"

Superficial fungal infection	
Dermatophytosis and tinea versicolor	Hyphae and spores in stratum corneum
Porokeratosis	Cornoid lamella
Ichthyosis	Slight hyperkeratosis, diminished or absent granular layer
Hypopigmentation	Diminished or absent basal layer melanin, melanocytes
Vitiligo	
Piebaldism	
Chemical leukoderma	
Nevus depigmentosus	
Hyperpigmentation	Increased basilar melanin and possibly melanocytes
Café-au-lait macule	
Freckle	
Melasma	
Lentigo	
Macular amyloidosis	Pink amorphous globules in papillary dermis
	Pigment incontinence
Onchocerciasis	Microfilaria in superficial dermis
Dermal melanocytosis	Dendritic melanocytes in dermis
Urticaria pigmentosa	Increased numbers of mast cells in dermis
Argyria	Deposition of silver granules in basement membranes, particularly surrounding eccrine sweat coils
Urticaria	Sparse perivascular infiltrate
	Edema
Anhidrotic ectodermal dysplasia	Absence of eccrine sweat glands
Anetoderma	Focal or diffuse absence of elastic tissue
	Inflammation present or absent
Cutis laxa	Absence of elastic fibers
Connective tissue nevus	Increased or decreased collagen and/or elastin
	Abnormal connective tissue
Dermal mucinosis	Increased dermal mucin
Myxedema	
Scleromyxedema	
Atrophoderma	Decreased thickness of dermis
Lipoatrophy	Fat lobules diminished in size

algorithm now considering noninflammatory conditions. Histologic alterations may suggest "normal skin" and may include the so-called invisible dermatoses (Table 1-8).[6,7] As already outlined earlier, one generally must resort to systemic study of the specimen beginning with the stratum corneum or perhaps with the subcutis in the reverse order. It goes without saying that the histopathologist should have some understanding of the regional microanatomy and age-related variations of skin in order to know what is within normal limits.

ALTERATIONS OF STRATUM CORNEUM AND EPIDERMIS The stratum corneum is studied for subtle abnormalities such as parakeratosis, hyperkeratosis, and fungal elements. The epidermis is inspected for acanthosis, atrophy, subtle alterations suggesting an inflammatory or vesicular reaction, alterations of the granular layer as in ichthyosiform dermatitides, peculiar processes such as epidermolytic hyperkeratosis, and finally, pigmentary alterations associated with hypo- and hyperpigmentation.

ALTERATIONS OF PAPILLARY DERMIS The papillary dermis is then studied for alterations such as deposition of amyloid, hyalinization of vessels as in porphyria, and incontinence of melanin (melanin-laden macrophages in papillary dermis).

ALTERATIONS OF RETICULAR DERMIS The reticular dermis is examined systematically for alterations of collagen as in morphea/scleroderma or scleredema, thickening or atrophy of the reticular dermis, alterations of elastic fibers, and deposition of materials such as mucin or amyloid.

REFERENCES

1. Ackerman A, Boer A, Bennin B, Gottlieb G. *Histologic Diagnosis of Inflammatory Skin Diseases: A Method of Pattern Analysis*. 3rd ed. Philadelphia, PA: Lea & Febiger; 2005.
2. Ackerman AB. An algorithmic method for histologic diagnosis of inflammatory and neoplastic skin diseases by analysis of their patterns. *Am J Dermatopathol*. 1985; 7(2):105-107.
3. Ackerman AB. Differentiation of benign from malignant neoplasms by silhouette. *Am J Dermatopathol*. 1989;11(4):297-300.
4. Murphy BW, Webster RJ, Turlach BA, et al. Toward the discrimination of early melanoma from common and dysplastic nevus using fiber optic diffuse reflectance spectroscopy. *J Biomed Opt*. 2005;10(6): 064020.
5. Nathwani B, Burke J, Winberg C. Architectural features of normal, neoplastic, and nonneoplastic lymph nodes: a practical diagnostic approach. In: Murphy G, Mihm M, eds. *Lymphoproliferative Disorders of the Skin*. Boston, MA: Butterworths; 1986.
6. Bernhard JD. Invisible dermatoses versus nonrashes. *J Am Acad Dermatol*. 1983;9(4): 599-600.
7. Brownstein MH, Rabinowitz AD. The invisible dermatoses. *J Am Acad Dermatol*. 1983;8(4):579-588.

CHAPTER 2

Spongiotic Dermatitis

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INTRODUCTION

The term spongiotic dermatitis refers to a large group of inflammatory disorders that share the histopathologic finding of spongiosis, characterized by impairment of cohesion between epidermal keratinocytes and intercellular edema (Fig. 2-1 and Table 2-1). Spongiosis is the hallmark of eczematous dermatitides, but can be seen in a variety of other skin conditions (Table 2-2). The mechanisms underlying the pathogenesis of spongiotic changes have only recently begun to be elucidated.[1,2] Skin-infiltrating T-cells damage the epidermis by releasing proinflammatory cytokines and induce keratinocyte apoptosis through "killer molecules."[1,2] There is subsequent cleavage of adhesion molecules, including E-cadherin, on keratinocytes.[1,2] Accumulation of extracellular fluid results in widening of the spaces between keratinocytes, causing the epidermis to resemble a sponge histologically.[1,2]

Other terms used to refer to these diseases include eczema, eczematous dermatitis, or simply dermatitis. The clinical appearance of the spongiotic dermatoses can vary significantly, depending on the duration, etiology, and location of the lesions and the presence of superimposed secondary changes such as excoriation. However, the salient clinical finding is that of epidermal alteration. These primary and secondary epidermal changes may include erythema, vesiculation, scaling, crusting, lichenification, hyperpigmentation, excoriation, oozing, erosions, or fissures. Most lesions of spongiotic dermatitis are poorly demarcated clinically, with the notable exceptions of nummular dermatitis (round well-defined, coin-shaped plaques) and some lesions of contact dermatitis. Collectively, the spongiotic dermatoses are among the most common cutaneous disorders presenting to dermatologists and primary care providers.

Spongiotic dermatitis is conventionally divided into acute, subacute, and chronic stages (Table 2-3). A single lesion may evolve through these three stages; however, not all lesions do this. The classic example of *acute spongiotic dermatitis* is acute allergic contact dermatitis, such as that caused by exposure to poison ivy. Acute spongiotic dermatitis is characterized histologically by significant intercellular edema with formation of spongiotic microvesicles or even macrovesicles (that can be seen clinically) (Figs. 2-2 to 2-3). An associated superficial, perivascular inflammatory infiltrate composed of lymphocytes, histiocytes, some eosinophils, and occasionally associated extravasated red blood cells is noted. Subepidermal edema may also be prominent. The stratum corneum may still be normally cornified without parakeratosis. The clinical lesion reflects these histologic features; appearing as edematous, inflamed oozing papules and plaques, often with visible vesicles. A lesion of *subacute spongiotic dermatitis* usually demonstrates spongiosis with formation of some microvesicles, and overlying parakeratosis (Figs. 2-4 to 2-6). Mild epidermal acanthosis may be a feature. A superficial perivascular inflammatory infiltrate of lymphocytes, histiocytes, with or without eosinophils is present in the dermis, but papillary dermal edema is not a prominent feature. Good examples of subacute spongiotic dermatitis are lesions of atopic dermatitis and nummular dermatitis present for several weeks. Clinically these lesions are scaling pink-to-red papules and plaques, often with secondary changes such as excoriation. Many lesions of subacute spongiotic dermatitis become chronic (such as the atopic dermatitis) (Figs. 2-7 to 2-9). *Chronic spongiotic dermatitis* describes lesions that have been present for a time and demonstrate changes of repair and/or secondary changes, in addition to spongiosis. Chronic spongiotic dermatitis lesions can show compact hyperkeratosis, acanthosis with hypergranulosis, spongiosis, and sometimes papillary dermal fibrosis due to chronic rubbing (Fig. 2-10). Spongiosis is usually minimal and only focal in chronic lesions. These lesions present as lichenified, firm papules and plaques with accentuation of skin lines and often with postinflammatory pigmentary changes (hyperpigmentation more commonly than hypopigmentation).

The most common inflammatory cells identified in the spongiotic epidermis are lymphocytes, often in association with Langerhans cell microvesicles (Fig. 2-11), but as discussed later in this chapter, other cells may predominate, including eosinophils and/or neutrophils, resulting in changes of *eosinophilic spongiosis* and *neutrophilic spongiosis*, respectively. A PAS stain to exclude dermatophytoses should be performed in all biopsies showing spongiosis, particularly those associated with neutrophil exocytosis (Fig. 2-12).

Secondary Changes

Because spongiotic dermatoses are often pruritic, secondary changes are common. The most frequently identified secondary changes seen in association with spongiosis include: (a) superimposed infection; (b) lichenification/lichen simplex chronicus, secondary to chronic rubbing (Fig. 2-13 and 2-14); (c) prurigo nodularis, secondary to chronic picking (Fig. 2-15); and (d) erosions or ulcers secondary to excoriations.

Patients chronically rub itchy spongiotic dermatoses. As a result, the skin clinically becomes thickened and papular with accentuation of normal skin markings, hyperpigmentation, and scaliness (Table 2-4).

Superimposed infection or secondary impetiginization is not an infrequent complication. This change is secondary to the scratching of these often intensely pruritic eruptions. The resultant bacterial infection overlying the changes of the spongiotic dermatitis results in abundant scale-crust laden with bacteria that can be identified on routine staining and highlighted with a Gram stain. In more severe cases vesiculopustules may be identified.

Eosinophilic Spongiosis

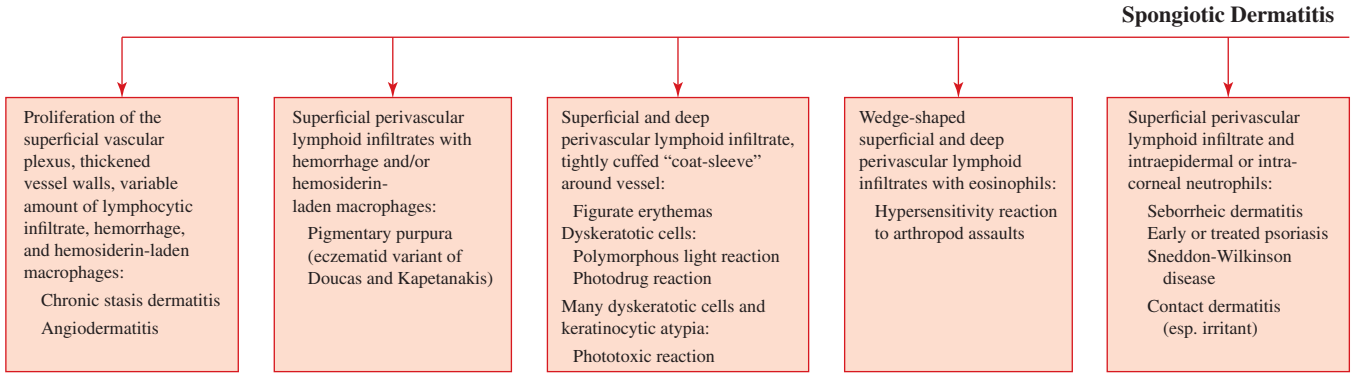
Eosinophilic spongiosis describes a reaction pattern in which there is exocytosis of eosinophils associated with changes of spongiosis (Figs. 2-16 to 2-17).[3-6] These changes can be seen in a variety of inflammatory dermatoses, described in other chapters (Table 2-5).

Neutrophilic Spongiosis

A heterogeneous group of dermatoses can demonstrate neutrophilic spongiosis (Figs. 2-12, 2-18, and 2-19), described as the presence of neutrophil exocytosis with epidermal spongiosis (Table 2-6).[4,7,8] Occasionally, neutrophils can form collections within the epidermis (ie, spongiform pustules).

Contact Dermatitis

Contact dermatitis describes an inflammatory skin reaction to an exogenous agent. Two variants have been described: (1) allergic contact dermatitis and (2) irritant contact dermatitis.[9-16] Allergic contact



▲ **FIGURE 2-1** Algorithm for spongiotic dermatitis.

Table 2-1
Differential Diagnosis of Spongiotic Dermatoses

ENTITY	DISTINGUISHING HISTOLOGIC FINDING
Allergic contact dermatitis	Eosinophilic spongiosis
	Spongiotic micro- and macrovesiculation
Irritant contact dermatitis	Neutrophils
	Ballooning
	Necrosis
Photoallergic contact dermatitis	Eosinophilic spongiosis
	Necrotic keratinocytes
Phototoxic dermatitis	Sunburn (necrotic) keratinocytes
	Pallor of keratinocytes
	Neutrophils
Dermal/protein contact dermatitis	Prominent papillary dermal edema
Atopic dermatitis	Epidermal acanthosis
	Prominent vasculature
	Secondary changes of LSC
Fox-Fordyce disease	Follicular infundibular spongiosis
Nummular dermatitis	None
Pompholyx	Vesiculopustules
Seborrheic dermatitis	Parakeratosis at lips of follicular ostia
Id reaction	None
Asteatotic eczema	None
Sulzberger-Garbe syndrome	Genital skin
Pityriasis rosea	Mounds of parakeratosis
	Extravasated red blood cells
Exfoliative erythroderma	Depends on underlying disease
Stasis dermatitis	Thick-walled venules
	Extravasated red blood cells
	Hemosiderin deposition
	Fibrosis
Spongiotic drug eruptions	Spongiotic ± interface changes
	Necrotic keratinocytes
	Eosinophils
Pityriasis alba	Follicular spongiosis
	Parafollicular parakeratosis
	Decreased melanization in basal layer
	Reduction in basal melanocytes
	Melanophages
Gianotti-Crosti syndrome	Spongiotic ± interface changes
	Lymphocyte exocytosis
	Papillary dermal edema
PUPPP	None
Incontinentia pigmenti	Eosinophilic spongiosis
	Dyskeratotic squamous cells
Miliaria	Involvement of eccrine duct

Table 2-2
Skin Diseases in which Spongiosis May be Seen

Dermatophytosis
Erythema neonatorum
Grover disease, spongiotic variant
Gyrate erythemas
Lichen striatus
Mycosis fungoides
Parapsoriasis
Pigmented purpuric dermatoses
Pityriasis lichenoides
Polymorphous light eruption
Primary syphilis
Psoriasis, early or treated
Reaction to arthropod assault

dermatitis is a type IV delayed hypersensitivity reaction in the skin of a patient who has been previously sensitized to an allergen. Common allergens include nickel, urushiol (poison ivy), and topical medications, including local anesthetics and topical antibiotics. Irritant contact dermatitis is due to exposure to chemical or physical agents that induce direct (non–immunologically mediated) damage to the skin. Common offending agents include detergents, soaps, some sunscreens, acids, and alkalis. Irritant contact dermatitis is the most common mechanism of occupational hand dermatitis. Irritant contact dermatitis occurs more quickly after exposure, tends to resolve more quickly, and is more common than allergic contact dermatitis, but it may be difficult to distinguish allergic and irritant contact dermatitis from each other or from other spongiotic dermatitides on the basis of clinical or histopathologic features. In addition, some agents may act as both an irritant and an allergen.